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SYNTHESIS OF N-(TOSYL)AZETIDIN-2-IMINES

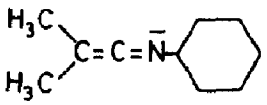
A. VAN CAMP, D. GOOSSENS, M. MOYA-PORTUGUEZ, J. MARCHAND-BRYNAERT and L. GHOSEZ*

Laboratoire de Chimie Organique de Synthèse, Université Catholique de Louvain
Place Louis Pasteur, 1, B-1348 LOUVAIN-LA-NEUVE, BELGIUM

Summary : A synthetic route for N-(tosyl)azetidin-2-imines 6, a novel class of derivatives of β-lactams, has been developed. The procedure is applicable to the synthesis of azetidin-2-imines related to penicillins and cephalosporins.

The biological activity of β-lactam antibiotics has been correlated with the chemical instability of the amide bond, resulting from a strongly reduced delocalization of the unshared electrons of the nitrogen atom into the adjacent carbonyl group[1]. It is therefore perhaps surprising that very few studies have dealt with the replacement of the carbonyl part of the amide linkage by unsaturated functions of different electrophilic character. To our knowledge the only report of such a modification deals with the synthesis albeit in very low yields, of β-thionolactam analogs of cephalosporins and penicillins[2]. The new compounds showed reduced antimicrobial activity in vitro. A few years ago, we set ourselves the task of preparing the iminium and imine analogs of β-lactams. A general methodology for the synthesis of azetidin-2-iminium salts has already been described[3]. We present here our preliminary results on the synthesis of azetidin-2-imines[4].

N-(alkyl)ketenimines are not sufficiently electrophilic to react with Schiff bases such as benzylideneaniline or N-methylbenzalimine : for instance, N-(cyclohexyl)dimethylketenimine 1[5] and benzylideneaniline did not condense after 96 hours at 100° in benzene (recovered Schiff base). Furthermore, the less stable N-(cyclohexyl)phthalimidoketenimine 2[6] did not give any adduct with N-methylbenzalimine (Δ,$CHCl_3$, recovered Schiff base).



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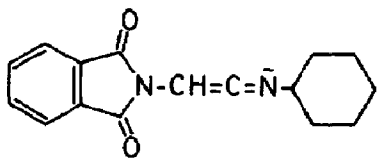
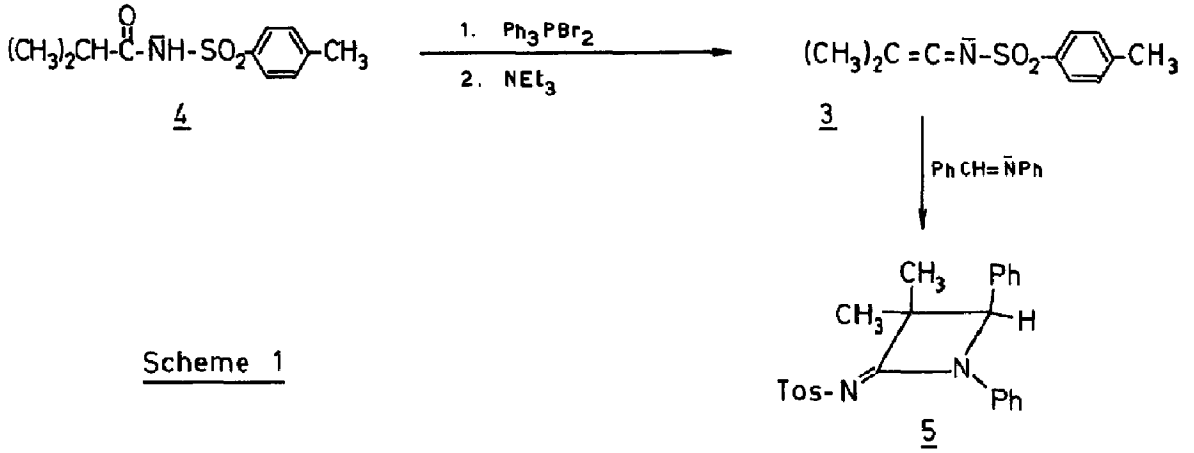


2

These preliminary observations led us to undertake the synthesis of ketenimines which would be susceptible to nucleophilic attack by Schiff bases. N-(tosyl)ketenimines were found to fulfil this requirement[7].

A solution of N-(tosyl)dimethylketenimine 3 (i.r. : 1990 cm^{-1}) was readily prepared from the sulfimide 4 by treatment with triphenylphosphine dibromide and triethylamine[8]. Addition of benzylideneaniline to this solution of 3, at 0°, resulted in the formation of a [2+2] adduct 5 in 86 % yield (Scheme 1).



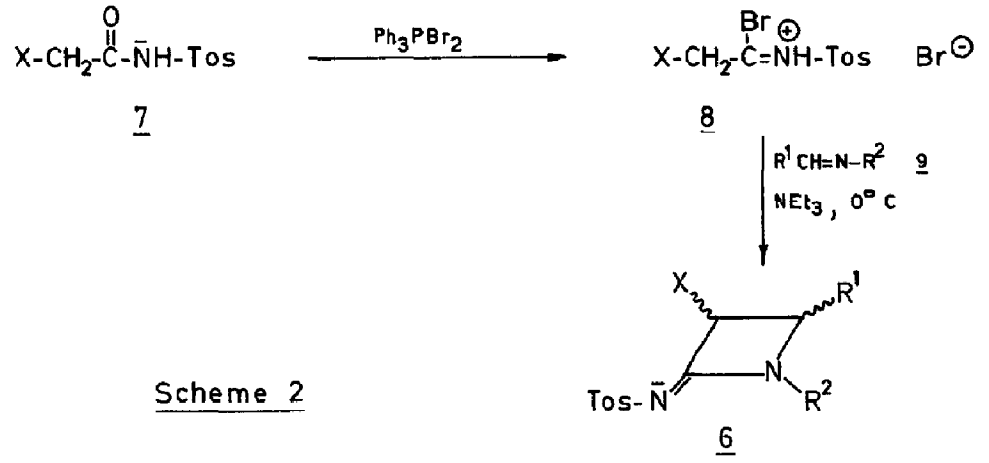
4 3 5

Scheme 1

The procedure has been extended to the preparation of various functionalized azetidin-2-imines 6 (Scheme 2).

Addition of sulfimides 7 to a suspension of triphenylphosphine dibromide in CH_2Cl_2 at 0°C yielded solutions of α-bromo-iminium bromides 8. These were treated at 0° with a dichloromethane solution of an imine 9 (1 eq.) and triethylamine (2 eq.). This one-pot procedure gave pure N-(tosyl)azetidin-2-imines 6 a-f in moderate yields (Table I). All azetidin-2-imines 6 showed a strong i.r. absorption band between 1630 and 1650 cm^{-1}.

Nmr spectra, mass fragmentations and analytical data supported the structures 6 a-f.



7 8 6

Scheme 2

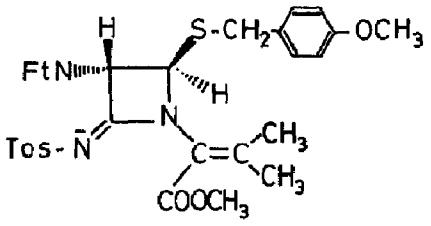
TABLE I

N-(tosyl)azetidin-2-imines 6

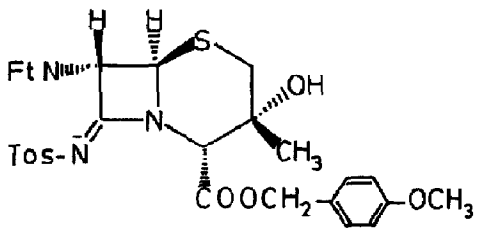
6	X	R^1	R^2	Yield (%)[b]	Config.	m.p.(°C)
a	Cl	Ph	Ph	38	trans	127 - 128
b	Br	$COOCH_3$	$CHPh_2$	38	c/t(3:1)	-
c	N_3	Ph	Ph	30	trans	219 - 225
d	N_3	$COOCH_3$	$CHPh_2$	47	c/t(1:1)	-
e	FtN[a]	PhS	C_6H_{11}	57	trans	129
f	FtN[a]	$COOCH_3$	$CHPh_2$	50	c/t(1:1)	-

(a) FtN : phthalimido (b) calculated from 7

The viability of the method is further demonstrated by the synthesis of more elaborate azetidin-2-imines such as 10[9], or 11[10].



10 (57 %)



11 (53 %)

The spectral data[11] are in agreement with the proposed structures. An X-ray diffraction analysis[12] confirms the structure of 11.

The further application of this approach for the synthesis of analogs of β-lactam antibiotics is under investigation.

Acknowledgments

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References and notes

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b) J. Marchand-Brynaert, M. Moya-Portuguez, D. Lesuisse, and L. Ghosez, J.Chem.Soc., Chem. Comm., 173 (1980)

(4) A few azetidinimines were mentioned in the previous litterature :
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b) J.K. Crandall, L.C. Crawley, J.B. Komin, J. Org. Chem. 40 2045 (1975).

(5) M.W. Barker and J.D. Rosamond, J. Heterocycl. Chem. 9 1419 (1972).

(6) Prepared from the corresponding α-chloro-imine and triethylamine in refluxing chloroform. i.r. : 2040 cm^{-1}.

(7) A recent paper describes the photochemical generation of N-(cyano) diphenyl aminoketenimine and its reaction with benzylideneaniline : B. Arnold, M. Regitz, Angew. Chem. Int. Ed. Engl. 18, 320 (1979).

(8) H.J. Bestmann, J. Lienert and L. Mott, Ann. 718, 24, (1968).

(9) The imine was synthetized according to the procedure of M.D. Bachi and O. Goldberg, J. Chem. Soc., Perkin Trans.I, 1184 (1974).

(10) The imine was synthetized according to the procedure of B.G. Christensen and R.W. Ratcliffe, (personal communication). See also R.W. Ratcliffe, and B.G. Christensen Tetrahedron Lett. 4645 (1973)

(11) 10 : m.p. 165°C
$\nu(CHCl_3)$: 1170(w), 1720(s), 1630(s) cm^{-1}
$\delta(CDCl_3)$: 1.93(s,3); 2.23(s,3); 2.30(s,3); 3.56(s,3); 3.70(s,3); 3.76(s,2); 5.60 (s,2); 6.5-7.8(m,12).

11 : m.p. : 117,3°C
ν(KBr) : 3200,1780(w),1720(s),1635(s)cm^{-1}
$\delta(CDCl_3)$: 1.48(s,3); 2.26(s,3); 2.50(d, J=13.5 Hz, 1); 3.16(d,J=13.5 Hz,1); 3.33 (s,1); 3.70(s,3); 4.55(s,1); 5.15(s,2); 5.53(d,J=1,5 Hz, 1); 5.66(d,J=1,5 Hz,1); 6.8-7.9(m,12).

(12) J.P. Declercq, G. Germain and M. Van Meerssche, unpublished results.

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