A 1,3-Dipolar Cycloaddition Route to 7-Azanorbornanes: Application to the Synthesis of *syn*-Facial *N*-Bridged Polynorbornanes[1]

Douglas N. Butler,* John R. Malpass,[2] Davor Margetic, Richard A. Russell,[3] Guangxing Sun, Ronald N. Warrener*
Centre for Molecular Architecture, Central Queensland University, Rockhampton, Queensland, 4702, Australia
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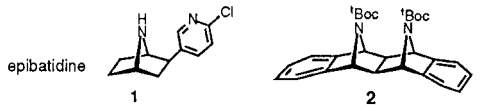
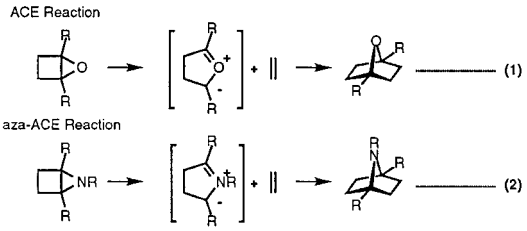
Abstract: Aziridinocyclobutenes react with electron-deficient or ring-strained alkenes to produce 7-azanorbornenes in a novel 1,3-dipolar cycloaddition reaction suitable for BLOCK assembly protocols. Benzo-7-azanorbornadiene and 7-heterobridged analogues react stereoselectively to produce compounds with *syn*-facial orientation of their bridges.

7-Azanorbornanes have received much interest following the discovery of the analgesic properties of epibatidine **1** (Scheme 1) and several specialist syntheses of this alkaloid have appeared in the recent literature.[4] Higher norbornalogues of 7-azanorbornanes, on the other hand, are uncommon and one of the rare examples is the doubly *N*-bridged adduct **2** reported by Sasaki *et al.* as the minor product (21%) in the cycloaddition of *N*-^{t}Boc-isoindole with *N*-^{t}Boc-7-aza-benzonorbornadiene.[5]



Scheme 1

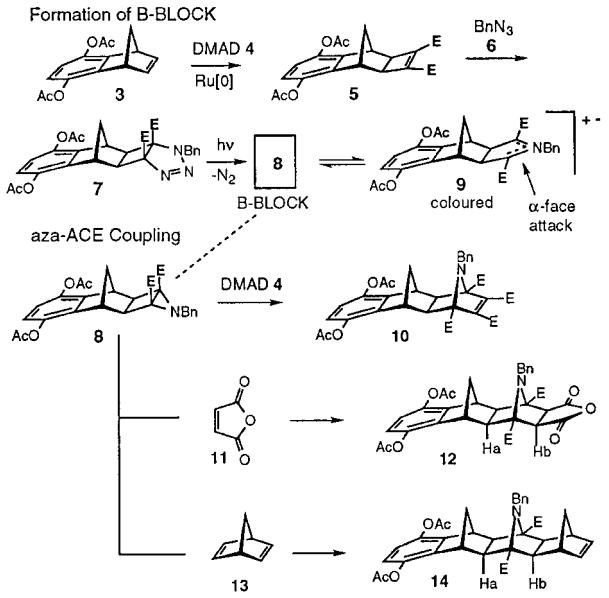
Following the success of our recently described ACE reaction (Scheme 2, equation 1) for the synthesis of 7-oxanorbornenes,[6] we reasoned that the development of an aziridine equivalent (aza-ACE reaction, Scheme 2, equation 2) held much potential for the synthesis of *N*-bridged alicyclics, especially 7-azanorbornanes. This is the subject of the present letter where we demonstrate the versatility of this new BLOCK reaction by the synthesis of the first examples of *syn*-facial polynorbornane systems containing multiple *N*-bridges.[7]



Scheme 2

The aziridinocyclobutane **8** required to test the potential of the aza-ACE coupling reaction was prepared as outlined in Scheme 3. Conversion of the benzonorbornadiene **3**[8] to the cyclobutene-1,2-diester **4** followed the established method of Mitsudo and co-workers, which employs the ruthenium-catalysed addition of dimethyl acetylene dicarboxylate **4** (DMAD).[9] Conversion of cyclobutene **5** to the triazoline **7**[10] was achieved by thermal addition of benzyl azide **6** and elimination of dinitrogen to produce aziridine **8**[10] was conducted photochemically (Hanovia 450 watt Hg lamp, quartz, benzene, RT). The synthesis of aziridinocyclobutane **8** was achieved in 40% overall yield for the three step process from the readily available benzonorbornadiene **3**.

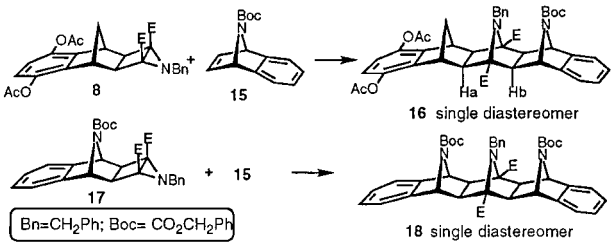
The reactivity of the *N*-benzyl aziridinocyclobutane **8** towards 1,3-dipolar cycloaddition was assessed initially by reaction with excess DMAD **4** (benzene at reflux) which produced the 1:1-adduct **10**.[10] The structure of **10** was supported by NMR data and presumed to arise *via* attack of the DMAD onto the α-face of the 1,3-dipolar intermediate **9**, formed by ring-opening of the aziridine (Scheme 3). Support for this proposal is provided by the formation of a yellow colour when aziridine **8** is heated alone in toluene.[11] Colour formation is lost on cooling and regenerated on heating, indicating the reversibility of the ring-opening process; further, the colour is discharged immediately on the addition of dipolarophiles like dimethyl fumarate.



Scheme 3

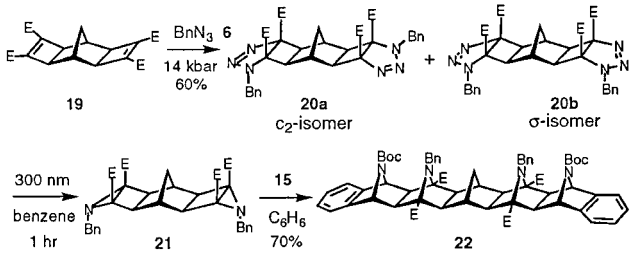
High stereoselectivity is observed in the reaction of the aziridine **7** with ethylenic dienophiles, eg maleic anhydride **11** forms a single product, shown to be the *exo*-fused adduct **12**[10] by the existence of an nOe between Ha and Hb (Scheme 3). Norbornadiene (in excess) also reacts smoothly with aziridine **8** to yield a single 1:1-adduct **14**.[10] An nOe observation between Ha and Hb again defines the stereochemistry as *exo,exo*-fused between the norbornene (*exo*-attack on the norbornadiene) and the newly-formed 7-azanorbornane subunit (diastereoselective attack at the α-face of the 1,3-dipole).

In order to assess the ability of the BLOCK reactions to produce [n]polynorbornanes containing multiple *N*-heterobridges, we have studied the aza-ACE reaction of the 7-aza-bridged dipolarophile **15** with aziridine **8** (Scheme 4). This reaction afforded a single diastereomer **16**[10] which was assigned the extended-frame structure on the basis of nOe enhancement between Ha and Hb, an experiment which was conducted at 60 °C because of *N*-substituent isomerisation.[13] It was possible to produce a polynorbornane with three juxtaposed *N*-bridges by employing the *N*-bridged aziridine **17**;[14] indeed reaction of A-BLOCK **15** with aziridine **17** formed the [3]polynorbornane **18**[10] in which the three nitrogen bridges are on the same face of the molecule. The structure of **18** rested on symmetry grounds where the NMR exhibited the expected C_{2v}-symmetry only at elevated temperature (67 °C) owing to *N*-inversions.



Scheme 4

We next turned our attention to introducing multiple nitrogen bridges into the polynorbornane via the dual aza-ACE reaction. The required *bis*-aziridine **21**[10] was prepared as outlined in Scheme 5. In this case, the cyclobutene-1,2-diester groups in **19**[9] are reluctant to add benzyl azide **6** under thermal conditions, but do so satisfactorily when compressed together at 14 kbar.[15] The resultant mixture of C_2-isomer **20a** and σ-isomer **20b** is not separated but deazetised photochemically to the common *bis*-aziridine **21**.[10] Reaction of **21** with *N*-Boc-7-aza-benzonorbornadiene **15** produced the [5]polynorbornane **22**[10] containing four aza-bridges. The structure of **22** was again determined by NMR spectral symmetry at elevated temperature.



Scheme 5

In conclusion, we have shown that the aza-ACE reaction is a versatile cycloaddition protocol and a worthy addition to our BLOCK coupling program. The high stereoselectivity of the coupling process should allow the production of polarofacial [n]polynorbornanes containing multiple heterobridges and these and other novel systems will be reported in due course.

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References and footnotes

(1) Building BLOCKs in Synthesis Part 4, for part 3, see Warrener, R. N.; Margetic, D.; Russell, R. A. *Synlett* **1998**, 585.

(2) on leave from Department of Chemistry, University of Leicester, LE1 7RH, UK

(3) Honorary visiting Professor CQU, from Department of Biological and Chemical Sciences, Deakin University, Geelong, Victoria, 3217, Australia.

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(7) For an earlier report on the preparation of polarofacial molecules based on 7-oxanorbornanes, see Warrener, R. N.; Butler, D. N.; Liao, W. Y.; Pitt, I. G.; Russell, R. A. *Tetrahedron Lett.* **1991**, *32*, 1889.

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(10) New compounds gave satisfactory ^{13}C NMR, MS and micro analytical data or high resolution mass spectra. Representative physical and ^1H NMR spectral data:
7: m.p. 149-150 °C (ethanol); ^1H NMR ($CDCl_3$) δ 1.74 (1H, d, *J* = 10.9 Hz); 2.03 (1H, d, *J* = 10.9 Hz); 2.31 (3H, s); 2.32 (3H, s); 2.35 (1H, d, *J* = 6.8 Hz); 2.47 (1H, d, *J* = 6.8 Hz); 3.53 (3H, s); 3.66 (1H, s); 3.84 (3H. s); 4.85 (2H, s); 6.80 (2H, s); 7.30-7.36 (5H, nm).
8: m.p. 135-136 °C (ethanol); ^1H NMR ($CDCl_3$) δ 1.92 (1H, d, *J* = 10.4 Hz); 2.16 (2H, d, *J* = 10.4 Hz); 2.33 (6H, s); 2.44 (2H, s); 3.77 (6H, s); 3.85 (2H, s); 3.98 (2H, s); 6.82 (2H, s); 7.25 (1H, t, *J* = 7.6 Hz); 7.31 (2H, t, *J* = 7.3 Hz); 7.39 (2H, d, *J* = 7.3 Hz).
10: m.p. 192-4 °C (methylene chloride/methanol). ^1H NMR ($CDCl_3$) δ 1.93 (1H, d, *J* = 8.9 Hz); 2.28 (6H, s); 2.48 (2H, s); 3.49 (6H, s); 3.55 (2H, s), 3.70 (1H, d, *J* = 8.9 Hz); 3.76 (2H, s); 3.79 (6H, s); 6.75(2H, s); 7.18-7.28 (5H, m).
12: m.p. 213–214 °C (methylene chloride/petroleum ether 40-60°C).^1H NMR ($CDCl_3$) δ 1.35 (1H, d, *J* = 9.4 Hz); 2.26 (2H, s); 2.28 (6H, s); 3.16 (2H, nm); 3.61 (1H, d, *J* = 9.4 Hz); 3.64 (2H, s); 3.90 (6H, s); 3.92 (2H, s); 6.77 (2H, s); 7.20 (1H, t, *J* = 7.9 Hz); 7.28 (2H, t, *J* = 7.2 Hz); 7.44 (2H, d, *J* = 7.2 Hz).
14: m.p. 199-200 °C (methylene chloride/methanol). ^1H NMR ($CDCl_3$) δ 0.88 (1H, d, *J* = 8.9 Hz); 1.21 (1H, d, *J* = 9.9 Hz); 1.96 (2H, s); 2.23 (2H, s); 2.26 (6H, s); 2.44 (2H, d, *J* = 8.9 Hz); 2.65 (2H, s); 2.67 (1H, d, *J* = 9.9 Hz); 3.21 (2H, s); 3.85 (6H, s); 4.36 (2H, s); 6.05 (2H, t, *J* = 1.3 Hz); 6.72 (2H, s); 7.17 (1H, t, *J* = 7.8 Hz); 7.26 (2H, t, *J* = 7.3 Hz); 7.47 (2H, d, *J* = 7.3 Hz).
16: m.p. 129-130 °C ^1H NMR (60 °C, $CDCl_3$) δ 1.09 (1H, d, *J* = 9.6 Hz), 1.90 (2H, s), 2.14 (6H, s), 2.27 (2H, s), 3.04 (2H, s), 3.41 (1H, d, *J* = 9.6 Hz), 3.74 (6H, s), 3.90 (2H, s), 4.91 (2H, bd s), 5.20 (2H, s), 6.58 (2H, s), 6.99-7.30 (14H, m).
17: not isolated. ^1H NMR ($CDCl_3$) δ 2.38 (2H, s), 3.72 (6H, sbr), 3.92 (2H, s), 5.01 (2H, sbr), 5.79 (2H, s), 7.16-7.35 (14H, m).
18: 33%, m.p. 172-173 °C, ^1H NMR ($CDCl_3$, 67 °C) δ 2.06 (4H, s), 3.68 (6H, s), 4.00 (2H, s), 4.94 (4H, s), 5.23 (4H, s), 7.02-7.30 (23H, m). Loss of symmetry occurs at ambient.
21: not isolated. ^1H NMR ($CDCl_3$) δ 1.90 (2H, s), 2.15 (4H, s), 3.30 (2H, s), 3.72 (12H, s), 3.99 (4H, s), 7.22-7.40 (10H, m).
22:m.p. 181-183 °C (ether/petroleum ether); ^1H NMR ($CDCl_3$) δ 1.40 (4H, s), 1.94 (2H, s), 2.23 (4H, s), 2.71 (2H, s), 3.69 (12H, s), 3.78 (4H, s), 4.94 (4H, dbr), 5.17 (4H, s), 7.10-7.26 (28H, m).

(11) While there is a precedent for the ring-opening and trapping for the ACE reaction (Gotthardt, H.; Huisgen, R.; Bayer, H. O. *J. Am. Chem. Soc.*, **1970**, *92*, 4340), there is none for the aziridino cyclobutane ring-opening. Of course, the ring opening of simple aziridines to 1,3-dipoles is well documented.[12]

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