1-Pyrrolidin-1-ylbuta-1,3-dienes as Potential 1,5-Dipoles; Synthesis of Pyrrolizines

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Tautomerization of 1-pyrrolidin-1-ylbuta-1,3-dienes and (hetero)aromatic compounds formally containing this moiety, to the corresponding 1,5-dipoles by a concerted [1,6] hydrogen shift is followed by a 1,5-electrocyclization to give pyrrolizine derivatives.

The *in situ* generation of 1,3-dipoles by prototropic equilibration of oxazolinones,[1] imines of α-amino-acid esters,[2] and arylhydrazones[3] and the subsequent intra- or inter-molecular reaction with 1,3-dipolarophiles provides a versatile method for synthesis of 5-membered heterocycles. We now report a synthesis of pyrrolizine derivatives which involves the tautomerization of 1-pyrrolidin-1-ylbuta-1,3-dienes to the corresponding 1,5-dipoles by a concerted [1,6] hydrogen shift, followed by a 1,5-dipolar cyclization.

Previously we have reported that reactions of 3-pyrrolidin-1-ylthiophens and pyrrolidine enamines with electron-deficient acetylenes like dimethyl acetylenedicarboxylate (DMAD) in protic solvents yield pyrrolizine derivatives instead of the cyclobutenes that are formed in apolar solvents.[4] Recently, in the reaction of the pyrrolidine enamine of α-tetralone[5] and DMAD in methanol at −7 °C, we observed two transient singlet ^{1}H n.m.r. absorptions of unequal intensities at δ 6.33 and δ 5.95, respectively, which we assigned to the *E*- and *Z*-isomer of the Michael adduct (**1**).[6] After a prolonged reaction, however, we isolated only the pyrrolizine (**2**) in a yield of 89%.[4c] This observation indicated that one or both of the Michael adducts containing the 1-pyrrolidin-1-ylbuta-1,3-diene moiety may be an intermediate in the formation of the pyrrolizine. Therefore we decided to investigate if this is a general reaction of 1-pyrrolidin-1-ylbuta-1,3-dienes.

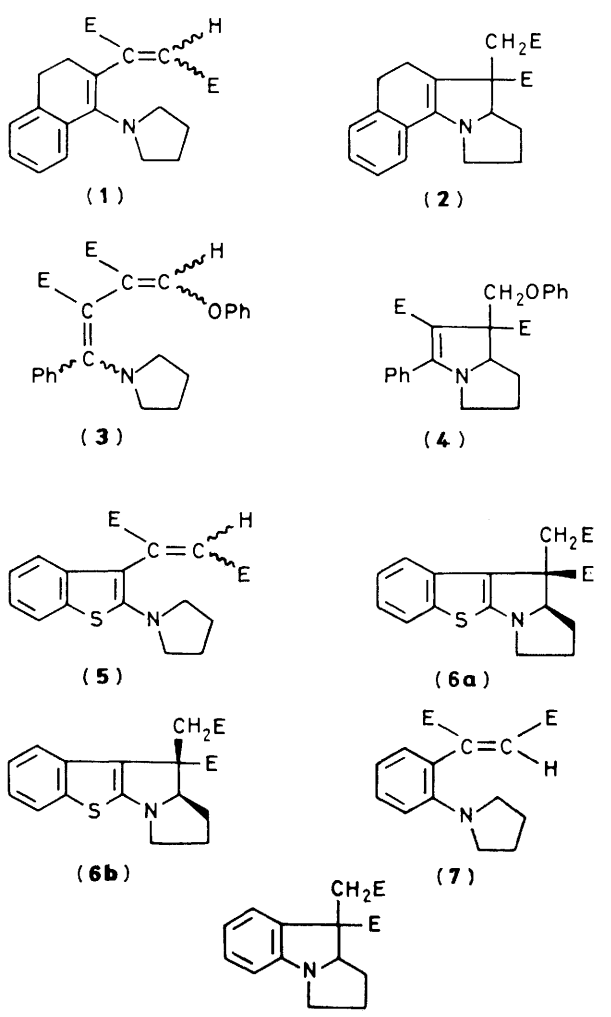
We found that (**3**)[4a] upon refluxing in butan-1-ol for 20 h gave the crystalline pyrrolizine (**4**)† (m.p. 143—144.5 °C) in a

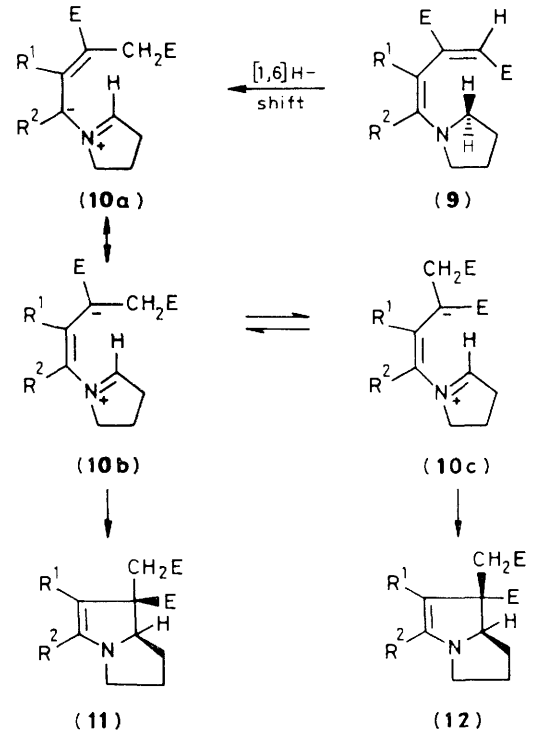
† Satisfactory elemental analyses were obtained for all new compounds.

Table 1. ^1H and ^{13}C N.m.r. data for pyrrolizines.

Compound	^1H N.m.r.[a] [$-CH_2R^b$/(ABq)]		J	N–CH<	J	^{13}C N.m.r.[a] N–CH<	$-CH_2R^b$	$C(CO_2Me)$-CH_2R^b
(4)	4.68	4.42	10	—[c]		70.6	67.3	59.2
(6a)	3.19	2.94	15.5	4.4—4.0[d]		81.2	43.3	55.5
(6b)	4.02	2.77	18	5.15[e]	6 and 10	78.4	36.6	53.9
(8)	3.63	2.72	18	4.65[e]	5 and 11	72.0	38.9	54.1

[a] In $CDCl_3$: δ values *vs.* Me_4Si, J in Hz. [b] R = OPh (**4**) or CO_2Me (**6a**, **6b**, **8**). [c] Coincides with ABq. [d] Multiplet. [e] Doublet of doublets.





Scheme 1

yield of 26%, and a mixture of stereoisomers of (**3**) which did not further react.‡ The structure of (**4**) was proven by comparison of its n.m.r. data (Table 1) with those of pyrrolizines, the *X*-ray structures of which have been reported.[4b,c] We investigated the scope of this cyclization by examining 1-pyrrolidin-1-ylbuta-1,3-dienes in which one of the double bonds constitutes part of a (hetero)aromatic system. Compound (**5**) was obtained, from the reaction of 2-pyrrolidin-1-ylbenzo[*b*]thiophen[7] with DMAD in methanol at room temperature, in a yield of 86%, as a 3:1 mixture of the *E*- and *Z*-isomers which were separated by column chromatography (Lobar, CH_2Cl_2–CCl_4, 4:1). The red *E*-isomer [m.p. 96.5—98.5 °C; δ 7.07 (=$CHCO_2Me$)] afforded after refluxing in butan-1-ol for 15 h a 1:2 mixture of two pyrrolizines [(**6a**), m.p. 94—96 °C, and (**6b**), m.p. 137—138 °C] in an overall yield of 86%. However refluxing a solution of the *E*-isomer of (**5**) in toluene for 15 h gave only (**6a**) in a yield of 73%. When the yellow *Z*-isomer of (**5**) [m.p. 114—116 °C; δ 5.93 (=$CHCO_2Me$)] was refluxed in toluene for 15 h neither cyclization nor *Z* to *E* isomerization occurred, whereas after refluxing in butan-1-ol for 15 h the *Z*-isomer was partially converted into a 1:2 mixture of (**6a**) and (**6b**), respectively.

In relation to our work on mitomycin C analogues it was of interest to discover if compound (**7**) [oil; δ 6.07 (=$CHCO_2Me$)],§ in which one of the double bonds of the diene moiety is part of a benzene ring, would cyclize. Heating (**7**) in butan-1-ol for 3.5 h at reflux temperature gave exclusively one isomer of

‡ There are four stereoisomers of (**3**) of which probably only one, the (*E*,*E*)-isomer, can cyclize (*vide infra*). The starting material was a mixture of two isomers.

§ This compound was prepared by addition of (2-pyrrolidin-1-yl-phenyl)copper to DMAD in THF.

the pyrrolizine (**8**) (m.p. 107—108 °C) in a yield of 74%, presumably *via* isomerization to the *E*-isomer, which was observed as a transient intermediate [δ 6.78 (=$CHCO_2Me$)], and subsequent cyclization.

The cyclization of the 1-pyrrolidin-1-ylbuta-1,3-dienes to pyrrolizines can be explained by assuming a two-step process. The first step is a prototropic equilibration of (**9**) (Scheme 1) to give a 1,5-dipole (**10**) *via* a thermal antarafacial [1,6] hydrogen shift of one of the α-methylene protons of the pyrrolidine moiety to the $C(CO_2Me)$=$CHCO_2Me$ group. This concerted sigmatropic rearrangement is electronically equivalent¶ to a thermal [1,7] hydrogen shift in a hepta-1,3,5-triene.[9] This type of hydrogen shift occurs *via* a helical transition state of the 6π-system. As can be seen from Dreiding models as well as from the NCH_2-signals in the ^1H n.m.r. spectra which show a distorted signal for the *E*-isomer of (**5**) compared with a sharp 'triplet' signal for the *Z*-isomer, only the *E*-isomer has the required helical conformation whereas the *Z*-isomer is much flatter. We have strong evidence that the [1,6] hydrogen shift is indeed a concerted process because after allowing both isomers of (**5**) to react in butan-1-[^2H]ol for 15 h at reflux temperature no incorporation of deuterium was observed.** The second step is a symmetry-allowed disrotatory 1,5-dipolar cyclization.[11] In the 1,5-dipole, stereomutation [(**10b**) to (**10c**)] can occur depending on structure, rate of cyclization, and probably the polarity of the solvent.[12] This would explain why in toluene only (**6a**) is formed, but in butan-1-ol both (**6a**) and (**6b**) are produced.

We believe that the *in situ* generation of a 1,5-dipole by a concerted hydrogen shift followed by a 1,5-electrocyclization is a more general process and can also account for the cyclization of a tricyanobutadienylidenebenzothiazoline derivative followed by elimination of malononitrile to yield 1-benzoyl-2-cyanopyrrolo[2,1-*b*]benzothiazole as reported by Tsuge *et al.*[13] The generation of a 1,5-dipole catalysed by base followed by a 1,5-dipolar cyclization has recently been reported by Speckamp *et al.*[14] and Pandit *et al.*[15]

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¶ *Cf.* the photochemical antarafacial [1,16] hydrogen shift in the corrin system[8] that can formally be regarded as a [1,17] hydrogen shift.

** Meth-Cohn *et al.*[10] have proved that in the acid-catalysed cyclization of a deuteriated anil to a dihydrobenzimidazole the [1,6] deuterium shift occurs without incorporation of hydrogen in the final product.

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