A Novel Efficient Three-Component One-Pot Synthesis of 1,3-Diazabicyclo[3.1.0]hex-3-ene System under Microwave Irradiation

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Received 15 April 2005

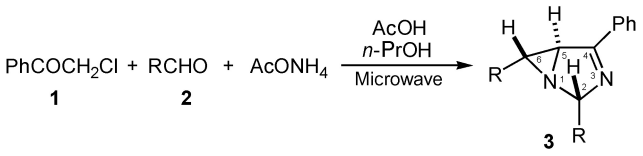
Abstract: Bridgehead aziridines **3** were synthesized in high yields and excellent diastereocontrol by a three-component reaction of an aldehyde, phenacyl chloride and ammonium acetate in acetic acid using microwave irradiation.

Key words: multicomponent, microwave, bicyclic aziridine, diastereocontrol

Functionalized aziridines are an extremely important class of compounds for a number of reasons: they are potentially the precursors of new biologically active compounds, they constitute the structural motif in many natural products and they are very useful synthetic intermediates.[1]

Exploration of new routes to the synthesis of aziridine derivatives has thus attracted considerable attention and the search for a means of rapid access to these heterocycles and their diverse biological properties is well documented in literature.[2]

Our research in this area has been concerned with the application of multicomponent reactions[3] to the one-pot synthesis[4] of the 1,3-diazabicyclo[3.1.0]hex-3-ene ring system.[5] Here we describe an efficient approach to the synthesis of stereodefined bridgehead aziridines **3** from commercially available low-cost compounds. This was achieved by the addition of phenacyl chloride **1** to aldehyde derivatives **2** in the presence of an excess of a mixture of AcOH/$AcONH_4$ in *n*-propanol under microwave-assisted conditions (Scheme 1).[6]



Scheme 1

From what appears to be a highly diastereoselective process, we only ever isolated the *exo*-isomer **3** in all cases studied. When extended to aliphatic aldehydes, the same procedure failed to produce any significant results. With aldehydes containing an α-hydrogen no reaction was observed to proceed, while with bulkier substrates, such as pivalaldehyde (entry 7), an analogous bicyclic product was obtained but with markedly reduced yields.

The same reactions, performed according to the classic method of heating under reflux,[7] were observed to proceed in a similar manner but took longer and gave less satisfactory yields. The results are summarized in Table 1.

Table 1 Synthesis of Aziridines **3**

Entry	**3**	R	Yield (%)[a]	Yield (%)[b]
1	**a**	Ph	92	86
2	**b**	2-MeC_6H_4	88	75
3	**c**	3-MeC_6H_4	78	65
4	**d**	3-$MeOC_6H_4$	75	63
5	**e**	3-ClC_6H_4	72	61
6	**f**	4-MeC_6H_4	79	67
7	**g**	$(CH_3)_3C$	35	–

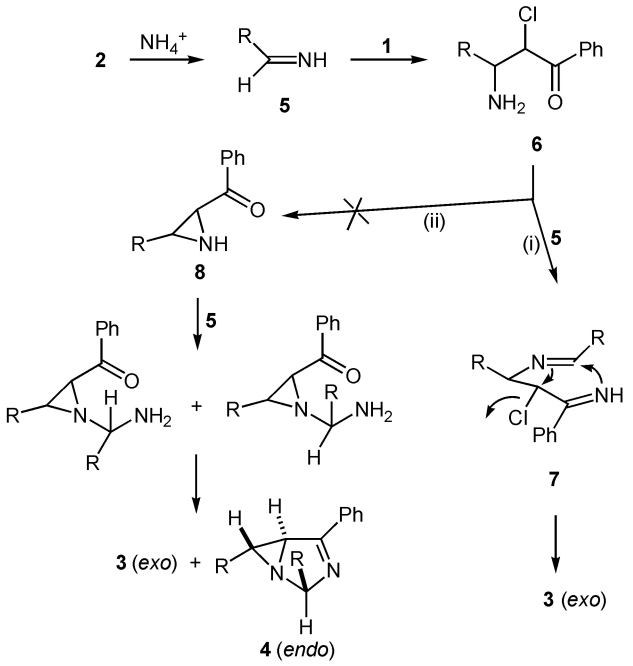
[a] Isolated yields under microwave irradiation; reaction time 5–10 min.
[b] Isolated yields under traditional conductive-heating method; reaction time 2–3 h.

The identification of compounds **3** was based on their spectral and analytical data,[8] and confirmed by X-ray crystallographic analysis carried out on **3a**.[9] Coupling constants and NOE measurements (irradiation of HC-2 gives rise only to enhancement of HC-6) provided exhaustive information on the *exo*-stereochemistry of the process.

In these reactions, three stereocenters are created and only one of the possible diastereoisomers is produced as a racemic mixture. Reaction process (i) seems most plausibly to explain the formation exclusively of *exo*-isomer **3** (Scheme 2). The alternative (ii), in which a key step is the in situ formation of derivative **8**, is not altogether satisfactory. Indeed, in line with previous research in which trans-aroylaziridines **8** were used as starting products,[10] we would have expected to see a consistent mixture of *exo* **3** and *endo* **4** isomers, with the latter prevalent. Moreover, the relatively lengthy formation times of **8** are not very consistent with the observed course of the reaction. Initially, therefore, (Scheme 2, path i) the amino ketone **6** is produced by means of a stereoselective intermolecular aldolization between phenacyl chloride **1** and the aldimine

SYNLETT 2005, No. 10, pp 1633–1635
Advanced online publication: 07.06.2005
DOI: 10.1055/s-2005-869859; Art ID: G11805ST

5, which has formed in the interim from the aldehyde in the presence of the AcOH/$AcONH_4$ mixture. Instead of cyclizing to **8**, this amine intercepts the aldehyde (or the aldimine) that is still present in the reaction environment and evolves, again stereoselectively, to *E*-imine **7**. In this the NH imine and the Schiff base moiety are appropriately dislocated in order to give rise to an 6-*endo*-trig cyclization,[11] which in turn guides the formation of aziridine functionality within the bicyclic ring system **3** by 3-*exo*-tet cyclization[11] between the nitrogen atom originally from the Shiff base and the electrophilic C-Cl fragment. This proposed ring-closure of the intermediate **7** is consistent with a chair-like transition state with R substituents disposed in a pseudo-equatorial manner.



Scheme 2

The advantage of this synthesis in comparison with previous ones is evident: it rests on a highly efficient reaction that is effectively diastereoselective, requires mild reaction conditions and for which work up is straightforward. The tedious preliminary preparation procedures required for type **8** N-unsubstituted aziridines are avoided.[12]

In conclusion, this easy route to stereodefined bridgehead aziridines opens the door to various applications for this attractive class of compounds.[5b,13]

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(6) **Microwave Irradiation.**
A mixture of phenacyl chloride **1** (463.7 mg, 3 mmol), aldehyde **2** (6 mmol), ammonium acetate (1.55 g, 20 mmol) and glacial acetic acid (10 mL) in *n*-PrOH (20 mL) in the presence of molecular sieves (4 Å) was irradiated for 5–10 min in a self-tunable CEM microwave synthesizer at 90 °C. After cooling the reaction to r.t., the solvent was removed under vacuum and the residue was crystallized from EtOH to give **3** as colorless crystals.

(7) **Conventional heating.**
As above procedure, but absolute EtOH was used as solvent and the reaction mixture was refluxed for 2–3 h.

(8) Selected data.
Compound **3a**: mp 155–156 °C (lit.[5a] mp 153–154 °C). IR (nujol): 1597, 1569, 1046 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.72 (d, *J* = 2.2 Hz, *H*C-6), 3.74 (dd, *J* = 2.2 and 2.9 Hz, *H*C-5), 6.22 (d, *J* = 2.9 Hz, *H*C-2), 7.30–8.01 (m, arom., 15 H). ^{13}C NMR ($CDCl_3$): δ = 49.0 (C-5), 56.4 (C-6), 97.4 (C-2), 170.4 (C-3). Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 85.31; H, 5.94; N, 9.14.
Compound **3b**: mp 134–135 °C. IR (nujol): 1601, 1578, 1050 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.43 (s, 3 H), 2.65 (s, 3 H), 2.85 (d, *J* = 2.1 Hz, *H*C-6), 3.65 (dd, *J* = 2.1 and 3.0 Hz, *H*C-5), 6.35 (d, *J* = 3.0 Hz, *H*C-2), 7.18–8.05 (m, arom., 13 H). ^{13}C NMR ($CDCl_3$): δ = 47.8 (C-5), 56.8 (C-6), 94.5 (C-2), 171.2 (C-3). Anal. Calcd. for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.40; H, 6.73; N, 8.11.
Compound **3c**: mp 152–153 °C. IR (nujol): 1599, 1573, 1048 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.43 (s, 3 H), 2.46 (s, 3 H), 2.72 (d, *J* = 1.8 Hz, *H*C-6), 3.78 (dd, *J* = 1.8 and 2.2 Hz, *H*C-5), 6.24 (d, *J* = 2.2 Hz, *H*C-2), 7.16–8.08 (m, arom., 13 H). ^{13}C NMR ($CDCl_3$): δ = 49.3 (C-5), 56.6 (C-6), 99.1 (C-2), 170.4 (C-3). Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found C, 85.32; H, 6.69; N, 8.38.
Compound **3d**: mp 148–149 °C. IR (nujol): 1599, 1580, 1040 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.66 (d, *J* = 1.9 Hz, *H*C-6), 3.70 (dd, *J* = 1.9 and 2.4 Hz, *H*C-5), 3.77 (s, 3 H), 3.79 (s, 3 H), 6.17 (d, *J* = 2.4 Hz, *H*C-2), 6.82–7.98 (m, arom., 13 H). ^{13}C NMR ($CDCl_3$): δ = 49.0 (C-5), 53.8 (C-6), 97.3 (C-2), 170.4 (C-3). Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.98; H, 6.08; N, 7.69.
Compound **3e**: mp 118–119 °C. IR (nujol): 1596, 1572, 1048 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.62 (d, *J* = 1.8 Hz, *H*C-6), 3.65 (dd, *J* = 1.8 and 2.7 Hz, *H*C-5), 6.12 (d, *J* = 2.7 Hz, *H*C-2), 7.23–7.95 (m, arom., 13 H). ^{13}C NMR ($CDCl_3$): δ = 48.2 (C-5), 56.5 (C-6), 96.7 (C-2), 170.5 (C-3). Anal. Calcd for $C_{22}H_{16}Cl_2N_2$: C, 69.67; H, 4.25; N, 7.39. Found: C, 69.80; H, 4.32; N, 7.21.
Compound **3f**: mp 135–136 °C. IR (nujol): 1600, 1581, 1049 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.29 (s, 3 H), 2.42 (s, 3 H), 2.69

(d, *J* = 2.0 Hz, *H*C-6), 3.65 (dd, *J* = 2.0 and 2.9 Hz, *H*C-5), 6.21 (d, *J* = 2.9 Hz, *H*C-2), 7.10–8.01 (m, arom., 13 H). ^{13}C NMR ($CDCl_3$): δ = 48.5 (C-5), 56.5 (C-6), 97.1 (C-2), 170.9 (C-3). Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.01; H, 6.42; N, 8.39.

Compound **3g**: mp 68–69 °C. IR (nujol): 1610, 1576, 1041 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.99 (s, 9 H), 1.02 (s, 9 H), 1.18 (d, *J* = 2.1 Hz, *H*C-6), 3.22 (dd, *J* = 2.1 and 3.3 Hz, *H*C-5), 4.49 (d, *J* = 3.2 Hz, *H*C-2), 7.39–7.51 (m, arom., 3 H), 7.85–7.88 (m, arom., 2 H). ^{13}C NMR ($CDCl_3$): δ = 49.8 (C-5), 56.2 (C-6), 104.3 (C-2), 170.2 (C-3). Anal. Calcd. for $C_{18}H_{26}N_2$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.78; H, 9.60; N, 10.49.

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