Pergamon

Tetrahedron Letters, Vol. 38, No. 33, pp. 5887-5890, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01311-7

Novel Ring Opening Reactions of Methyleneaziridines

Julie Ince and Michael Shipman*

Department of Chemistry, Stocker Road, University of Exeter, Exeter, Devon, EX4 4QD, U.K.

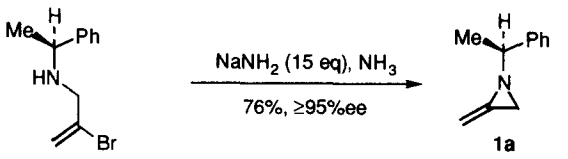
David S. Ennis

SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, U.K.

Abstract: Treatment of 2-methyleneaziridines with chloroformates (MeO_2CCl, $PhCH_2O_2CCl$) or acid chlorides (AcCl, p-$NO_2C_6H_4COCl$) at room temperature in a variety of nonpolar solvents (CH_2Cl_2, THF, toluene) produces ring opened enamine products in moderate to good yields.

Methyleneaziridines are small but densely functionalised heterocycles[1] which can be readily prepared by sodium amide induced cyclisation of the corresponding *N*-(2-bromoallyl)alkylamines.[2,3] We have recently used this chemistry to prepare a variety of chiral, nonracemic methyleneaziridines such as **1a** without racemisation at the adjacent stereogenic centre (Scheme 1).[4,5] Despite the strained nature of the methyleneaziridine ring system, surprisingly few reports concerning the ring opening reactions of these heterocycles have been disclosed.[3,6-8] Bottini and Roberts have shown that treatment of 1-ethyl-2-methyleneaziridine with hydrochloric acid gives chloroacetone *via* a ring opening / hydrolysis process. Chloroacetone from this reaction was isolated as its 2,4-dinitrophenylhydrazone derivative although the overall yield for this sequence was not disclosed.[3] A detailed mechanistic study relating to the protonation and subsequent ring opening reactions of 1-methyl-2-methyleneaziridine using FSO_3H/SbF_5 has been described.[6] In other work relating to the chemistry of methyleneaziridines, it has been postulated that the decomposition of 3-lithio-1-*tert*-butyl-2-methyleneaziridine involves nucleophilic ring opening of 1-*tert*-butyl-2-methyleneaziridine by this organolithium species.[7]

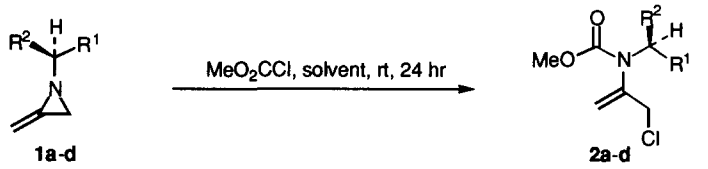
In this Letter, we disclose studies from our laboratories which establish that methyleneaziridines can be induced to undergo smooth nucleophilic ring opening reactions in the presence of a variety of chloroformates and acid chlorides under relatively mild reaction conditions.



1a

Scheme 1

Treatment of methyleneaziridine (*S*)-**1a** with methyl chloroformate in dichloromethane at room temperature gave enamine **2a** in 85% yield (Table 1, Entry 1).[9,10] ^{1}H NMR data for this enamine closely agree with the chemical shift values reported for related enamine structures prepared by an alternative route.[11] Additional studies have established that this ring opening reaction of methyleneaziridines is quite general. The reaction can be conducted in a variety of solvents (Table 1, Entries 1-3) and considerable variation in the structure of the methyleneaziridine can be accommodated without detrimental effects (Table 1, Entries 1, 4, 5 & 7).[12]

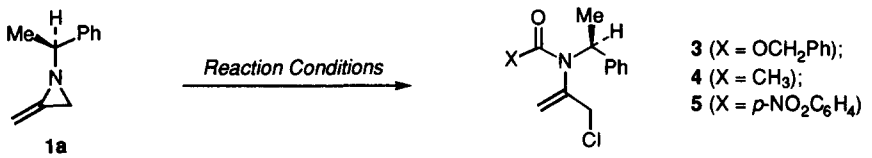


1a-d **2a-d**

Entry	Methyleneaziridine	R^1	R^2	Solvent	Product	% Yield[§]
1	(*S*)-**1a**	Ph	CH_3	CH_2Cl_2	**2a**	85
2	(*S*)-**1a**	Ph	CH_3	THF	**2a**	70
3	(*S*)-**1a**	Ph	CH_3	toluene	**2a**	63
4	(*S*)-**1b**	CH_2OBn	Ph	toluene	**2b**	50
5	(*S*)-**1c**	CH_2OBn	$CH(CH_3)_2$	toluene	**2c**	64
6	(*S*)-**1c**	CH_2OBn	$CH(CH_3)_2$	CH_2Cl_2	**2c**	74
7	**1d**	$-CH_2(CH_2)_3CH_2-$		toluene	**2d**	69

Table 1. [§]Isolated yields after column chromatography on silica gel.

To further probe the generality of this procedure, we treated methyleneaziridine **1a** with a variety of related reagents capable of ring opening the aziridine in an analogous fashion. Other chloroformates and acid chlorides can be used to effect similar ring opening reactions (Table 2). However, treatment of methyleneaziridine **1a** with 1.1 equivalents of acetic anhydride in toluene, even at elevated temperatures, yielded only recovered starting material. Other reagents such as methanesulfonyl chloride (1.1 eq, CH_2Cl_2, rt) and diphenylphosphoryl azide (1.1 eq, CH_2Cl_2, rt) produced complex mixtures of products.

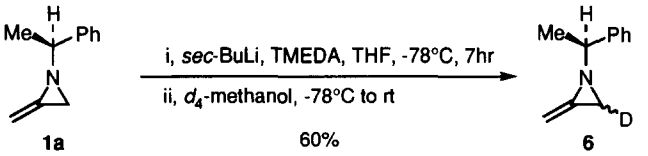


1a

Entry	Reaction Conditions	X	Product	% Yield[§]
1	$PhCH_2O_2CCl$, toluene, rt, 24 hr	$PhCH_2O$	**3**	63
2	$MeCOCl$, CH_2Cl_2, rt, 3 hr	CH_3	**4**	68
3	p-$NO_2C_6H_4COCl$, CH_2Cl_2, rt, 4 hr	p-$NO_2C_6H_4$	**5**	77

Table 2. [§]Isolated yields after column chromatography on silica gel.

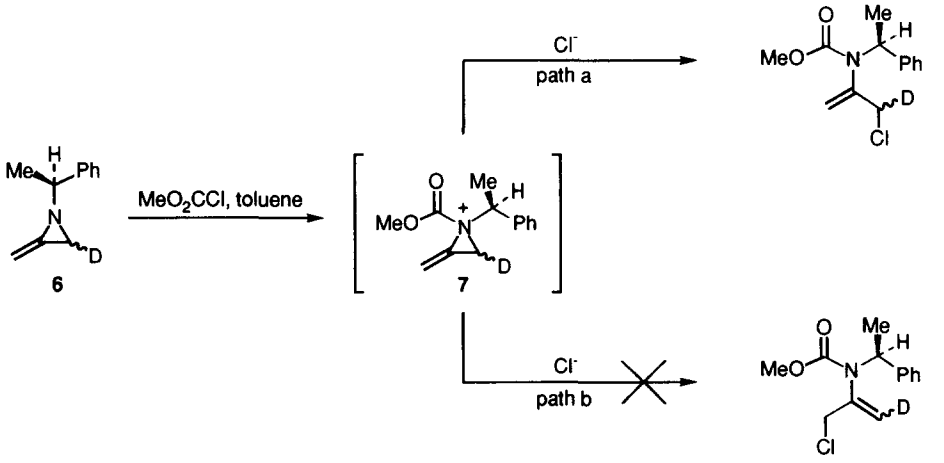
In order to help elucidate the mechanism of this reaction, we required deuterium labelled methyleneaziridine **6**. This compound was prepared by lithiation of methyleneaziridine **1a** with 1.1 equivalents of *sec*-butyllithium and subsequent deuteration with d_4-methanol (Scheme 2).[7,13] The extent of deuterium incorporation in the product was determined to be approximately 82% by ^{1}H NMR analysis. Interestingly, this compound was obtained as a 65:35 mixture of diastereomers indicating that the chiral grouping on nitrogen exerts some influence on this lithiation / deuteration process.



Scheme 2

We postulate that the ring opening reactions proceed *via* *N*-acyl aziridinium cation **7** which is subsequently ring opened by chloride anion generated in the reaction mixture. In principle, the observed products could be produced by direct nucleophilic attack at the methylene carbon atom of the aziridine ring (Scheme 3, path a), or alternatively by an SN' process involving chloride anion attack at the exocyclic carbon of the double bond (Scheme 3, path b). On the basis of the work undertaken by Jongejan *et al* one must also consider the possible involvement of an intermediate cyclopropaniminium cation.[6] To differentiate between these mechanistic possibilities, deuterated methyleneaziridine **6** was treated with methyl chloroformate in toluene, which gave the expected enamine product in 65% yield. ^{1}H NMR spectroscopy located the deuterium exclusively at the sp^3 hybridised carbon atom in the product suggesting that this reaction proceeds *via* direct ring opening of the aziridine ring (Scheme 3, path a).

In summary, we have established that methyleneaziridines can readily be ring opened to functionalised enamine products using a variety of chloroformates and acid chlorides under mild reaction conditions. Studies to use such ring opening reactions in organic synthesis are ongoing and will be disclosed in due course.



Scheme 3

Acknowledgements. We are grateful to SmithKline Beecham Pharmaceuticals for their generous financial support. We are indebted to Dr J.A. Ballantine and his staff at the EPSRC Mass Spectrometry Service for high resolution mass spectra.

REFERENCES & NOTES

1. For a leading reference on the preparation and chemistry of methyleneaziridines, see De Kimpe, N.; De Smaele, D.; Sakonyi, Z. *J. Org. Chem.* **1997**, *62*, 2448-2452.
2. Pollard, C. B.; Parcell, R. F. *J. Am. Chem. Soc.* **1951**, *73*, 2925-2927.
3. Bottini, A. T.; Roberts, J. D. *J. Am. Chem. Soc* **1957**, *79*, 1462-1464.
4. Ince, J.; Ross, T. M.; Shipman, M.; Slawin, A. M. Z.; Ennis, D. S. *Tetrahedron* **1996**, *52*, 7037-7044.
5. Ince, J.; Ross, T. M.; Shipman, M.; Ennis, D. S. *Tetrahedron: Asymmetry* **1996**, *7*, 3397-3406.
6. Jongejan, E.; Steinberg, H.; De Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 66-69.
7. Quast, H.; Weise Vélez, C. A. *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 342-343.
8. Crandall, J. K.; Crawley, L. C.; Komin, J. B. *J. Org. Chem.* **1975**, *40*, 2045-2047.
9. All new compounds gave satisfactory spectroscopic and high resolution mass spectral data.
10. ***Typical procedure:*** To a stirred solution of (*S*)-*N*-(1-phenylethyl)-2-methyleneaziridine (0.20 g, 1.26 mmol) in dichloromethane (10 ml) was added methyl chloroformate (0.11 ml, 1.38 mmol) and the reaction mixture stirred at room temperature for 24 hours. Water (10 ml) was added and the reaction mixture extracted with dichloromethane (3 x 10 ml). The combined organic layers were washed with water (2 x 5 ml), dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (10 % ethyl acetate / petroleum ether) gave **2a** (0.27 g, 85%) as a pale yellow oil. $[\alpha]_D$ = -15.7° (*c* 1.0, $CHCl_3$); ν_{max} (film) 1701, 1654, 1486, 1191 cm^{-1}; δH (300 MHz; $CDCl_3$) 7.37-7.25 (5H, m, Ph), 5.48 (1H, q, 7.0 Hz, C<u>H</u>Me), 5.40 (1H, s, =CH), 4.91 (1H, s, =CH), 3.93 (1H, d, A of AB, 13.5 Hz, CHCl), 3.79 (3H, s, OCH_3), 3.67 (1H, d, B of AB, 14.0 Hz, CHCl), 1.62 (3H, d, 7.0 Hz, CH_3); δC (100.6 MHz; $CDCl_3$) 155.3 (s), 141.6 (s), 141.3 (s), 128.4 (d), 127.5 (d), 127.2 (d). 116.0 (t), 56.1 (d), 52.9 (q), 44.9 (t), 17.8 (q); *m / z* 255 / 253 (M^+), 218 (M^+-Cl), 105, 77, 51. Observed 253.0875; $C_{13}H_{16}ClNO_2$ requires 253.0870.
11. Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Akiba, T.; Terashima, S. *Tetrahedron* **1994**, *50*, 3889-3904.
12. Attempts to react sterically encumbered *N*-trityl methyleneaziridine under these reaction conditions were unsuccessful. The starting methyleneaziridine was recovered unchanged.
13. Quast, H.; Weise Vélez, C. A. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 213-214.

(*Received in UK* 9 *June* 1997; *accepted* 27 *June* 1997)