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2-Azabicyclo[2.2.2]octa-3,5-dione via a Nitrile Diels−Alder Reaction

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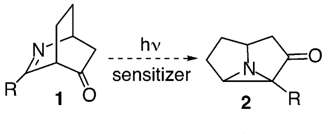
Abstract: The hetero-Diels−Alder reaction of an electron-deficient nitrile, *p*-toluenesulfonyl cyanide, with the silyl enol ether of cyclohexenone produced a hydrolytically sensitive [4 + 2] adduct in good yield. Use of Mander's reagent, ethyl cyanoformate, with the same diene, produced an unstable adduct. Hydrolysis of the tosyl cyanide adduct resulted in the isoquinuclidinone 2-aza[2.2.2]octa-3,5-dione as a crystalline compound in excellent yield from the nitrile.

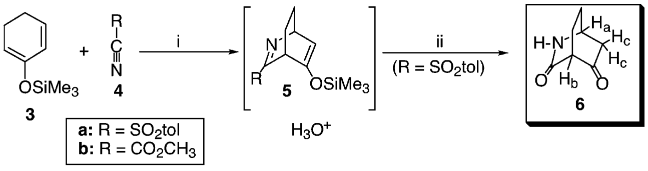
We are currently developing a new synthetic method to prepare interesting nitrogen heterocycles via the oxa-di-π-methane photochemical rearrangement of variously substituted azabicyclo[2.2.2]octenones.[1] Toward this goal, we needed an efficient synthetic route to the 2-azabicyclo-[2.2.2]oct-2-en-4-one photoprecursors, **1** (Scheme 1). Access to these compounds could be envisioned via the Diels−Alder reactions of substituted nitriles with a suitable diene. Use of the Diels−Alder reaction to produce bicyclo[2.2.2]octenones is well-precedented in the literature.[2] However, to our knowledge, the use of a nitrile to produce 2-azabicyclo[2.2.*n*]alk-2-ene compounds is limited to the production of 2-azabicyclo[2.2.1] systems.[3,4]

SCHEME 1



R = alkyl; EWG; -XR[1]

SCHEME 2[a]



[a] (i) For R = SO_2tol: CH_2Cl_2, 40 °C, 24 h; for R = CO_2CH_3: Et_2O, $MgBr_2{\cdot}OEt_2$ (25 mol %), rt, 15 h. (ii) HOAc, H_2O, 0 °C, 3 h.

The Diels−Alder reactions of *unactivated* nitriles are known to proceed under harsh conditions (high temperature and pressure)[2,5] or via metal catalysis[6] and generally produce aromatic nitrogen compounds. Therefore, the Diels−Alder reactions of the activated nitriles *p*-toluenesulfonyl cyanide (**4a**) and Mander's reagent (ethyl cyanoformate, **4b**) with the diene **3** were investigated to produce **1**.[3,7] The reaction of the nitrile **4a** with the known 2-trimethylsiloxy-1,3-cyclohexadiene,[8] **3**, using the conditions shown in Scheme 2 produced the Diels−Alder product **5a** in excellent crude yield and purity by NMR (∼90% pure after removal of all volatiles). NMR analysis also indicated the formation of only one regioisomer. However, further attempts to purify **5a** or to convert the silyl enol ether to the ketone without affecting the sensitive imine functionality led to decomposition. In our hands, the Diels−Alder product **5b** from ethyl cyanoformate (**4b**) (ether, $MgBr_2{\cdot}OEt_2$, Et_2O, rt) decomposed upon purification or silyl enol ether hydrolysis attempts.

To prove the regiochemistry of the Diels−Alder reaction and also provide azabicyclooctenones that we could utilize to produce other photoprecursors, the *p*-toluenesulfonyl cyanide Diels−Alder product **5a** was hydrolyzed in situ with aqueous acetic acid[3a] to produce the novel bicycloketo-amide **6** (an isoquinuclidinone) as a crystalline solid in 77% overall yield from the nitrile. The 1-D proton NMR of the keto-amide **6** did not conclusively prove the regiochemistry of the Diels−Alder reaction. However, a 2-D COSY spectrum clearly indicated that the bridgehead proton H_a α to the amide nitrogen was clearly coupled to the methylene protons (H_c) α to the ketone and that the bridgehead proton (H_b) α to the amide carbonyl was not coupled to the H_c's.

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Thus, we have been able to produce a novel isoquinuclidinone in excellent overall yield from the Diels−Alder reaction of *p*-toluenesulfonyl cyanide with an electron-rich cyclic diene. Conversions of the keto-amide, **6**, to imidate photoprecursors and their subsequent photolyses will be reported elsewhere.

Experimental Section

NMR Scale Reaction To Prepare 2-Aza-3-(4-methylphenylsulfonyl)-5-trimethylsiloxybicyclo-[2.2.2]octan-2,5-diene (5a). A 25-mL round-bottomed flask was charged with the silyl enol ether **3**[8] (0.0177 g, 0.105 mmol), *p*-toluenesulfonyl cyanide (0.0191 g, 0.105 mmol), and $CDCl_3$ (0.50 mL). After stirring at room temperature for 58 h, ^1H NMR analysis showed disappearance of the silyl enol ether. The solvent was removed under a stream of argon to yield **5a** as a colorless oil which was ~90% pure by ^1H NMR analysis (0.037 g, 0.105 mmol, 99% crude). ^1H NMR ($CDCl_3$): 7.75 (d, 2H, $J = 8.3$ Hz), 7.33 (d, 2H, $J = 8.0$ Hz), 5.18 (dd, 1H, $J = 5.9$, 2.5 Hz), 5.06 (dd, 1H, $J = 5.8$, 2.2 Hz), 4.14 (t, 1H, $J = 2.3$ Hz), 2.42 (s, 3H), 1.66−1.20 (m, 4H), 0.12 (s, 9H). ^{13}C NMR ($CDCl_3$): 175.6, 155.9, 145.8, 134.0, 131.3, 130.2, 129.7, 103.6 (C1), 61.5, 43.7, 25.2, 23.6, 0.2. HRMS: calcd for $C_{15}H_{18}NO_3SSi$ ($M - C_2H_5^+$) 320.077669, found 320.077988. MS: 320 (1), 306 (5), 257 (39), 242 (23), 194 (65), 149 (12), 139 (10), 121 (9), 91 (13), 73 (100). IR (NaCl, cm^{-1}): 2957, 1645, 1598, 1329, 1255, 1204, 1153, 909, 849.

2-Azabicyclo[2.2.2]octan-3,5-dione (6) from Nitrile 4a. A 25-mL round-bottomed flask was charged with silyl enol ether **3**[8] (2.38 g, 14.1 mmol), *p*-toluenesulfonyl cyanide (2.68 g, 14.7 mmol), and CH_2Cl_2 (10 mL). After stirring at reflux for 24 h, the mixture was cooled to 0 °C, and the flask was charged with glacial acetic acid (4 mL) and H_2O (8 mL). After stirring at 0 °C for 3 h, the mixture was neutralized with NaOH, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The organic washes were combined and dried with $MgSO_4$, and the solvent was removed under reduced pressure to yield an oily yellow solid (2.3 g). Trituration with Et_2O yielded a pale yellow solid (1.51 g, 10.9 mmol, 77%), mp 143.4−143.7 °C (EtOAc/Hex, 1:2). ^1H NMR ($CDCl_3$): 7.71 (bs, 1H, N-*H*), 4.00 (m, 1H), 3.24 (m, 1 H), 2.46 (dt, 1H, $J = 18.6$, 2.7 Hz), 2.27 (dd, 1H, $J = 18.3$, 2.0 Hz), 2.13−1.79 (m, 4H). ^{13}C NMR ($CDCl_3$): 205.7, 171.2, 57.4, 47.4, 43.3, 26.7, 21.1. HRMS: calcd for $C_7H_9NO_2$ 139.064022, found 139.063329. IR (KBr, cm^{-1}): 3182, 2796, 1740, 1682, 1450, 1398, 1337, 1309, 1096, 1010.

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Supporting Information Available: General experimental methods and ^1H, ^{13}C, and COSY NMR spectra of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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