Tetrahedron Letters No. 42, pp 4093 - 4096.

0040-4039/78/1015-4093$02.00/0

TOWARDS POLYAZAAZULENES. THE SYNTHESIS OF 3,7-DIHYDROPYRROLO [3,4-d] [1,2] DIAZEPINES

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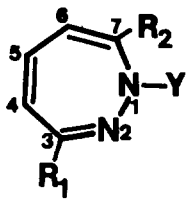
The synthesis of polyazaazulenes is of interest when studying the effect of methine group replacement by nitrogen atoms upon the spectroscopic and chemical properties of the parent azulene[1]. Along these lines[2] and as part of our continuing studies of cycloadditions to 1,2-diazepines[3], we investigated their reactivity with tosylmethyl isocyanide (TOSMIC).

TOSMIC has been used in recent years as a powerful synthon for the preparation of a number of five-membered heterocyclic systems, ranging from pyrroles to imidazoles, from oxazoles to thiazoles, to cite but a few[4-9]. Multistep mechanisms have been proposed in order to account for the addition of TOSMIC to polarized double bonds, like imines and aldehyde- and ketone-carbonyls, as well as to conjugated double bonds[8,10]. 1,2-Diazepines exhibit one imine double bond and two conjugated double bonds, all three of which could in principle add TOSMIC after treatment of the latter with sodium hydride.

Sodium hydride, being a strong base, cleaves 1,2-diazepines which are not substituted at C-3 whereby dienaminonitrile isomers are obtained[11]. Therefore we chose 3-substituted diazepines as our starting material, not expecting any addition of TOSMIC to the imine double bond, since imidazole formation will be prevented by the presence of the C-3 substituent. Furthermore the TOSMIC anion addition process to any polarized double bond is likely to be reversible[10]. We surmised that TOSMIC would add, if at all, either to the Δ^4 or to the Δ^6 double bond of diazepines 1, leading eventually to pyrrole derivatives.

In a typical experiment a dimethoxyethane solution of TOSMIC and of diazepine 1a is treated at -35° with sodium hydride until hydrogen evolution ceases. The reaction mixture is then poured on ice. Extraction with methylene chloride, followed by column chromatography over silicic acid with cyclohexane/ethyl acetate 1/1 v/v, leads to pyrrolodiazepine 2a, m.p.141-142° in 53% yield. Spectral data and elemental analysis[12] fully support the structure of 1-methyl-3-ethoxycarbonyl-3,7-dihydropyrrolo[3,4-d] [1,2] diazepine for compound 2a [UV (EtOH) λ_{max} 254 (ε:20,500) and 225 nm (ε:14,700); IR (KBr) 3240 (N-H), 1635 (C=O), 1615 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 1.33 (3H; t; CH_2-$\underline{CH_3}$), 2.3 (3H;s;CH_3),

4.3 (2H; q; $\underline{CH_2}$-CH_3), 6.15 (1H; d; H-4; J_{45}=8Hz), 6.32 (1H; d; H-5; J_{54}=8Hz), 6.9 (1H; m; H-3), 7.3 (1H; m; H-1) and 9.9 ppm (1H; broad singlet, exchangeable with D_2O); MS m/e 219]. One notices in particular in the ^1H NMR spectrum two unresolved multiplets at δ 6.9 and 7.3. After exchange of the N-H proton with deuterium the multiplets become finely resolved doublets (J=2Hz) which are typical for the α and α' hydrogen atoms (H-1 and H-3 in 2a) of a pyrrole substituted at C-3 and C-4[13]. The AB pattern which we observe in the NMR spectrum of 2a is characteristic for H-6 and H-7 protons of diazepines 1[14]. One concludes therefore that the pyrrole ring is site-specifically built upon the Δ^4 double bond of the starting diazepine.



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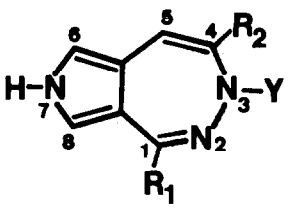

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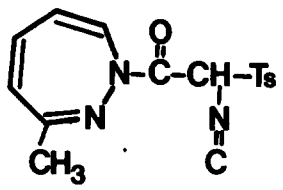

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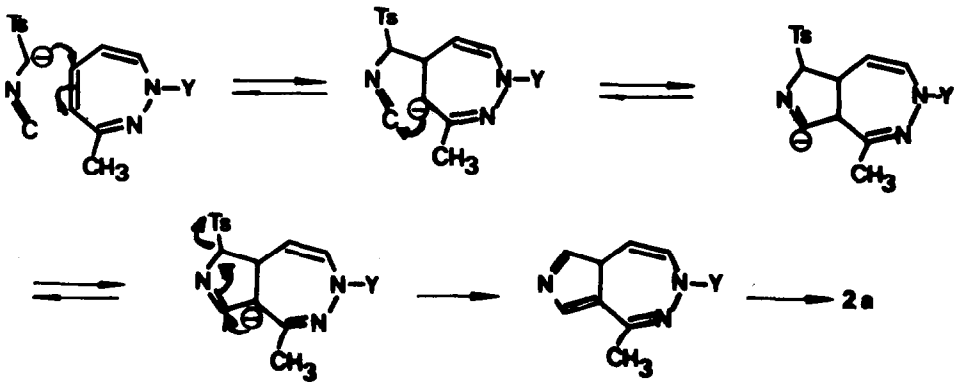
All 3-substituted 1,2-diazepines investigated undergo the same type of reaction with TOSMIC leading in moderately good yields (except for 1e) to the corresponding pyrrolodiazepines (Table 1)

Table 1. 3,7-Dihydropyrrolo[3,4-d] [1,2] diazepines 2 obtained from reaction of TOSMIC anicn with 1,2-diazepines 1

	Y	R_1	R_2	m.p. °C	Yield %
2a	CO_2Et	CH_3	H	141-142	52
2b	$COCH_3$	CH_3	H	170-172	53
2c	COPh	CH_3	H	104-106	50
2d	Ts	CH_3	H	180 dec.	49
2e	$CO_2CH_2CCl_3$	CH_3	H	oil	20
2f	$COCH_3$	CH_3	CH_3	190-192	48

As a working hypothesis the following multistep mechanism can be proposed for the buildup of the pyrrole ring (Scheme 1). The regiospecificity of the first step is tentative only since a substituted TOSMIC reagent would be required in order to check the hypothesis. In our opinion the first three steps should be reversible which would also account for the fact that the fully substituted imine double bond does not add TOSMIC. The last two steps of the mechanistic hypothesis are obviously irreversible.

Scheme 1



When diazepine 1e is reacted with TOSMIC, besides the pyrroldiazepine 2e one isolates also a yellow compound m.p.124° decomp. (yield: 11%) which is not stable [IR (KBr) 2150 (N≡C) and 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.7 (2H; d; J=9Hz), 7.25 (2H; d; J=9Hz), 6.35 (3H; m; H-4, H-5, H-7), 5.8 (1H; m; H-6), 2.4 (3H; s; CH_3) and 2.15 ppm (3H; s; CH_3)]. From these spectral data one assigns tentatively structure 3 for this compound. The TOSMIC anion obviously underwent nucleophilic attack on the electron deficient carbonyl of the trichlorocarboethoxy moiety, whereby the trichloroethoxy group is extruded.

Pyrrolodiazepines 2 are readily available compounds which seem ideally suited for the synthesis of 2,5,6-triazaazulenes.

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(Received in UK 29 August 1978; accepted for publication 4 September 1978)