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Cycloaddition reactions of azomethine ylides with a 9-fluorenone-malononitrile Knöevenagel adduct

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ABSTRACT

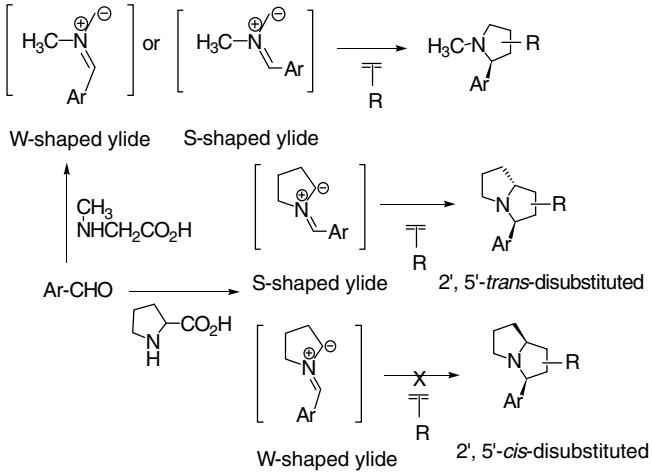
Numerous derivatives of spiropyrrolidines and spiropyrrolizines containing cyano groups were successfully synthesized via condensation of sarcosine and proline Schiff bases of several aromatic aldehydes with the Knöevenagel adduct of 9-fluorenone-malononitrile prepared through a modified procedure. Assignment of the molecular structure was carried out by single crystal X-ray diffraction, as well as by HMBC and ROSEY spectroscopy.

Cycloadditions are an important group of reactions in organic synthesis.[1] The azomethine ylide represents one of the most reactive and versatile classes of 1,3-dipoles and is trapped readily by a range of dipolarophiles, either inter or intramolecularly, forming substituted pyrrolidines.[2] The three atom C-N-C unit containing four π-electrons affords a zwitterionic system with the nitrogen and one of the carbon atoms carrying positive and negative charges, respectively. As such, this species in combination with two π-electrons of an alkene or alkyne constitutes a six - electron system capable of undergoing a [π4s + π2s] reaction according to Woodward-Hoffmann rules.[3]

The Knöevenagel condensation is a well-established method for the synthesis of α,β-unsaturated compounds. It is utilized in various synthetic transformations and thus we have used this procedure for the synthesis of a 9-fluorenone-malononitrile adduct.[4]

The simplest approach to an azomethine ylide is the reaction of a secondary amine such as sarcosine or proline with an aldehyde (Scheme 1).[5] Reaction of the resulting ylide with an alkene either present in solution or as a functional group present within the aldehyde structure, via inter- or intramolecular cycloaddition results in the formation of the corresponding pyrrolidine and pyrrolizine heterocycles (Scheme 1).[6] Spiropyrrolidines and spiropyrrolizines have gained much attention due to their interesting biological activities.[7]

Our recent interest in pyrrolidine and pyrrolizine derivatives containing substituents at C3′ on the ring prompted us to prepare



Scheme 1. Formation of a single product from sarcosine and a 2′,5′-*trans*-disubstituted product from proline.

them via reaction of an azomethine ylide with the Knöevenagel adduct of 9-fluorenone-malononitrile. This reaction was expected to yield a pyrrolidine or a pyrrolizine derivative with the negative carbon of the azomethine ylide attached to the 9-fluorene carbon since reaction of an azomethine ylide with double bonds containing electron-withdrawing groups has been reported to follow the Michael type addition.[8] Subsequent transformation of the cyano substituent to other functional groups and formation of the corresponding aldehydes, ketones, esters, and amino acids with potential biological activities could be carried out easily. Herein,

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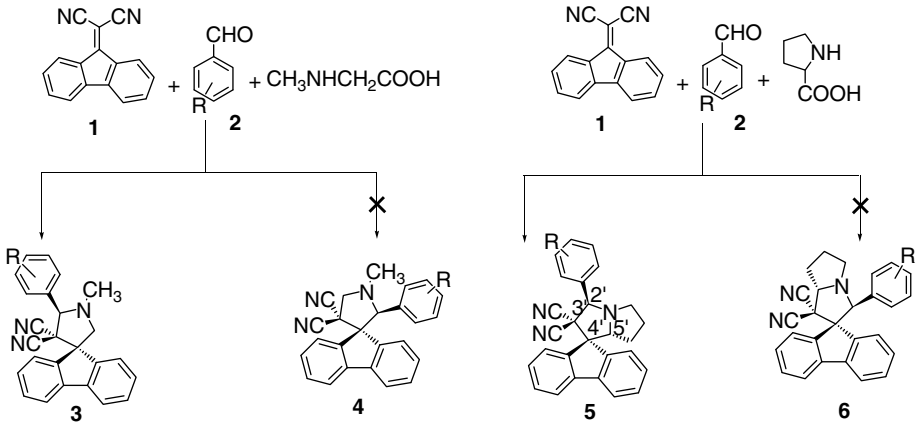

R: (a) 4-Me; (b) 4-OMe; (c) 4-Cl; (d) 4-Br; (e) 4-H; (f) 3,4-OMe; (g) 3,4,5-OMe; (h) 4-NO_2

3	Time (h)	Yield (%)
a	8	78
b	5	70
c	8	68
d	6	74
e	5	77
f	4	73
g	6	77
h	10	44

5	Time (h)	Yield (%)
a	7	76
b	7	73
c	8	68
d	6	74
e	5	73
f	7	71
g	6	73
h	10	trace

Scheme 2. Synthesis of spiropyrrolidines and spiropyrrolidines.

we are pleased to report the synthesis of a number of pyrrolidine and pyrrolizine derivatives via condensation of the Knöevenagel adduct of 9-fluorenone-malononitrile **1** with sarcosine and proline Schiff bases of several aromatic aldehydes.

The Knöevenagel adduct was prepared via modification[9] of the previously reported procedure.[10] Utilization of our modified method reduced the reaction time with a concomitant increase in the reaction yield (vide antara). This adduct was subsequently treated with the Schiff bases obtained from condensation of either sarcosine or proline with a number of aromatic aldehydes **2a**–**h** in refluxing toluene for the appropriate amount of time (Scheme 2).[11] The solid products were filtered and recrystallized from methanol resulting in spiropyrrolidines **3a**–**h** and spiropyrrolizines **5a**–**h**. Identification of the products was carried out by spectroscopic methods.[12] The results are presented in Scheme 2.

The ^{1}H NMR spectrum of **3a** exhibited a singlet at δ 2.42 for the 4-CH_3 protons and another singlet at δ 2.55 for the *N*–CH_3 protons. The *N*–CH_2 protons of the pyrrolidine ring appeared as two doublets at δ 3.26 and δ 3.73. The benzylic proton resonated as a singlet at δ 4.36. The ^{13}C NMR showed a signal at δ 66.31 due to the spiro carbon. The structure of compound **3a** was further confirmed by mass spectrometry which exhibited a molecular ion peak at *m*/*z* 375.

The ^{1}H NMR spectrum of **5a** showed a singlet at δ 2.13 for the 4-CH_3 protons. The *N*–CH proton of the pyrrolizine ring (H5′) appeared as a triplet at δ 4.85 and the benzylic proton (H2′) resonated as a singlet at δ 5.12.

As shown in Scheme 2, two possible Michael-type and anti-Michael type additions can be envisaged for the addition of azomethine ylides to **2a**–**h** leading either to **3a**–**h** and **5a**–**h** or **4a**–**h** and **6a**–**h**, respectively. Confirmation of the product structure was obtained by single crystal X-ray diffraction of **3a** (Fig. 1).[13] The reaction proceeded exclusively via Michael-type addition of the azomethine ylide to the dipolarophile.

Based on the HMBC spectrum of **3a** (Fig. 2) and the observation of the 1,3-coupling of the CN groups (appearing at δ 113.2 and δ 114) with the benzylic CH (resonating at δ 4.36), the structure of

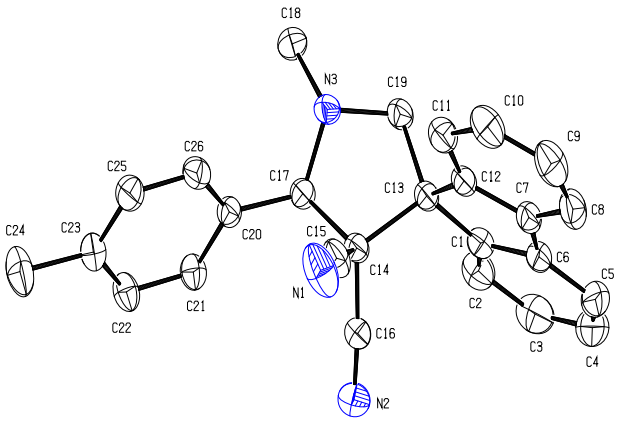

Figure 1. ORTEP diagram of compound **3a**.

3a was confirmed unequivocally. Therefore, the observation of a long range coupling in the HMBC spectrum, seems to be a reliable tool for determination of molecular structure whenever obtaining the single crystal X-ray structure is not possible.

The configuration of the stereocenter in **5a** was assigned using ROSEY spectroscopy. Protons H2′ and H5′ (see Scheme 2) showed no correlation in the ROSEY spectrum (Fig. 3), which implied a *trans* arrangement between C-2′ and C-5′.

In addition to regioselectivity issues (vide supra), the dipolar cycloaddition reaction can lead to mixtures of stereoisomers. From the two possible W- and S-shaped ylide geometries obtained from proline (Scheme 1), the 2′,5′-*cis*-disubstituted and the 2′,5′-*trans*-disubstituted products respectively, are anticipated to be formed via a suprafacial reaction.[2] Inspection of the other reported examples[2] and product **5a** (Scheme 2), perhaps show some general preference for cycloaddition through an S-shaped ylide.[2]

In summary, pyrrolidine and pyrrolizine derivatives containing two cyano groups at positions 3′ and 3′, respectively, were successfully prepared and identified. Transformation of the cyano groups

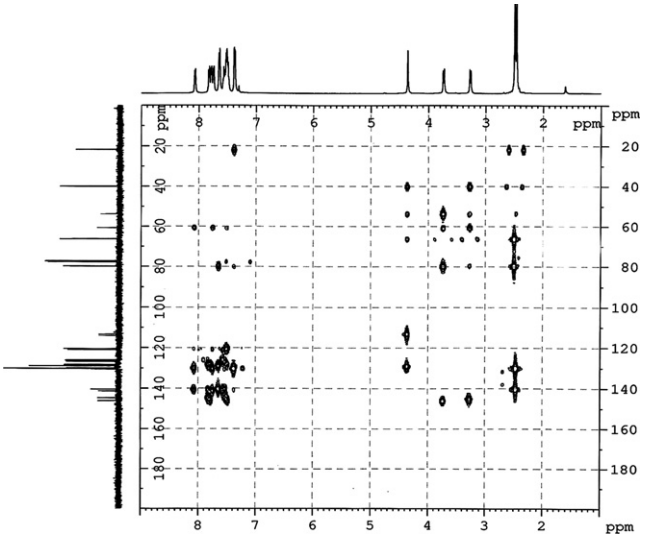

Figure 2. HMBC spectrum of compound **3a**.

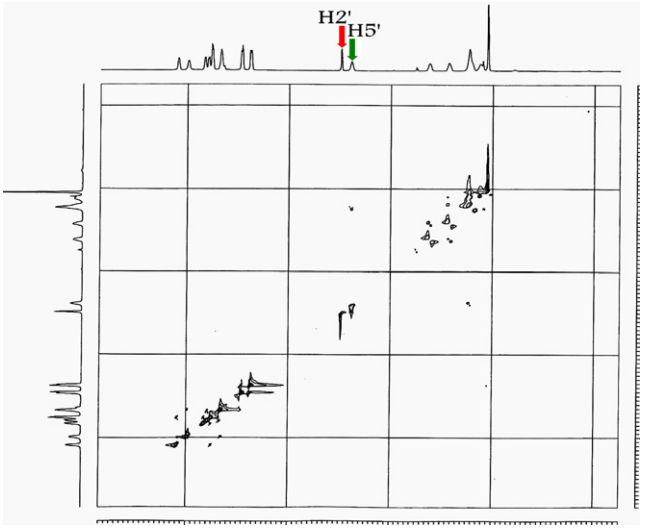

Figure 3. ROSEY spectrum of compound **5a**.

to other functionalities is currently under investigation in our research group and is expected to furnish other new pyrrolidine and pyrrolizine derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.127.

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9. *Modified procedure for the preparation of the 9-fluorenone-malononitrile adduct*: To a solution of 9-fluorenone (1 mmol) in absolute ethanol (5 mL) containing 3 drops of piperidine, malononitrile (1.1 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. The resulting orange precipitate was then filtered and recrystallized from ethanol to afford the product (yield 87%, mp: 230–232 °C).
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11. *Representative procedure for the preparation of fluorene spiro*[*9.4′*]-*1-N-methyl* (*2′–arylidene*)-*3′,3′–dicyano-pyrrolidine*: A mixture of sarcosine (178 mg, 2.0 mmol), aldehyde (2.0 mmol), and **1** (456 mg, 2.0 mmol) in dry toluene (20 mL) containing molecular sieves (1000 mg, 3 Å) was refluxed with stirring for the appropriate time (see Scheme 2). The progress of the reaction was followed by TLC. After completion, the solvent was removed under reduced pressure and the resulting solid was recrystallized from methanol to afford a white crystalline product.
12. *Fluorene spiro*[*9.4′*]-*1-N-methyl*(*2′–p-methylphenyl*)-*3′,3′–dicyano-pyrrolidine* (**3a**): White crystals, mp: 217–219 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.55 (s, 3H), 3.26 (d, J = 10.1 Hz, 1H), 3.73 (d, J = 10.1 Hz, 1H), 4.36 (s, 1H), 7.30–8.08 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.77, 40.04, 53.82, 60.71, 66.31, 79.92, 113.37, 114.02, 120.53, 120.97, 126.10, 126.75, 128.25, 128.50, 128.92, 129.99, 130.20, 130.24, 130.57, 140.41, 140.48, 141.30, 144.67, 146.10; IR(KBr): 2245 cm^{-1}; mass m/z: 375 (M^+); Anal. Calcd for $C_{26}H_{21}N_3$: C, 83.2; H, 5.6; N, 11.2. Found: C, 83.12; H, 5.73; N, 11.35. *Fluorene spiro* [*9.4′*]-*1-N-methyl*(*2′–p-methylphenyl*)-*3′,3′–dicyano-pyrrolizine* (**5a**): White crystals, mp: 234–237 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (m, 1H), 1.63 (m, 1H), 2.13 (s, 3H), 2.18 (m, 2H), 2.88 (m, 1H), 3.26 (m, 1H), 4.85 (t, J = 6.3 Hz, 1H), 5.12 (s, 1H),7.05–8.04 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.34, 27.93, 30.06, 49.63, 52.69, 54.01, 67.75, 71.11, 112.92, 114.24, 120.69, 120.89, 121.48, 125.94, 127.37, 127.99, 128.10, 128.71, 129.95, 130.02, 130.48, 137.58, 139.04, 140.92, 141.56, 142.49; mass m/z: 401 (M^+); Anal. Calcd for $C_{28}H_{23}N_3$: C, 83.79; H, 5.73; N,10.47. Found: C, 83.91; H, 5.84; N, 10.67.
13. Crystallographic data for **3a** have been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 693980. Copies of these data can be obtained free of charge via www.ccdc.ca-m.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).