

HOMOLYTIC ALKYLATION OF HETEROAROMATIC BASES :
THE PROBLEM OF MONOALKYLATION .

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Abstract - The silver-catalyzed decarboxylation of carboxylic acids by persulphate leads to alkyl radicals , which have been utilized for the selective alkylation of heteroaromatic bases . The method is particularly efficient in a water-chlorobenzene two-phase system for two reasons : it considerably increases the selectivity in monoalkylation when more positions of high nucleophilic reactivity (i.e. α and γ) are available in the heterocyclic ring (i.e. quinoline , 4-cyano- and 4-ethylpyridine , pyrazine , quinoxaline etc.) and it determines a much higher efficiency for the radical sources when the silver salt catalysis is deactivated by complexation of the salt with the heterocyclic compound . The high selectivity in monoalkylation has been obtained by the combination of polar effects and the increased lipophilicity of the alkylated product , which makes its extraction from the aqueous solution by the organic solvent easier .

The substitution of protonated heteroaromatic bases by nucleophilic alkyl and carbonyl radicals reflects most of the aspects of the Friedel-Crafts aromatic substitution , but with opposite reactivity and selectivity¹ . Both reactions can be divided , in a generalized sense , into alkylations and acylations , which include reactions of considerable diversity . Also the synthetic advantages and disadvantages are , therefore , opposite . Thus , in the electrophilic process , acylation is much more selective than alkylation , for two reasons : i) the acylating electrophiles are characterized by an intrinsically higher regio- and chemoselectivity compared with the alkylating species ; ii) the introduction of an acyl

group strongly deactivates the aromatic ring towards further acylation so that selective monoacylation is easy to obtain at high conversions of the aromatic substrate, whereas the introduction of an alkyl group activates the substrate towards further alkylation, thus favouring polysubstitution.

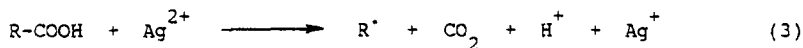
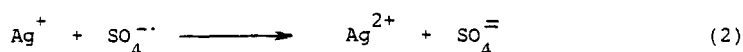
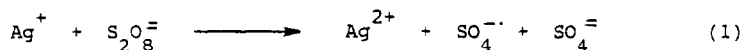
In the substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals the behaviour is opposite, due to the opposite character of the reacting species: carbonyl groups activate (i.e. the 2-position of 4-cyanoquinoline is about 130 times more reactive than the corresponding position in 4-methylquinoline towards the benzoyl radical) and alkyl groups deactivate the heterocyclic ring, so that polysubstitution by carbonyl radicals easily occurs when more than one position of high nucleophilic reactivity is available in the heterocyclic ring (i.e. α and γ), whereas it is difficult to stop the reaction to monosubstitution¹. On the other hand, the polar character of the alkyl groups is relatively poor as compared to that of the carbonyl groups (i.e., the σ_m , σ_p , and σ_+ Hammett constants for the ethyl group are respectively - 0.07, - 0.15 and - 0.30, whereas the σ_m , σ_p and σ_+ for the acetyl group are + 0.38, + 0.50 and + 0.87) and the degree of deactivation is not sufficient to arrest the alkylation to monosubstitution at high conversions of the substrate, when more reactive positions (α and γ) are available. The problem of polysubstitution is, therefore, important also for homolytic alkylation.

These limitations are much less severe as compared with electrophilic alkylation, because in any case only the α and γ positions of protonated heterocyclic rings are attacked by alkyl and acyl radicals and, when only one of these positions is free, only monosubstitution takes place in high yields at complete conversions; that is, a carbonyl group is much less activating than the protonated heterocyclic nitrogen and that is not surprising, because, treating the heterocyclic nitrogen atom of pyridine as a substituent in the benzene ring, the exceptionally high value of 4 was estimated² for the σ -Hammett constant of the para position in protonated pyridine, 0.5 being the corresponding value for the acetyl group.

We have already shown how it is possible to overcome the difficulty for the selectivity in monoacylation by using α -ketoacids as source of acyl radicals and by taking advantage of the decreased basicity and increased lipophilicity of the monoacylated products in a two-phase system³ similar to the modification introduced by G.Heinisch⁴ to our⁵ method of alkoxy carbonylation by alkoxy carbonyl radicals, $\cdot\text{COOR}$, in aqueous solution. Now we report the synthetic advantages obtained by a two-phase system in the homolytic alkylation of protonated heteroaromatic bases for what concerns the selectivity of monoalkylation and the efficiency of the procedure.

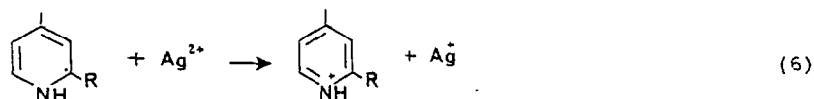
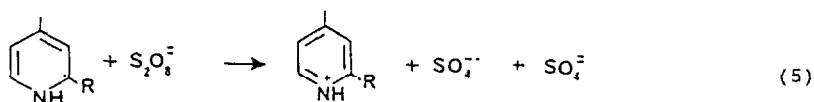
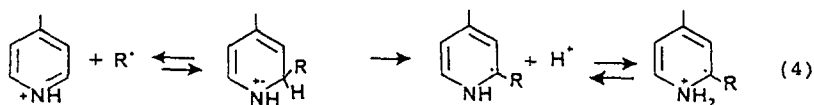
Results and discussion

Among the numerous sources of alkyl radicals, developed by us for the alkylation of heteroaromatic bases¹, the silver-catalyzed oxidative decarboxylation of carboxylic acids by persulphate^{1,6} revealed to be particularly suitable for a two-phase procedure. The generation of the alkyl radical takes place according to eqs. 1-3 and has a general character for carboxylic acids.



The reaction 3 takes place in aqueous solution and it is particularly selective: a small concentration of the carboxylic acid in aqueous solution is sufficient for the reaction to proceed effectively; this makes the use of a two-phase system possible, even when the carboxylic acid is much more soluble in organic solvents than in water.

The alkylation takes place according to a chain process (eqs. 4-6), whose features are general for substitutions of protonated heteroaromatic bases by nucleophilic radicals¹.



Reaction 6 should be very fast ; however , reaction 3 keeps the stationary concentration of the Ag(II) salt very low and the chain process is maintained more by reaction 5 than by reaction 6 .

The results on Table 1 indicate that an alkyl group always deactivates heterocyclic rings towards further alkylation and that the degree of deactivation increases with the nucleophilic character of the attacking radical (methyl < primary < secondary < tertiary alkyl) . The data of Table 1 were determined by the competitive method in aqueous solution ; they only have a qualitative meaning and do not reflect the actual relative rates the addition of alkyl radicals to the heterocyclic ring being reversible , expecially with secondary and tertiary alkyl radicals , as shown by the isotopic effect⁷ . However , these data clearly show that , at high conversions of the heterocyclic compound , polysubstitution becomes a significant process .

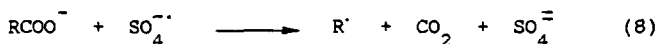
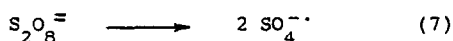
Table 1 - Relative rates in homolytic alkylation of heteroaromatic bases .

Radical	4-Me-pyridine : Pyridine	Lepidine : Quinoline	2-c-hex-4-CN-Pyridine : 4-Cyanopyridine
Me	0.53	-	-
n-Bu	0.32	0.70	0.33
i-Bu	0.28	0.60	0.20
t-Bu	0.15	0.16	< 0.10
c-Hex	0.23	-0.48	-

We have , therefore , utilized a two-phase procedure : one phase was formed by the aqueous solution and the other by chlorobenzene . The results with quinoline , 4-cyanopyridine , 4-ethylpyridine , pyrazine and quinoxaline , as heteroaromatic bases bearing more than one free reactive position , and valeric , isovaleric , pivalic and cyclohexanecarboxylic acids as sources of primary , secondary and tertiary alkyl radicals are reported in Tables 2-6 .

These results show that the two-phase system offers a twofold advantage : it allows a considerable increase in selectivity for monosubstitution and , at the same time , it significantly increases the synthetic potentiality of this radical source . This is due to the fact that , in acidic aqueous medium , the decarboxylation of carboxylic acids by persulphate does not occur in the absence of silver salt , because oxidation takes place according to eq. 3 . Besides , the silver catalysis is deactivated in aqueous solution by heterocyclic derivatives bearing two heteroatoms in the ring , such as diazines , which complex the silver salt , thus reducing its catalytic activity . The degree of deactivation is strictly connected with the rate of decarboxylation , which is related to the stability of the generated carbon-centered radical . Thus , deactivation is moderate with tertiary carboxylic acids , while it is substantial with secondary , and almost complete with primary , carboxylic acids .

Some years ago , we ⁸ tried to overcome this difficulty by using an aqueous solution of carboxylic acid and sodium carboxylate ; decarboxylation occurs , in this case , also in the absence of silver salt , according to eqs. 7 and 8 .



This method , however , is less useful than the silver-catalyzed process , mainly for two reasons : reaction 8 is much less selective than reaction 3 , so that the presence of relatively high concentrations of carboxylate

is necessary in order to obtain good results , whereas with silver catalysis low concentrations of carboxylic acids in acidic aqueous solution give excellent results . Moreover , the low acidity in the absence of silver salt reduces protonation , reactivity and selectivity of weak bases , such as diazines .

Now , the two-phase system allows to overcome all these problems and makes the silver-catalyzed decarboxylation of carboxylic acids very effective also in the presence of heterocyclic derivatives bearing more than one heteroatom , as the results of Tables 5 and 6 show : under the same conditions and utilizing an excess of persulphate , the conversions of quinoxaline are in all cases complete with a two-phase system , but they are less than 10 % with primary and 65 % with secondary carboxylic acids in aqueous solution . The higher efficiency of the two-phase system is noteworthy also with the less reactive heteroaromatic bases , such as 4-ethylpyridine , as shown by the results in Table 3 . With the same amount of persulphate and the same acidity , the conversions are always higher in the two-phase system than in aqueous solution ; the phenomenon becomes more marked with tertiary than with primary alkyl radicals : with *t*-butyl radical no attack occurs in aqueous solution , whereas a 33 % conversion is obtained by the two-phase procedure . This is related to the facts that the addition of alkyl radicals to the heterocyclic ring is reversible , that the reversibility increases from primary to tertiary alkyl radicals⁷ and that it becomes particularly important with the less reactive substrates . Considering that pivalic acid is faster oxidized than primary and secondary carboxylic acids , the two-phase system appears to provide higher efficiency for the alkyl radical source (eq.3) , but also for the rearomatization of the heteroaromatic radical adduct (eqs. 5 and 6) .

The fact that the rate of decarboxylation increases with the stability of the generated alkyl radical suggests an inner-sphere electron-transfer mechanism , in which either the breaking of the O-Ag^+ bond is simultaneous to the breaking of the R-CO bond , or a contribution of the bond breaking occurs in the transition state of electron transfer (eqs. 9 and 10)

Table 2 - Alkylation of quinoline by RCOOH and $S_2O_8^{2-}$.

R	Acid (mol) ^a	Persulphate (mol) ^a	Solvent	Conversion (%)	Monoalkyl (%)	Dialkyl (%)
n-Bu	H ₂ SO ₄ (2)	1	H ₂ O	38	100	-
n-Bu	H ₂ SO ₄ (2)	2	H ₂ O	87	2(46);4(54)	33
n-Bu	CF ₃ COOH(1)	1	PhCl/H ₂ O	31	67	-
n-Bu	CF ₃ COOH(1)	2	PhCl/H ₂ O	63	2(41);4(59)	-
i-Bu	H ₂ SO ₄ (2)	1	H ₂ O	64	100	14
i-Bu	H ₂ SO ₄	2	H ₂ O	100	2(43);4(57)	57
i-Bu	CF ₃ COOH(1)	1	H ₂ O	68	86	10
i-Bu	CF ₃ COOH(1)	1	PhCl/H ₂ O	56	2(38);4(62)	-
i-Bu	CF ₃ COOH(1)	2	PhCl/H ₂ O	100	43	18
t-Bu	H ₂ SO ₄ (2)	2	H ₂ O	96	2(30);4(70)	-
t-Bu	CF ₃ COOH(1)	2	PhCl/H ₂ O	88	90	-
c-Hex	H ₂ SO ₄ (2)	1	H ₂ O	67	2(40);4(60)	12
c-Hex	H ₂ SO ₄ (2)	2	H ₂ O	100	2(37);4(63)	60
c-Hex	CF ₃ COOH(1)	2	H ₂ O	100	82	44
c-Hex	CF ₃ COOH(1)	1	PhCl/H ₂ O	63	2(34);4(66)	-
c-Hex	CF ₃ COOH(1)	2	PhCl/H ₂ O	100	100	17

a) moles per mole of heteroaromatic base

 Table 3 - Alkylation of 4-cyanopyridine by RCOOH and $S_2O_8^{2-}$.

R	Acid (mol) ^a	Persulphate (mol) ^a	Solvent	Conversion (%)	Monoalkyl (%)	Dialkyl (%)
n-Bu	H ₂ SO ₄ (1)	2	H ₂ O	97	30	70
n-Bu	CF ₃ COOH(1)	2	PhCl/H ₂ O	93	65	35
n-Bu ^b	CF ₃ COOH(1)	2	PhCl/H ₂ O	18	100	-
i-Bu	H ₂ SO ₄ (1)	2	H ₂ O	83	67	33
i-Bu	CF ₃ COOH(1)	2	PhCl/H ₂ O	90	87	13
t-Bu	H ₂ SO ₄ (1)	2	H ₂ O	100	23	77
t-Bu	CF ₃ COOH(1)	2	PhCl/H ₂ O	100	77	23
t-Bu ^b	CF ₃ COOH(1)	2	PhCl/H ₂ O	100	85	15
t-Bu ^B	-	2	PhCl/H ₂ O	35	75	25
c-Hex	H ₂ SO ₄ (1)	2	H ₂ O	98	52	48
c-Hex ^b	CF ₃ COOH(1)	2	PhCl/H ₂ O	100	92	8
c-Hex ^b	CF ₃ COOH(1)	1.1	H ₂ O	73	84	16
c-Hex ^b	H ₂ SO ₄ (1)	2	H ₂ O	100	38	62
c-Hex ^b	H ₂ SO ₄ (0.5)	3	H ₂ O	100	-	100
c-Hex ^b	CF ₃ COOH(1)	3	PhCl/H ₂ O	100	70	30
c-Hex ^b	CF ₃ COOH(1)	2	PhCl/H ₂ O	71	97	3
c-Hex ^b	-	4	PhCl/H ₂ O	100	49	51

a) mol for mol of heterocyclic compound ; b) at 50°C

Table 4 - Alkylation of 4-ethylpyridine by RCOOH and $S_2O_8^{2-}$ (3 mol per mol of base) .

R	Solvent	Acid (mol) ^a	Conversion (%)	Monoalkyl (%)	Dialkyl (%)
n-Bu	H ₂ O	H ₂ SO ₄ (2)	65	62	38
n-Bu	PhCl/H ₂ O	CF ₃ COOH(1)	76	75	25
i-Bu	H ₂ O	H ₂ SO ₄ (2)	54	75	25
i-Bu	PhCl/H ₂ O	CF ₃ COOH(1)	90	96	4
t-Bu	H ₂ O	H ₂ SO ₄ (2)	0	-	-
t-Bu	PhCl/H ₂ O	CF ₃ COOH(1)	3	100	-
c-Hex	H ₂ O	H ₂ SO ₄ (2)	58	73	27
c-Hex	PhCl/H ₂ O	CF ₃ COOH(1)	94	97	3

a) mol for mol of heteroaromatic compound .

Table 5 - Alkylation of pyrazine with RCOOH and $S_2O_8^{2-}$.

R	Acid (mol) ^a	Conversion (%)	Solvent	Monoalkyl (%)	Dialkyl (%)
n-Bu	H ₂ SO ₄ (2)	45	H ₂ O	62	38
n-Bu	CF ₃ COOH(1)	65	PhCl/H ₂ O	100	-
i-Bu	H ₂ SO ₄ (2)	65	H ₂ O	51	49
i-Bu	CF ₃ COOH(1)	100	PhCl/H ₂ O	86	14
t-Bu	H ₂ SO ₄ (2)	90	H ₂ O	40	60
t-Bu	CF ₃ COOH(1)	100	PhCl/H ₂ O	90	10

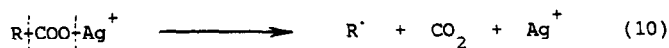
a) mol per mol of pyrazine

Table 6 - Alkylation of quinoxaline by RCOOH and $S_2O_8^{2-}$.

R	Acid (mol) ^a	Persulphate (mol) ^a	Solvent	Conversion (%)	Monoalkyl (%)	Dialkyl (%)

n-Bu	CF ₃ COOH(1)	2	H ₂ O	4	100	-
n-Bu	H ₂ SO ₄ (1)	2	H ₂ O	8	100	-
n-Bu	CF ₃ COOH(1)	2	PhCl/H ₂ O	100	84	16
n-Bu	CF ₃ COOH(1)	1.3	PhCl/H ₂ O	67	93	7
i-Bu	H ₂ SO ₄ (1)	2	H ₂ O	65	85	15
i-Bu	CF ₃ COOH(1)	2	PhCl/H ₂ O	100	52	48
i-Bu	CF ₃ COOH(1)	1.3	PhCl/H ₂ O	87	92	8
t-Bu	H ₂ SO ₄ (1)	2	H ₂ O	90	100	-
t-Bu	CF ₃ COOH(1)	2	PhCl/H ₂ O	100	100	-
c-Hex	H ₂ SO ₄ (1)	2	H ₂ O	58	84	16
c-Hex	CF ₃ COOH(1)	2	PhCl/H ₂ O	100	78	22
c-Hex	CF ₃ COOH(1)	1.3	PhCl/H ₂ O	75	91	9
c-Hex	CF ₃ COOH(1)	2	PhCl/H ₂ O	56	100	-

a) mol for mol of quinoxaline ; b) at 50°C



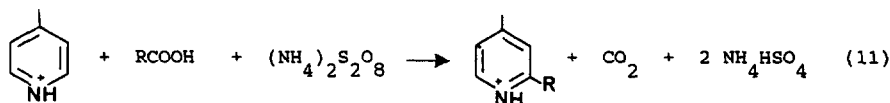
As the energy of the C-O bond decreases , the electron transfer reaction becomes faster .

The results of Tables 2-6 indicate that in all cases , under the same conditions , the selectivity of monoalkylation is higher by the two-phase procedure than in aqueous solution . The conversion of the heterocyclic compound obviously influences the ratio between mono- and polyalkylation ; the higher the conversions , the lower these ratios will be , all the other conditions being equal . The comparison between the two procedures is therefore significant only at similar conversions . When the conversions in the reactions of Tables 2-6 are quantitative , which can be achieved by using an excess of persulphate , the ratios between mono- and dialkylation are affected by the fact that we do not know the excess of reagent after complete conversions in the two different procedures , which have different efficiency for what concerns silver salt catalysis , and the comparison is less significant .

Another important factor , which affects selectivity in monoalkylation , is the lipophilicity of heteroaromatic bases and of their alkyl derivatives , which determines the ease of extraction of the reaction products from the aqueous solution by the organic solvent : thus , selectivity is higher with quinoxaline than with pyrazine . On the other hand , the introduction of an alkyl group does not significantly affect the basicity of the heteroaromatic substrate , while it considerably increases its lipophilicity , thus favouring the extraction of the product by the organic layer .

On the purpose of making the extraction of the unprotonated alkylation product by the organic solvent easier , thus favouring monosubstitution , the medium acidity should be the lowest consistent with the need for protonation , at least partial , of the starting heteroaromatic base . We have , in most cases , utilized equimolar amounts of CF_3COOH , but heteroaromatic bases in Tables 2-6 have quite different strenghts ; thus , for instance , quinoxaline (pK_a 0.56) being much less basic than quinoline

(pK_a 4.94) , it is less protonated under the same reaction conditions , so that it shows higher selectivity in monoalkylation . It should be also considered that the acidity of the medium varies during the reaction , according to the alkylation stoichiometry (eq. 11)



The steric effect can as well be important in the selectivity of monoalkylation for quinoxaline , in which positions 2 and 3 are particularly reactive towards nucleophilic alkyl radicals . The introduction of an alkyl group in position 2 reduces reactivity for position 3 not only for polar , but also for steric reasons ; the effect increases with the bulk of the alkyl group . Steric effects are also important with quinoline : t-butyl radical only attacks position 2 , the steric hindrance of hydrogen in position 5 preventing it from attacking position 4 , so that a highly selective monoalkylation takes place in any case ; with pyridine this steric effect is not present , and position 4 is as reactive as position 2 towards t-butyl radical .

Compared with alkoxycarbonylation and acylation³ , in which the selectivity of monosubstitution is mainly due to the decreased basicity and increased lipophilicity of the acylated product , with elimination or minimization of the effects of polar activation , selectivity in monoalkylation is favoured in a two-phase system by the combination of polar deactivation and increased lipophilicity of the alkylated product .

The two-phase system , combined with a suitable acidity of the medium , is therefore a considerable general improvement for substitution of hetero-aromatic bases by nucleophilic carbon-centered radicals , not only for the increased selectivities , but also for the higher efficiency , and it contributes to make this reaction , even more , one of the most important ones for this class of aromatic compounds .

Experimental section

The heteroaromatic bases and the carboxylic acids are commercial products. All the reaction products were identified by comparison (g.l.c. , IR , NMR and MS) with authentic samples , previously⁶ prepared by the same procedure in aqueous solution .

General procedure of alkylation - A mixture of heteroaromatic base (2.5 mmol) , carboxylic acid (7 mmol) , AgNO_3 (0.2 mmol) , ammonium persulphate and CF_3COOH or H_2SO_4 in the amounts reported in Tables 2-6 in 25 ml of water and 25 ml of chlorobenzene was refluxed for 2h . The aqueous solution was made basic with NaOH , the organic solvent was separated and the aqueous solution further extracted with CH_2Cl_2 . The extract was analyzed by g.l.c. with the same procedures previously⁶ utilized ; the reaction products were isolated by flash chromatography on silica gel (6:1 hexane/ethyl acetate) . Some experiments were carried out at 50°C . The results are reported in Tables 2-6 .

The relative rates were determined by the same procedure , using 2 mmol of pairs of heterocyclic derivatives , 2 mmol of H_2SO_4 and only 0.2 mmol of persulphate , in order to keep conversions low (3-8 %) as necessary for the competitive method to be valid . The results are reported in Table 1 .

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