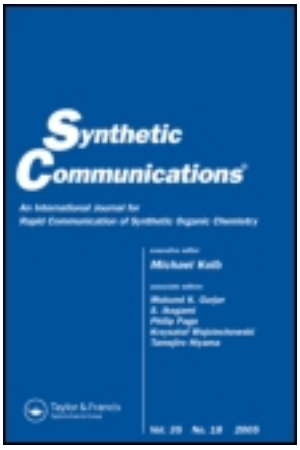

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Novel Synthesis of N-Methyl Spiropyrrolidines by 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylides

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Novel Synthesis of N-Methyl Spiropyrrolidines by 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylides

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Abstract: A series of novel N-methyl spiropyrrolidines have been synthesized in good yield by the cycloaddition reaction of azomethine ylides generated by a decarboxylative route from sarcosine and paraformaldehyde with conformationally locked s-trans enone functionality present in the (*E*)-3-arylidene-4-chromanone as dipolarophiles. The structure of the title compound was established by spectroscopic techniques.

Keywords: 1,3-dipole, azomethine, ylide, spiropyrrolidines

INTRODUCTION

The intermolecular 1,3-dipolar cycloaddition reaction of azomethine ylides with olefins represents an efficient and convergent method for the construction of the pyrrolidine structural unit.[1–3] Their ease of generation coupled with the highly regio- and stereoselective nature of their cycloaddition has resulted in a number of syntheses that utilize such a reaction as the key step. This method is widely used in the synthesis of natural products such as alkaloids and pharmacologically active compounds.[4] Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties.[5–7] 4-Chromanones are versatile intermediates for the synthesis of many natural products such as

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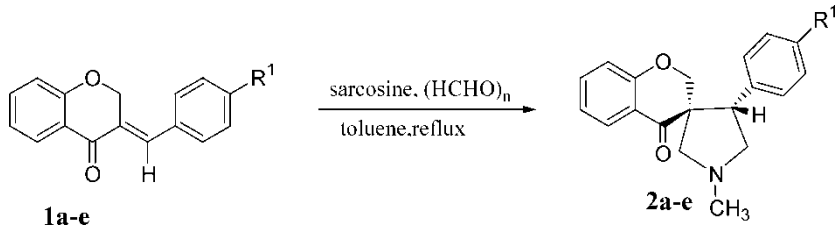
brazilin, hematoxylin, ripariochromene, clausenin, calonilide (A), and nopyhyllum (B).[8,9] Chromanone heterocycles have also drawn much attention because of their important pharmacological properties.[8] Many natural products containing chromanone, chromane, and chromene moiety have been isolated, of particular interest is eucomine, the first member of arylidene chromanone found in nature.[10] As a part of our ongoing research program in the area of cycloaddition reactions[11] and with a view to synthesizing a rare class of spiroheterocyclic derivatives,[12–14] we herein report the facile synthesis of N-methyl spiropyrrolidines through the cycloaddition reaction of azomethine ylides generated by a decarboxylation route with conformationally locked s-trans enone functionality present in the (*E*)-3-arylidene-4-chromanones as dipolarophile.

RESULTS AND DISCUSSION

Azomethine ylides can be generated by a number of methods of which the decarboxylation route is convenient for the synthesis of substituted pyrrolidines.[15] In this method an aldehyde and a secondary amino acid are condensed to generate the reactive intermediate, which is then trapped by dipolarophiles. The required dipolarophile (*E*)-3-arylidene-4-chromanones **1a–e** were prepared by the acid-catalyzed reaction of 4-chromanone with various benzaldehydes, and the products were assigned *E*-configuration on the basis of their NMR spectra, in accordance with the literature.[16] The arylidene proton signal is observed around δ 7.85 in all cases, more deshielded than in the *Z* isomer, which is reported to resonate around δ 6.0.[17]

The 1,3-dipolar cycloaddition reaction of azomethine ylides generated by decarboxylative condensation of sarcosine with paraformaldehyde in the presence of (*E*)-3-arylidene-4-chromanmone **1a–e** in toluene under reflux afforded the novel 1-*N*-methyl-spiro[3.3^1]chroman-4^1-one-4-aryl-pyrrolidines **2a–e** in good yield (Scheme 1). The structure of the cycloadducts **2a–e** were confirmed with the help of spectral and analytical data.



Scheme 1. R^1 = a) H, b) CI, c) Me, d) OMe, e) NO_2.

The IR spectrum of **2a** revealed the presence of carbonyl peak at 1681 cm^{-1}, an increase of 13 cm^{-1} from the normal value observed for benzylidene chromanone, which indicates the loss of conjugation. The ^1H NMR spectrum of **2a** showed a singlet at δ 2.44 because of the N-methyl group in the pyrrolidine ring. One doublet of a doublet appeared at δ 4.39 with the *J* values of 7.8 and 5.9 as a result of benzylic protons. It also showed two well separated doublets at δ 3.60 and 4.13 with coupling constant value of 11.7 Hz because of the OCH_2 protons in the chromanone ring. Nine aromatic protons resonated as multiplets in the region of δ 6.82–7.95. The ^{13}C NMR spectrum of **2a** showed a peak at 193.8 ppm because of chromanone carbonyl. It showed six sp^3 carbons, including one spiro carbon at 55.0 ppm, and the rest of the peak well account for the proposed structure of **2a**. This compound gave satisfactory microanalysis.

Identical results were obtained with other derivatives of benzylidene chromanones **1(b–e)**. In conclusion, an efficient synthesis of a series of novel spiropyrrolidine derivatives has been achieved via the [3 + 2] cycloaddition reaction of azomethine ylides generated by decarboxylative condensation of sarcosine and paraformaldehyde with (*E*)-3-arylidene-4-chromanones.

EXPERIMENTAL

General

All melting points are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8300 instrument. Mass spectra were recorded on JEOL DX 303 HF spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard on the JEOL instrument at 400 MHz and 100 MHz respectively. Elemental analyses were carried out on a Perkin-Elmer 240 B instrument.

General procedure for the cycloaddition reaction of benzylideneflavanone with azomethine ylide generated from decarboxylation route using sarcosine and paraformaldehyde: A mixture of sarcosine (0.22 g, 2.5 mmol), paraformaldehyde (0.36 g, 6 mmol), and arylidenechromanone (1 mmol) was heated under reflux in 10 ml of toluene. The water formed in the reaction was continuously removed with the aid of Dean–Stark apparatus. After completion of the reaction (12–24 h) the solvent was evaporated in vacuo. The residue was chromatographed over silica gel (100–200 mesh) using petroleumether-ethylacetate (4 : 1) to give pyrrolidine derivatives.

1-*N*-Methyl-spiro[3.3^1]flavan-4^1-one-4-phenyl-pyrrolidine (2a): Yield 85%, colorless solid, mp 118–119°C; reaction time: 12 h; Found: C, 77.65; H, 6.68; N, 4.85. $C_{19}H_{19}NO_2$ requires C, 77.79; H, 6.53, N, 4.77. IR (KBr): 1681 cm^{-1}; ^1H NMR: 2.44 (s, 3H), 2.59 (d, $J = 9.3$, Hz, 1H), 3.01–3.11

(m, 3H), 3.60 (d, $J = 11.7$ Hz, 1H), 4.13 (d, $J = 11.7$ Hz, 1H), 4.39 (dd, $J = 7.8$, 5.9 Hz, 1H), 6.82–7.43 (m, 8H, Ar-H), 7.95 (dd, $J = 7.8$, 1.5 Hz, 1H); ^{13}C NMR: 41.80, 45.67, 55.03, 61.84, 62.20, 72.38, 117.56, 120.12, 121.17, 126.91, 127.88, 128.29, 128.52, 135.74, 138.75, 160.98, 193.89; CIMS m/z: 293 (M^+).

1-*N*-Methyl-spiro[3.3^1]flavan-4^1-one-4-(4-chlorophenyl)-pyrrolidine (2b): Yield 74%, semi solid; reaction time: 15 h; Found: C, 69.77; H, 5.39; N, 4.33. $C_{19}H_{18}ClNO_2$ requires C, 69.62; H, 5.53, N, 4.27. IR (KBr): 1679 cm^{-1}; ^{1}H NMR: 2.33 (s, 3H), 2.52 (d, $J = 9.7$, Hz, 1H), 2.91–3.03 (m, 3H), 3.53 (d, $J = 11.7$ Hz, 1H), 4.03 (d, $J = 11.7$ Hz, 1H), 4.22 (dd, $J = 7.8$, 5.4 Hz, 1H), 6.76–7.37 (m, 7H, Ar-H), 7.86 (dd, $J = 7.8$, 1.5 Hz, 1H); ^{13}C NMR: 42.06, 45.61, 55.34, 62.00, 62.07, 72.37, 117.95, 120.30, 121.65, 128.19, 128.76, 130.20, 133.05, 136.28, 137.64, 161.29, 194.00; CIMS m/z: 327 (M^+).

1-*N*-Methyl-spiro[3.3^1]flavan-4^1-one-4-(4-methylphenyl)-pyrrolidine (2c): Yield 68%, semi solid; reaction time: 24 h; Found: C, 78.29; H, 7.05; N, 4.70. $C_{20}H_{21}NO_2$ requires C, 78.14; H, 6.88, N, 4.56. IR (KBr): 1681 cm^{-1}; ^{1}H NMR: 2.17 (s, 3H), 2.29 (s, 3H), 2.49 (d, $J = 9.7$, Hz, 1H), 2.89–2.96 (m, 3H), 3.51 (d, $J = 11.7$ Hz, 1H), 4.02 (d, $J = 11.7$ Hz, 1H), 4.26 (dd, $J = 7.9$, 5.8 Hz, 1H), 6.71–7.28 (m, 7H, Ar-H), 7.82 (dd, $J = 7.8$, 1.5 Hz, 1H); ^{13}C NMR: 20.82, 41.72, 45.11, 54.81, 61.56, 62.02, 72.26, 117.43, 120.00, 121.03, 127.74, 128.24, 128.86, 135.24, 135.61, 136.33, 160.88, 193.74; CIMS m/z: 307 (M^+).

1-*N*-Methyl-spiro[3.3^1]flavan-4^1-one-4-(4-methoxyphenyl)-pyrrolidine (2d): Yield 60%, semi solid; reaction time: 18 h; Found: C, 74.12; H, 6.75; N, 4.45. $C_{20}H_{21}NO_3$ requires C, 74.28; H, 6.55, N, 4.33. IR (KBr): 1685 cm^{-1}; ^{1}H NMR: 2.31 (s, 3H), 2.52 (d, $J = 9.3$, Hz, 1H), 2.92–2.97 (m, 3H), 3.53 (d, $J = 11.7$ Hz, 1H), 3.64 (s, 3H), 4.04 (d, $J = 11.7$ Hz, 1H), 4.25 (dd, $J = 7.8$, 5.4 Hz, 1H), 6.69–7.33 (m, 7H, Ar-H), 7.84 (dd, $J = 7.8$, 1.5 Hz, 1H); ^{13}C NMR: 41.84, 44.98, 54.99, 55.11, 61.94, 62.15, 72.41, 113.64, 117.55, 120.12, 121.15, 127.86,129.49, 130.54, 135.74, 158.46, 161.02, 194.05; CIMS m/z: 323 (M^+).

1-*N*-Methyl-spiro[3.3^1]flavan-4^1-one-4-(4-nitrophenyl)-pyrrolidine (2e): Yield 75%, semi solid; reaction time: 24 h; Found: C, 67.25; H, 5.44; N, 8.19. $C_{19}H_{18}N_2O_4$ requires C, 67.44; H, 5.36, N, 8.28. IR (KBr): 1685 cm^{-1}; ^{1}H NMR: 2.33 (s, 3H), 2.54 (d, $J = 9.3$, Hz, 1H), 3.00–3.12 (m, 3H), 3.55 (d, $J = 11.7$ Hz, 1H), 4.12 (d, $J = 11.7$ Hz, 1H), 4.33 (dd, $J = 7.8$, 5.4 Hz, 1H), 7.40–7.53 (m, 7H, Ar-H), 8.19 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR: 41.84, 45.12, 54.98, 61.82, 62.24, 72.48, 117.52, 120.18, 121.25, 128.33, 130.42, 135.74, 138.24, 143.66, 147.42, 160.88, 194.04; CIMS m/z: 338 (M^+).

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