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Generation and Diels–Alder Reactions of t-Butyl 2*H*-Azirine-3-carboxylate

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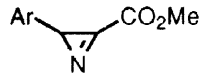
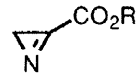
Abstract: The azirinyl ester **2** (R = Bu^t) has been generated by thermolysis of t-butyl 2-azidoacrylate. It is too unstable to allow its full characterisation but it has been intercepted by Diels–Alder cycloaddition to several dienes. Addition to a chiral diene **8** is highly diastereoselective. © 1998 Elsevier Science Ltd. All rights reserved.

We have recently described some Diels–Alder reactions of methyl 2-aryl-2*H*-azirine-3-carboxylates **1**.[1] These azirines were found to act as dienophiles towards several electron rich dienes at room temperature and in the absence of a catalyst. The combination of a strained C=N double bond and an activating alkoxycarbonyl substituent evidently promotes the Diels–Alder cycloaddition, since less activated azirines do not react under these conditions.[2]

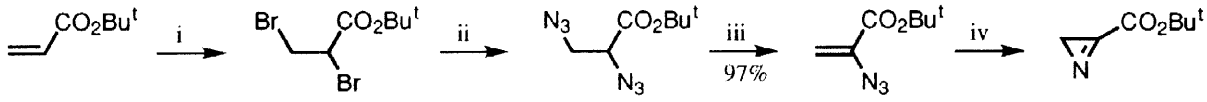


1



2

There are very few 2*H*-azirine-3-carboxylic esters described in the literature.[3] We set out to prepare an ester **2** that is unsubstituted at C-2; no azirines of this type with an activating substituent at C-3 are known. The Diels–Alder reactions of such an ester offer the possibility of preparing chiral, non racemic cycloadducts by using a chiral auxiliary or a chiral catalyst. The obvious precursor is a 2-azidoacrylic ester, and both the methyl[4] and the ethyl[5] esters have been prepared before from methyl and ethyl acrylate, respectively. Preliminary experiments were carried out on methyl 2-azidoacrylate but the product generated on thermolysis of the azide proved to be both highly unstable and volatile. t-Butyl 2-azidoacrylate was then prepared by the route shown in Scheme 1.[6] It was decomposed by heating in dry heptane under nitrogen[7] and the progress of the reaction was monitored by TLC until the starting azide was no longer detectable (5 hours). The azirine **2** (R = Bu^t) was isolated in impure form[8] by rapid evaporation of the solution but it proved to be very unstable, and decomposed within an hour in the condensed phase.

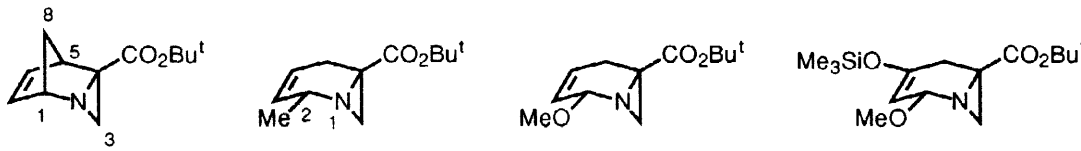


Reagents and conditions: i, Br_2, CH_2Cl_2, 5 °C; ii, NaN_3 (3 eq.), RT, 7 d; iii, DBU, ether, RT, 15 min.; iv, heptane, 98 °C, 5 h.

Scheme 1

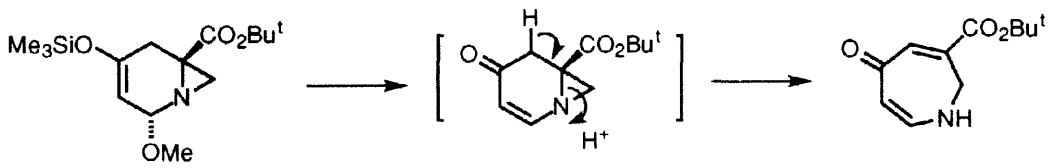
PII: S0040-4039(98)01617-7

Diels–Alder cycloaddition reactions were carried out by repeating the thermolysis of t-butyl 2-azidoacrylate then immediately adding a conjugated diene, in excess, to the solution of the azirine in heptane at room temperature. The aziridines **3–6** were isolated and characterised from reactions with cyclopentadiene, 1,3-pentadiene, 1-methoxybutadiene and 1-methoxy-3-trimethylsilyloxybutadiene repectively.[9] These structures are analogous to those of the adducts that were isolated and characterised earlier from the aryl substituted azirines **1**.[1] The NMR spectra of the compounds all show signals with a zero geminal coupling constant between the hydrogen atoms of the three membered ring. This is also a feature of the spectra of 1-azabicyclo[4.1.0]heptanes in the literature.[10]



3 **4** **5** **6**

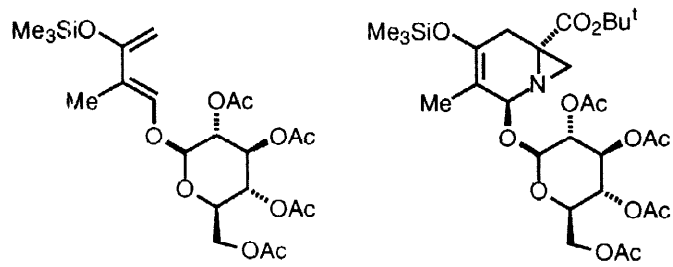
The silyl enol ether **6** slowly decomposed at room temperature to give a yellow solid that was isolated and characterised as the azepinone **7**.[11] This structure is the result of opening of the the three membered ring; a possible mechanism is shown in Scheme 2.



6 **7**

Scheme 2

The facial selectivity of the cycloaddition to a chiral diene was then investigated. The diene chosen was the silyloxydiene **8**, bearing a chiral auxiliary derived from glucose. This diene has been prepared and studied by Stoodley and co-workers, who showed that reactions with carbon dienophiles are highly diastereoselective.[12] The reaction with the diene **8** was carried out by heating it in heptane for 1 hour with a twofold excess of the azirine **2** (R = Bu^t). An NMR spectrum of the crude reaction mixture revealed, besides a small amount of unreacted diene and signals due to decomposition products of the azirine, a single cycloadduct (within the limits of detection at 200 MHz). This compound was then isolated by flash chromatography and characterised.[13] It has been assigned the structure **9**.



8 **9**

This structure is assigned on the basis that it will be formed by *endo* addition to the less hindered face[12] of the diene (Figure).

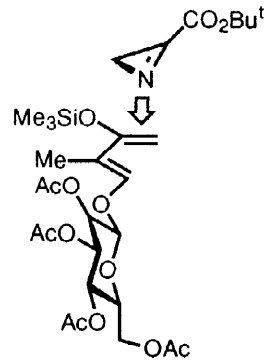


Figure. Likely direction of approach of the azirine **2** to the diene **8**.

The high degree of *endo* selectivity displayed in these cycloadditions, combined with the structural rigidity of the azirine, make the reactions excellent potential candidates for asymmetric catalysis. We are currently investigating this possibility and other related cycloadditions, as a route to chiral bicyclic aziridines.

1 Alves, M.J.; Gilchrist, T.L. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 299–303.

2 Anderson, D.J.; Hassner, A. *Synthesis*, **1975**, 483–495.

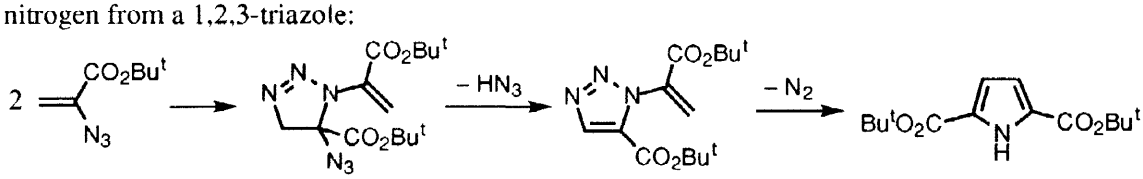
3 Smolinsky, G.; Pryde, C.A. *J. Org. Chem.*, **1968**, *33*, 2411–2416; Bestmann, H.J.; Kunstmann, R. *Chem. Ber.*, 1969, **102**, 1816–1832: Shin, C.; Yonezawa, Y.; Suzuki, K.; Yoshimura, J. *Bull. Chem. Soc. Jpn.*, **1978**, *51*, 2614–2617; L'abbe, G.; Dekerk, J.P.; Van Stappen, P. *Bull. Soc. Chim. Belg.*, **1981**, *90*, 1073–1074; Knittel, D. *Synthesis*, **1985**, 186–188; Hickey, D.M.B.; Moody, C.J.; Rees, C.W. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 1119-1122; Watanabe, T.; Takahashi, H.; Kamakura, H.; Sakaguchi, S.; Osaki, M.; Toyama, S.; Mizuma, Y.; Ueda, I.; Murakami, Y. *Chem. Pharm. Bull.* 1991, **39**, 3145–3152.

4 Hassner, A.; Fowler, F.W. *J. Org. Chem.*, **1968**, *33*, 2686–2691.

5 Kakimoto, M-.a.; Kai, M.; Kondo, K. *Chem. Lett.*, **1982**, 525–526; Ghosh, S.K.; Verma, R.; Ghosh, U.; Mamdapur, V.R. *Bull. Chem. Soc. Jpn.*, **1996**, *69*, 1705–1711.

6 The product from step ii in Scheme 1 was a 3:1 mixture of t-butyl 2,3-diazidopropionate and t-butyl 2-azidoacrylate. By reaction with DBU the mixture was converted completely into t-butyl 2-azidoacrylate; ν_{max} (film) 2135, 2104, 1720 and 1615 cm^{-1}, δ ($CDCl_3$) 1.53 (9 H, s), 5.26 (1 H, s) and 5.71 (1 H, s).

7 A dilute (44 millimolar) solution in heptane was used. In more concentrated solutions there are significant amounts of a by-product, which has been identified as di-t-butyl pyrrole-2,5-dicarboxylate. This is probably formed by dimerisation of the azide through 1,3-dipolar cycloaddition, followed by loss of nitrogen from a 1,2,3-triazole:



8 The azirine was identified by NMR: δ 1.56 (9 H, s) and 1.93 (2 H, s).

9 Compound **3**, isolated (50%) by flash chromatography as an oil that crystallises below RT; ν_{max} (film) 1720 cm^{-1}; δ (300 MHz, $CDCl_3$) 1.45 (9 H, s), 1.57 (1 H, s, H-3), 1.76 (1 H, br dd, *J* 7.9 and 3.0, H-8), 2.12 (1 H, dt, *J* 7.9 and 1.8, H-8), 2.38 (1 H, d, *J* 3.0, H-3), 3.43 (1 H, m, H-5), 4.08 (1 H, br s, H-1). 5.62 (1 H, ddd, *J* 5.2, 2.4 and 0.9, H-7) and 6.13–6.16 (1 H, m, H-6). Compound **4**, isolated (43%) as an oil; ν_{max} (film) 1710 cm^{-1}; δ (300 MHz, $CDCl_3$) 1.20 (3 H, d, *J* 7.2), 1.47 (9 H, s), 1.87 (1 H, s, H-7), 1.90 (1 H, t, *J* 1.2, H-7), 2.53 (1 H, ddt, *J* 18.3, 6.1,and 1.2 H, H-5), 2.65 (1 H, dddd, *J* 18.3, 5.5, 3.0 and 0.9, H-5), 3.73–3.80 (1 H, m, H-2), 5.25 (1 H, dtt, J 10.3, 1.2 and 1.2, H-3) and 5.59–5.66 (1 H, m, H-4). Compound **5**, isolated (67%) as an oil; ν_{max} (film) 1720 cm^{-1}; δ (300 MHz, $CDCl_3$) 1.47 (9 H), 1.99 (2 H, s, 2 H-7), 2.62–2.63 (2 H, m, 2 H-5), 3.63 (3 H, s), 4.80 (1 H, br s, H-2), 5.38–5.44 (1 H, m, H-3) and 5.57–5.74 (1 H, m, H-4). Compound **6**, isolated (30%) as an oil; ν_{max} (film) 1720 cm^{-1}; δ (300 MHz, $CDCl_3$) 0.21 (9 H, s), 1.48 (9 H, S), 1.98 (2 H, s, 2 H-7), 2.47 (1 H, d, *J* 18.0, H-5), 2.66 (1 H, d, *J* 18.0, H-5), 3.51 (3 H, s), 4.48 (1 H, br s, H-3) and 4.91 (1 H, s, H-2).

10 Bernet, B.; Murty, A.R.C.B.; Vasella, A. *Helv. Chim. Acta*, **1990**, *73*, 940–958; Paulsen, H.; Matzke, M.; Orthen, B.; Nuck, R.; Reutter, W. *Liebigs Ann. Chem.*, **1990**, 953–963.

11 Compound **7**, m. p. 173–174.5 °C; ν_{max} (nujol) 3183 and 1704 cm^{-1}; δ (300 MHz, $CDCl_3$) 1.50 (9 H, s), 4.11 (2 H, d, *J* 5.1, coupling removed by D_2O shake, 2 H-2), 5.21 (1 H, dt, *J* 8.2 and 1.8, H-6), 5.80 (1 H, br, NH) and 7.03–7.08 (2 H, m, H-4 and H-7); δ_C (75 MHz, $CDCl_3$) 27.95 (3 CH_3), 42.58 (C-2), 82.30 (CMe_3), 104.36 (C-6), 131.30 (C-3), 141.42 and 148.02 (C-4 and C-7), 164.80 (CO_2Bu^t) and 189.99 (C-5).

12 Gupta, R.C.; Larsen, D.S.; Stoodley, R.J.; Slawin, A.M.Z.; Williams, D.J. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 739–749.

13 Compound **9** (84% after chromatography), m.p 138–140.5 °C (sample recrystallised from ether–hexane); δ (400 MHz, $CDCl_3$) 0.19 (9 H, s), 1.49 (9 H, s), 1.52 (3 H, s), 1.88 (1 H, s, H-7), 1.92 (1 H, s, H-7), 2.00, 2.03, 2.05 and 2.08 (each 3 H, s), 2.52 (1 H, d, *J* 17.9, H-5), 2.76 (1 H, d, *J* 17.9, H-5), 3.75 (1 H, ddd, *J* 9.4, 4.9 and 2.4, H-5'), 4.13 (1 H, dd, *J* 12.1 and 2.4, H-6'), 4.25 (1 H, dd, *J* 12.1 and 4.9, H-6'), 5.01 (1 H, dd, *J* 9.6 and 8.1, H-2'), 5.11 (1 H, approx. t, *J* 9.8, H-3'), 5.24 (1 H, t, *J* 9.4, H-4'), 5.26 (1 H, d, *J* 8.1, H-1') and 5.27 (1 H, s, H-2).