A Convenient Synthesis of Azetidine-2-thiones and Azetidin-2-imines

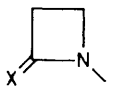
Jacqueline Marchand-Brynaert, Manuel Moya-Portuguez, Isabelle Huber, and Léon Ghosez*

Laboratoire de Chimie Organique de Synthèse, Université Catholique de Louvain, Place Louis Pasteur, 1, B–1348 Louvain-La-Neuve, Belgium

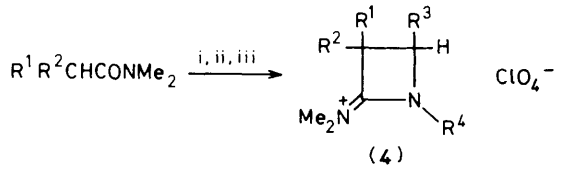
Azetidin-2-iminium salts, which are readily available from tertiary amides, can be easily converted into the corresponding thiones or imines.

In spite of the amount of research into the synthesis of β-lactams (**1**), very few papers have been devoted to the preparation of the thioxo (**2**)[1–4] and imino (**3**)[5–9] analogues. We report here a general method for the synthesis of azetidine-2-thiones and azetidin-2-imines from the readily available azetidin-2-iminium salts (**4**).

Compounds (**4**) were prepared from tertiary amides and Schiff bases by a previously described procedure[10–12] (Scheme



(1) X = O
(2) X = S
(3) X = NR
(4) X = $\overset{+}{N}R_2$



a; $R^1 = R^2 = Me$, $R^3 = R^4 = Ph$ (97%)
b; $R^1 = R^2 = Me$, $R^3 = SCH_2Ph$, $R^4 = Bu^t$ (38%)
c; $R^1 = H$, $R^2 = Me$, $R^3 = Ph$, $R^4 = CHPh_2$ (95%)[a]
d; $R^1 = R^2 = R^3 = H$, $R^4 = CHPh_2$ (50%)
e; $R^1 = H$, $R^2 = R^3 = R^4 = Ph$ (91%)[b]
f; $R^1 = H$, $R^2 = CO{\cdot}C_6H_4CO{\cdot}N$, $R^3 = CO_2Me$, $R^4 = CHPh_2$ (72%)[b]

Scheme 1. *Reagents:* i, $COCl_2$–HCl; ii, $R^3CH{=}NR^4{-}NEt_3$; iii, aqueous $KClO_4$. Yields, given in parentheses, are for the perchlorates, purified by crystallization in methanol. [a] Mixture of *trans* (75%) and *cis* (25%) isomers. [b] <3% of *cis* isomer.

Table 1

	Yields of products from (4), %			
	(1)	(3)	(7)	(2)
a	89[a]	100	100	95[a]
b	97[a]	85[b]	90[b]	70[a]
c	80[b,c]	40[g]	traces	91[b,c]
d	86[b,d]	traces	*ca.* 0	92[a]
e	*ca.* 0[e]			84[b,h,i]
f	10[b,f]			41[b,j]

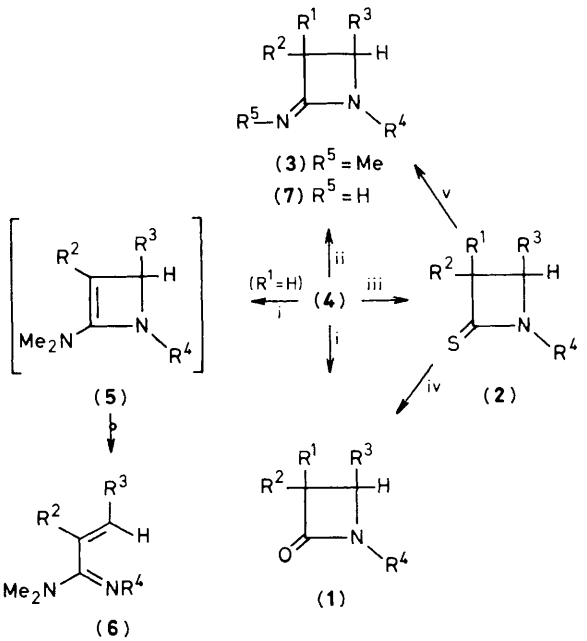
	Yields of products from (2), %		
	(1)	(3)	(7)
c	100[c]	85[c]	45[g]
d	100	58	28[g]
e	100[j]	95[k]	60[g]
f	100[j]		

[a] Crystallized from MeOH. [b] Chromatographed on silica gel. [c] Mixture of *trans* (75%) and *cis* (25%) isomers. [d] Some $Ph_2CH{-}NHCH_2CH_2C(O)NMe_2$ is isolated (*ca.* 10% yield). [e] 87% yield of (6) after crystallization from MeOH. [f] Mixture of *trans* (50%) and *cis* (50%) isomers. [g] Yield calculated from ^1H n.m.r. spectra of crude mixtures. [h] Mixture of *trans* (87%) and *cis* (13%) isomers. [i] Some $PhNHCHPhCHPhC(S)NMe_2$ is isolated (*ca.* 15% yield). [j] <3% of *cis* isomer. [k] Mixture of *trans* (80%) and *cis* (20%) isomers.

1). The reaction of (**4**) with a solution of potassium hydroxide does not lead to the cleavage of the four-membered ring but usually[11,12] gives the β-lactams (**1**) (Table 1). However, the presence of a phenyl or phthalimido substituent at C-3 (**4e, f**) increases the rate of deprotonation of the iminium salts, giving the enamines (**5**) which undergo a fast electrocyclic rearrangement into the α,β-unsaturated amidines (**6**) (Scheme 2).

We have also attempted the direct conversion of (**4**) into the corresponding imines in the presence of ammonia or methylamine. This was successful only with azetidin-2-iminium salts bearing no hydrogen at C-3 (Table 1).

In contrast the reaction of less basic sodium hydrogen sulphide with (**4**) gave the azetidine-2-thiones (**2**) in all cases (Table 1). These could be quantitatively converted into the corresponding β-lactams (**1**) in the presence of *m*-chloroperbenzoic acid (Table 1). Furthermore, the thiolactams could be readily activated toward nucleophilic attack. Thus the reaction of (**2c—e**) with methylamine in the presence of mercury acetate and with ammonia in the presence of silver trifluoromethanesulphonate gave the azetidin-2-imines (**3c—e**) and (**7c—e**), respectively, which could not be prepared by direct aminolysis of the corresponding iminium salts (Table 1).



Scheme 2. *Reagents:* i, Aqueous KOH–CH_2Cl_2; ii, R^5NH_2–CH_2Cl_2; iii, NaSH–MeCOMe; iv, *m*-chloroperbenzoic acid–CH_2Cl_2; v, $Hg(OAc)_2$–$MeNH_2$–CH_2Cl_2 or CF_3SO_3Ag–NH_3–CH_2Cl_2.

Thus the thioxo and imino analogues of β-lactams are now readily accessible by the routes outlined in Scheme 2.

We thank the Fonds National de la Recherche Scientifique (J. M-B) and the Université Catholique de Louvain (M. M-P) for fellowships, and the Service de la Programmation de la Politique Scientifique for financial support.

Received, 16th May 1983; Com. 618

References

1 R. Shabana, S. Schelbye, K. Clausen, S. O. Olesen, and S. O. Lawesson, *Nouv. J. Chim.*, 1980, **4**, 47.
2 P. W. Wojtkowski, J. E. Dolfini, O. Kocy, and C. M. Cimarusti, *J. Am. Chem. Soc.*, 1975, **97**, 5628.
3 E. Schaumann, *Chem. Ber.*, 1976, **109**; 906.
4 A. K. Bose and G. L. Mina, Abstract Papers 151st Meeting Am. Chem. Soc., 1966, ch. 22, p. 1.
5 R. Graf, D. Guenther, R. Jensen, K. Matterstock, Ger. Offen, 1963, 1 144 718; *Chem. Abstr.*, 1963, **59**,6368.
6 J. K. Crandall, L. C. Crawley, and J. B. Komin, *J. Org. Chem.*, 1975, **40**, 2045.
7 N. Goasdoue and M. Gaudemar, *J. Organomet. Chem.*, 1977, **125**, 9.
8 A. Van Camp, D. Goossens, M. Moya-Portuguez, J. Marchand-Brynaert, and L. Ghosez, *Tetrahedron Lett.*, 1980, **21**, 3081.
9 B. Arnold and M. Regitz, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 320.
10 B. Haveaux, A. Dekoker, M. Rens, A. R. Sidani, J. Toye, and L. Ghosez, *Org. Synth.*, 1980, **59**, 26.
11 M. De Poortere, J. Marchand-Brynaert, and L. Ghosez, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 267.
12 J. Marchand-Brynaert, M. Moya-Portuguez, D. Lesuisse, and L. Ghosez, *J. Chem. Soc., Chem. Commun.*, 1980, 173.