Methyl 2*H*-Azirine-3-carboxylates as Dienophiles: Synthesis of Methyl 1-Azabicyclo[4.1.0]-hept-3-ene-6-carboxylates

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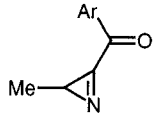
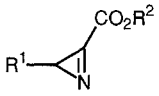
Methyl 2-aryl-2*H*-azirine-3-carboxylates are good dienophiles. They react with cyclopentadiene, cyclohexa-1,3-diene and 2,3-dimethylbuta-1,3-diene at or below 50 °C to give products of [4+2]-cycloaddition to the carbon–nitrogen double bond.. The cycloadditions are *endo* selective and the dienophiles approach from the less hindered face of the azirines.

The strained carbon–nitrogen double bond of 2*H*-azirines is much more reactive than that of normal imines.[1] There are, however, relatively few reports of Diels–Alder reactions in which 2*H*-azirines participate as dienophiles.[2] The reactivity of imines as dienophiles is enhanced by the presence of an electron-withdrawing substituent on carbon, but there is only one report of the Diels–Alder reaction of a 2*H*-azirine bearing a conjugative electron-withdrawing substituent at C-3.[3] Hemetsberger and Knittel found that the ketones **1** (Ar = phenyl and *p*-tolyl) reacted exothermically with cyclopentadiene to give a single cycloadduct in each case, but they were unable to determine which one of the four possible diastereoisomers was being formed. We considered that the esters **2**, which are prepared by the thermal decomposition of vinyl azides **3**,[4] should be good dienophiles. With the exception of some [2 + 2]-cycloaddition reactions of dimethyl 2*H*-azirine-2,3-dicarboxylate,[5] no cycloaddition reactions of these activated azirine esters have been reported. The Diels–Alder reactions of the azirines **2a** and **2b** with cyclopentadiene, cyclohexa-1,3-diene and 2,3-dimethylbuta-1,3-diene are described in this paper.



1



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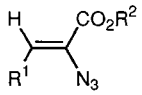


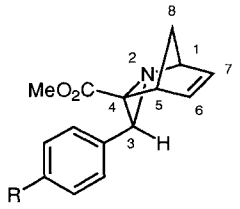
3

2, 3 a: R^1 = 4-ClC_6H_4, R^2 = Me

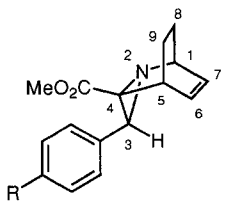
2, 3 b: R^1 = 4-MeC_6H_4, R^2 = Me

The azirines **2a** and **2b** were generated from the corresponding methyl 2-azidocinnamates[4] **3** by heating in heptane solution (bp 98 °C) for 2–3 hours. The solvent was then distilled off and the crude azirine was dissolved in an excess of the appropriate diene. The solutions were allowed to stand at room temperature for 24 hours and, when necessary, were then heated at 50 °C for 2 hours to ensure that the reactions were complete. With cyclopentadiene, no heating was necessary. In each case a major product was detected. The major products were isolated either by recrystallisation or by column chromatography.

The products isolated from the reactions with cyclopentadiene were shown to have the structures **4a** and **4b**. The stereochemistry was established by COSY and NOE experiments. In particular, irradiation of the 3-H signal of both **4a** and **4b** caused enhancement of the signals for 6-H and 7-H. Structures **4** are those that would result from *endo* cycloaddition to the less hindered face of the azirine esters **2**. There are four stereoisomers that could be formed in this Diels–Alder reaction but structure **4** is the only one in which the hydrogens on C-6 and C-7 are close in space to that on C-3. The analogous structures **5a** and **5b** were deduced for the adducts formed with cyclohexa-1,3-diene. With 2,3-dimethylbuta-1,3-diene there are two possible structures for a cycloadduct. The products have been assigned structures **6a** and **6b**, which are consistent with addition to the less hindered face of the azirines.



4



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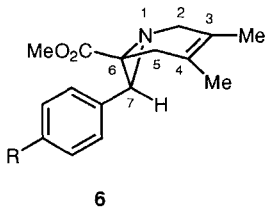

6

4, 5, 6 a: R = Cl; **4, 5, 6 b**: R = Me

These experiments show that the azirines **2** are, as expected, good dienophiles and that their Diels–Alder reactions are stereoselective. The cycloaddition reactions provide a route to the 1-azabicyclo[4.1.0]hept-3-ene ring system, the chemistry of which is relatively unexplored. Since it is not necessary to purify the azirines it should be possible to extend the reactions to other substituted α-azido esters, and to other types of cycloaddition process, such as 1,3-dipolar cycloaddition.

Generation and Cycloaddition Reactions of Azirines; General Procedure:

A solution of the azidocinnamate ester **3** (2.0 mmol) in heptane (10 mL) was heated under reflux for 2–3 h, its decomposition being monitored by IR. It was then cooled and evaporated to leave the crude azirine as a yellow solid. The appropriate diene was added

in large excess (2–3 mL) and the resulting solution was left at r.t. for 18 h. If any azirine remained, as indicated by TLC, the solution was then heated at 50 °C for 2 h to complete the reaction. The product was isolated either by column chromatography (EtOAc-hexane) followed by crystallisation or by direct crystallisation of the product remaining after removal of the excess of diene. Yields are based on the starting azidocinnamate ester.

Methyl 3-(4-Chlorophenyl)-2-azatricyclo[3.2.1.0^{2,4}]oct-6-ene-4-carboxylate **(4a)**:

Isolated by chromatography as a yellow oil which after crystallisation gave a yellow solid (40%), mp 73–74 °C (from Et_2O-hexane).

MS (CI): $m/z = 276$ ($M^+ + 1$).

IR (KBr): $\nu = 1744$ and 1723 cm^{-1}.

^1H NMR (300 MHz): $\delta = 1.77$ (1 H, d, $J = 8.0$ Hz, 8-H), 2.16 (1 H, d, $J = 8.0$ Hz, 8-H), 2.61 (1 H, s, 3-H), 3.49 (3 H, s, CH_3), 3.58 (1 H, br s, 5-H), 4.37 (1 H, br s, 1-H), 5.81–5.84 (1 H, m, 7-H), 6.29–6.32 (1 H, m, 6-H), 7.20–7.26 (4 H, m, Ar-H).

^{13}C NMR (75 MHz): $\delta = 48.17$ (5-C), 51.46 (4-C), 52.18 (CH_3), 53.93 (3-C), 58.91 (8-C), 66.95 (1-C), 128.07 and 128.94 (Ar-CH), 128.49 (7-C), 132.79 (6-C), 132.96 and 134.42 (Ar-C), 170.95 (C=O).

Methyl 3-(4-Methylphenyl)-2-azatricyclo[3.2.1.0^{2,4}]oct-6-ene-4-carboxylate **(4b)**:

Isolated by chromatography as a yellow oil which after crystallisation gave a yellow solid (51%), mp 83–84 °C (from Et_2O-hexane).

MS (CI): $m/z = 256$ ($M^+ + 1$).

IR (KBr): $\nu = 1725$ cm^{-1}.

^1H NMR (300 MHz): $\delta = 1.76$ (1 H, d, $J = 8.0$ Hz, 8-H), 2.08 (1 H, d, $J = 8.0$ Hz, 8-H), 2.29 (3 H, s, Ar-CH_3), 2.62 (1 H, s, 3-H), 3.49 (3 H, s, CH_3), 3.56 (1 H, br s, 5-H), 4.36 (1 H, br s, 1-H), 5.80–5.83 (1 H, m, 7-H), 6.28–6.31 (1 H, m 6-H), 7.06 (2 H, d, $J = 7.7$ Hz, Ar-H), 7.19 (2 H, d, $J = 7.7$ Hz, Ar-H).

^{13}C NMR (75 MHz): $\delta = 21.15$ (Ar-CH_3), 48.21 (5-C), 51.38 (4-C), 52.07 (CH_3), 54.59 (3-C), 58.74 (8-C), 66.86 (1-C), 127.37 and 128.63 (Ar-CH), 128.40 (7-C), 132.77 (6-C), 132.63 and 136.76 (Ar-C), 171.31 (C=O).

Methyl 3-(4-Chlorophenyl)-2-azatricyclo[3.2.2.0^{2,4}]non-6-ene-4-carboxylate **(5a)**:

Isolated by crystallisation as a colourless solid (48%), mp 94 °C (from EtOAc-hexane).

MS (CI): $m/z = 290$ ($M^+ + 1$).

IR (Nujol): $\nu = 1741$ and 1725 cm^{-1}.

^1H NMR (300 MHz): $\delta = 1.15$–1.25 (1 H, m, 9-H), 1.38–1.48 (1 H, m, 8-H), 1.55–1.65 (1 H, m, 9-H), 2.09–2.17 (1 H, m, 8-H), 2.55 (1 H, s, 3-H), 3.33–3.35 (1 H, m, 5-H), 3.44 (3 H, s, CH_3), 4.07–4.10 (1 H, m, 1-H), 5.78–5.93 (1 H, approx. t, 7-H), 6.28–6.34 (1 H, approx. t, 6-H), 7.19–7.24 (4 H, m, Ar-H).

^{13}C NMR (75 MHz): $\delta = 22.37$ (9-C), 25.64 (8-C), 31.31 (4-C), 33.24 (5-C), 40.92 (3-C), 50.36 (1-C), 53.59 (CH_3), 127.71 (7-C), 129.64 and 130.74 (Ar-CH), 132.02 (6-C), 134.35 and 136.16 (Ar-C), 172.16 (C=O).

Methyl 3-(4-Methylphenyl)-2-azatricyclo[3.2.2.0^{2,4}]non-6-ene-4-carboxylate **(5b)**:

Isolated by crystallisation as a colourless solid (19%), mp 96–97 °C (from EtOAc-hexane).

MS (CI): $m/z = 270$ ($M^+ + 1$).

IR (Nujol): $\nu = 1737$ cm^{-1}.

^1H NMR (300 MHz): $\delta = 1.12$–1.30 (1 H, m, 9-H), 1.36–1.48 (1 H, m, 8-H), 1.54–1.67 (1 H, m, 9-H), 2.06–2.20 (1 H, m, 8-H), 2.28 (3 H, s, CH_3), 2.50 (1 H, s, 3-H), 3.32–3.39 (1 H, m, 5-H), 3.47 (3 H, s, CH_3), 4.08–4.16 (1 H, m, 1-H), 5.78–5.86 (1 H, approx. t, 7-H), 6.28–6.38 (1 H, approx. t, 6-H), 7.09 (2 H, d, $J = 7.5$ Hz, Ar-H), 7.20 (2 H, d, $J = 7.5$ Hz, Ar-H).

^{13}C NMR (75 MHz): $\delta = 20.82$ (9-C), 21.11 (Ar-CH_3), 24.11 (8-C), 31.71 (4-C), 35.49 (5-C), 39.83 (3-C), 48.62 (1-C), 51.93 (OCH_3), 126.12 (7-C), 127.54 and 128.61 (Ar-CH), 130.39 (6-C), 132.80 and 136.51 (Ar-C), 171.00 (C=O).

Methyl 7-(4-Chlorophenyl)-3,4-dimethyl-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate **(6a)**:

Isolated by chromatography as a yellow solid (58%), mp 100–102 °C (from EtOAc-hexane).

MS (CI): $m/z = 292$ ($M^+ + 1$).

IR (Nujol): $\nu = 1746$ cm^{-1}.

^1H NMR (300 MHz). $\delta = 1.50$ (3 H, s, CH_3); 1.64 (3 H, s, CH_3), 2.45 (1 H, d, $J = 18.0$ Hz, 5-H), 2.78 (1 H, d, $J = 18.0$ Hz, 5-H), 3.11 (1 H, s, 7-H), 3.33 (1 H, d, $J = 16.2$ Hz, 2-H), 3.35 (3 H, s, CH_3), 3.74 (1 H, d, $J = 16.2$ Hz, 2-H), 7.14–7.22 (4 H, m, Ar-H).

^{13}C NMR (75 MHz): $\delta = 16.43$ (4-CH_3), 18.76 (3-CH_3), 29.03 (5-C), 43.41 (7-C), 48.20 (6-C), 51.84 (OCH_3), 52.49 (2-C), 120.07 and 120.48 (3-C and 4-C), 128.04 and 128.86 (Ar-CH), 132.85 and 134.79 (Ar-C), 170.56 (C=O).

Methyl 3,4-Dimethyl-7-(4-methylphenyl)-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate **(6b)**:

Isolated by chromatography as a yellow oil (56%) that crystallised on standing; mp 40–41 °C.

MS (CI): $m/z = 272$ ($M^+ + 1$).

IR (Nujol): $\nu = 1750$ and 1723 cm^{-1}.

^1H NMR (300 MHz): $\delta = 1.50$ (3 H, s, 4-CH_3), 1.63 (3 H, s, 3-CH_3), 2.22 (3 H, s, Ar-CH_3), 2.43 (1 H, d, $J = 18.0$ Hz, 5-H), 2.79 (1 H, d, $J = 18.0$ Hz, 5-H), 3.10 (1 H, s, 7-H), 3.32 (1 H, d, $J = 17.3$ Hz, 2-H), 3.35 (3 H, s, OCH_3), 3.74 (1 H, d, $J = 17.3$ Hz, 2-H), 6.98 (2 H, d, $J = 8.0$ Hz, Ar-H), 7.25 (2 H, d, $J = 8.0$ Hz, Ar-H).

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