A Concise Synthesis of 4-Unsubstituted Azetidin-2-ones†

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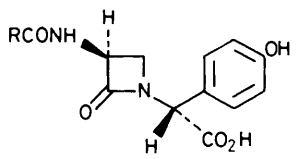
On catalysis by trimethylsilyl trifluoromethanesulphonate, 4-acetoxy-β-lactams react with hydrosilanes to give 4-unsubstituted-β-lactams in good to excellent yields.

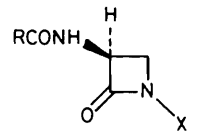
β-Lactam antibiotics are of current widespread interest because of their applications.[1] Monolactams such as nocardicins (**1**), monobactams (**2**), and tabtoxin (**3**) are characterized by the absence of substituents at the 4-position of the β-lactam ring. Despite numerous suitable methods for the synthesis of β-lactams, *e.g.* the annelation of an imino compound with an activated acetic acid is a versatile procedure for the construction of the azetidinone ring,[2] the innaccesibility of monomeric formaldehyde imines[3] has necessitated the development of new strategies for the preparation of monocyclic 4-unsubstituted β-lactams.[4]

We first prepared 4-acetoxy-β-lactams by the acetic acid–imine approach[5] and since the acetoxy group is readily removed by several reagents[6] we investigated the conversion of 4-acetoxy-β-lactams into 4-unsubstituted β-lactams (see Scheme 1).

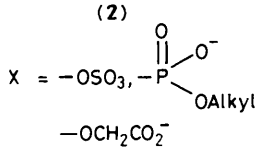
We found that the reaction between a 4-acetoxyazetidin-2-one and a sixfold excess of a hydrosilane, in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulphonate (triflate), cleanly afforded a 4-unsubstituted β-lactam in good yield. Of the hydrosilanes examined, *i.e.* triethylsilane, polymethylhydrosiloxane, and tetramethyldisiloxane, only tetramethyldisiloxane gave satisfactory results.‡ Of the catalysts zinc iodide, boron trifluoride, and trimethylsilyl triflate, only trimethyl triflate proved to be effective.

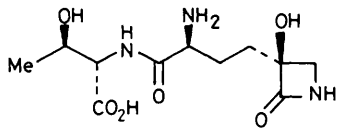


(**1**)



(**2**)

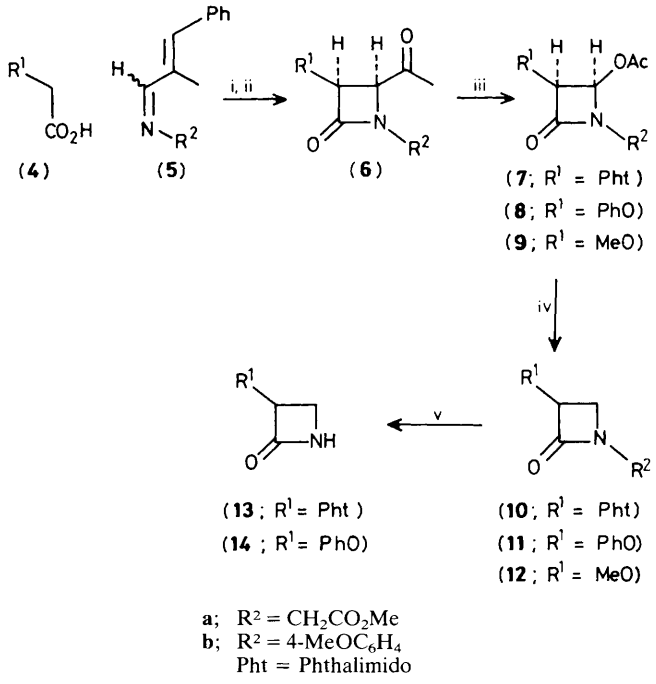




(**3**)

† For Part 62 of the series Reagents and Synthetic Methods see F. P. Cossío, I. Ganboa, J. M. García, B. Lecea, and C. Palomo, *Tetrahedron Lett.*, 1987, **28**, 1945.

‡ See R. D. G. Cooper in 'Topics in Antibiotic Chemistry', Vol. 3, ed. P. G. Sammes, Ellis Horwood Limited, Chichester, 1980, p. 156.



a; $R^2 = CH_2CO_2Me$
b; $R^2 = 4\text{-}MeOC_6H_4$
Pht = Phthalimido

Scheme 1. *Reagents and conditions:* i, $PhOPOCl_2$, NEt_3, CH_2Cl_2, room temp., 20—24 h; ii, O_3, −78 °C, CH_2Cl_2, then Me_2S; iii, *m*-chloroperbenzoic acid, C_6H_6, reflux; iv, $HMe_2SiOSiMe_2H$, C_6H_6, $F_3CSO_3SiMe_3$, reflux; v, cerium(IV) ammonium nitrate, $MeCN\text{–}H_2O$, ref. 7.

A representative procedure is as follows. A mixture of the 4-acetoxyazetidin-2-one (**7a**)[5] (1 mmol), 1,1,3,3-tetramethyldisiloxane (6 mmol), and trimethylsilyl triflate (two drops) in benzene (5 ml) was refluxed for 57 h under nitrogen. The reaction mixture was evaporated and the waxy residue was treated with methanol. The solid product was filtered off affording (**10a**) in 70% yield: 60 MHz ^1H n.m.r. δ ($CDCl_3$) 8.02—7.33 (m, 4H, ArH), 5.47 (d,d, *J* 4.5 Hz, *J'* 3 Hz, 1H, CH), 4.33 (d, *J* 18 Hz, 1H, CH), 3.90 (d, *J* 18 Hz, 1H, CH), 3.95–3.58 (m, 2H, CH_2), 3.75 (s, 1H, OMe). Further examples are listed in Table 1. The β-lactams (**10b**)—(**12b**) were easily transformed into their corresponding *N*-unsubstituted β-lactams; thus removal of the *p*-methoxyphenyl group[7] in (**10b**) led to (**13**) in 94% yield, m.p. 199—200 °C (decomp.); similarly (**14**), m.p. 109—110 °C (decomp.), was obtained in 86% yield. Using this synthesis diverse 4-unsubstituted β-lactams should be readily available.

Table 1. 4-Unsubstituted β-lactams prepared.

Compound[a]	*t*/h	Yield (%)	m.p./°C[b]
(**10a**)	57	70	164—165
(**10b**)	15	95	226—228
(**11a**)	25	53	—[c]
(**11b**)	15	96	112—114
(**12b**)	15	70	74—75

[a] All compounds were racemic mixtures and gave satisfactory spectral and analytical data. [b] From EtOH unless noted otherwise. [c] Colourless oil isolated by column chromatography. [d] From AcOEt–hexane.

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