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1-Amino-2-chloromethylene-2,3-dihydropyrroles by Unusual Reaction of Conjugated Azoalkenes with 2-Chloro-1,3-dicarbonyl Compounds

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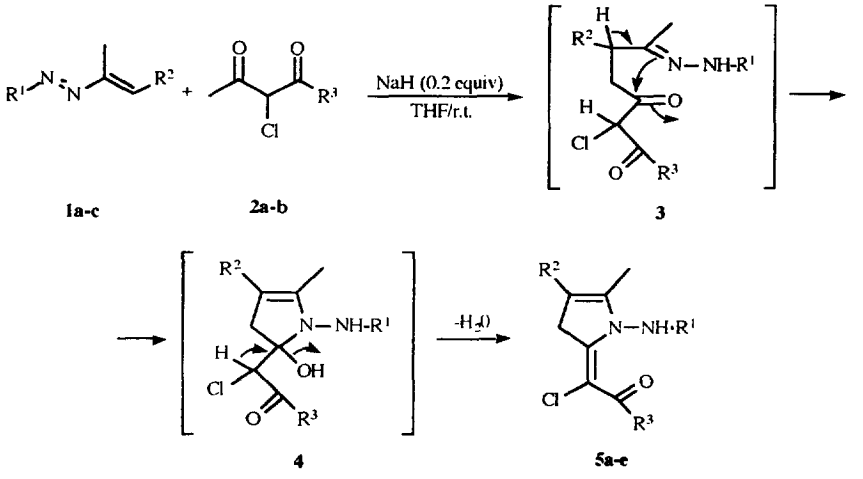
Abstract: New 1-amino-2-chloromethylene-2,3-dihydropyrroles, predominantly as *E* isomers, have been obtained in good yields and under mild conditions by the sodium hydride catalyzed reaction of some conjugated azoalkenes with 2-chloro-1,3-dicarbonyl compounds.

In previous papers, we reported the nucleophilic attack of various compounds containing activated methylene or methine groups to the azo-ene system of conjugated azoalkenes, to give polyfunctionalized pyrrole derivatives.[1,2] These studies have confirmed that conjugated azoalkenes are interesting products and powerful tools in organic chemistry.[3,4]

We now report the singular behaviour of the reaction between alkoxycarbonyl- (**1a**) or aminocarbonyl-azoalkenes (**1b-c**) and 3-chloro-2,4-pentanedione (**2a**), as well as methyl 2-chloroacetoacetate (**2b**) which, surprisingly, afford 1-amino-2-chloromethylene-2,3-dihydropyrroles (**5a-e**) predominantly as *E* isomers. The reaction occurs rapidly under mild conditions (room temperature) in tetrahydrofuran, with catalytic amount (0.2 equiv) of sodium hydride.[5] The mechanism seems to involve a nucleophilic attack on the heterodienic system of conjugated azoalkenes by the terminal carbanion of the β-dicarbonyl compounds, instead of the expected attack by the highly-stabilized central carbanion, as normally observed in previous analogous investigations.[1] This attack first determines the formation of the hydrazonic intermediate (**3**) by 1,4-conjugate addition of Michael-type. This adduct then gives rise to the heteroring closure (**4**) due to an internal nucleophilic attack of the lone pair of >C=N-NH- nitrogen atom on the ketonic function. Finally, the exocyclic olefination process takes place by loss of a water molecule, producing unknown 1-amino-2-chloromethylene-2,3-dihydropyrroles (**5a-e**) in good to excellent yields (see Scheme and Table). The *E/Z* isomers of these derivatives were unequivocally revealed mainly by ^{1}H-NMR spectroscopy exhibiting two doublets (J=12 Hz) centered at nearly 4.5 ppm and two doublets with the same coupling constant centered at nearly 4.8 ppm attributable to two hydrogen atoms in the position 3 of the pyrroline ring for the *Z* and *E* form, respectively. ^{13}C-NMR spectroscopy show a triplet (J=155 Hz) in the region of 34-40 ppm ascribable to the C(3) heterocyclic carbon atom.[6]



1a-c **2a-b** **3** **4** **5a-e**

Scheme

Table. Yields, melting points and reaction times of 1-amino-2-chloromethylene-2,3-dihydropyrroles **5a-e**.

Azoalkene 1	β-Dicarbonyl 2	Pyrrole 5	R^1	R^2	R^3	Yields[a] (%)	Mps[b] (°C)	Reaction times (min)
1a	**2a**	**5a**	$COOBu^t$	COOMe	Me	71	198-199	45
1a	**2b**	**5b**	$COOBu^t$	COOMe	OMe	74	212-214	40
1b	**2a**	**5c**	$CONH_2$	COOEt	Me	90	183-185	30
1b	**2b**	**5d**	$CONH_2$	COOEt	OMe	89	240-242	5
1c	**2b**	**5e**	CONHPh	COOMe	OMe	73	170-172	30

[a]Yields of pure isolated product. [b]Melting points are uncorrected and occur with decomposition.

Therefore, these reactions manifest a high degree of regio- and stereochemical specificity and the compounds obtained are both interesting products and useful intermediates in organic synthesis because of their suitability for several structural modifications. It is noteworthy that the reactions realised under the same conditions by utilizing as nucleophilic agents β-dicarbonyl compounds, without the chlorine atom or with a methyl group in its place, provided the previously described 1-aminopyrroles or 1-amino-2,3-dihydropyrrol-2-ols, respectively.[1] Hence, the chlorine atom clearly seems to play a determining role in favouring the terminal carbanion rather than the centralized dicarbonyl carbanion. This preferential formation cannot be explicated in terms of dicarbanion production, because of the use of 0.2 equivalents of sodium hydride.[7]

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References and Notes

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5. General procedure for the synthesis of 1-amino-2-chloromethylene-2,3-dihydropyrroles (**5a-e**). To a stirred solution of the 2-chloro-1,3-dicarbonyl compounds **2a-b** (2 mmol) in tetrahydrofuran (10 ml) was added sodium hydride (0.4 mmol, 0.2 equiv). After 10 min. at room temperature, the conjugated azoalkenes **1a-c** in tetrahydrofuran (10 ml) were added dropwise and their red colour rapidly disappeared. The reaction was monitored by silica gel TLC. After the times reported in Table, tetrahydrofuran was evaporated under reduced pressure and the crude reaction product was crystallized from ethyl ether-petroleum ether (40-60 °C). In the case of the conjugated azoalkene **1c** the reaction was carried out by adding simultaneously both reagents and catalyst. The subsequent work-up procedure remains the same as described above.
6. IR, MS, ^{1}H- and ^{13}C-NMR spectra, as well as elemental analysis data of all 1-amino-2-chloromethylene-2,3-dihydropyrroles (**5a-e**) are in agreement with the structures reported. For **5c**: IR 3411, 3312, 3257, 3207, 1705, 1688, 1661, 1589 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.26 and 1.28 (2t, 3H, Me, J=7.0 Hz), 2.11 (s, 3H, Me), 2.32 and 2.35 (2s, 3H, Me), 4.22 and 4.25 (2q, 2H, OCH_2, J=7.0 Hz), 4.47 and 4.61 (2d, 1H, CH_2,J=12.0 Hz), 4.71 and 4.92 (2d, 1H, CH_2,J=12.0 Hz), 6.50 (bs, 2H, NH_2, D_2O ex); 9.58 and 9.76 (bs, 1H, NH, D_2O ex). ^{13}C-NMR (DMSO-d_6): δ 9.7 and 10.2 (Me), 13.9 and 14.0 (Me), 30.9 and 31.0 (Me), 34.2 and 34.4 (C3), 59.9 and 60.3 (OCH_2), 108.1 and 110.8 (C5), 120.6 and 123.2 (C2), 129.6 and 132.4 (C4), 135.2 and 136.1 (CCl), 156.6 and 157.1 (NC=O), 163.4 and 163.8 (OC=O), 196.6 and 197.2 (C=O). MS: m/z (%) 301 (35) [M^+], 265 (40), 256 (85), 236 (100). Anal. Calcd. for $C_{12}H_{16}ClN_3O_4$: C, 47.77; H, 5.34; N, 13.93. Found: C, 47.91; H, 5.27; N, 13.75. For **5c** the *E/Z* ratio was calculated to be 80:20, while the other compounds **5a,b,d,e** were detected in nearly pure *E* isomeric form.
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