Tetrahedron Vol. 40, No. 5, pp. 811 to 850, 1984
Printed in Great Britain

0040-4020/84 $5.00 + .00
Pergamon Press Ltd.

TETRAHEDRON REPORT NUMBER 160

ELECTROORGANIC CHEMISTRY IN ORGANIC SYNTHESIS

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(*Received in the UK* 1 *March* 1983)

CONTENTS

INTRODUCTION

Since electroorganic chemistry seems rather unfamiliar to those investigating organic synthesis,[1] the purpose of this review is to show that electroorganic chemistry is one of the promising tools for organic synthesis.

Electroorganic chemistry can be said to be a new area of organic chemistry, and hence its definition has not necessarily been established yet. Although the electrolysis of organic compounds has been studied rather extensively, the concept of electrolysis is not always the same as that of electroorganic chemistry. Electroorganic chemistry can be classified into two categories, that is, direct and indirect reactions. In both categories, the reaction is initiated by transfer of electron between electrode and a substrate A, and, as shown in eqn (1), the substrate A is transformed to an anion radical or a cation radical depending on the direction of the transfer of electron. When the starting substrate A is a radical or ionic species, the pattern of transformation of A is such as shown in eqn (2), where $-e$ means the removal of one electron, and $-2e$ means removal of two electrons; $-[e]$ means removal of electrons in appropriate numbers.

$$A^{2-} \underset{+e}{\overset{-e}{\rightleftharpoons}} A^{-\cdot} \underset{+e}{\overset{-e}{\rightleftharpoons}} A \underset{+e}{\overset{-e}{\rightleftharpoons}} A^{+\cdot} \underset{+e}{\overset{-e}{\rightleftharpoons}} A^{2+} \tag{1}$$

$$A^{-} \underset{+e}{\overset{-e}{\rightleftharpoons}} A\cdot \underset{+e}{\overset{-e}{\rightleftharpoons}} A^{+} \tag{2}$$

Thus, the definition of electroorganic chemistry is to investigate the chemical behavior of an activated species of A in solution. The generation of the similar activated species may be possible by using common organic reactions. The chemical behavior of the same activated species is, however, often different between electroorganic chemistry and common organic chemistry. One of the major causes of this difference is that in an electroorganic reaction, the activated species is not formed uniformly in homogeneous solution, but is generated only on the surface of electrode, whereas in common organic reactions, the active species is uniformly distributed in the solution.

This difference in location of generation of activated species and in distribution of activated species brings about great difference in the reaction of the activated species.

Viewed from the standpoint of organic synthesis, electroorganic chemistry has a remarkable characteristic. In common organic reactions the reaction generally takes place between nucleophilic reagents (Nu) and electrophilic reagents (E), while reaction between reagents of the same polarity is not possible. Therefore, the inversion of polarity of one of the reagents is essential for carrying out the reaction between Nu and Nu or E and E. The inversion of polarity of reagents (Umpolung) is, however, not facile in common organic reactions, whereas in electroorganic reaction, the process of formation of the activated species is the Umpolung itself as shown in eqns (1) and (2). Thus, one of the major characteristics of electroorganic chemistry is the facility of Umpolung, which makes a variety of organic syntheses possible.

Since it is impossible to show all the areas of electroorganic chemistry in this rather short paper, the anodic oxidation of amine derivatives and its application to organic synthesis are described as one of the examples of the direct reaction, and also indirect anodic reactions are briefly surveyed. Because of the difficulty of citing all the references related to this review, many of the data are collected from the studies carried out in the author's laboratory to make this review concise.

ELECTROOXIDATION OF AMINES AND THEIR DERIVATIVES

Oxidation of simple aliphatic amines

The oxidation potentials of simple aliphatic amines are relatively low. Among them, primary amines show higher oxidation potentials, whereas tertiary amines are the most easily oxidizable as shown in Table 1.[2,3] The reaction pathway of simple aliphatic amines is relatively complex and is highly affected by reaction conditions such as solvent, electrode material, and anode potential.

(i) *Reaction in acetonitrile.* Acetonitrile is a commonly used solvent in the study on the mechanism of the oxidation of amines. Amines are generally oxidatively dealkylated in acetonitrile containing a neutral supporting electrolyte like sodium perchlorate.

Primary amine[4]

$$n\text{-PrNH}_2 \xrightarrow[\substack{1.2\text{ V vs Ag/Ag}^+\\ \text{CH}_3\text{CN-NaClO}_4\\ \text{two compartment cell}}]{-[e]}$$

$$\underset{Y=52\%}{n\text{-PrNH}_2} + \underset{Y=14\%}{\text{NH}_4\text{ salt}} + \underset{Y=25\%}{\text{NH}_3} + \underset{Y=4\%}{\text{CH}_3\text{CH}_2\text{CHO}} + \underset{Y=22\%}{\text{N}_2} \qquad (3)$$

Table 1. Oxidation potentials of simple aliphatic amines

Compound	E_p (V *vs.* NHE)[2]	E_p (V *vs.* Ag/Ag^+)[3]
n-$PrNH_2$	1.63	1.58
n-$BuNH_2$	1.63	—
t-$BuNH_2$	1.64	—
$(n\text{-Pr})_2NH$	1.26	—
$(n\text{-Bu})_2NH$	1.31	—
$(PhCH_2)_2NH$	1.49	—
$(n\text{-Pr})_3N$	1.02	0.64
$(n\text{-Bu})_3N$	1.02	—
$(PhCH_2)_3N$	1.27	—

Sweep rate 10 V/sec. 25 °C. 0.100 M $NaClO_4$ in CH_3CN.
2 - 7 mM amine concentration.

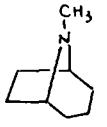
Secondary amine[5]

$$(n\text{-Pr})_2NH \xrightarrow[\substack{CH_3CN\text{-}NaClO_4 + H_2O \\ 1.40\ V\ vs\ Ag/Ag^+}]{-[e]}$$

$$CH_3CH_2CHO + n\text{-}PrNH_2 + n\text{-}PrNH_3^+ \qquad (4)$$
$$Y = 25.3\% \quad Y = 16.9\% \quad Y = 49\%$$

Tertiary amine[6].

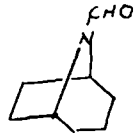
$$(n\text{-Pr})_3N \xrightarrow[\substack{CH_3CN\text{-}NaClO_4 \\ 1.00\ V\ vs.\ Ag/Ag^+}]{-2e} (n\text{-Pr})_3\overset{+}{N}H + (n\text{-Pr})_2\overset{+}{N}H_2 \qquad (5)$$
$$Y = 65\% \qquad Y = 15\%$$



tropane

$$\xrightarrow[CH_3CN\text{-}NaClO_4]{-2e}$$

+ tropane +



(6)[7]

Y = 13.6% Y = 57.6% Y = 5.3%

nortropane

The addition of water into the reaction medium increases the formation of carbonyl compounds.[6,8]

$$(n\text{-Pr})_3N \xrightarrow[\substack{10\%\ H_2O\text{-}CH_3CN\text{-}NaClO_4 \\ 0.80\ V\ vs\ Ag/Ag^+}]{-2e}$$

$$(n\text{-Pr})_3NH^+ + (n\text{-Pr})_2\overset{+}{N}H_2 + CH_3CH_2CHO \qquad (7)$$
$$Y = 54\% \qquad Y = 53\% \qquad Y = 48\%$$

The oxidation is initiated by the direct removal of one electron from the lone pair electrons of nitrogen.[8] Water hydrolyses the intermediate iminium ion to the carbonyl compound.

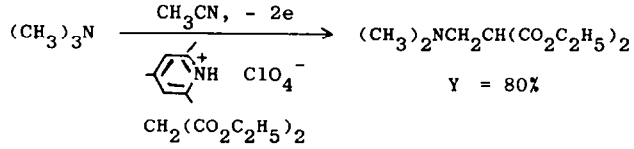
$$(n\text{-Pr})_3N \xrightarrow{-e} (n\text{-Pr})_3\overset{+\cdot}{N} \xrightarrow{-e,\ -H^+} (n\text{-Pr})_2\dot{N}\text{-}\overset{+}{C}H\text{-}C_2H_5$$

$$\xrightarrow[\text{base (B)}]{H_2O} (n\text{-Pr})_2N\text{-}CH(OH_2)\text{-}CHCH_3 \longrightarrow$$

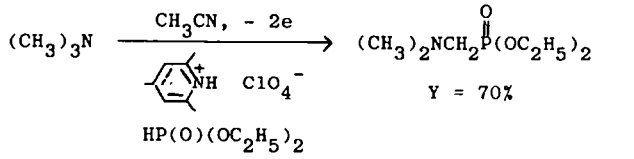
$$(n\text{-Pr})_2NH + CH(OH)\text{=}CH\text{-}CH_3 + BH^+ \qquad (8)$$

The intermediary formation of a cation radical has been observed by ESR method in the oxidation

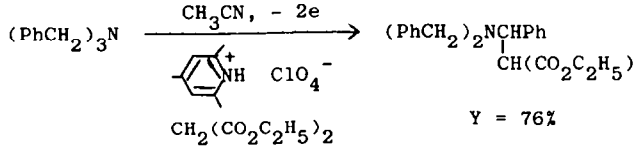
of 1,4-diazabicyclo[2.2.2]octane[9] and the intermediate iminium cation can be trapped by nucleophiles as exemplified below.[10]



(9)

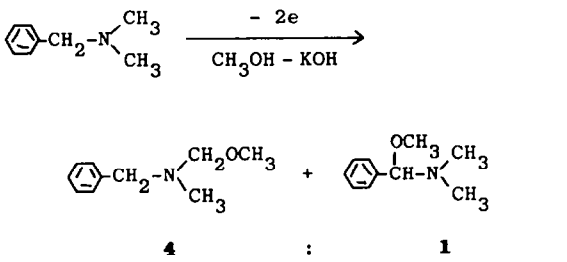


(10)



(11)

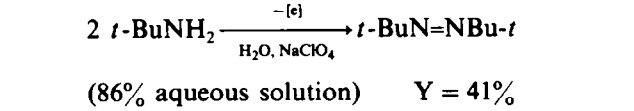
(ii) *Reaction in methanol or water.* In the reaction carried out in acetonitrile using neutral salts like $NaClO_4$ as supporting electrolyte, a proton generated through deprotonation of the cationic intermediate obstructs the oxidation and decreases the yield, since the proton adds to the starting amine to form a protonated amine which is inactive in the anodic oxidation. Also, the reaction carried out in acetonitrile often yields a complex mixture of products, so that it is not always useful as a tool in organic synthesis. On the other hand, under basic conditions, the reaction carried out in a nucleophilic solvent or in the presence of a nucleophile gives the oxidized products in reasonable yields. For instance, benzyldimethylamine gives the methoxylated products (12).[11]



(12)

The cyanation of amines has been achieved by carrying out the reaction in aqueous methanol using sodium cyanide as an electrolyte (Table 2).[12] The mechanism of cyanation is almost the same as eqn (8) except that the iminium cation intermediate reacts with cyanide anion rather than with water, as cyanide anion is sufficiently nucleophilic. The regioselectivity of this cyanation has not been explained clearly, but it has been proposed that the conformation of the adsorbed amine on the anode plays an important role in the determination of the regioselectivity.

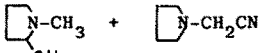
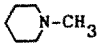
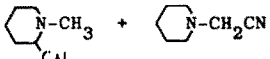
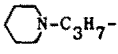
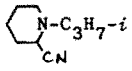
(iii) *Formation of a nitrogen–nitrogen bond.* When the concentration of amine is sufficiently high, the amine behaves as a nucleophile to yield a hydrazine derivative or an azo compound.[13]



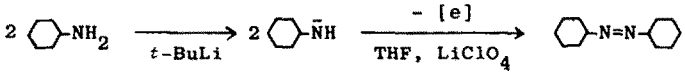
(13)

If the concentration of amine is low, the yield of azo compound is only trace. Some of the other reactions are shown below.

Table 2. Anodic cyanation of tertiary amines[a]

Amine	Anode potential (V *vs.* SCE)	Product	Yield (%)[b]
$(CH_3)_3N$	1.2 - 1.4	$(CH_3)_2NCH_2CN$	53
$(C_2H_5)_3N$	1.1 - 1.2	$(C_2H_5)_2NCHCN$ (CH$_3$)	53
$(C_2H_5)_2NCH_3$	1.0 - 1.2	$(C_2H_5)_2NCH_2CN$ (57) + $C_2H_5N(CH_3)CHCNCH_3$ (43)	37
$(i\text{-}C_3H_7)_2NCH_3$	0.9 - 1.1	$(i\text{-}C_3H_7)_2NCH_2CN$	55
	1.0 - 1.3	 (81) (19)	59
	1.1 - 1.4	 (62) (38)	66
	1.0 - 1.2		62

[a]Anolyte: amine (0.10 mol) + NaCN (0.15 mol) in 75ml of $CH_3OH - H_2O$ (1:1)
[b]GLC



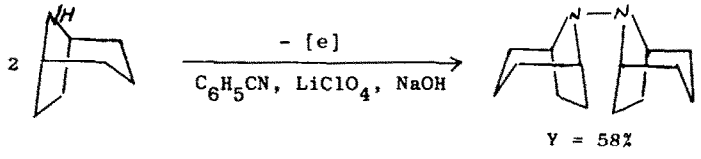
Y = 23%

(14)[14]

$$2(n\text{-}C_4H_9)_2NH \xrightarrow[THF,\ LiClO_4]{-[e]} (n\text{-}C_4H_9)_2N\text{-}N(n\text{-}C_4H_9)_2$$

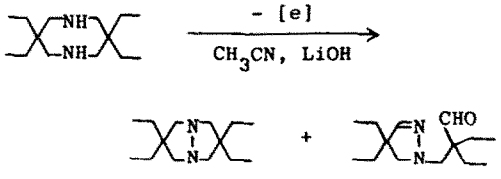
Y = 38%

(15)[14]



Y = 58%

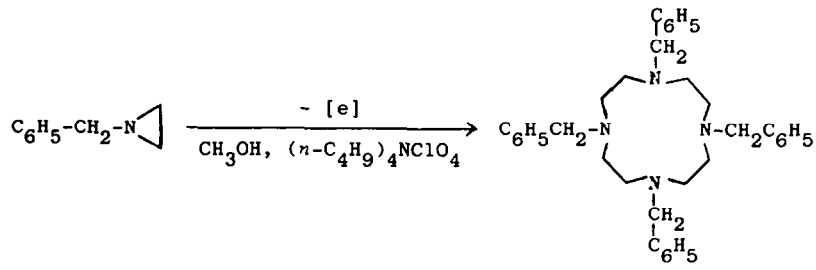
(16)[15]



Y = 14% Y = 10%

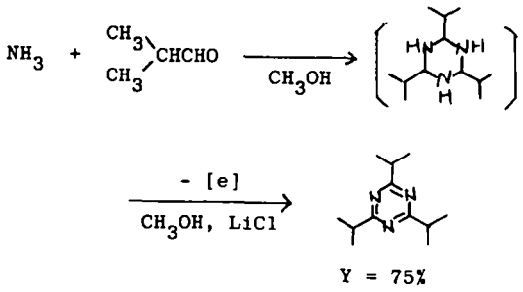
(17)[16]

Azirizine yields a tetramer.[17]



(18)

(iv) *Aromatization.* When the amine has an appropriate structure for aromatization, anodic oxidation may give an aromatic compound.[18]

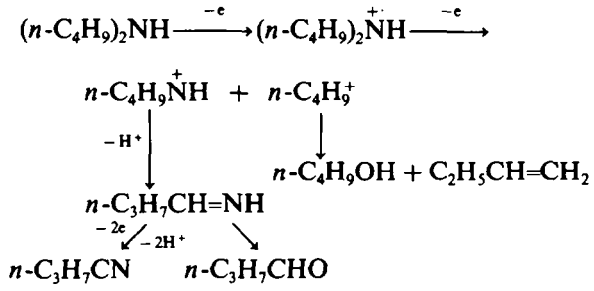


(19)

(v) *Effect of electrode materials.* The reaction pathway of the oxidation of aliphatic amines is considerably affected by the material of electrode. Formation of nitrile is the typical nature of silver electrode.[19,20]

$$(n\text{-}C_4H_9)_2NH \xrightarrow[\text{Ag electrode}]{-[e]} n\text{-}C_3H_7CHO + n\text{-}C_3H_7CN + n\text{-}C_4H_9OH \tag{20}$$

Formation of nitrile is explained by the following reaction scheme.



(21)

Nickel electrode also gives nitrile.[21]

$$C_2H_5NH_2 \xrightarrow[\text{Ni electrode}]{-[e]} CH_3CN \tag{22}$$

$$Y = 68\%$$

Regioselectivity in the oxidation of aliphatic amines

Some regioselectivity has been observed in the anodic oxidation of asymmetric amines. For example, in the oxidation of diisopropylethylamine or dicyclohexylethylamine, the reaction mainly

takes place at the ethyl group.[5,6] The anodic methoxylation of benzyldimethylamine shows a peculiar regioselectivity, which is one of the most extensively studied problems to discuss the regioselectivity of anodic oxidation of amines.[11,22]

$$C_6H_5CH_2N(CH_3)_2 \xrightarrow[CH_3OH,\,KOH]{-2e} C_6H_5\underset{\displaystyle OCH_3}{\underset{|}{C}}HN(CH_3)_2 + C_6H_5CH_2\underset{\displaystyle CH_3}{\underset{|}{N}}-CH_2OCH_3 \qquad (23)$$

1 : **4**

In the usual chemical reaction, the carbonium ion on a benzylic position is much more stable than that on a terminal carbon atom, and hence the benzylic position seems to be the most favorable position for the methoxylation. The results obtained in the anodic reaction are, however, remarkably different. The methoxylation mainly takes place at the terminal methyl group. This peculiar regioselectivity has been explained by a steric hindrance at the benzylic position, since benzyldimethylamine is adsorbed on the anode at both the aromatic ring and nitrogen atom. This explanation, however, has not been established yet, since similar regioselectivity has also been observed in the photochemical oxidation of amines carried out in a homogeneous solution.[23] The regioselectivity of anodic oxidation of asymmetric amines is affected by types of the supporting electrolyte and anode potential. For instance, the ratio between the reactions at benzylic position and at terminal methyl group in the anodic oxidation of benzyldimethylamine changes with

$$C_6H_5CH_2N\begin{matrix}CH_3\\CH_3\end{matrix} \xrightarrow[CH_3OH]{-2e} \underset{\mathbf{A}}{C_6H_5CHO} + \underset{\mathbf{B}}{C_6H_5CH_2NHCH_3} + \underset{\mathbf{C}}{C_6H_5CH_2NH_2} \qquad (24)$$

A : Product of oxidation at the benzylic position

B,**C** : Product of oxidation at the methyl group

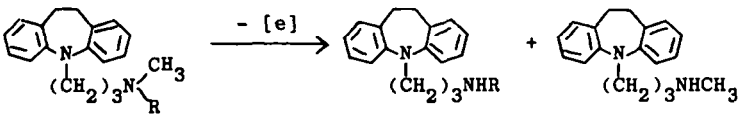
changing supporting electrolytes and anode potentials as shown in Table 3.[24] These results have been explained by the difference of basicity of the reaction medium.

The regioselectivity observed in the anodic oxidation of some aliphatic amines shows a remarkable similarity with that in the enzymatic reaction catalyzed by cytochrome P-450 monooxygenase system. For example, the anodic and liver microsomal N-dealkylation of derivatives of imipramine are shown in Table 4, in which the regioselectivity observed in both reactions shows reasonable similarity.[25]

Table 3. Effect of supporting electrolytes and anode potentials on the regioselectivity

Supporting electrolyte	Potential (V *vs.* SCE)	Ratio $\frac{\text{attack on mehtyl}^a}{\text{attack on benzyl}}$
n-Bu_4NBF_4	+ 1.05	10.1
	+ 1.60	7.0
	+ 1.90	5.8
	+ 2.30	5.6
KOH	+ 1.0	2.0
	+ 1.1	2.3
	+ 2.3	2.3

[a]Not corrected on the number of α-hydrogens.



(25)

R : C_2H_5, n-C_3H_7, n-C_4H_9

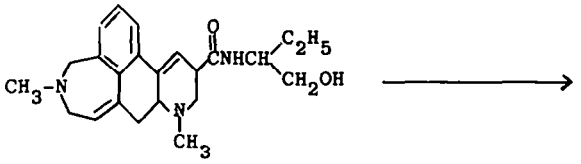
A : Demethylated product

B : Dealkylated product

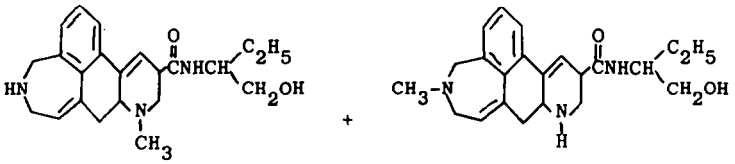
Table 4. Ratio of A/B

R	Microsomal method	Anodic Method
C_2H_5	2.02 ± 0.07	2.34 ± 0.06
i-C_3H_7	3.40 ± 0.12	4.09 ± 0.08
n-C_4H_9	2.05 ± 0.09	2.51 ± 0.07

A similar similarity has also been observed in the anodic and microsomal N-dealkylation of N-alkylamides. This similarity suggests that the electron transfer process is involved in the microsomal N-dealkylation of amines. The similarity between anodic and microsomal N-dealkylation has also been observed in the regioselectivity of N-demethylation of a compound having two N-methyl groups.[26]



methysergide

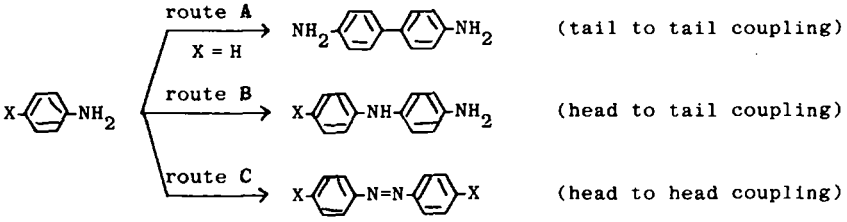


(26)

microsomal method (conversion 20%)	1.66	:	1
anodic method (conversion 42%)	1.40	:	1

Oxidation of aromatic amines

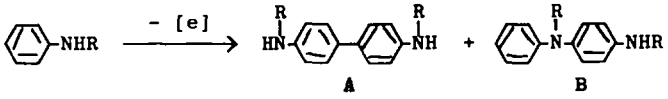
In contrast with aliphatic amines, the anodic oxidation of aromatic amines shows relatively complex reaction patterns, depending on the reaction conditions. The reaction patterns of oxidation of aniline and its derivatives are summarized in the following eqn (27).[27] The first



(27)

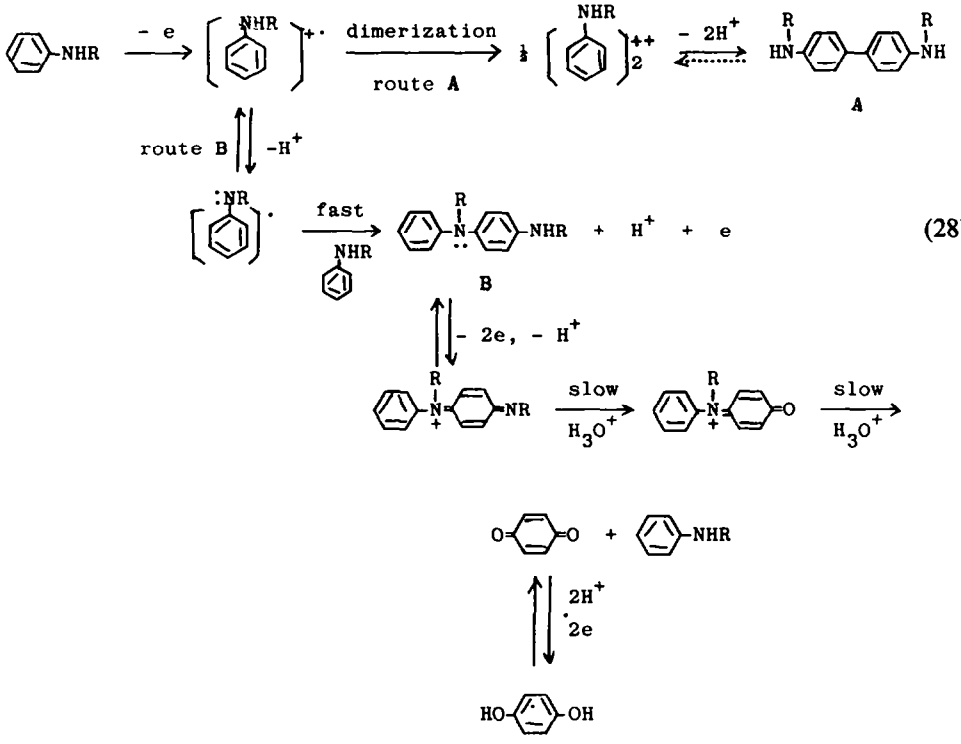
products formed in the route **B** are often oxidized further and isolated as *p*-benzoquinone.

The factors which control the ratio of the routes **A** and **B** have been studied using the following



(28a)

reaction [eqn (28)] as the model reaction.[28] The proposed mechanism of this reaction is as follows.



(28b)

According to this reaction mechanism, the following factors will favor the route **B**. (i) The size of R is small, (ii) the pH value of reaction medium is high, (iii) the concentration of starting material is high, and (iv) low current density.

Thus, the high pH value facilitates removal of proton from the intermediate cation radical, and high concentration of the starting material and low current density increase the ratio of starting material/cation radical. All of these factors favor the route **B**. On the other hand, high current density, low concentration of the starting material, and low pH value are favorable reaction conditions for the route **A**.

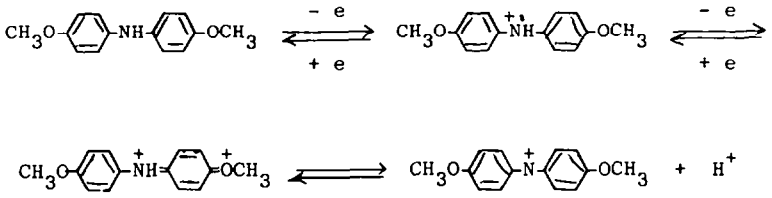
Table 5. Effect of R on the ratio A/B

R in 	A (%)	B (%)
CH_3	50	50
C_2H_5	60	40
i-C_3H_7	65	35
t-C_4H_9	100	0

For example, the anodic oxidation of aniline in 0.05 M H_2SO_4 gives *p*-benzoquinone, the product of route **B** in almost quantitative yield, whereas the same oxidation carried out in 6 M H_2SO_4 yields benzidine, the product of route **A**, in 10–20% yield together with *p*-benzoquinone.

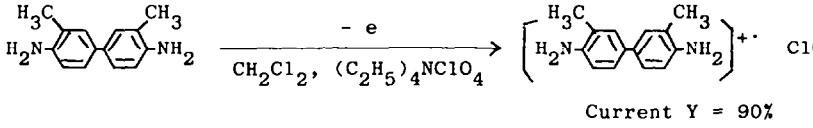
The effect of bulkiness of the group R on the ratio of **A** and **B** is summarized in Table 5, which shows clearly that the bulky R group favors the route **A**. Further reaction of the products of route **B** often gives polymeric compounds.[29] *o*- and *m*-Substituted anilines show similar behavior to the *p*-substituted anilines.

The reaction mechanism shown above in the eqn (28) proposes the formation of a cation radical as the first intermediate, which is in fact observed in the following reaction [eqn (29)] by using CV method.[30,31]



(29)

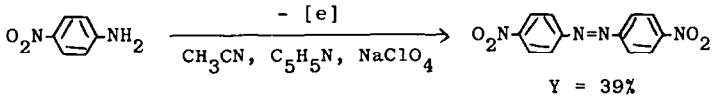
The products of route **A** formed by tail to tail coupling are sometimes oxidized to stable cation radicals as shown in eqn (30).[32]



Current Y = 90%

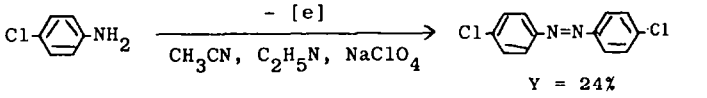
(30)

The formation of head to head coupling products through the route **C** has been observed by carrying out the reaction in a mixture of acetonitrile and pyridine.[33]



Y = 39%

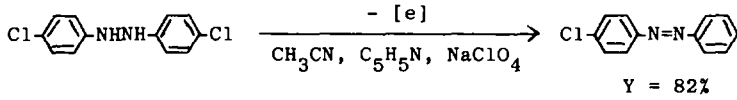
(31)



Y = 24%

(32)

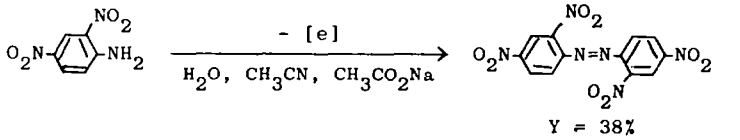
The fact that the anodic oxidation of hydrazo compounds under the same reaction conditions yields the corresponding azo compounds suggests that the hydrazo compounds are the inter-



Y = 82%

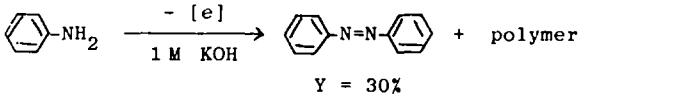
(33)

mediates for the formation of azo compounds in the route **C**. The route **C** has also been observed in the following reactions.



Y = 38%

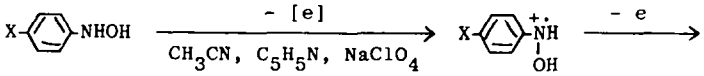
(34)[34]



Y = 30%

(35)[35]

The anodic oxidation of phenylhydroxyamines also gives small amounts of products of the route C, though the main products are nitroso compounds.[36]

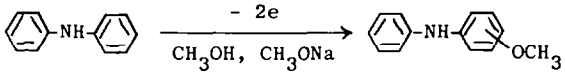


(36)

Y = 8% (X = H) Y = 78% (X = H)
Y = 10% (X = Cl) Y = 80% (X = Cl)

The oxidation of naphthylamine shows a similar reaction pathway.[37]

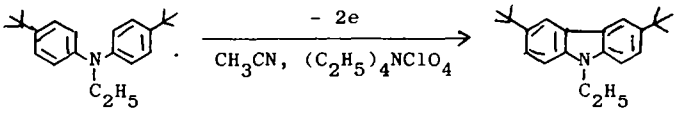
The other patterns of reaction than those shown in eqn (27) are often observed in the anodic oxidation of aromatic amines. For instance, the aromatic nucleus is methoxylated in the oxidation



(37)

Y = 7.6%
(*o* : *p* = 1 : 20)

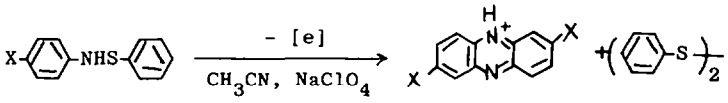
of diphenylamine in methanol.[38] An intramolecular coupling between two phenyl rings has also taken place as exemplified in eqn (38).[39]



(38)

Y = 15%

Benzenesulphenanilides show a unique pattern of coupling yielding 2,7-disubstituted phenazines.[40,41]

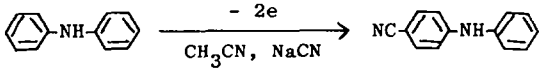


(39)

Y = 39% (X = OCH_3)
Y = 42% (X = CH_3)

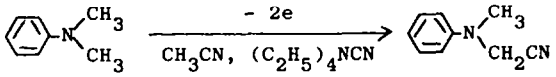
Cyanation and methoxylation of N,N-dialkylanilines

Among the anodic reactions of aromatic amines, the anodic cyanation and methoxylation of *N,N*-dialkylanilines are rather rare reactions which are useful in organic synthesis. The cyanation takes place at both phenyl ring and methyl group.



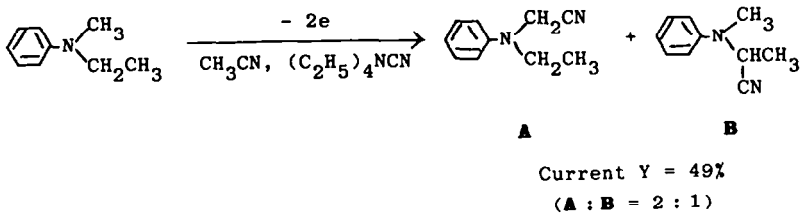
(40)[42]

Y = 61%



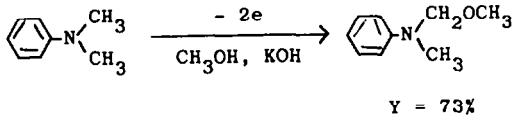
(41)[43]

Current Y = 19%

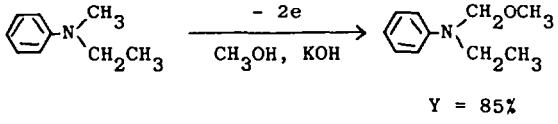


(42)[43]

Methoxylation of *N,N*-dimethyl- or *N*-methyl-*N*-alkyl-aniline takes place at the methyl group predominantly.[44]

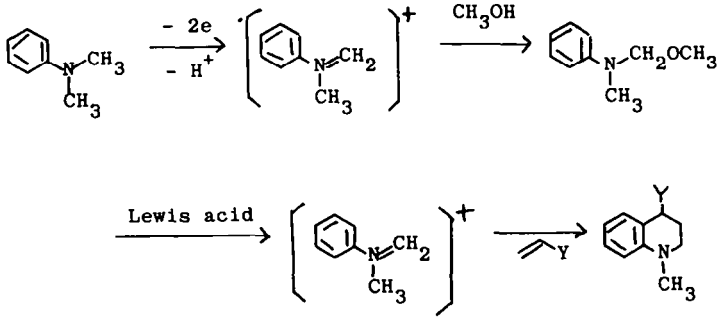


(43)



(44)

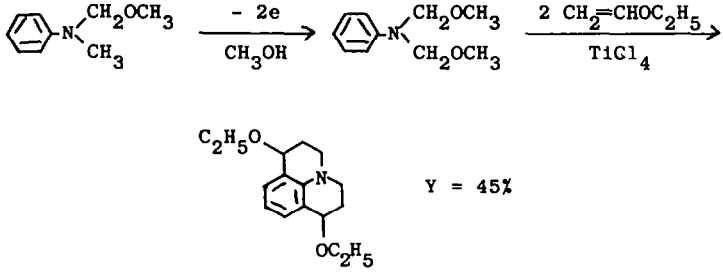
The methoxylated *N,N*-dimethylaniline shows high potentiality as a starting material in organic synthesis, since the treatment of the methoxylated compound with Lewis acid easily regenerates the iminium ion intermediate, which can be trapped *in situ* with a variety of nucleophiles such as



(45)

electron-rich olefins, the products being tetrahydroquinolines. Typical results are summarized in Table 6.

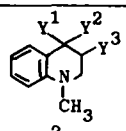
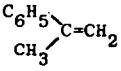
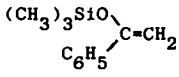
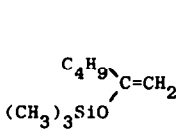
Further anodic oxidation of α-methoxy-*N,N*-dimethylaniline in methanol yields α,α′-dimethoxy-*N,N*-dimethylaniline, which gives julolidine derivatives upon reaction with two molecules of ethyl vinyl ether.



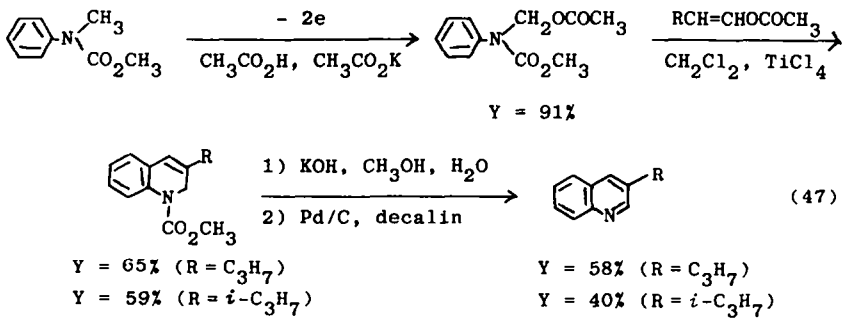
(46)

As described above, the reaction of α-methoxy-*N,N*-dimethylaniline with electron-rich olefins gives the corresponding tetrahydroquinoline derivatives. On the other hand, with using *N*-carbomethoxy-*N*-acetoxymethylaniline as the starting material, the similar reaction yields quin-

Table 6. Synthesis of tetrahydroquinolines from α-methoxy-*N*,*N*-dimethylaniline with using $TiCl_4$ as a catalyst

Electron-rich olefin	Product			Yield (%)
	Y^1	Y^2	Y^3	
$C_6H_5CH=CH_2$	C_6H_5	H	H	84
	C_6H_5	CH_3	H	89
$n\text{-}C_6H_{13}CH=CH_2$	$n\text{-}C_6H_{13}$	H	H	58
$C_2H_5OCH=CH_2$	OC_2H_5	H	H	64
$C_2H_5CH=CHOSi(CH_3)_3$	$OSi(CH_3)_3$	H	C_2H_5	61
	$OSi(CH_3)_3$	C_6H_5	H	31
	$OSi(CH_3)_3$	C_4H_9	H	29
	OCH_3	C_4H_9	H	11
	OH	C_4H_9	H	21
$C_2H_5CH=CH-N$		H	C_2H_5	81
$CH_2=CHOAc$	OCH_3	H	H	11
	OH	H	H	69

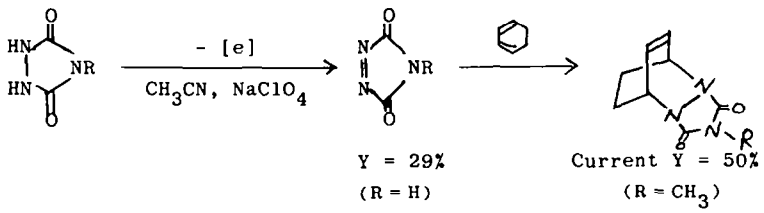
oline derivatives in reasonable yields, though the detail of the anodic oxidation of carbamates is described in the following section.



(47)

Oxidation of miscellaneous amine derivatives

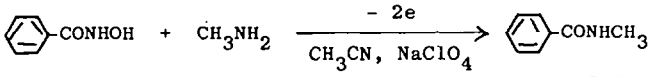
The anodic oxidation of urazoles gives 1,2,4-triazoline-3,5-diones.[45] Usual chemical oxidation of urazoles using *t*-butyl hypochlorite, trichloroacetyl isocyanate, dinitrogen tetraoxide, or NBS



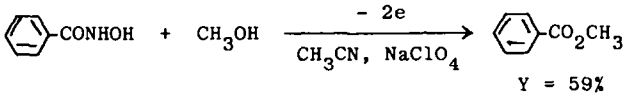
(48)

as the oxidizing agent often gives by-products which are not easily separable. The same reaction carried out in the presence of cyclohexadiene gives the Diels–Ader adduct in 75% yield (R=CH_3).

When benzohydroxamic acid is oxidized anodically in the presence of suitable nucleophiles such as amines or alcohols, benzoylation of the nucleophiles takes place as exemplified below.[46]

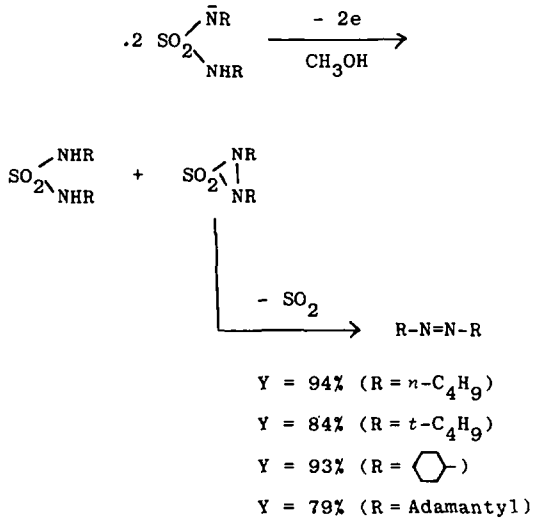


(49)



(50)

The anodic oxidation of *N*,*N*-dialkylsulphamides in the presence of base leads to the formation of azoalkanes.[47]



(51)

Oxidation of amides and carbamates

As described in the previous section, due to the instability of intermediates, anodic oxidation of aliphatic amines is not necessarily useful in organic synthesis, whereas amides and carbamates of aliphatic amines yield relatively stable intermediates which are sufficiently promising as the starting materials in organic synthesis.

The anodic oxidation of ϵ-aminocaprolactam and *N*-methyl-ϵ-aminocaprolactam is the first study which shows that the oxidative transformation of a methyl or a methylene group to a carbonyl group takes place at the position adjacent to the amine nitrogen atom.[48] Since then, a variety of studies have been carried out as the results are briefly surveyed in Table 7.

The reaction mechanism of the α-methoxylation or α-acetoxylation of amides[65–67] and carbamates[56] has been shown to involve the direct one electron removal from lone pair electrons of nitrogen in the initial step when inert supporting electrolytes are used.

Table 7. Anodic oxidation of amides, carbamates and lactams

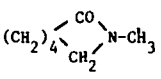
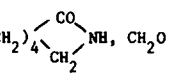
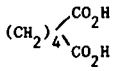
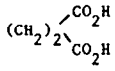
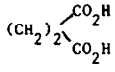
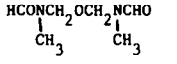
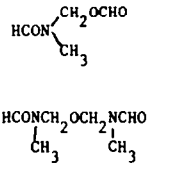
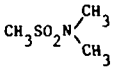
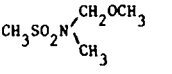
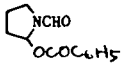
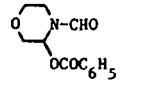
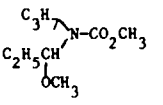
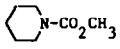
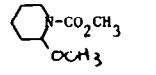
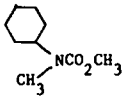
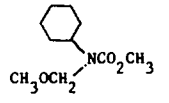
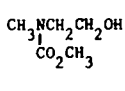
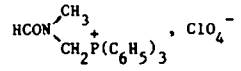
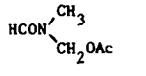
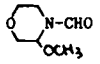
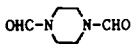
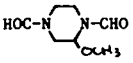
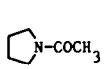
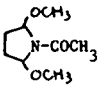
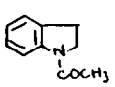
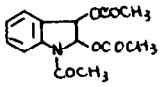
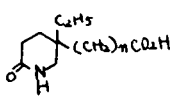
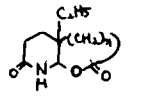
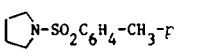
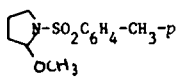
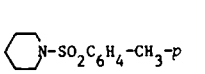
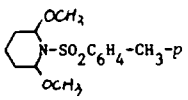
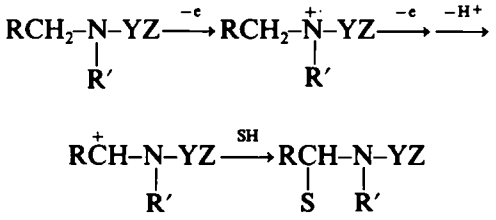
Substrate	Product	Yield (%)	Reference	Year
		—	48	1954
		—		
$(CH_3)_2CHNHCOCH_2CH_2CONH_2$	$(CH_3)_2C{=}O$	77.5	49	1960
		76.4		
$CH_3OCNH(CH_2)_4NHCOCH_3$		62.8	50	1961
		—	51	1964
		33 21	52	1964 1966
		81	53	1972
		52	54	1972
		—	55	1973
		—	55	1973
$(C_3H_7)_2NCO_2CH_3$		68	56 54	1975 1972
		72	56	1975
		78	56	
		60	56	
$HCON(CH_3)_2$		60	57	1975
$HCON(CH_3)_2$		92	58	1975

Table 7. (*Contd.*)

Substrate	Product	Yield (%)	Reference	Year
		97	59	1976
		96	59	1976
		91	59	
		—	60	1978
		77	61	1978
		54.6	62	1979
		64.3	62	
		n=1 76 n=2 58	63	1980
		79	64	1981
		93	64	1981



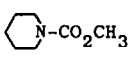
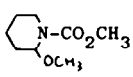
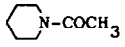
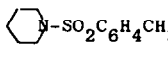
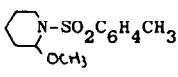
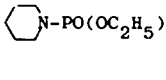
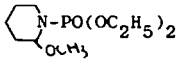
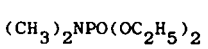
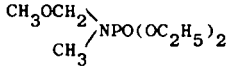
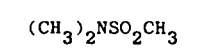
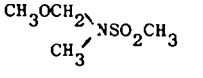
(52)

SH: solvent (CH_3OH, CH_3CO_2H, etc.), Y: CO, PO, or SO_2
Z: R or OR

The fact that as shown in Table 8, the oxidation potentials of a variety of amides depend on the structures of Y and Z also suggests the mechanism of direct removal of electron from lone pair electrons of nitrogen.[68]

On the other hand, when the oxidation potentials of supporting electrolytes are lower than those of amides, the participation of radical species generated by the oxidation of the supporting electrolytes has been suggested.[67]

Table 8. Oxidation potential of carbamates and amides

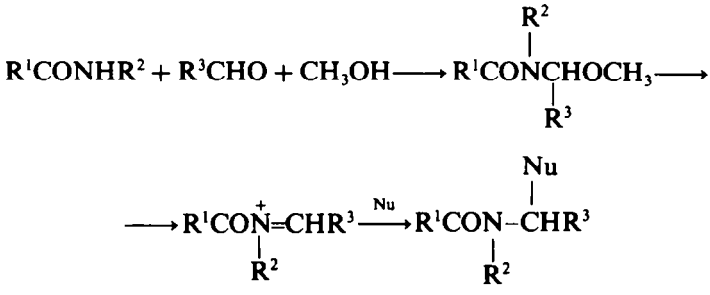
Carbamate and amide	Oxidation potential ($E_{\frac{1}{2}}$ *vs.* SCE)	α-Methoxylated carbamate and amide	Yield (%)
	1.96		86
	1.88	—	—
	2.14		21.5
	1.96		64
	2.02		72
	2.07-2.08[a]		81[b]

[a] Peak potential (V *vs.* Ag/Ag^+).[53]

[b] Ref. 53.

Application of α-methoxy- or α-acetoxy-amides or -carbamates to organic synthesis

The products obtained by the anodic oxidation of amides or carbamates in methanol have the same structures as the compounds which can be synthesized from amides (carbamates), aldehydes, and methanol. The regeneration of iminium cations from these α-methoxy-amides, and subsequent reactions of the iminium cations with nucleophiles such as active methylene compounds or nucleophilic aromatic nuclei have been well known under the name of amidoalkylation (eqn 53).[69]

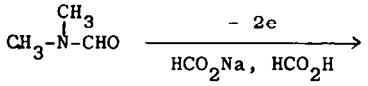


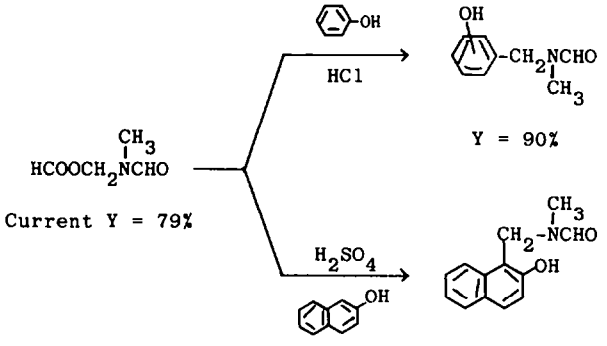
(53)

In the amidoalkylation, however, preparation of the starting α-methoxyamides often encounters difficulty, since using aldehydes higher than formaldehyde is not necessarily successful, and also even in the case of using formaldehyde, yields and purity of the α-methoxyamides are not always satisfactory. On the other hand, the anodic α-methoxylation of amides and carbamates are generally very successful, and also in this anodic method, it is possible to synthesize α-methoxyamides (carbamates) which can not be prepared by the method shown in the eqn (53).

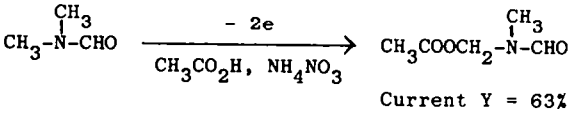
Since the first proposal of using the anodically prepared α-formyloxy-*N*,*N*-dimethylformamide as an electrophilic reagent,[70] and the first finding that the α-methoxylation is highly successful with respect to carbamates of a variety of higher aliphatic amines and alicyclic amines,[56] extensive studies have been carried out in the utilization of the anodically synthesized α-methoxy- or α-acyloxy-amides and -carbamates as electrophiles in organic synthesis.[71]

(i) *Formation of carbon–carbon bond.* Aromatic compounds being sufficiently reactive as nucleophiles can be used in the amidoalkylation.

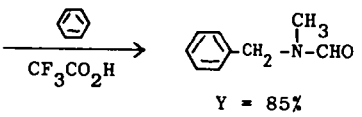




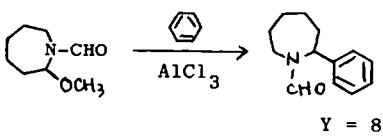
(54)[70]



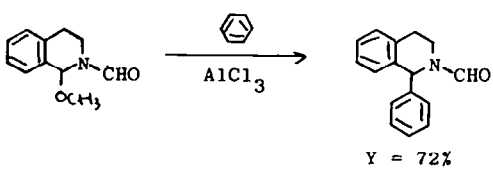
(55)[72]



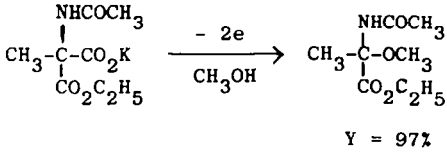
(56)[73]



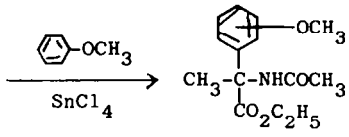
(57)[74]



(58)[74]



Y = 97%

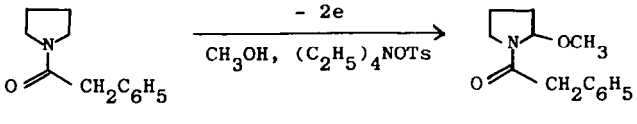


(59)[75]

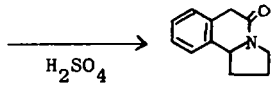
Y = 58% (*para*)

Y = 29% (*ortho*)

The intramolecular reaction of the iminium cation with an aromatic ring existing in the same compound has also been observed.[76]



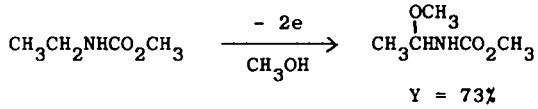
Y = 85%



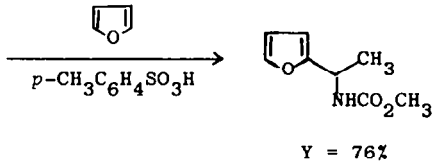
(60)

Y = 85%

Heteroaromatic rings such as furan are utilizable as nucleophiles in the amidoalkylation.

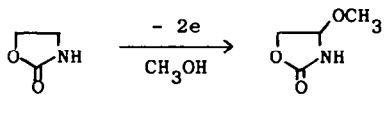


Y = 73%

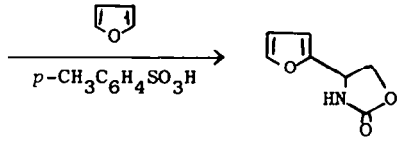


(61)[77]

Y = 76%

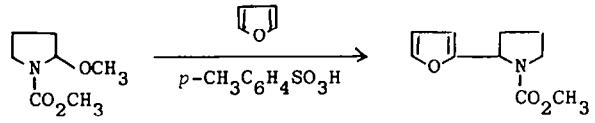


Y = 89%



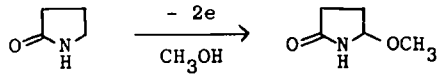
(62)[77]

Y = 71%

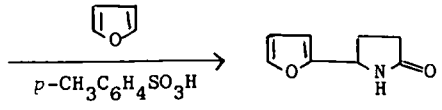


(63)[77]

Y = 89%

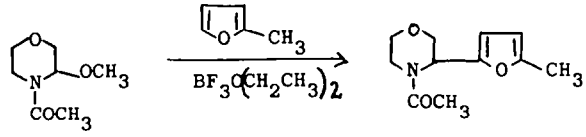


Y = 67%



(64)[77]

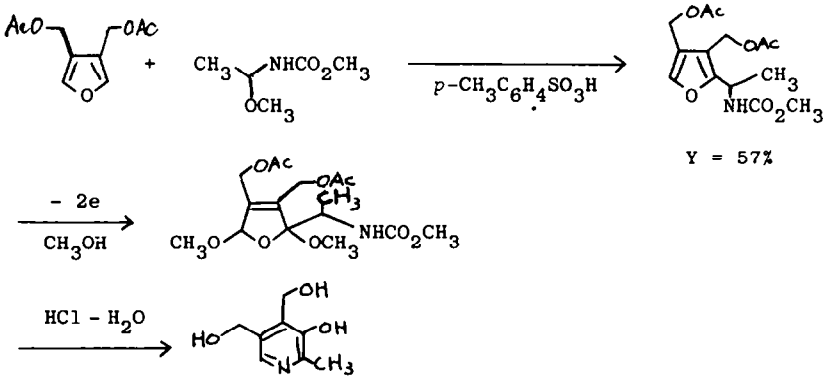
Y = 67%



(65)[78]

Y = 70%

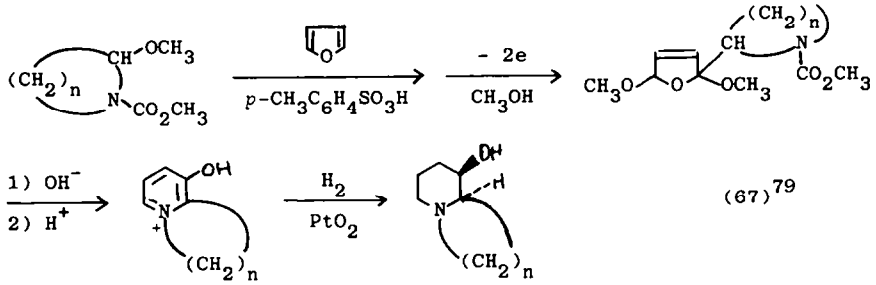
The furan ring in the products is transformable further to other skeletons as exemplified in the following three reactions. In the first example, pyridoxine is synthesized in a reasonable yield. Two



(66)[77]

pyridoxine, Y = 31% (two steps)

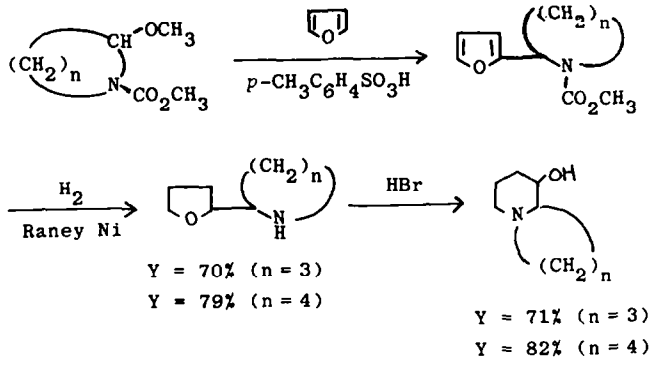
examples clearly show that these reactions are typical and useful methods for the synthesis of 1-azabicyclo[4.n.0.]systems.



(67)[79]

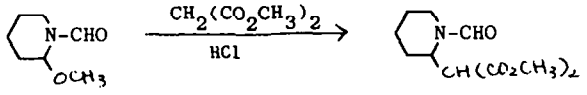
Y = 70% (n = 3)
Y = 66% (n = 4)
Y = 54% (n = 5)

Y = 73% (n = 3)
Y = 73% (n = 4)

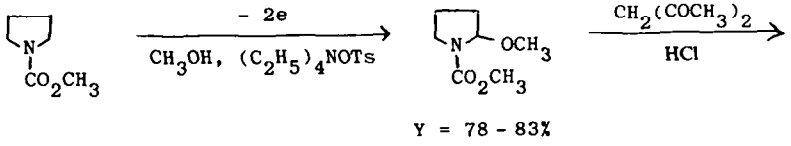


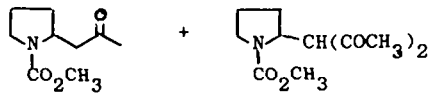
(68)[80]

Active methylene compounds such as dimethyl malonate also behave as nucleophiles in the amidoalkylation.



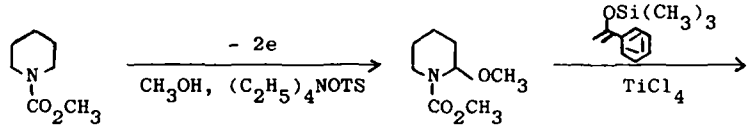
(69)[81]

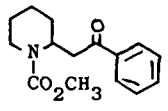




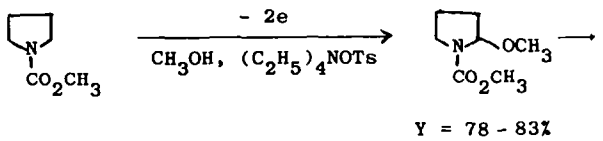
(70)[76]

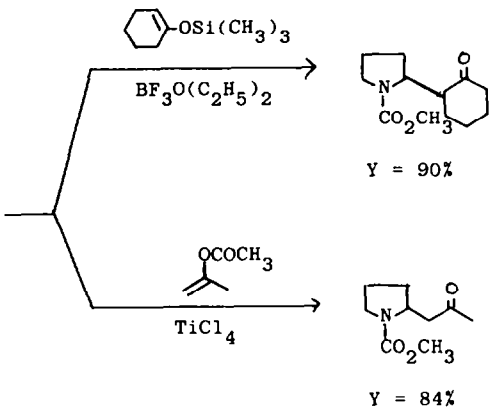
The nucleophiles unstable under acidic conditions, such as enol ethers or enol esters, require Lewis acids rather than Brönsted acids as catalysts.





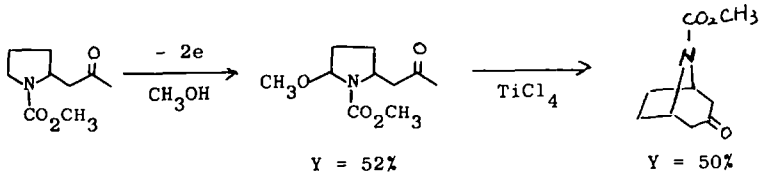
(71)[76]





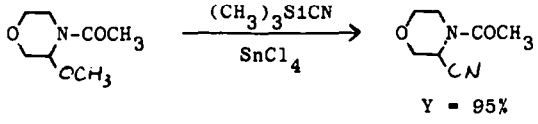
(72)[76]

Since the anodic methoxylation of these products takes place at the less substituted α-position, the intramolecular reaction of this methoxylated compound gives tropanone type skeleton. A



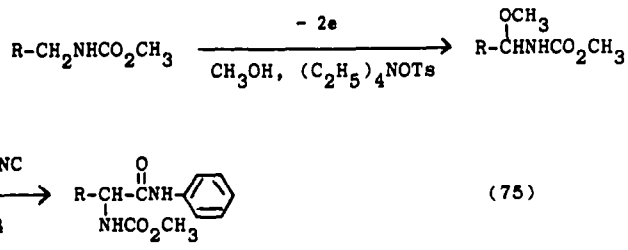
(73)[76]

cyano group is introduced by using trimethylsilyl cyanide as the cyanation agent.



(74)[78]

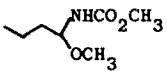
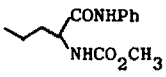
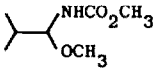
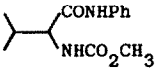
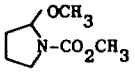
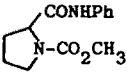
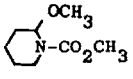
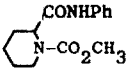
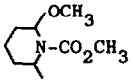
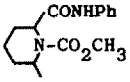
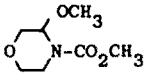
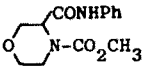
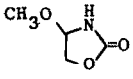
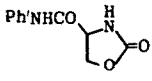
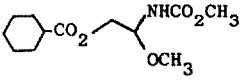
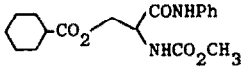
On the other hand, with using isocyanides as nucleophiles, *N*-alkyl- or *N*-arylamino-carbonyl groups are introduced to the α-position to yield α-amino acid derivatives (Table 9).[82]

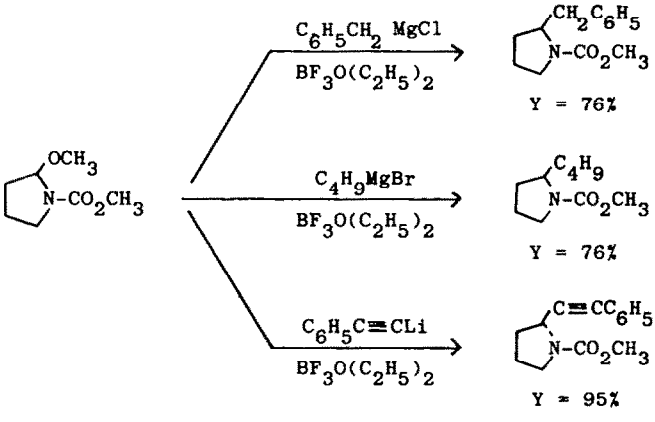


(75)

Although the Grignard reagents are the most common nucleophiles, they are highly unstable under acidic conditions. Hence, the treatment of α-methoxylated carbamates with Lewis acid catalysts is necessary before the addition of the Grignard reagents to the reaction system. The reaction of the Grignard reagents with α-methoxylated carbamates gives poor results without using the Lewis acid catalysts.

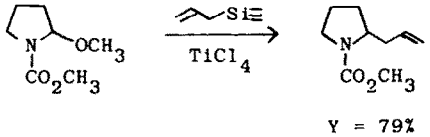
Table 9. Synthesis of α-amino acid derivatives

α-Methoxylated carbamate	Yield (%)	α-Amino acid derivative	Yield (%)
	50		64
	70		82
	80		64
	86		73
	69		50
	55		48
	89		34
	39		49

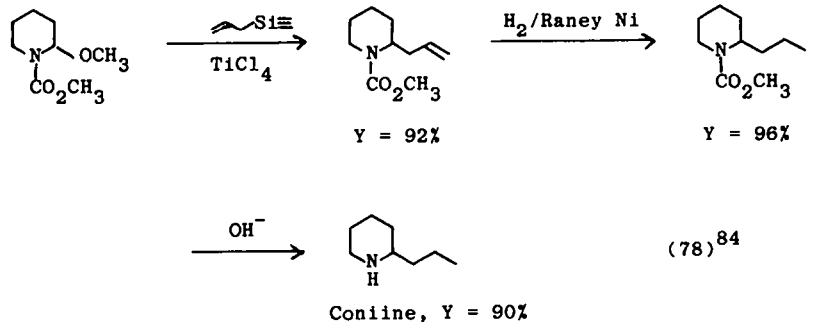


(76)[83]

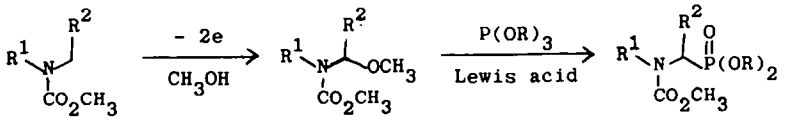
The reaction of allylmagnesium chloride with α-methoxycarbamates is not satisfactory, whereas allyltrimethylsilane yields the allylated products in high yields.



(77)[84]

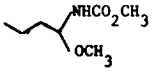
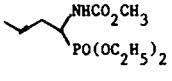
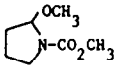
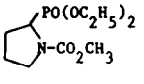
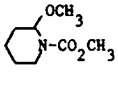
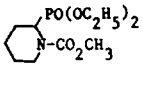
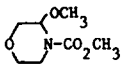
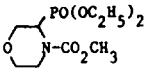
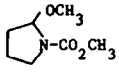
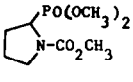
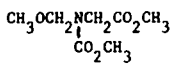
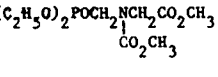


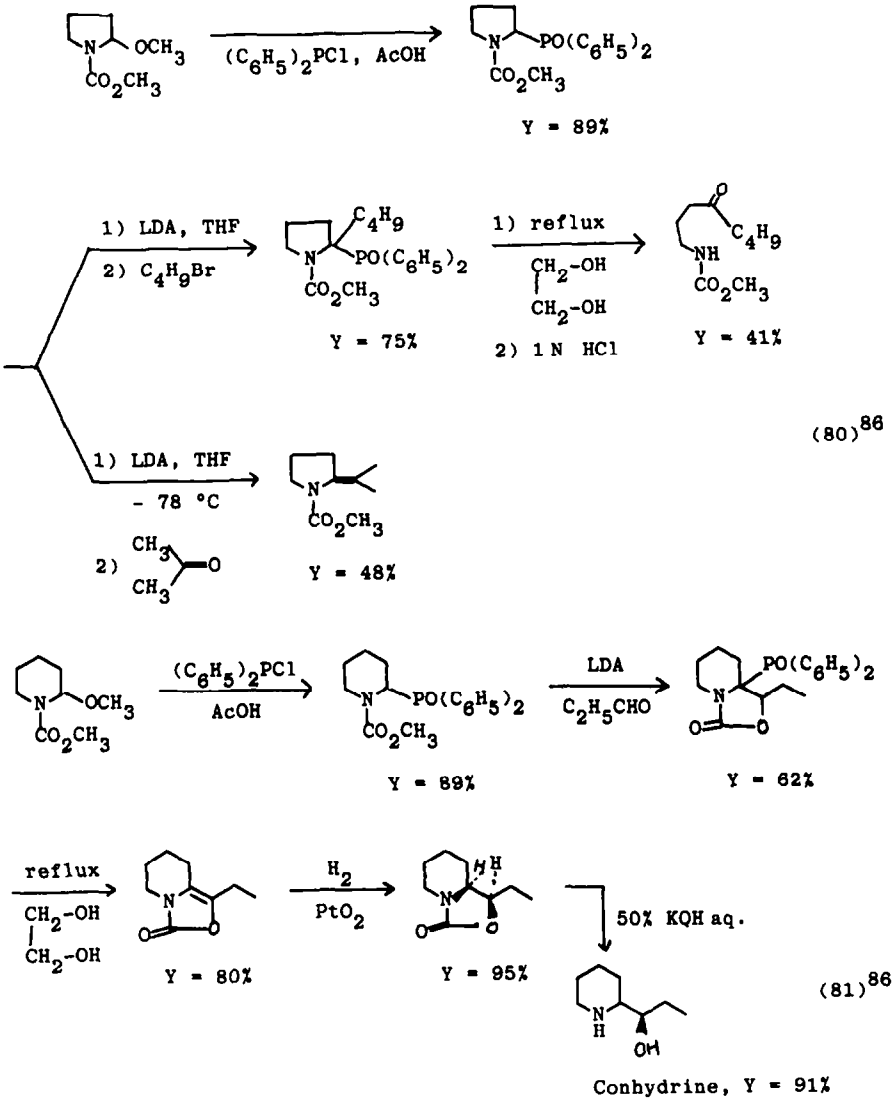
(ii) *Formation of bonds between carbon and heteroatoms.* The reaction of trialkyl phosphites with α-methoxycarbamates leads to the formation of carbon–phosphorous bond (Table 10).[85] The



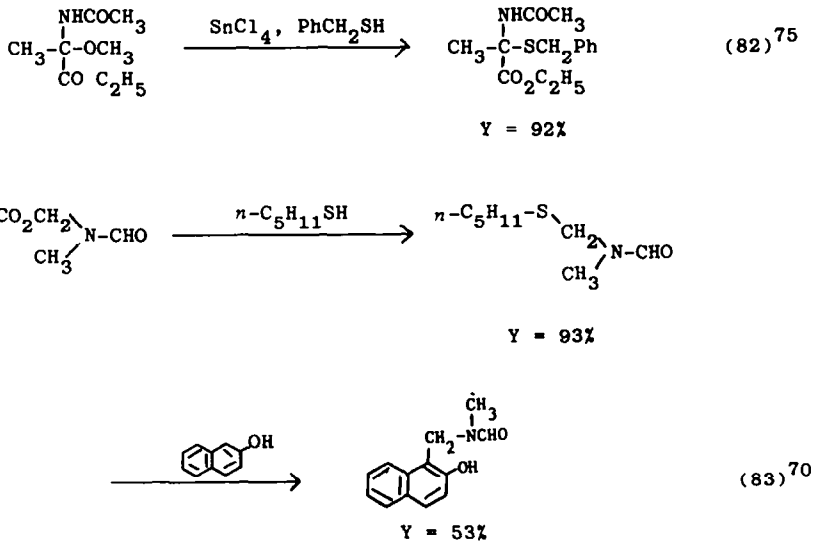
phosphine oxides prepared through the reaction of α-methoxycarbamates with chlorodiphenylphosphine show a variety of reactions, in which it is remarkable that the α-positions of carbamates can behave as nucleophiles.

Table 10. The reaction of α-methoxylated carbamates with trialkyl phosphites

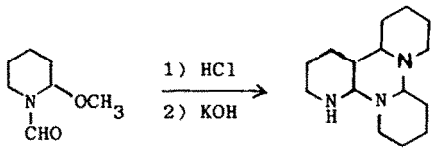
α-Methoxylated carbamate	$R(OR)_3$ R	Lewis acid	Aminoallylphosphonate	Yield (%)
	C_2H_5	$BF_3O(C_2H_5)_2$		100
	C_2H_5	$BF_3O(C_2H_5)_2$		98
	C_2H_5	$TiCl_4$		93
	CH_3	$BF_3O(C_2H_5)_2$		~100
	CH_3	$BF_3O(C_2H_5)_2$		~100
	C_2H_5	$BF_3O(C_2H_5)_2$		81



The formation of carbon–sulphur bonds is exemplified in the following two reactions. The

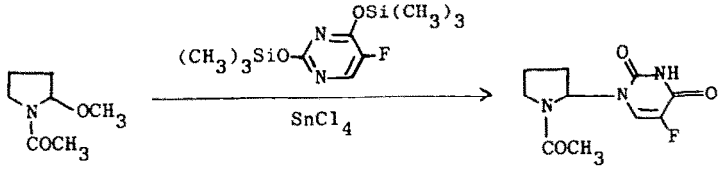


following examples show the formation of carbon–nitrogen bond and carbon–oxygen bond.



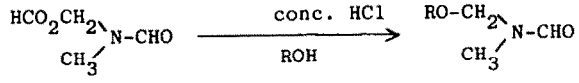
Y = 80%

(84)[87]



Y = 81%

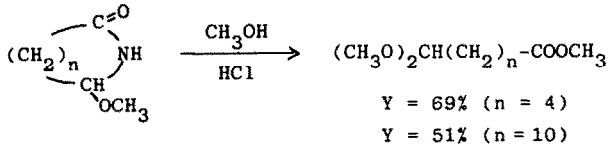
(85)[88]



Y = 68% (R = C_2H_5)
Y = 77% (R = i-C_3H_7)
Y = 88% (R = C_6H_{11})

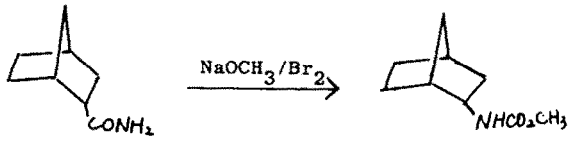
(86)[70]

(iii) *Reaction using the α-methoxylated amides and carbamates as masked carbonyl compounds.* Since the α-methoxylated amides and carbamates are equivalent to carbonyl compounds, treatment of these α-methoxyl compounds with acidic methanol yields the corresponding acetals and ketals.

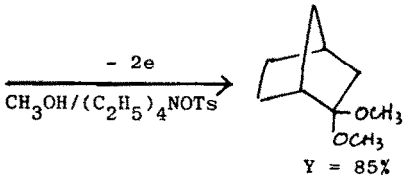


Y = 69% (n = 4)
Y = 51% (n = 10)

(87)[89]



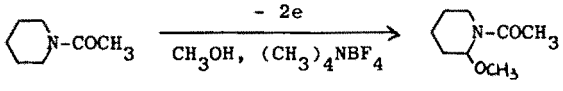
Y = 85%



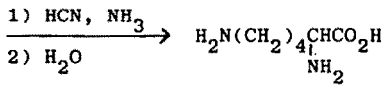
Y = 85%

(88)[90]

The following example shows the reaction in which the α-methoxylated compound is used as the masked aldehyde.



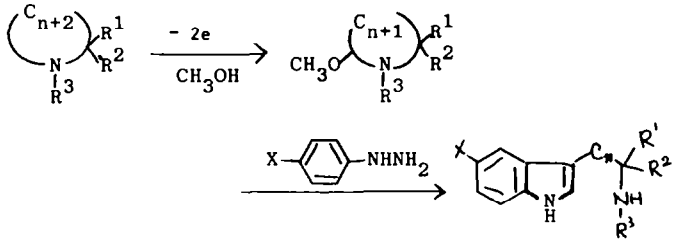
Y = 92%



Y = 38%

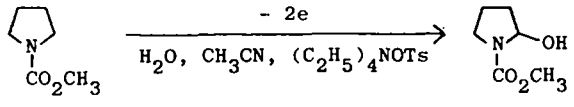
(89)[91]

β-Substituted indoles such as indoleacetic acid, tryptamine, and L-tryptophan are easily synthesized utilizing the masked aldehydes (Table 11).[92]

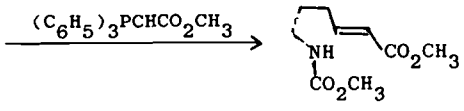


(90)

Using the α-methoxylated compounds as the masked aldehydes requires acidic catalysts, whereas α-hydroxylated amides and carbamates are usable as aldehydes without using catalysts.



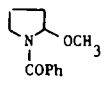
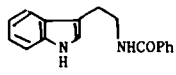
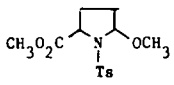
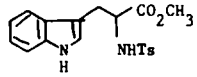
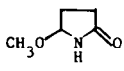
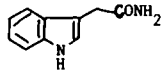
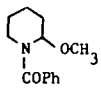
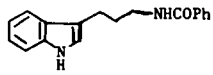
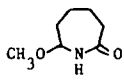
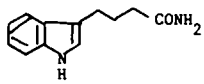
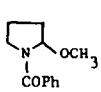
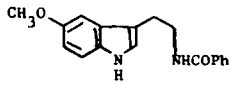
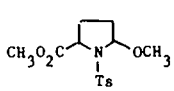
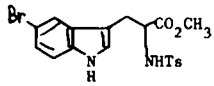
Y = 80%



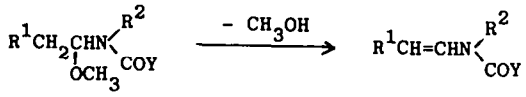
(91)[93]

Y = 79%

Table 11. Synthesis of β-substituted indoles

Masked aldehyde	Yield (%)	X-⟨⟩-NHNH$_2$ X	β-Substituted indole	Yield (%)
	80	H		76
	83	H		73
	67	H		40
	97	H		79
	94	H		70
	80	OCH_3		87
	83	Br		63

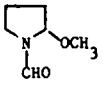
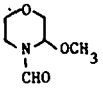
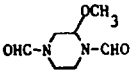
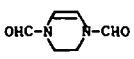
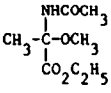
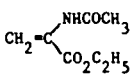
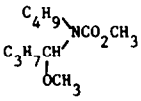
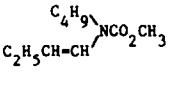
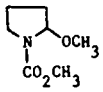
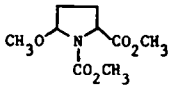
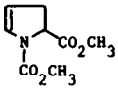
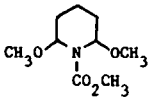
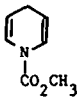
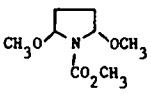
(iv) *Formation of enecarbamates and their reaction.* The α-methoxylated carbamates are easily transformed to unsaturated carbamates (enecarbamates) through elimination of methanol (Table 12).

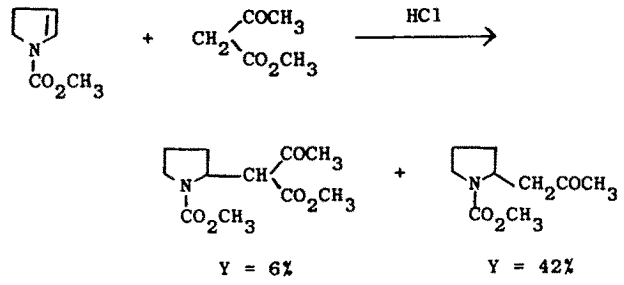


(92)

A variety of substituents are introduced to the α- or β-position of carbamates by reaction of the enecarbamates with nucleophiles or electrophiles. For example, active methylene compounds add to the α-position of enecarbamates under the conditions catalyzed by Brönsted acids.

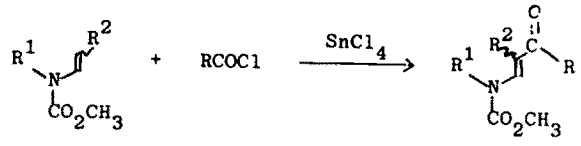
Table 12. Formation of enecarbamates and enamides from anodically prepared α-methoxycarbamates and α-methoxyamides

Carbamate, amide	Catalyst	Product	Yield (%)	Reference
	none		55	54
	NH_4Br		76	94
	NH_4Br		73	94
	NH_4Br		46	94
	NH_4Br		76	75
	NH_4Cl		94	95
	NH_4Cl		91	95
	NH_4Cl		70	97
	NH_4Cl		86	97
	NH_4Cl		62	97



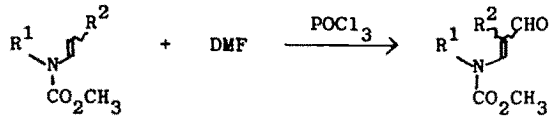
Y = 6% Y = 42% (93)[76]

Friedel–Crafts type reaction of the enecarbamates gives β-acylated enecarbamates.[95,97]



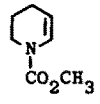
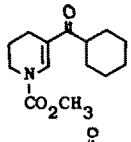
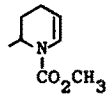
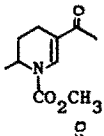
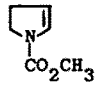
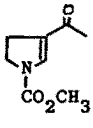
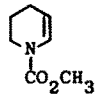
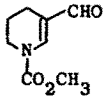
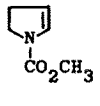
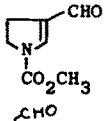
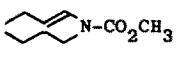
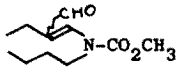
(94)

Similarly to the Friedel–Crafts reaction, Vilsmeyer reaction yields β-formyl-enecarbamates (Table 13).[95,97]

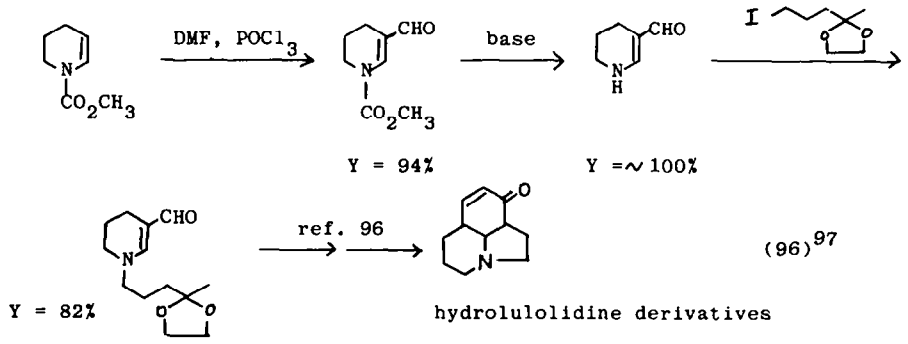


(95)

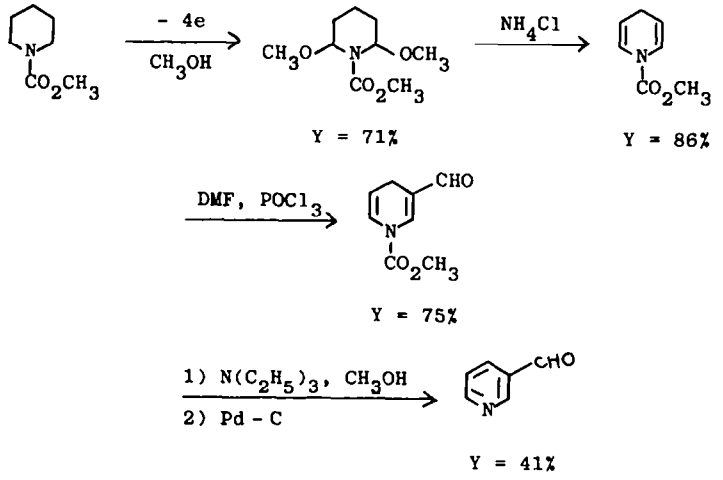
Table 13. Acylation and formylation of enecarbamates

Enecarbamate	R in R-COCl or DMF-$POCl_3$	Product	Yield (%)
	cyclo C_6H_{11}		85
	CH_3		70
	CH_3		32
	DMF - $POCl_3$		94
	DMF - $POCl_3$		66
	DMF - $POCl_3$		91

The β-formyl-enecarbamates are useful starting materials to the synthesis of heterocyclic compounds as exemplified below.

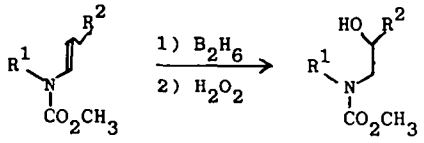


(96)[97]



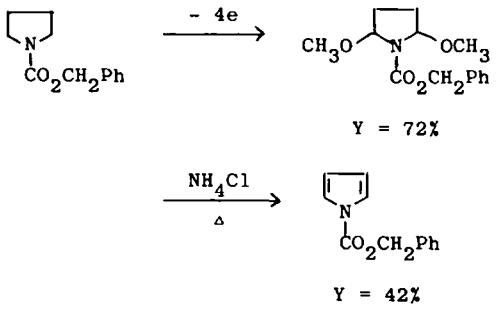
(97)[97]

The hydroboration of enecarbamates gives the corresponding β-hydroxy-carbamates in reason-



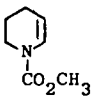
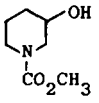
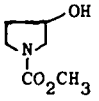
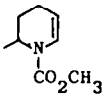
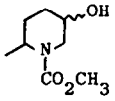
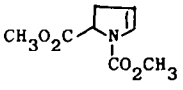
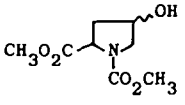
(98)

able yields (Table 14).[97] Pyrrole derivatives are obtainable from pyrrolidine carbamates through dimethoxylation followed by elimination of two molecules of methanol.



(99)[97]

Table 14. Hydroboration of enecarbamates

Enecarbamate	Product	Yield (%)
		60
		62
		60
		45

OXIDATION USING MEDIATORS

Principle

In electroorganic reactions, the generation of active species by the direct electron transfer between electrode and substrates highly depends on the oxidation and reduction potentials of the substrates. When the oxidation and reduction potentials of a substrate are beyond the range accessible by the usual technique of electrochemical reaction, the direct electron transfer between the substrate and electrode is not expectable, and hence it is necessary to devise some other method to oxidize or reduce the substrate. Also, even if the oxidation and reduction potentials of substrates are in the accessible range of the electrochemical method, it is more desirable to oxidize or reduce the substrates with using some indirect method at much lower potential than that in the direct method. Electroorganic synthesis using mediators has been devised to actualize these ideas. Figure 1 represents a diagram of the reaction system using a mediator.

The substrate S shown in Fig. 1 has a high oxidation potential, so that the direct electron transfer from S to anode hardly takes place and the high oxidation potential necessary for the oxidation of S brings about unexpected side reactions being resulted from oxidation of solvents and supporting electrolytes. On the other hand, when the reaction system contains a compound M_{red} (a reduced form of M) oxidizable at sufficiently lower potential than S, the oxidation of M_{red} to M_{ox} (an oxidized form of M) will take place prior to the oxidation of S. Provided that M_{ox} is able to oxidize S to the product P, the oxidation of S will be achieved at lower potential than that necessary in the direct oxidation of S. There are two types of reaction in the oxidation of S with M_{ox}. One of them is direct electron transfer (homogeneous electron transfer) from S to M_{ox} in solution, while the other is chemical oxidation of S with M_{ox}. The former is called homomediatory system and the latter is heteromediatory (or chemomediatory) system in this review. The compound M is called a mediator or an

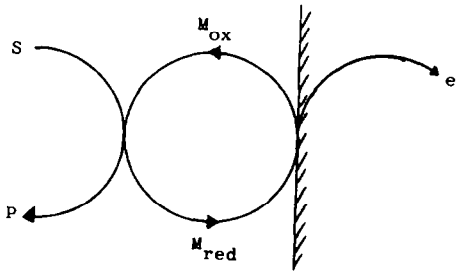


Fig. 1.

electron carrier, since M mediates electron transfer between S and anode. When M_{ox} oxidizes S in solution, M_{ox} is reduced to M_{red} which is again oxidized at anode to regenerate M_{ox}. Thus, if the life of the redox system $M_{ox} \rightleftarrows M_{red}$ is sufficiently long, only a catalytic amount of mediator can promote the entire reaction. As a matter of course, the idea of a mediatory system is not only applicable to oxidation exemplified by Fig. 1, but also effective in reduction. Although the term mediator or electron carrier has been introduced rather recently, many types of reaction system involving a compound which behaves as a mediator are already known.

Homomediatory system

The homomediatory system is representable by eqn (100), in which a substrate S is oxidized with using a mediator M.

$$M \xrightarrow{-e} M^{+\cdot} \tag{100a}$$

$$M^{+\cdot} + S \rightleftharpoons M + S^{+\cdot} \tag{100b}$$

$$S^{+} \longrightarrow P_1^{+} + P_2\cdot \tag{100c}$$

Since the oxidation potential of S is more positive than M, the equilibrium (100b) shifts largely to the left side. Hence, the rate of whole reaction highly depends on the rate of the irreversible reaction (100c). In fact, the oxidation shown in eqn (100) effectively proceeds only when $S^{+\cdot}$ collapses fast into products.

When the oxidation potential of S is extremely more positive than M, the oxidation shown in eqn (100) is almost impossible, even though the rate of irreversible collapse of $S^{+\cdot}$ is fast. In such a case, some further activation of $M^{+\cdot}$ may be necessary to make the oxidation possible.

The anodic oxidation of *tris*-(*p*-bromophenyl)amine (M) in the presence of carboxylate anions is one of the earliest typical reactions using the homomediatory system (101).[98]

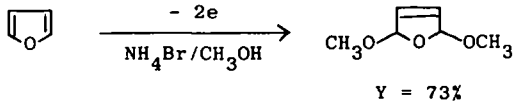
$$\begin{gathered} M \xrightarrow{-e} M^{+\cdot}, \\ M^{+\cdot} + RCO_2^{-} \rightleftharpoons M + RCO_2\cdot \\ RCO_2\cdot \longrightarrow R\cdot + CO_2 \end{gathered} \tag{101}$$

Since the oxidation half-wave potential of M(1.30 V vs NHE) is sufficiently low to be oxidized prior to the oxidation of carboxylate anions and generally the collapse of acyloxy radical is very fast (half-life, about 10^{-10} sec), the oxidation of carboxylate anions is able to be promoted by the mediator. Some other studies are summarized in Table 15.

Heteromediatory system

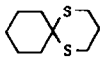
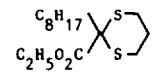
In the heteromediatory system, the substrate S is not oxidized by direct electron transfer from S to M_{ox} but chemical reaction between S and M_{ox}. Many of the mediatory systems being useful in organic synthesis are classifiable into this category. Although some indirect oxidations using heavy metal ions as oxidizing agents have been known as rather classical types of mediatory systems, the most interesting and promising reactions are those using new mediators which are not easily preparable by the usual chemical methods. Among a variety of mediators, the redox system between halide anion and a positive species of halogen is one of the most interesting mediators from the view point of organic synthesis.

One of the early synthetic studies which uses halide anion as the mediator is the anodic methoxylation of furan in the presence of 0.05 equivalent of ammonium bromide, though the reaction has not been described as the oxidation using a mediator (102).[103]



(102)

Table 15. Homomediatory oxidation

Substrate	Product	Yield (%)	Mediator	Reference
$C_8H_{17}OCH_3$-C$_6$H$_4$-OCH_3	$C_8H_{17}OH$	95	$(Br\text{-}C_6H_4)_3N$	99
$CH_2{=}CH{-}CH{=}CH_2$	$BrCH_2CH(OCH_3)CH{=}CH_2$	97	$(Br\text{-}C_6H_4)_3N$	100
		95	$(CH_3\text{-}C_6H_4)_3N$	101
	$C_8H_{17}COCO_2C_2H_5$	70	$(CH_3\text{-}C_6H_4)_3N$	101
	—	—	$(Br\text{-}C_6H_4)_3N$	102

The reaction is not the direct oxidation of furan, but bromide anion is oxidized first to form bromine which reacts with furan. The intermediate bromide is solvolyzed with methanol to yield the product and to regenerate bromide anion.

A catalytic amount (0.01 equiv) of potassium iodide has been successfully used in the anodic coupling of active methylene compounds such as ethyl malonate and ethyl acetoacetate (103).[104,105]

$$I^- \xrightarrow{-e} \tfrac{1}{2}I_2 \qquad K^+ \xrightarrow{+e} K\cdot$$

$$K\cdot + CH_3COCH_2CO_2C_2H_5 \longrightarrow CH_3COC^-HCO_2C_2H_5 + K^+ + \tfrac{1}{2}H_2 \qquad (103)$$

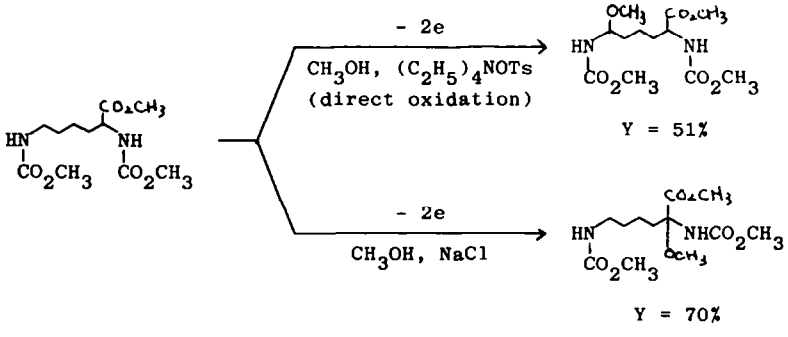
$$CH_3COC^-HCO_2C_2H_5 + \tfrac{1}{2}I_2 \longrightarrow CH_3COCH(CH_3COCHCO_2C_2H_5)CO_2C_2H_5 + I^-$$

$$Y = 40\%$$

The reaction without using potassium iodide leads to an unsatisfactory result. The dimerization of anions of active methylene compounds using iodide as the mediator has been extended to the paired reaction system in which ethyl acrylate dimerizes as the cathodic reaction and diethyl malonate anion dimerizes as the anodic reaction.[106,107]

After these early investigations, a variety of oxidations using the redox system of halide ion as the mediator have been studied as some of them are briefly surveyed in Table 16.

The reaction using a mediator sometimes gives an entirely different result from the direct oxidation. The direct oxidation of *N,N'*-biscarbamate of methyl ester of lysine in methanol yields a methoxylated product at the carbon α to the ω-amino group. On the other hand, the reaction of the same compound in methanol containing sodium chloride gives a methoxylated product at the α position to the carbomethoxyl group.[123] This difference may be explained as follows (eqn 104).



(104)

Table 16. Oxidation using halide ion as the mediator

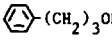
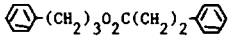
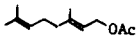
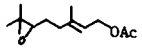
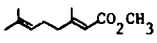
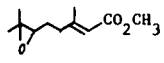
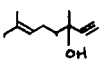
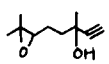
Substrate	Mediator	Solvent	Product	Yield (%)	Reference
CH_3CONH_2	NaBr, NaOH	—	$CH_3CONHCONHCH_3$	68	108
C_6H_{13}-CH(I)-CH_3	I_2	CH_3CN	$C_6H_{13}CH(NHCOCH_3)CH_3$	54	109
			$C_5H_{11}CH(NHCOCH_3)C_2H_5$	22	
1-Adamantyl-I	I_2	CH_3CN	1-Adamantyl-$NHCOCH_3$	60	109
CH_3OH, CO	NH_4Br	CH_3OH	$(CH_3O)_2CO$	80	110
$(C_2H_5)_2POH$	LiCl	C_2H_5OH	$(C_2H_5O)_2P(=O)C_2H_5$	70	111
$(CH_2)_{10}$CH-OH, CH_2	KI	t-C_2H_5OH-C_6H_{14}-H_2C	$(CH_2)_{10}$C=O, CH_2	91	112
C_6H_{13}CH(OH)-CH_3	KI	t-C_4H_9OH-H_2O	$C_6H_{13}C(=O)CH_3$	99	112
$C_8H_{17}OH$	KI	H_2O	$C_8H_{17}O_2CC_7H_{15}$	83	112
	KI	t-C_4H_9OH-C_6H_{14}-H_2O		84	112
$(C_2H_5O)_2POH$ + $(C_2H_5)_2NH$	NaI	CH_3CN	$(C_2H_5O)_2P(=O)N(C_2H_5)_2$	92	113
	NaBr	CH_3CN-THF-H_2O -$(C_2H_5)_3N$		75	114
	NaBr	CH_3CN-THF-H_2O		74	114
	NaBr	CH_2CN-H_2O-HCO_2H		77	114

Table 16 (*Contd*)

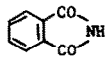
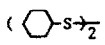
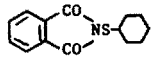
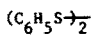
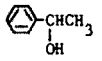
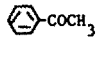
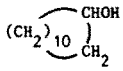
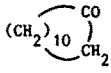
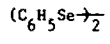
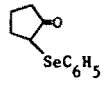
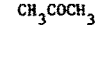
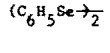
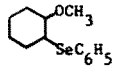
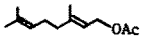
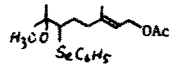
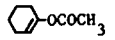
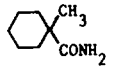
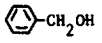
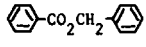
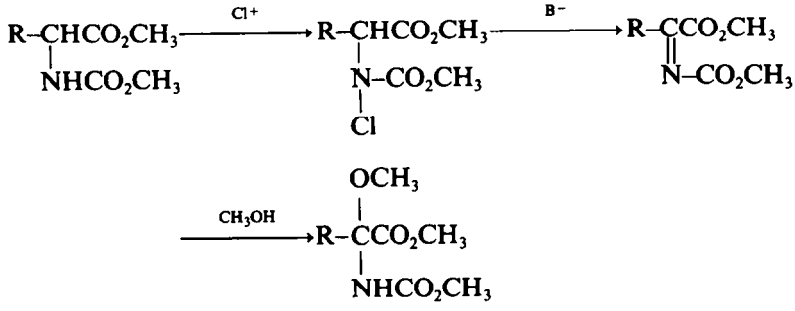
Substrate	Mediator	Solvent	Product	Yield (%)	Reference
 	NaBr	CH_3CN		99	115
$(C_2H_5O)_2POH$ 	NaBr	CH_3CN	$(C_2H_5O)_2\overset{O}{\overset{\|}{P}}S\text{-}C_6H_5$	91	116
$C_6H_{13}CHCH_3$ OH	poly-4-vinylpyridine hydrobromide (PVH)	CH_3CN	$C_6H_{13}COCH_3$	98	117
	PVH	CH_3CN		91	117
	PVH	CH_3CN		82	117
$C_8H_{17}OH$	PVH	CH_3OH	$C_7H_{15}CO_2H$	59	117
 	$(C_2H_5)_4NBr$ $MgBr_2$	CH_3CO_2H		97	118
CH_3COCH_3 	$(C_2H_5)_4NBr$ $MgBr_2$	$CH_3CO_2H\text{-}H_2SO_4$	$CH_3COCH_2SeC_6H_5$	88	118
 	$(C_2H_5)_4NBr$	$CH_3OH\text{-}H_2SO_4$		96	119
	$(C_2H_5)_4NBr$	$CH_3OH\text{-}H_2SO_4$		83	119

Table 16 (*Contd*)

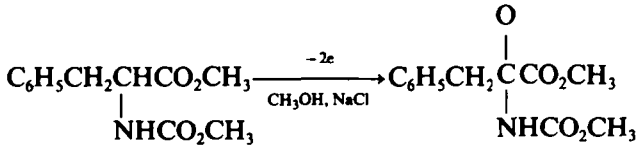
Substrate	Mediator	Solvent	Product	Yield (%)	Reference
	$(C_2H_5)_4NBr$	CH_3OH		95	119
$C_8H_{17}CONH_2$	KBr	CH_3OH	$C_8H_{17}NHCO_2CH_3$	73	120
	KBr	CH_3OH		80	120
	KI	t-C_4H_9OH-H_2O		73	121
CH_2O $(CH_3)_2NH$	KI	H_2O	$(CH_3)_2NCHO$	95	122
CH_2O 	KI	H_2O		93	122
$C_6H_{13}CHO$ $(CH_3)_2NH$	KI	t-C_4H_9OH-H_2O	$C_5H_{11}COCH_2N(CH_3)_2$	56	122

It is reasonable that the oxidation potential required for the removal of one electron from the lone-pair electrons of the nitrogen of ω-amino group is lower than that of α-amino group, and hence the direct methoxylation takes place at the neighboring carbon of the ω-amino group. On the other hand, in the reaction carried out in the presence of sodium chloride, chloride ion and its oxidized species behave as the mediator. The active species of the mediator reacts with α-amino group to yield *N*-chloro compound which turns out an imino compound upon the reaction with a base. The addition of methanol to the imino group gives the α-methoxylated compound.



(105)

The α-methoxylation is also effective for synthesis of a variety of α-amino acid derivatives.



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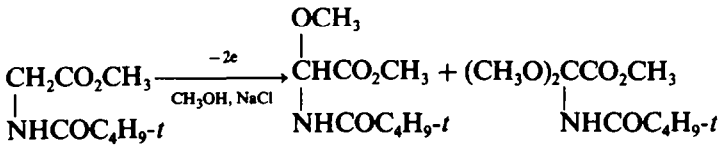
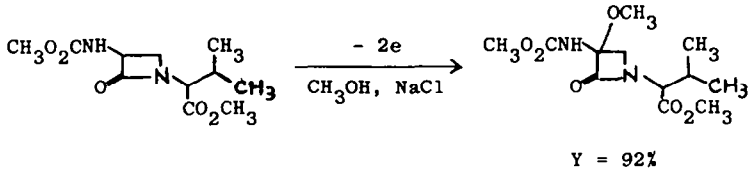


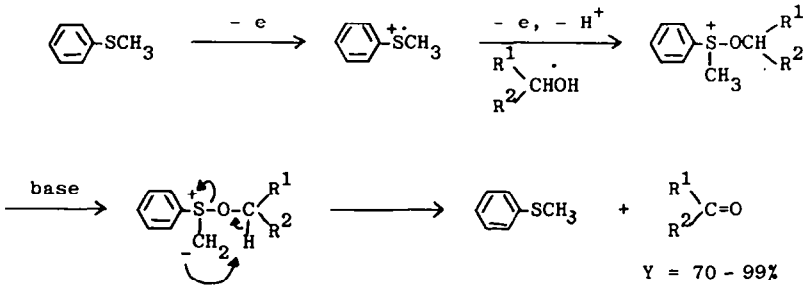
(107)

This α-methoxylation is highly useful for the methoxylation of some β-lactams.



(108)

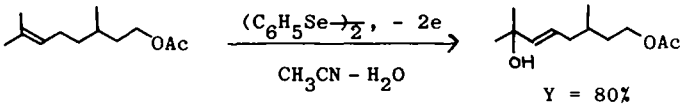
Organic sulfides are the other effective mediators than halide ion. The oxidation of secondary alcohols to ketones has been successfully achieved by using methyl phenyl sulfide as the mediator



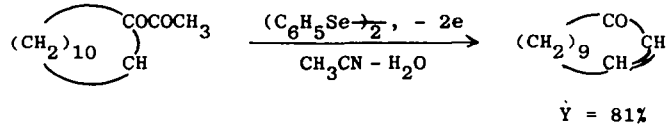
(109)

(109).[124] It is remarkable that carbon–carbon double bond is completely inert in this oxidation.

The compound, C_6H_5SeOH is able to be used as a mediator in the following reactions (110, 111).[125]

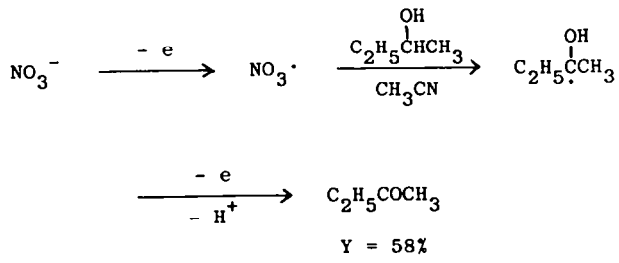


(110)



(111)

Using lithium or tetraethylammonium nitrate as a mediator has also been shown in the oxidation of 2-butanol (112).[126]

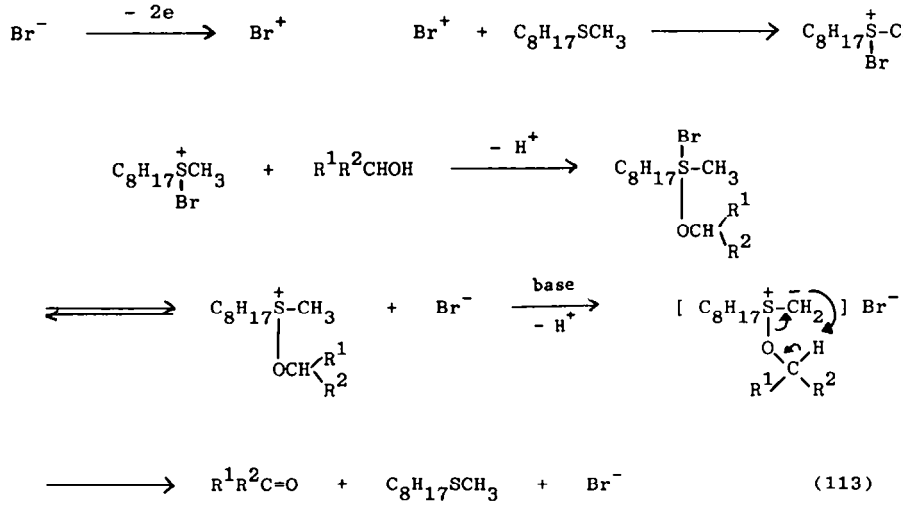


(112)

Double mediatory systems

As described above, the mediatory system is an effective tool to oxidize substrates being hardly oxidizable by the direct method. Further development of this idea leads to a new idea exemplified in Fig. 2, in which two types of mediator are combined to achieve the oxidation of substrates at the potential which is far lower than the potential required in the mediatory system using one type of mediator.[127]

In this system, the oxidation potential (E_p 1.1 V vs SCE) of Br^- to Br^+ is the lowest, and the oxidation of R'_2S to $R'_2S^{+\cdot}$ does not take place at this potential. As described above, alcohols R^1R^2CHOH is oxidizable by $R'_2S^{+\cdot}$, whereas Br^+ is not so reactive as to oxidize alcohols satisfactorily. When both mediators are combined as depicted in Fig. 2, however, the oxidation of alcohols is achievable at far lower potential than that necessary for the oxidation of R'_2S to R'_2S^+. The reaction pathway is shown in eqn (113), in which *n*-octyl methyl sulfide (E_p 1.93 V vs SCE)



(113)

is used as the mediator. The yield of ketones are in the range of 80–94%. The mediatory system shown in Fig. 2 can be called a double mediatory system.

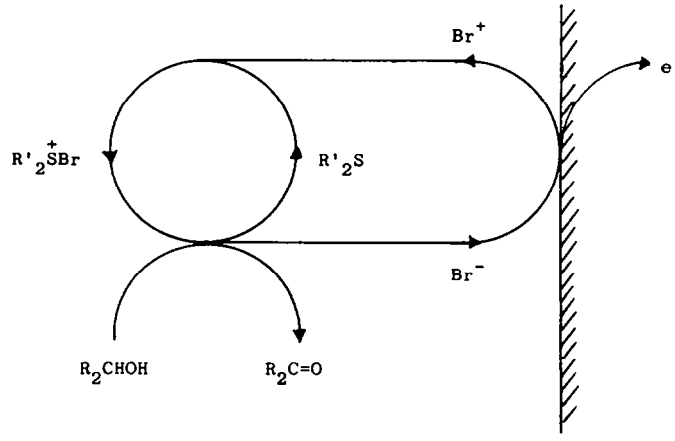


Fig. 2.

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