A New Synthetic Methodology for the Pyrrolidine Ring

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Abstract: An unprecedented synthesis of pyrrolidine rings has been accomplished by the reaction of azidoacetyl derivatives with maleate and fumarate esters.

Key words: azides, enamines, pyrrolidine, phenothiazine

Phenothiazines, which are inexpensive and widely available, belong to an important class of tricyclic nitrogen–sulfur heterocycles; they possess a broad spectrum of pharmacological activities including psychotropic, immunopotentiating, antimicrobial, antifungal, antiproliferative, and antitumor activities, and stimulation of the penetration of anticancer agents through the blood–brain barrier.[1–9] One important modification of the parent phenothiazine structure is the introduction of a substituent at the thiazine nitrogen atom. This includes the azide moiety, a grouping that leads to energy-rich and flexible intermediates and has enjoyed considerable interest since its discovery in 1864.[10–13] In spite of their explosive properties, organic azides are valuable intermediates in organic synthesis.[14] Thus they are used in the synthesis of anilines and *N*-alkyl-substituted anilines,[15] as precursors for nitrenes and as dipoles in cycloadditions.[16]

Following our interest in the synthesis of new phenothiazine derivatives with various substituents in search of better medicinal agents, we have investigated the cycloaddition reactions of 10-(azidoacetyl)-10*H*-phenothiazine with various olefinic dipolarophiles. We wish to report here an unprecedented interaction of azidoacetyl derivatives **1** as *C*-nucleophiles with maleate and fumarate esters, leading to pyrrolidine derivatives. Highly substituted pyrrolidines are found in pharmaceuticals and natural alkaloids and are privileged building blocks in organic synthesis.[17,18] The reaction of 10-(azidoacetyl)-10*H*-phenothiazine (**1a**, Scheme 1) with an equimolecular amount of dimethyl maleate in boiling toluene provided a mixture of two compounds that were separated by column chromatography (silica gel, EtOAc–hexane = 1:1). The minor compound (14% isolated yield) was easily identified as enamine derivative **3a** by mass spectrometry and NMR analysis.[19] The *Z*-stereochemistry around the double bond was indicated by the chemical shift of the amine hydrogen (δ = 8.47 ppm), implying an intramolecular hydrogen bond with the oxygen atom of the ester group. The structure of the major compound (45% isolated yield) **2a** was unambiguously proved by X-ray analysis (Figure 1).[20] This is consistent with the NMR spectrum, which unexpectedly indicated four different methyl ester groups.[21] In view of the above results we performed the same reaction using two equivalents of methyl maleate. Regardless of the azide/maleate ratio, the reaction output

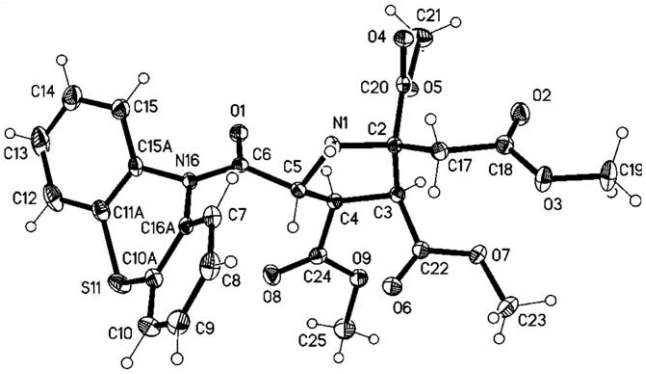
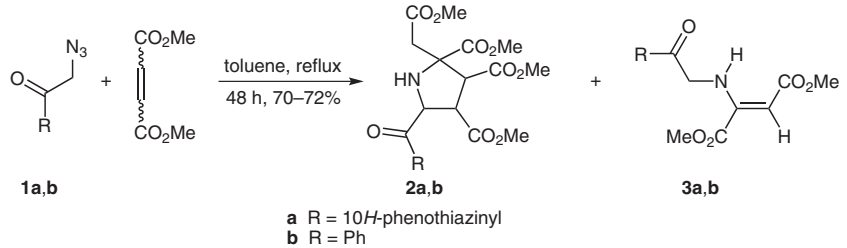


Figure 1 Molecular structure of pyrrolidine **2a**; the ellipsoids represent 50% probability levels



Scheme 1

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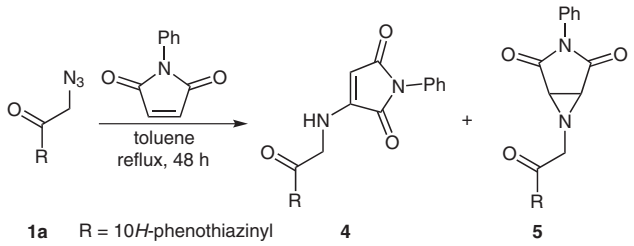
was unchanged, with an improved yield for pyrrolidine derivative (58%) when two equivalents of dimethyl maleate were used.

These studies were extended by the treatment of phenacyl azide **1b** with dimethyl maleate in toluene. After 48 hours reflux two products were detected in the reaction mixture, the pyrrolidine derivative **2b** (60%) and enamine **3b** (12%).

Again, the major product was pyrrolidine **2b** with a ratio of the two products of 4:1. These results are in contrast to those obtained from the reaction of azide **1a** with *N*-phenyl maleimide (Scheme 2). Thus, heating an equimolecular mixture of 10-(azidoacetyl)-10*H*-phenothiazine and *N*-phenyl maleimide in toluene for 48 hours produced a mixture of enamine **4** and aziridine **5** in a 3:1 ratio and 70% total isolated yield.

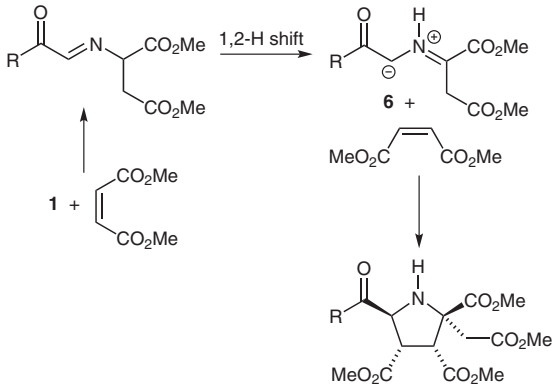


Scheme 2

The formation of enamines in both sequences and an aziridine in the latter can be explained by a Michael-type addition of nucleophilic N1 atom to the olefinic double bond. A simultaneous or subsequent elimination of molecular nitrogen opens the way for the aziridine ring closure or for a 1,2-hydride shift to the nitrogen atom. The latter process, which leads to the enamines, appears to be favored. The formation of a nitrene compound before the Michael-type interaction of azide with the olefinic dipolarophiles was ruled out by heating the azide **1a** alone in toluene. Regardless of the concentration (10^{-3} or 1 M), after 48 hours reflux the azide was recovered in quantitative yields.

From the mechanistic point of view the unexpected formation of pyrrolidine derivatives **2** can be explained through the enamines as intermediates or via a sequence involving dipolar cycloaddition. The first alternative was ruled out by subjecting the pure enamines **3a**,**b** and dimethyl maleate to the same reaction conditions. After 48 hours reflux the stating materials were recovered in quantitative yields.

A literature survey on azide chemistry revealed no direct transformation to a pyrrolidine ring or a related system. Further inspection of the X-ray structure shows that the two ester groups on the pyrrolidine are *cis* related. Although no experimental evidence in support of a detailed mechanism for the conversion of azides into pyrrolidines has been obtained, based on the above facts we can assume that a 1,3-dipolar cycloaddition between the ylide **6** and dimethyl maleate closes the pyrrolidine ring through an *exo*-TS (Scheme 3). The configuration of the azomethine ylide is controlled by favorable interactions between the acidic hydrogen atom and the two flanking carbonyl groups. The formation of intermediate **6** can be explained by an initial cycloaddition reaction of azide with maleate that provides the corresponding 4,5-dihydro-1,2,3-triazole. Thermal decomposition of the triazole followed by a 1,2-prototropic shift is a reasonable pathway for the formation of azomethine ylide, which leads to the observed stereochemical outcome.



Scheme 3

Several facts support the above suppositions. The reaction of azides **1a**,**b** with dimethyl fumarate, under conditions described for dimethyl maleate, led to the same mixture of reaction products with an identical distribution and yields. A comparison of the NMR spectra with those of **2a**,**b** revealed small shifts for several signals. Most likely, the dipolar cycloaddition of azomethine ylide **6** with dimethyl fumarate leads to an isomeric pyrrolidine where the two esters groups are *trans* to each other.

In conclusion, we have disclosed an unprecedented synthesis of the pyrrolidine ring from organic azides and maleate and fumarate esters. This reaction can serve for the synthesis of various substituted pyrrolidines since the positions 2 and 5 can be easily functionalized. The scope and limitations of this new synthetic methodology are under investigation.

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(19) **Analytical Data of Enamine 3a**
Yield 0.28 g, 14%; R_f = 0.47; mp 163–164 °C. IR (ATR): 2941, 1743, 1676, 1602, 1443, 1335, 1220, 1116, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.66 (s, 3 H, CH_3), 3.77 (s, 3 H, CH_3), 4.39 (br s, 2 H, CH_2), 5.40 (s, 1 H, CH), 7.23–7.54 (m, 8 H, 8 × CH_{ar}), 8.47 (s, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 46.9 (t), 50.9 (q), 52.6 (q), 90.4 (d), 120.9 (s), 126.9 (d), 127.1 (d), 127.3 (d), 128.1 (d), 133.2 (s), 137.6 (s), 164.1 (s), 168.6 (s), 170.0 (s). MS (EI): *m/z* (%) = 398 (12)[M^+], 331 (12), 199 (100). Anal. Calcd for $C_{20}H_{18}N_2O_5S$: C, 60.29; H, 4.55; N, 7.03. Found: C, 60.57; H, 4.61; N, 7.28.
(20) (a) **Crystal Structure Determination of 2a**
Crystal Data
Monoclinic, space group $P2_1/c$, *a* = 8.9732 (3), *b* = 21.1876 (7), *c* = 13.1662 (4) Å, *β* = 94.560 (4)°, *Z* = 4, *T* = 100 K.
Data Collection
A crystal ca. 0.3 × 0.25 × 0.2 mm^3 was used to record 64269 intensities on a Oxford Diffraction Xcalibur E diffractometer using MoKα radiation (λ = 0.71073 Å).
Structure Refinement
The structure was refined anisotropically on F^2 (program SHELXL-97)[20b] to *wR*2 = 0.0854, *R*1 = 0.0346 for 351 parameters and 7192 unique reflexions. Data have been deposited in Cambridge under the number CCDC-756944.
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(21) **Analytical Data of Pyrrolidine 2a**
Yield 1.57 g, 58%; R_f = 0.25; mp 192–193 °C. IR (ATR): 3342, 1734, 1723, 1675, 1432, 1342, 1297, 1031, 771, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.75 (s, 2 H, CH_2), 3.23 (s, 1 H, NH), 3.54 (s, 3 H, CH_3), 3.62 (s, 3 H, CH_3), 3.66 (m, 1 H, CH), 3.69 (s, 3 H, CH_3), 3.75 (m, 1 H, CH), 3.79 (s, 3 H, CH_3), 4.70 (m, 1 H, CH), 7.20–7.70 (m, 8 H, 8 × CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 40.2 (t), 51.4 (q), 51.9 (q), 52.1 (q), 52.2 (q), 53.0 (d), 59.0 (d), 69.3 (s), 126.3 (d), 126.9 (d), 127.0 (d), 127.3 (d), 127.4 (d), 127.8 (d), 128.1 (d), 133.5 (s), 133.4 (d), 138.0 (s), 138.2 (s), 170.3 (s), 170.4 (s), 170.6 (s), 171.1 (s), 173.1 (s). MS (EI): *m/z* (%) = 542 (5)[M^+], 483 (3), 451 (3), 316 (16), 284 (12), 224 (18), 199 (100). Anal. Calcd for $C_{26}H_{26}N_2O_9S$: C, 57.56; H, 4.83; N, 5.16. Found: C, 57.79; H, 4.99; N, 5.47.