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

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ABSTRACT

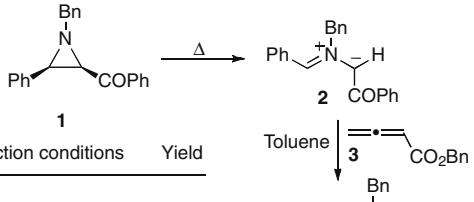
The reactivity of buta-2,3-dienoates toward aziridines is reported. Allenoates react as 2π-component in the [3+2] cycloaddition with the azomethine ylide generated from *cis*-1-benzyl-2-benzoyl-3-phenylaziridine affording 4-methylenepyrrolidines in a site-, regio-, and stereoselective fashion. Under 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.

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 procedure[6] 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-dienoate[8] (**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.

^{1}H and ^{13}C 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



Reaction conditions	Yield
Reflux, 1.5 h	31.5%
Reflux, 24 h	----
MW, 120 °C, 15 min	19%
MW, 150 °C, 10 min	59%
MW, 150 °C, 15 min	73%
MW, 150 °C, 20 min	60%
MW, 160 °C, 5 min	58%
MW, 160 °C, 15 min	67%

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

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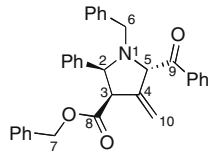
Table 1
^{1}H and ^{13}C NMR data for pyrrolidine **4**[a]



4

C	^{1}H NMR	^{13}C NMR
C-6	3.58 (1H, d, *J* = 13.2 Hz) 3.84 (1H, d, *J* = 13.2 Hz)	51.5
C-3	4.18 (1H, d, *J* = 8.0 Hz)	54.9
C-7	4.41 (1H, d, *J* = 12.4 Hz) 4.78 (1H, d, *J* = 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, *J* = 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).

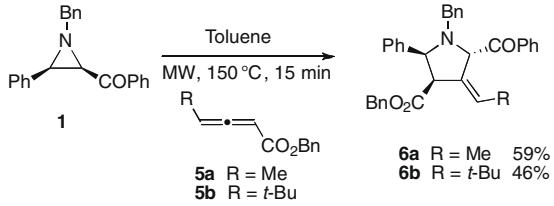
The work was extended to the reaction of aziridine **1** with benzyl penta-2,3-dienoate (**5a**)[8] and 5,5-dimethylhexa-2,3-dienoate (**5b**)[8] under microwave irradiation. Using the optimized reaction conditions the target molecules **6** were also selectively obtained (Scheme 2). It is worth noting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

trans-2-Benzoyl-1-cyclohexyl-3-phenylaziridine **7** was also synthesized by a known procedure[11] 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.

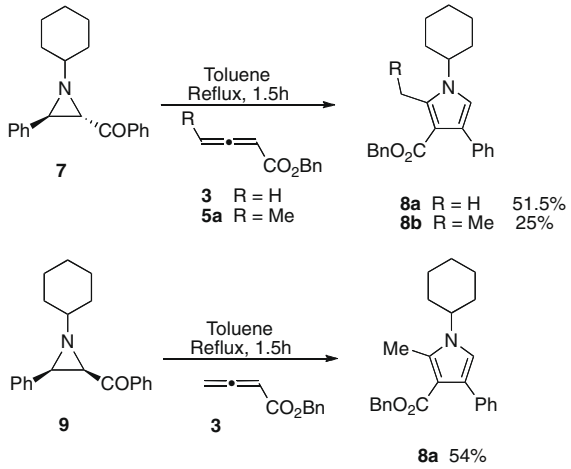
Based on the ^{1}H and ^{13}C NMR spectra we concluded that compound **8a** did not retain the benzoyl substituent. In fact, no signal with the chemical shift expected for a carbonyl carbon of a benzoyl group could be observed. On the other hand, the ^{1}H NMR spectrum shows a singlet at 6.61 ppm corresponding 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-methylenepyrrolidines **6** via reaction of aziridine **1** and allenoates **5**.

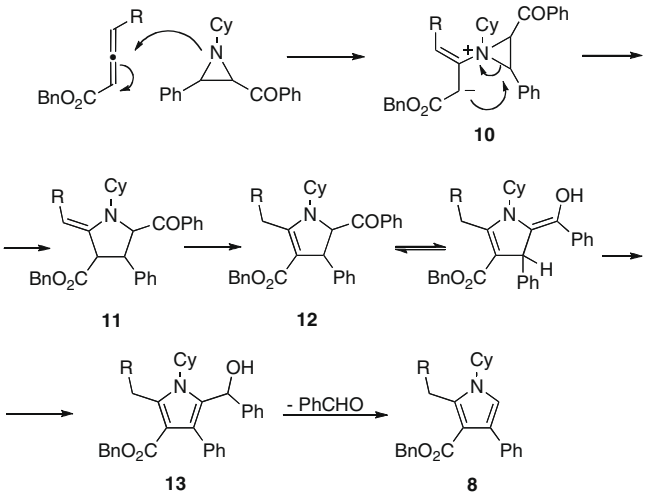


Scheme 3. Synthesis of pyrroles **8** via formal [3+2] cycloaddition of aziridines and allenoates.

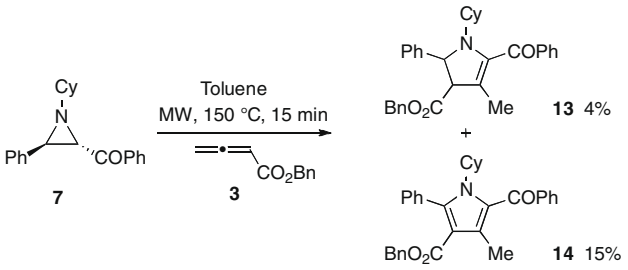
to the synthesis of pyrrole **8a** in 54% yield (Scheme 3). This result allowed us to conclude that the nature of N-substituent of the benzoyl-3-phenylaziridines determines the chemical behavior of these three-membered heterocycles toward allenoates.

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-hydoxybenzyl)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 allenoate **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 allenoates 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

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6. 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.
7. Crystallography data of aziridine **1** will be disclosed in due time.
8. 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.
9. *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 ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 ($C_{33}H_{30}NO_3$ [MH^+], 488.21810).
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11. 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.
12. *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 ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 ($C_{25}H_{28}NO_2$ [MH^+], 374.20753).
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