



Reactivity of allenates toward aziridines: [3+2] and formal [3+2] cycloadditions

Fernanda M. Ribeiro Laia, Teresa M. V. D. Pinho e Melo*

Department of Chemistry, University of Coimbra, 3004-535 Coimbra, Portugal

ARTICLE INFO

Article history:

Received 19 June 2009

Revised 7 August 2009

Accepted 26 August 2009

Available online 1 September 2009

Keywords:

Aziridines

Allenes

Pyrroles

Pyrrolidines

[3+2] cycloaddition

Formal [3+2] cycloaddition

Microwave

ABSTRACT

The reactivity of buta-2,3-dienoates toward aziridines is reported. Allenates react as 2π -component in the [3+2] cycloaddition with the azomethine ylide generated from *cis*-1-benzyl-2-benzoyl-3-phenylaziridine affording 4-methylenepyrrolidines in a site-, regio-, and stereoselective fashion. Under conventional thermolysis, *cis*- and *trans*-2-benzoyl-1-cyclohexyl-3-phenylaziridines showed a different reactivity. These aziridines participate in formal [3+2] cycloadditions with allenes via C–N bond cleavage of the three-membered ring leading to functionalized pyrroles.

© 2009 Elsevier Ltd. All rights reserved.

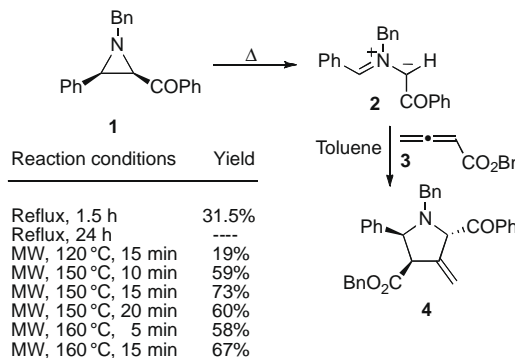
Allenes are interesting dipolarophiles due to the presence of two cumulative unsaturations. In fact, both C=C bonds are suitable positions for dipolar attack which can proceed with two opposite orientations. Hence, in the 1,3-dipolar cycloadditions of allenes both site- and regioselectivity can be involved. Allenes participate in cycloadditions with a variety of 1,3-dipoles, namely, nitrile oxides, nitrones, carbonyl ylides, nitrile imines, azides, and diazomethanes. However, the 1,3-dipolar cycloaddition of allenes with azomethine ylides is an unexplored research topic.^{1–5} Therefore, we set out to explore the cycloaddition of azomethine ylides generated from aziridines via conrotatory electrocyclic ring opening with buta-2,3-dienoates.

Aziridine **1** was prepared following a known synthetic procedure⁶ and its X-ray structure was determined in order to unambiguously establish the stereochemistry.⁷ Thermolysis of aziridine **1** in the presence of benzyl buta-2,3-dienoate⁸ (**3**) in refluxing toluene for 24 h did not lead to the target cycloadduct (Scheme 1). However, 4-methylenepyrrolidine **4**⁹ could be obtained as single stereoisomer in moderate yield (31.5%) when a significantly shorter reaction time was used (1.5 h). These results indicate the lack of stability of compound **4** to prolonged heating.

¹H and ¹³C NMR data for pyrrolidine **4** are given in Table 1 (chemical shifts of the aromatic groups are not included). The assignment was supported by two-dimensional COSY, NOESY, HMQC, and HMBC spectra (400 MHz). From the HMQC spectrum, it was established that the carbon with the chemical shift

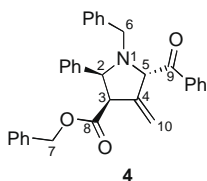
112.6 ppm corresponds to a methylene group since it shows connectivity with two protons with different chemical shifts, 4.99 ppm and 5.15 ppm. In the HMBC spectrum, carbon C-8 (170.8 ppm) correlates with H-2 and H-3. On the other hand, the carbon C-5 correlates with protons H-10 and H-2. In the NOESY spectrum H-2 shows connectivity with H-3 but no connectivity was observed between H-2 and H-5 or between H-3 and H-5.

We have recently reported that the microwave methodology for the conrotatory ring opening of an aziridine leading to the corresponding 1,3-dipole and the subsequent cycloaddition is more efficient than the conventional heating.¹⁰ Thus, the microwave-assisted 1,3-dipolar cycloaddition of azomethine ylide **2** with benzyl buta-2,3-dienoate (**3**) was carried out under different reaction



Scheme 1. Synthesis of 4-methylenepyrrolidine **4** via [3+2] cycloaddition of azomethine ylide **2** and allenolate **3**.

* Corresponding author. Tel.: +351 239 854475; fax: +351 239 826068.
E-mail address: tmelo@ci.uc.pt (T.M.V.D. Pinho e Melo).

Table 1
¹H and ¹³C NMR data for pyrrolidine **4**^a

C	¹ H NMR	¹³ C NMR
C-6	3.58 (1H, d, <i>J</i> = 13.2 Hz) 3.84 (1H, d, <i>J</i> = 13.2 Hz)	51.5
C-3	4.18 (1H, d, <i>J</i> = 8.0 Hz)	54.9
C-7	4.41 (1H, d, <i>J</i> = 12.4 Hz) 4.78 (1H, d, <i>J</i> = 12.4 Hz)	66.6
C-10	4.99 (1H, br s) 5.15 (1H, br s)	112.6
C-2	5.17 (1H, d, <i>J</i> = 8.0 Hz)	68.8
C-5	5.35 (1H, s)	67.2
C-4	—	136.7
C-8	—	170.8
C-9	—	201.3

^a Chemical shifts of the aromatic groups are not included.

conditions in order to optimize the synthetic procedure. We observed that the 1,3-dipolar cycloadduct **4** was obtained in 73% yield in a site-, regio-, and stereoselective fashion under microwave irradiation at 150 °C for 15 min (Scheme 1).

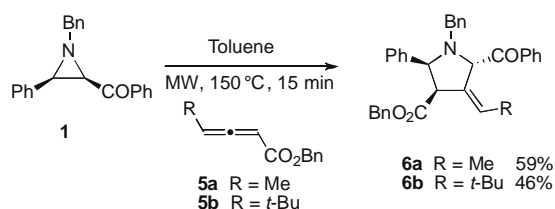
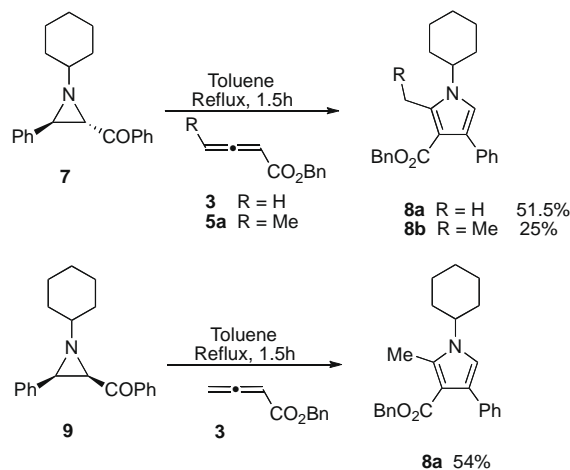
The work was extended to the reaction of aziridine **1** with benzyl penta-2,3-dienoate (**5a**)⁸ and 5,5-dimethylhexa-2,3-dienoate (**5b**)⁸ under microwave irradiation. Using the optimized reaction conditions the target molecules **6** were also selectively obtained (Scheme 2). It is worth noting that the isolation of 4-methylene-pyrrolidines **4** and **6** only requires crystallization from methanol.

trans-2-Benzoyl-1-cyclohexyl-3-phenylaziridine **7** was also synthesized by a known procedure¹¹ and its reactivity toward buta-2,3-dienoate was studied (Scheme 3). The reaction of aziridine **7** with benzyl buta-2,3-dienoate (**3**) in refluxing toluene led to an unexpected result. Pyrrole **8a**¹² was obtained in 51.5% yield. Carrying out the reaction with longer reaction time leads to significantly lower yield.

Based on the ¹H and ¹³C NMR spectra we concluded that compound **8a** did not retain the benzoyl substituent. In fact, no signal with the chemical shift expected for a carbonyl carbon of a benzoyl group could be observed. On the other hand, the ¹H NMR spectrum shows a singlet at 6.61 ppm corresponding to a pyrrolic proton. In the NOESY spectrum no connectivity was observed between the protons of the methyl group and the pyrrolic proton, which is in agreement with the proposed structure.

A similar reactivity was observed when aziridine **7** was reacted with allene **5a** in refluxing toluene. Pyrrole **8b** was isolated in 25% yield (Scheme 3).

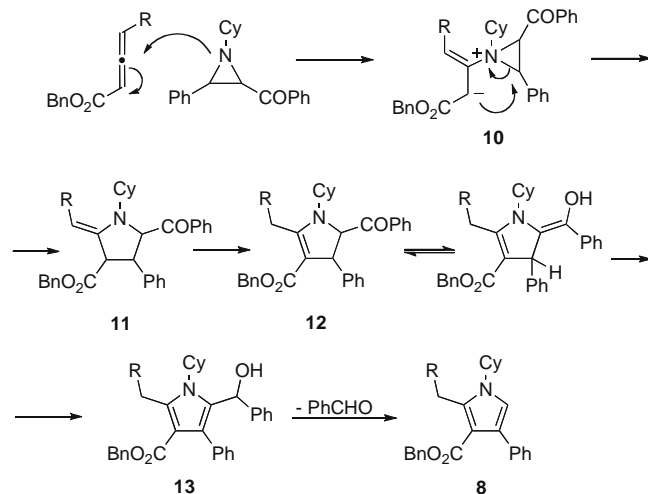
The reaction of *cis*-2-benzoyl-1-cyclohexyl-3-phenylaziridine **9**⁶ with benzyl buta-2,3-dienoate (**3**) was carried out and it led

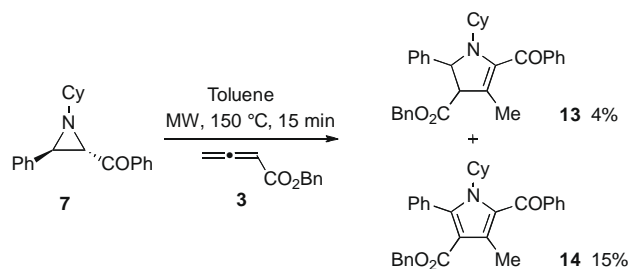
**Scheme 2.** Synthesis of 4-methylene-pyrrolidines **6** via reaction of aziridine **1** and allenoates **5**.**Scheme 3.** Synthesis of pyrroles **8** via formal [3+2] cycloaddition of aziridines and allenoates.

to the synthesis of pyrrole **8a** in 54% yield (Scheme 3). This result allowed us to conclude that the nature of *N*-substituent of the benzoyl-3-phenylaziridines determines the chemical behavior of these three-membered heterocycles toward allenoates.

The formation of pyrroles **8** can be explained as outlined in Scheme 4. Nucleophilic addition of aziridines **7** or **9** to the activated allene double bond giving intermediate **10** followed by the intramolecular attack of the carbanion center on the aziridine ring affords the five-membered heterocycles **11** via C–N bond cleavage. Tautomerisms and the subsequent aromatization lead to pyrrole **13** bearing a hydroxybenzyl sidechain, which is converted into benzaldehyde and the final product. The conversion of 2-(1-hydroxybenzyl)thiamin into thiamin and benzaldehyde involves a similar fragmentation step.¹³

It is known that *trans*- and *cis*-2-benzoyl-1-cyclohexyl-3-phenylaziridines (**7** and **9**) undergo thermal ring opening affording azomethine ylides which participate in [3+2] cycloadditions as dipole.¹⁴ However, the reactivity of aziridines participating in formal [3+2] cycloadditions via C–N bond cleavage with activated acetylene derivatives has been reported.¹⁵ Mattay and Gaebert demonstrated that the dipolar intermediate formed from *N*-butyl-2-phenylazirine and diethyl acetylenedicarboxylate could be trapped by carrying out the reaction in methanol.^{15a} Therefore,

**Scheme 4.** Mechanism proposal of the formal [3+2] cycloaddition of aziridines and allenoates.



Scheme 5. Microwave-assisted reaction of aziridine **7** and allenolate **3**.

the reaction of aziridine **7** with allene **3** in methanol was also performed. However, we were unable to trap intermediate **10** since at room temperature no reaction was observed and the reaction in refluxing methanol gave only pyrrole **8a** in 31% yield.

The microwave-induced reaction of aziridine **7** and allene **3** with the temperature set to 150 °C for 15 min afforded pyrrole **14** and dihydropyrrole **13** in 15% and 4% yield, respectively. Therefore, under these reaction conditions only products resulting from the 1,3-dipolar cycloaddition of the azomethine ylide generated in situ from aziridine **7** could be isolated (Scheme 5).

In conclusion, the site-, regio-, and stereoselective synthesis of 4-methylenepyrrolidines was achieved via [3+2] cycloaddition of allenolates with the azomethine ylide generated from *cis*-1-benzyl-2-benzoyl-3-phenylaziridine.

This reaction proved to be more efficient under microwave irradiation than with conventional heating.

The conventional thermolysis of *cis*- and *trans*-2-benzoyl-1-cyclohexyl-3-phenylaziridines in the presence of buta-2,3-dienoates allows us to report, for the first time, formal [3+2] cycloadditions of allenes and aziridine via C–N bond cleavage leading to functionalized pyrroles.

Acknowledgments

Thanks are due to FCT (Project PTDC/QUI/64470/2006) and FED-ER for financial support. We acknowledge the Nuclear Magnetic Resonance Laboratory of the Coimbra Chemical Centre (www.nmrccc.uc.pt), University of Coimbra for obtaining the NMR data.

References and notes

- Pinho e Melo, T. M. V. D. *Curr. Org. Chem.* **2009**, *13*, 1406–1431.
- Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; WILEY-VCH GmbH & Co. KgaA: Weinheim, 2004.
- Ma, S. *Chem. Rev.* **2005**, *105*, 2829–2871.
- Ma, S. *Aldrichimica Acta* **2007**, *40*, 91–102.
- Hassan, H. H. A. M. *Curr. Org. Chem.* **2007**, *4*, 413–439.
- Aziridine **1** (mp 105–107 °C; lit. 108 °C) and aziridine **9** (mp 107.5–109 °C; lit. 107 °C) were prepared as described in Cromwell, N. H.; Badson, R. D.; Harris, C. E. *J. Am. Chem. Soc.* **1943**, *65*, 312–315.
- Crystallography data of aziridine **1** will be disclosed in due time.
- Buta-2,3-dienoates were prepared via Wittig reaction of benzyl(triphenylphosphoranylidene)acetate with ketene following the general procedure described in (a) Pinho e Melo, T. M. V. D.; Cardoso, A. L.; Rocha Gonsalves, A. M. d'A.; Costa Pessoa, J.; Paixão, J. A.; Beja, A. M. *Eur. J. Org. Chem.* **2004**, 4830; (b) Lambert, T. H.; MacMillan, D. C. W. *J. Am. Chem. Soc.* **2002**, *124*, 13646–13647.
- Benzyl 5-benzoyl-1-benzyl-4-methylene-2-phenylpyrrolidine-3-carboxylate 4*. A suspension of aziridine **1** (100 mg, 0.32 mmol) and buta-2,3-dienoate **3** (84 mg, 0.48 mmol) in toluene (1 mL) was irradiated in the microwave reactor (CEM-Focused Synthesis System, Discover S-Class) for 15 min with the temperature set to 150 °C. The solvent was removed under reduced pressure and the crude product was recrystallized from methanol. Pyrrolidine **4** was obtained as a yellow solid in 73% yield. Mp 111.0–113.0 °C (methanol). IR (film) 3030, 1734, 1680, 1218 and 1157 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) 3.58 (1H, d, *J* = 13.2 Hz), 3.84 (1H, d, *J* = 13.2 Hz), 4.18 (1H, d, *J* = 8.0 Hz), 4.41 (1H, d, *J* = 12.4 Hz), 4.78 (1H, d, *J* = 12.4 Hz), 4.99 (1H, br s), 5.15 (1H, br s), 5.17 (1H, d, *J* = 8.0 Hz), 5.35 (1H, s), 7.02 (2H, br s, Ar-H), 7.18 (5H, br s, Ar-H), 7.28–7.36 (8H, m, Ar-H), 7.46–7.58 (5H, m, Ar-H); ¹³C NMR (CDCl₃, 100 MHz) 51.5, 55.0, 66.6, 67.2, 68.8, 112.6, 127.1, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 129.0, 133.0, 135.4, 136.7, 138.3, 138.5, 144.3, 170.8, 201.3; LC-MS (ESI) *m/z* 488 (MH⁺, 57%), 470 (35), 396 (100) and 380 (73). HRMS (ESI) *m/z* 488.22202 (C₃₃H₃₀NO₃ [MH⁺], 488.21810).
- Lopes, S. M. M.; Beja, A. M.; Silva, M. R.; Paixão, J. A.; Palacios, F.; Pinho e Melo, T. M. V. D. *Synthesis* **2009**, 2403–2407.
- Aziridine **7** (mp 100–102 °C; lit. 101–102 °C) was prepared as described in Southwick, P. L.; Christman, D. R. *J. Am. Chem. Soc.* **1952**, *74*, 1886–1891.
- Benzyl 1-cyclohexyl-2-methyl-4-phenyl-1H-pyrrole-3-carboxylate 8a*. A solution of aziridine **7** (80 mg, 0.26 mmol) and buta-2,3-dienoate **3** (54 mg, 0.31 mmol) in toluene (5 mL) was heated at reflux for 1.5 h. The solvent was removed under reduced pressure and the crude product was purified by preparative thin layer chromatography [ethyl acetate/hexane (1:10)]. Pyrrole **8a** was obtained as a yellow oil in 51.5% yield. IR (film) 2932, 1696, 1411, 1272 and 1155 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) 1.21–2.01 (10H, m), 2.55 (3H, s), 3.88 (1H, t, *J* = 12.0 Hz), 5.14 (2H, br s), 6.61 (1H, s), 7.06 (2H, br s, Ar-H), 7.22–7.32 (8H, m, Ar-H); ¹³C NMR (CDCl₃, 100 MHz) 11.3, 25.4, 25.8, 34.0, 55.3, 65.2, 109.9, 116.0, 126.0, 127.5, 127.6, 127.9, 128.2, 129.3, 135.8, 136.4, 136.5, 165.8; GC-MS (EI) *m/z* 373 (M⁺, 72%), 283 (25), 282 (100), 200 (55) and 91 (21). HRMS (ESI) *m/z* 374.21146 (C₂₅H₂₈NO₂ [MH⁺], 374.20753).
- Kluger, R. *Pure Appl. Chem.* **1997**, *69*, 1957–1967.
- (a) Amal Raj, A.; Raghunathan, R. *Tetrahedron* **2003**, *59*, 2907–2911; (b) Boruah, A.; Baruah, B.; Prajapati, D.; Sandhu, J. S.; Ghosh, A. *Tetrahedron Lett.* **1996**, *37*, 4203–4204; (c) Padwa, A.; Hamilton, L. *Tetrahedron Lett.* **1965**, *48*, 4363–4367.
- (a) Gaebert, C.; Mattay, J. *Tetrahedron* **1997**, *53*, 14297–14316; (b) Dalili, S.; Yudin, A. K. *Org. Lett.* **2005**, *7*, 1161–1164; (c) Zhu, W.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 5545–5548.