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X=Y-ZH Systems as Potential 1,3-Dipoles. Part 38[1]. 1,5-Electrocyclisation of Vinyl-and Iminyl-azomethine Ylides. 2-Azaindolizines and Pyrrolo-dihydro-isoquinolines.

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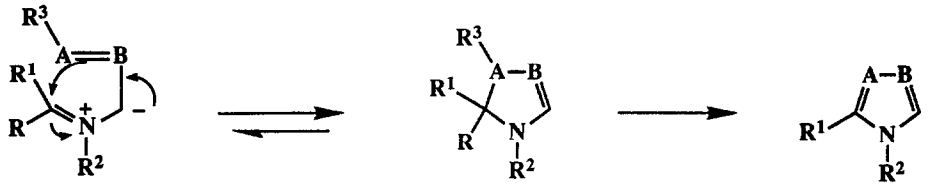
Abstract: Azomethine ylides generated by the decarboxylation of imines of a- amino acids and 2,2'- dipyridyl ketone undergo 1,5-electrocyclisation and subsequent aromatisation to generate 1,3- disubstituted-2-azaindolizines. Azomethine ylides generated from 1,2,3,4- tetrahydroisoquinoline and diarylidene acetone undergo 1,5- electrocyclisation and subsequent prototropic rearrangement. to give pyrrolo-5,6-dihydroisoquinolines.

When a 1,3-dipole is conjugated to a homo-or hetero-polar double bond or 1,3-diene moiety a 1,5- or 1,7-electrocyclisation reaction channel becomes available provided the π- electron array has, or can easily attain, the required configuration. Scheme 1 illustrates the 1,5-electrocyclisation of such an azomethine ylide derived species.

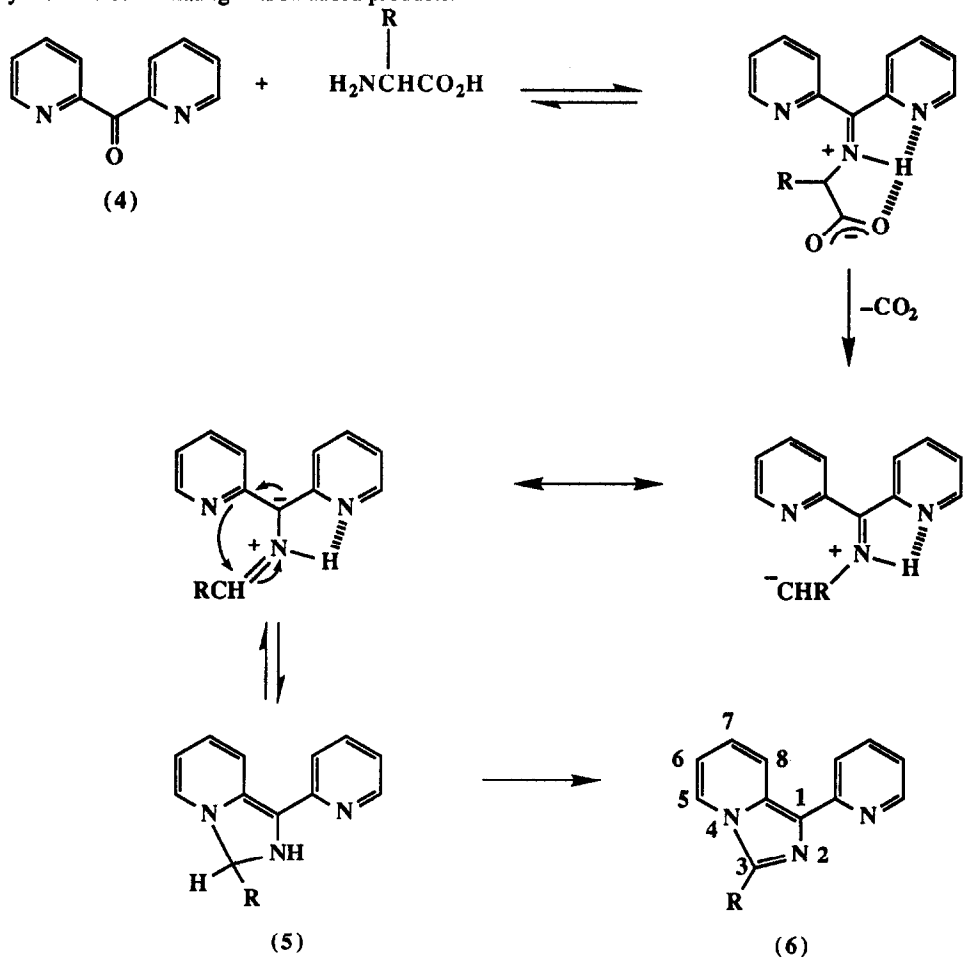


(1) a. A = CR_2, B = CR
b. A = NR, B = CR

Scheme 1

Our interest in 1,5-electrocyclisation reactions of 1,3-dipole derived species arises from an ongoing program which seeks to devise simple new methods for generating 1,3-dipoles.[2] Thus we have described the 1,5-electrocyclisation of vinyl azomethine ylides generated from imines by 1,2- prototropy and by deprotonation of iminium ions[3]. The latter process formed part of a tandem 1,5-electrocyclisation- aldol type condensation process[3]. These processes involved intermediates of type(1a) and analogous intermediates are involved in a range of silver carbonate induced oxidative 1,5-electrocyclisations of N-allyl-1,2,3,4-tetrahydroisoquinolines and- tetrahydro- β-carbolines[4]. In these latter process oxidative (air) aromatisation (Scheme1) of the product of 1,5-electrocyclisation

occurs. We now report two additional 1,5-electrocyclisation processes proceeding via azomethine ylides and culiminating in aromatised products.

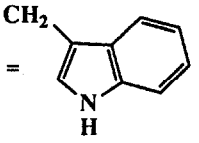
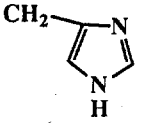
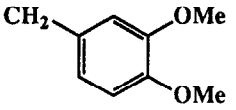


Scheme 2

Conceptually the 1,5-electrocyclisation of vinyl azomethine ylides can incorporate a heteroatom at either or both positions of the vinyl group A=B in Scheme1. We now report examples of (1b) →(3) utilising our decarboxylative route to azomethine ylides. In extensive earlier studies we have shown that aldehydes and ketones condense with α-amino acids, with subsequent decarboxylation, to generate azomethine ylides.[5] Thus 2,2'-bipyridyl ketone(4) was selected as a precursor of azomethine ylides of type(1b).

When α-amino acids (1mol) were heated with dipyridyl ketone (4) (1mol) in methanol containing a few drops of acetic acid the cascade process depicted in Scheme 2 occurred to furnish a series of 3-substituted-1-(2'-pyridyl)-2-azaindolizines in which the 3- substituent is derived from the α- amino acid chain (Table1). Under the reaction conditions employed none of the intermediate dihydro-compound(5) was detected.

Table 1 2-Azaindolizines (6) from the reaction of (4) with α- amino acids[a].

Amino Acid	Azaindolizine (6)	Yield(%)	m.p.(°C)
glycine	a. R = H	50	115-116
alanine	b. R = Me	64	94-96
phenylalanine	c. R = CH_2Ph	42	oil
valine	d. R = i-Pr	62	88-89
leucine	e. R = CH_2CHMe_2	56	38.5-39.5
tryptophan[b]	f. R = 	44	240-242
histidine[b]	g. R = 	30	230-232
O-dimethyl dopa	h. R = 	48	oil

a. Reactions carried out in boiling methanol containing a few drops of acetic acid.
b. Acetic acid omitted from reaction medium to supress Pictet-Spengler cyclisation of the intermediate imine

The addition of a small amount of acetic acid to the methanol solvent had a noticeable catalytic effect on the rate of the cascade process. However, in the case of tryptophan and histidine the acetic acid was omitted to supress the Pictet-Spengler cyclisations of their imines to (7) and (8) respectively.

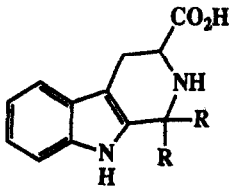
Table 2 Pyrrolo - dihydroisoquinolines from the reaction of (9a,b) and (10a-c)[a].

Amine	Ketone	Time (h)	Product	Yield(%)
9a	10a	48	13a	60
9b	10a	48	13b	40
9a	10b	60	13c	50
9a	10c	60	13d	40

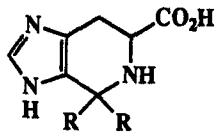
a. All reactions carried out in boiling toluene in the presence of n- Bu_2SnCl_2(1mol)

A second series of 1,5-electrocyclisations was investigated which proceed via an intermediate vinyl iminium species(11) and which involves a radically different aromatisation step. Thus the tetrahydroisoquinolines(9a,b) react slowly (toluene, 110°C, 48-60h) with the divinyl

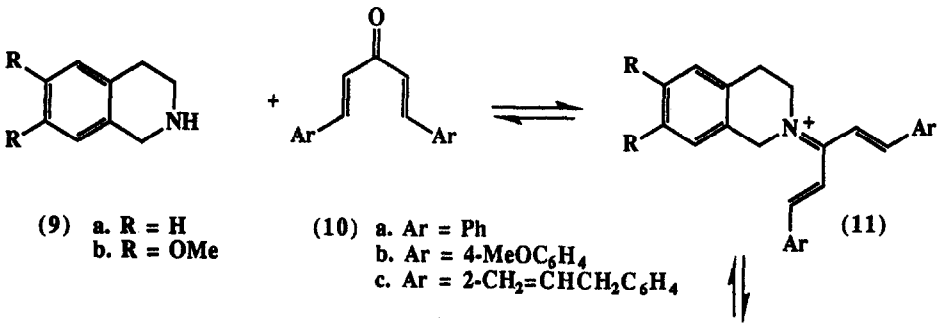
ketones(10a-c) in the presence of dibutyltin dichloride, as a mild Lewis acid, to give the



(7) R = 2-pyridyl



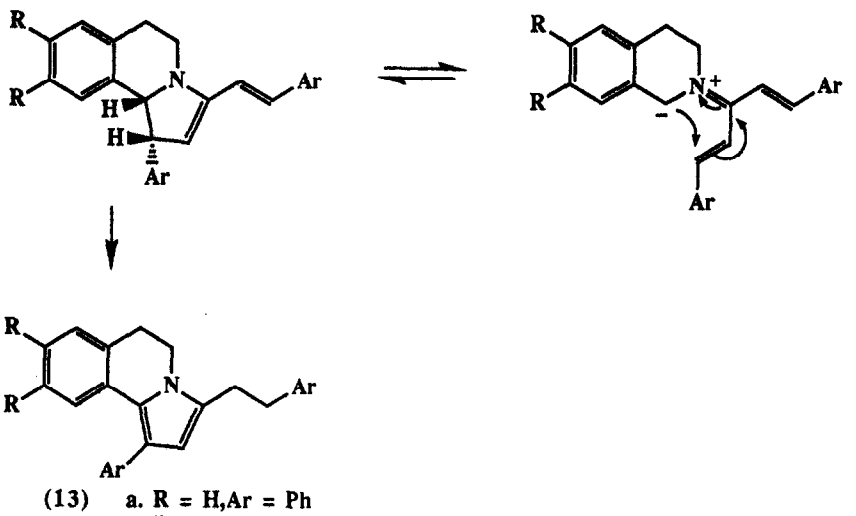
(8) R = 2-pyridyl



(9) a. R = H
b. R = OMe

(10) a. Ar = Ph
b. Ar = 4-$MeOC_6H_4$
c. Ar = 2-CH_2=$CHCH_2C_6H_4$

(11)

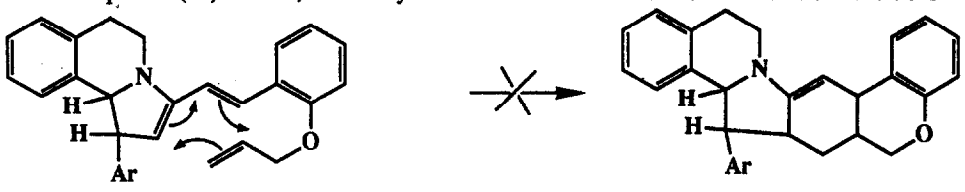


(13) a. R = H,Ar = Ph
b. R = MeO, Ar = Ph
c. R = H,Ar = 4-$MeOC_6H_4$
d. R = H, Ar = 2-CH_2=$CHCH_2OC_6H_4$

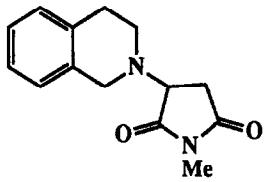
Scheme 3

pyrrolo-dihydroisoquinolines(13a-d)(40-60%) (Table2). In the absence of the dibutyltin dichloride the reaction does not occur. The function of the dibutyltin dichloride is to promote the formation of iminium ion(11) although it is also believed to have a role in the aromatisation process(see below).

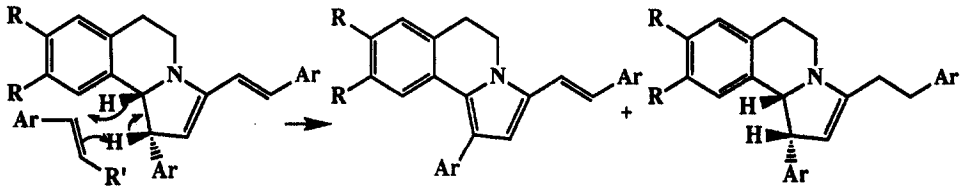
The initial product(12) of the 1,5-electrocyclisation was not observed under the reaction conditions



(12d)

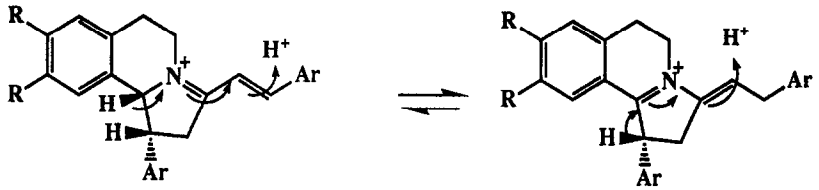


(14)



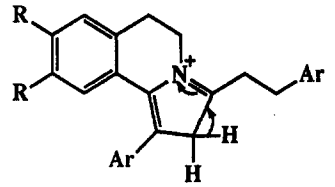
(15) (16)

2(13)



(17)

(13)



Scheme 4

employed, nor was it trapped by an intramolecular Diels-Alder reaction in the case of(12d). Attempts to intercept(12a) by a Diels-Alder reaction with N-methylmaleimide led only to Michael adduct(14).

There are several possible mechanisms for the hydrogen redistribution process(12)→(13). The 6π- electron disrotatory electrocyclisation process should furnish the cis-dihydropyrrole(12). The hydrogen redistribution process (12)→(13) could then occur by two successive dyotropic hydrogen rearrangements(15, arrows).[6] However, this is judged unlikely on entropy grounds and the absence of any(16) in the product. We consider the most likely mechanism for the hydrogen redistribution process is that depicted in Scheme(4). Thus protonation of the intermediate enamine(12) would furnish(17). Subsequent prototropy then leads to (13) (Scheme4).

The reaction of dibutyltin dichloride with the water produced in the initial ketone-amine condensation is the source of the Bronsted acid required to protonate(12). A related multiple prototropic process leading to aromatisation was observed by us in a closely related electrocyclisation process.[3]

Experimental

General experimental details were as previously noted[7].

General Procedure for the Preparation of 2-Azaindolizines

A mixture of dipyridyl ketone(3.8 mmol) and amino acid(3.8 mmol) in methanol(20 ml) containing a few drops of acetic acid was boiled under reflux for 12h. The solvent was then removed under reduced pressure and the residue chromatographed(SiO_2) eluting with ethyl acetate or 9:1v/v methylene chloride-methanol (for the tryptophan and histidine derived products). The yields and m.p.'s of the products are collected in Table 1. All solid products were crystallised from ether-petroleum ether (6a,6b,6c,6d) or methanol-ether(6f,6g) and all formed pale yellow rhombs.

1-(2'-pyridyl)-2-azaindolizine(6a). (Found: C,74.1; H,4.65; N,21.4. $C_{12}H_9N_3$ requires C,73.85; H, 4.6; N,21.5%); δ8.63 and 8.16(2xm,2x2H), 7.95(d,1H), and 7.73, 7.10, and 6.67(4xt,4x1H); m/z(%) 195(M^+,100), 168(12), 140(8) and 78(7).

1-(2'-pyridyl)-3-methyl-2-azaindolizine(6b).(Found: C,74.65; H,5.2; N,20.0. $C_{13}H_{11}N_3$ requires C,74.65; H,5.25; N,20.1%); δ 8.60(m,2H), 8.10(d,1H), 7.70(m,2H), 7.05, 6.88 and 6.55(3xt,3x1H), and 2.70(s, 3H, Me); m/z(%) 209(M^+,100), 169(28), 156(17), 140(18), and 78(41).

1-(2'-Pyridyl)-3-benzyl-2-azaindolizine(6c). HRMS: 285.1253. $C_{19}H_{15}N_3$ requires 285.1266. δ 8.62(m,2H), 8.20(d,1H), 7.70(t,1H), 7.58(d,1H), 7.23(m,5H), 7.08, 6.83 and 6.50 (3xt, 3x1H), and 4.50(s, 2H, CH_2); m/z(%) 285(M^+, 100), 208(58), 142(26), 105(24), 91(21), and 77(32).

1-(2'-Pyridyl)-3-isopropyl-2-azaindolizine(6d).(Found: C,76.05; H,6.5; N,17.85. $C_{15}H_{15}N_3$ requires C,75.95; H,6.35; N,17.7%); δ 8.58(m,2H), 8.15 and 7.80(2xd,2x1H), 7.64(t,1H), 7.02(m,1H), 6.83 and 6.61(2xt,2x1H), 3.36(m,1H,C<u>H</u>Me_2) and 1.48 (d,6H, CH<u>Me_2</u>); m/z(%) 237(M^+,56), 222(100), 165(41), 140(10), and 78(15).

1-(2'-Pyridyl)-3-(2'-methyl)propyl-2-azaindolizine(6e). (Found: C,76.4; H,6.9; N,16.75. $C_{16}H_{17}N_3$ requires C,76.5; H,6.75; N,16.75%); δ 8.59(m,2H), 8.12 and 7.79(2xd, 2x1H),7.69, 7.06, 6.85 and 6.60 (4xt,4x1H), 2.92(d,2H, <u>CH_2</u>CH), 2.27(m, 1H,<u>CH</u>Me_2), and 1.0(d,6H,CHMe_2); m/z(%) 251(M^+,97), 208(100), 181(10), 168(15), 140(12), 104(28), and

78(26)

1-(2'-Pyridyl) -3-(3'-indolylmethyl)-2-azaindolizine(6f). (Found: C,77.35; H,5.1; N,17.25. $C_{21}H_{16}N_4$ requires C, 77.8; H,4.95; N,17.3%); δ (DMSO-d_6) 10.92(s,1H,NH), 8.55, 8.45, 8.22 and 8.11(4xd, 4x1H), 7.80(t,1H), 7.52(d,1H), 7.32(m,2H), 7.14 and 7.0(2xt,2x1H), 6.92(m,2H), 6.69(t,1H) and 4.56(s,2H,CH_2); m/z(%) 324(M^+, 100), 246(20),194(34), 169(17), 130(67), 103(14) and 77(15).

1-(2'-Pyridyl)-3-(3'-imidazoylmethyl)-2-azaindolizine(6g).(Found C,69.5; H,4.7; N,25.2. $C_{16}H_{13}N_5$ requires, C,69.8; H,4.75; N,25.45%); δ(DMSO-d_6) 8.60(m,2H), 8.07 and 7.96(2xd,2x1H), 7.71(t,1H), 7.60(s,1H,NH), 7.09(t,1H), 6.89(m, 2H), 6,65(t,1H) and 4.48(s,2H,CH_2); m/z(%) 275(M^+, 100), 208(43), 194(14), 140(5) and 78(13).

1-(2'-Pyridyl)- 3-(3',4'-dimethoxyphenyl)-2-azaindolizine(6h). HMRS: 345.1465. $C_{21}H_{19}N_3O_2$ requires 345.1465. δ 8.57(br s and d,2H), 8.17(d,1H), 7.72(t,1H), 7.60(d,1H), 7.08 and 6.86 (2xt,2x1H), 6.74(m,3H), 6.55(t,1H), 4.45(s,2H,CH_2), and 3.84 and 3.78(2xs,2x3H,2xOMe); m/z(%) 345(M^+,100) 330(11), 208(13), 173(7), 151(17), and 78(8).

General Procedure for Preparation of Pyrrolo - dihydroisoquinolines.

A mixture of the diarylidine acetone (0.05mol), the tetrahydroisoquinoline(0.05mol) and di-n-butyltin dichloride(0.05mol) in dry toluene (75ml) was boiled under reflux for 48-60h using a Dean - Stark trap. The toluene was removed under reduced pressure, the residue taken up in ether(150ml), washed with saturated aqueous sodium carbonate(100ml) and brine(100ml) After drying($MgSO_4$) the ether was evaporated under reduced pressure and the residue purified by flash chromatography(SiO_2) eluting with an ether - petroleum ether mixture.

1-(2'-Phenylethyl)-3-phenylpyrrolo[2,1-a]-5,6-dihydroisoquinoline(13a). Obtained as off-white prisms from ether-petroleum ether, m.p. 72-73°C (Found: C,89.1; H,6.25; N,3.65. $C_{26}H_{23}N$ requires C, 89.4; H, 6.55; N,4.0%); δ(C_6D_6) 7.4-6.6(m,14H,ArH), 5.82(s,1H,pyrrole-H), 2.8(t,2H,NCH_2), and 2.5, 2.3 and 2.2 (3xt, 3x2H, 3XCH_2); m/z(%) 349(M^+,24), 269(12), 258(100), 256(6) and 235(1).

1-(2'-Phenylethyl)-3-phenylpyrrolo[2,1-a]-5,6-dihydro-7,8-dimethoxyisoquinoline (13b). Obtained as pale yellow prisms from ether-petroleum ether, m.p. 124-125°C (Found: C,81.95; H,6.75, N,3.2. $C_{28}H_{27}NO_2$ requires C,82.15; H,6.6; N,3.4%); δ 7.6-7.2(m,10H,ArH), 6.9 and 6.7 (2xs,2x1H,ArH), 6.1(s,1H,pyrrole-H), 3.9(s,3H,OMe), 3.9(t,2H,NCH_2), 3.4(s,3H,OMe), and 3.0(m,6H,3xCH_2); m/z(%) 409(M^+,22), 318(83),91(91) and 78(100).

1-(2'-(4''-methoxyphenyl))-3-(4'-methoxyphenyl)pyrrolo[2,1-a]-5,6-dihydro-isoquinoline(13c). Obtained as colourless needles from ether - petroleum ether, m.p. 128-130°C (Found: C,75.55; H,6.3, N,2.95. $C_{28}H_{27}NO_2.2H_2O$ requires C, 75.55; H,6.0; N,3.1%); δ 7.4-6.8(m,12H, ArH), 6.0(s,1H,pyrrole-H), 3.95(s,3H,OMe), 3.9(t, 2H,NCH_2), 3.8(s,3H,OMe) and 2.9(m, 6H, 3xCH_2; m/z(%) 409(M^+,15), 289(29), and 288(100).

1-(2'-(2''-allyloxyphenylethyl)-3-(2-allyloxyphenyl)pyrrolo[2,1-a]-5,6-dihydroiso quinoline(13d). Obtained as a thick pale yellow gum. HRMS: 461.2368. $C_{32}H_{31}NO_2$ requires 461.2355. δ 7.4-6.8(m,12H, ArH), 6.2(s,1H, pyrrole-H), 6.0 and 5.6 (2xm,2x1H,2x$C\underline{H}$=CH_2), 5.4, 5.3, 5.2, and 5.1(4xd,4x1H,2xCH=$C\underline{H_2}$),4.6 and 4.4 (2xd, 2x2H,2xOCH_2),

4.0(t,2H,NCH_2) and 3.0 (m,6H,3xCH_2); m/z(%) 461(M^+, 40), 314(100), 263(60), 262(38), 256(25), 299(12), and 91(11).

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