Pergamon

Tetrahedron Letters, Vol. 36, No. 19, pp. 3401-3404, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00492-0

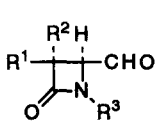
The Unusual Baeyer-Villiger Rearrangement of β-Lactam Aldehydes: Totally Stereoselective Entry to *cis*-3-Substituted 4-Formyloxy-2-azetidinones

Benito Alcaide,* Moustafa F. Aly[1] and Miguel A. Sierra

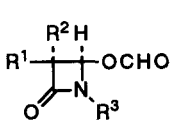
Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040-Madrid. Spain.

Abstract.- Baeyer-Villiger oxidation of 4-formyl-β-lactams **1** with *m*-chloroperbenzoic acid in dichloromethane at room temperature is shown to be a convenient method for the preparation of 4-formyloxy-β-lactams **2**. Some reactions of novel compounds **2** are also described.

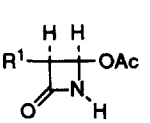
The Baeyer-Villiger oxidation of carbonyl compounds is a classical reaction in organic chemistry.[2] Aldehydes rearrange to carboxylic acids due to preferential migration of hydrogen. Alternative migration of the carbon group would give formates, which seldom occurs. Aryl aldehydes having hydroxy or methoxy groups are the only exceptions and are converted to aryl formates upon peroxyacid treatment.[3] We report here the unique behaviour of β-lactam aldehydes **1**[4] which exclusively give the corresponding formates, namely the 4-formyloxy-β-lactams **2**, under Baeyer-Villiger oxidation. Compounds **2** are unprecedented and closely related to 4-acetoxy-2-azetidinones **3**. Then, it is foreseeable that compounds **2** will be as useful building blocks in β-lactam chemistry.[5] Thus, 4-formyl-β-lactams **1** reacted smoothly with *m*-chloroperbenzoic acid (50-60%) in dichloromethane at room temperature to give the corresponding 4-formyloxy-β-lactams **2** in excellent yields (Table).[6] Retention of both the relative and the absolute stereochemistry of the starting β-lactam was observed in the oxidation of 4-formyl-β-lactams to compounds **2**[7] as can be deduced from the values of the vicinal



1



2

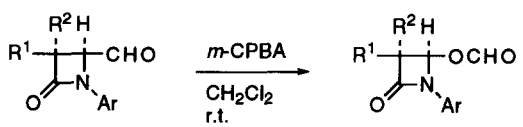


3

coupling constants ($J_{3,4}$ = 3.5 - 4.3 Hz). An attractive feature of this transformation is its high chemoselectivity and occurs even in the presence of other oxidizable groups, e. g. **2a-d**.[8] This fact makes Baeyer-Villiger oxidation even more profitable in β-lactam chemistry.

To test the chemical behaviour of the formyloxy group and to set analogies and differences with the classical 4-acetoxy substituent, some preliminary aspects of the chemistry of compounds **2** were studied. Firstly, compatibility of the formyloxy group with the manipulation of the group attached at N1 was addresed using compounds **2h** and **2i** as models (Scheme). Oxidative cleavage (CAN)[9] of the *p*-methoxyphenyl group attached to nitrogen yielded the corresponding *N*-unsubstituted formates **4a** and **4b** in good yields. Compound **4a** underwent reductive reaction with $NaBH_4$ in aqueous 2-propanol or methanol at 0°C to give the corresponding C4-unsubstituted *NH*-β-lactam **5a** in excellent yield.[10] Thus, 4-formyloxy-β-lactams are as suitable for standard manipulations as the related 4-acetoxy derivatives.

Table. Synthesis of 4-formyloxy-β-lactams 2

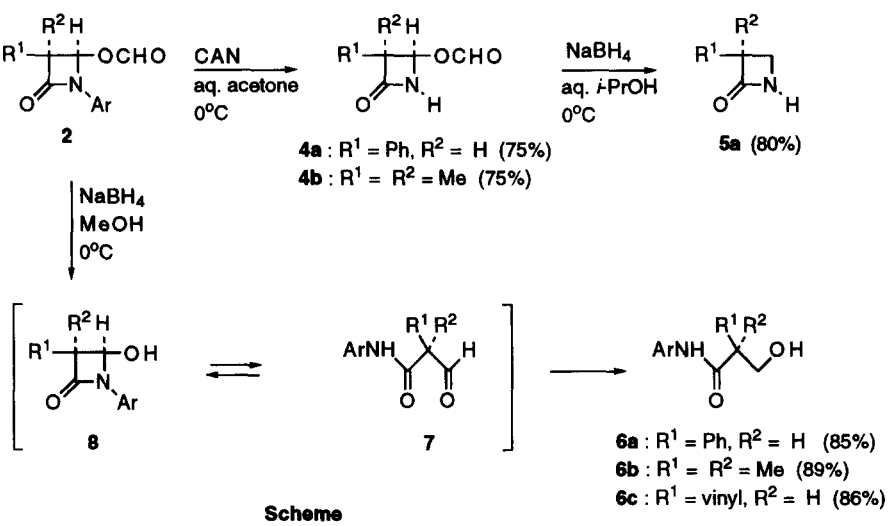


1 2

Comp.[a]	R^1	R^2	Reaction time (h)[b]	Yield (%)[c]	M.p. (°C)[d]
2a	CH_2=CH	H	3	91	105-107
2b	CH_2=C(Me)	H	20	70	62-64
2c	$(CH_3)_2C$=	H	2	90	104-106
2d	Md[e]	H	18	73	140-142
2e	Et	H	2.5	94	46-48
2f	*i*-Pr	H	18	72	120-122
(+)-**2g**[f]	BnO	H	2	94	92-94
2h	Ph	H	18	94	98-100
2i	CH_3	CH_3	6	93	37-39

[a] In all cases Ar = 4-methoxyphenyl. With exception of **2g**, all compounds **2** were racemic mixtures. [b] At room temperature. [c] Yield of pure, isolated product with correct analytical and spectral data. [d] Crystallized from CH_2Cl_2/hexanes, except for **2i** from diethyl ether/hexanes. [e] Md = Maleimidyl. [f] Prepared from optically pure (+)-(3*R*, 4*S*)-4-formyl-3-benzyloxy-2-azetidinone (**1g**).

On the other hand, reduction of different 4-formyloxy-β-lactams **2** with $NaBH_4$ in methanol at 0°C gave the corresponding α-substituted β-hydroxyamides **6** in high yields.[11] β-Hydroxyamides related to **6** are intermediates in the synthesis of malonamide derivatives and are useful retroamide isosteres in biologically relevant peptidomimetics.[12] The reduction of the formyloxy group should occur sequentially to afford first the α-formylamide **7**, the open tautomer of the 4-hydroxy-β-lactam **8**, which is further reduced to give the corresponding β-hydroxyamide **6**. While this work was in progress, the synthesis of a 4-hydroxy-β-lactam (type **8**) was reported from (3*R*)-4-acetoxy-3-benzyl-3-fluoro-β-lactam.[12] In our hands, the hydrolysis of compound **2i** under analogous conditions gave the corresponding open chain aldehyde tautomer (type **7**, R^1 = R^2 = Me) in 71% yield.[13] 4-Formyl-β-lactams can be very efficiently transformed into compounds **6** in only two steps following our procedure, in contrast with the reported method which requires four steps to effect the analogous transformation in related systems.



Scheme

In conclusion, the Baeyer-Villiger oxidation of 4-formyl-β-lactams provides a facile, efficient and totally stereoselective entry to *cis*-4-formyloxy-β-lactams which in turn are suitable building blocks for β-lactam antibiotics.

Acknowledgements. Support for this work by the DGICYT (Project PB93-0442) is gratefully acknowledged. One of us (M.F.A.) acknowledges the receipt of a post-doctoral fellowship by the Ministerio de Educación y Ciencia (Spain).

References and Notes

1. Permanent address: Chemistry Department, Faculty of Science at Qena, Assiut University, Egypt.

2. For recent reviews of Baeyer-Villiger reaction, see: (a) Krow, G. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 7, p 671.(b) Krow, G. R. *Organic Reactions*; Paquette, L. A. Ed.; John Willey and Sons: New York. 1993, Vol. 43; pp. 251. (c) Krow, G. R. *Tetrahedron*, **1981**, *37*, 2697. For recent papers, see: (a) Kaneda, K.; Ueno, S.; Imanaka,

T.; Shimotsuma, E.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.*, **1994**, *59*, 2915. (b) Chida, N.; Tobe, T.; Ogawa, S. *Tetrahedron Lett.*, **1994**, *35*, 7249.

3. (a) Ogata, Y.; Sawaki, Y. *J. Org. Chem.*, **1969**, *34*, 3985. (b) Godfrey, I. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Perkin Trans I*, **1974**, 1353. (c) Camps, F.; Coll, J.; Messeguer, A.; Pericás, M. A. *Tetrahedron Lett.*, **1981**, *22*, 3895.

4. 4-Formyl-2-azetidinones are easily available substrates both in the racemic and in the optically pure forms. See, for instance: (a) Alcaide, B.; Martín-Cantalejo, Y.; Plumet, J.; Rodriguez-López, J.; Sierra, M. A. *Tetrahedron Lett.*, **1991**, *32*, 803.(b) Alcaide, B.; Martín-Cantalejo, Y.; Pérez-Castells, J.; Rodriguez-López, J.; Sierra, M. A.; Monge, A.; Pérez-García, V. *J. Org. Chem.*, **1992**, *57*, 5921. (c) Evans, D. A.; Williams, J. M. *Tetrahedron Lett.*, **1988**, *29*, 5065. (d) Hubschwerlen, C.; Schmid, G. *Helv. Chim. Acta*, **1983**, *66*, 2206.(e) Jarayaman, M.; Deshmukh, A. R. A. S.; Bhawal, B. M. *J. Org. Chem.*, **1994**,

5. 4-Acetoxy-2-azetidinones are recognized as the most useful starting substrates for synthetic work in β-lactam chemistry, because the acetoxy group can be replaced by many different nucleophiles. See, for example: (a) Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles*, **1982**, *17*, 463. (b) Nagahara, T.; Kametani, T. *Heterocycles*, **1987**, *25*, 729. (c) Arrieta, A.; Cossio, F. P.; García, J. M.; Lecea, B.; Palomo, C. *Tetrahedron Lett.*, **1988**, *29*, 3129. (d) Wild, H. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers Inc., New York, 1993; Ch. 2, p 49.

6. Typical experimental procedure: A mixture of the 4-formyl-β-lactam (0.462g, 2mmol) and *m*-CPBA (calc. 0.414g, 2.4 mmol) [commercially available from Aldrich Company in 50-60% concentration] in dichloromethane (40 mL) was stirred at room temperature for 3 h. The reaction mixture was then washed with 5% aqueous $NaHCO_3$ solution (2x30 mL) and brine (2x30 mL), and finally dried over Na_2SO_4. Removal of the solvent afforded a residue, which was purified by silica gel chromatography with hexanes-EtOAc (3:1) to give the product.

7. Determined by high field (300 MHz) ^{1}H-NMR analysis of the crude reaction mixtures. No traces of the *trans*-isomer were detected in any case.

8. The sole exception was the 3-phenylthio-4-formyl-β-lactam, which give the corresponding sulfone after prolongued reaction time under the same reaction conditions , without change in the formyl group.

9. Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

10. For $NaBH_4$ reduction on related 4-acetoxy-β-lactams, see: Pfaendler, H. R.; Hoppe, H. *Heterocycles*, **1985**, *23*, 265. For another reduction method, see: Arrieta, A.; Lecea, B.; Cossio, F. P.; Palomo, C.*J. Org. Chem.* **1988**, *53*, 3784.

11. β-Hydroxy *N*-arylamides related to **6** have been used for the synthesis of relevant C4-unsubstituted-β-lactams. See, for example: (a) Bose, A. K.; Sahu, D. P.; Manhas, M. S. *J. Org. Chem.* **1981**, *46*, 1229. (b) Hanessian, S.; Couture, C.; Wyss, H. *Can. J. Chem.*, **1985**, *63*, 3613.

12. Abouabdellah, A.; Welch, J. T. *Tetrahedron: Asymmetry*, **1994**, *5*, 1005.

13. α-Formyl acetanilides related to **7** have been obtained from 4-amino-β-lactams. See, for instance: (a) Perelman, E.; Mizsak, S. A. *J. Am Chem. Soc.*, **1962**, *84*, 4988. (b) Opitz, G.; Koch, J. *Angew. Chem.*, **1963**, *75*, 167. (c) Bose, A. K.; Kugajevsky, I. *Tetrahedron*, **1967**, *23*, 957.

(*Received in UK* 27 *January* 1995; *revised* 15 *March* 1995; *accepted* 17 *March* 1995)