2,2,2-Trichloroethylsulphonyl, 2,2,2-Trichloroethoxysulphonyl, and Trifluoroacetyl Isocyanates in β-Lactam Synthesis

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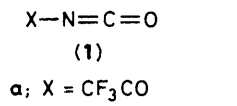
Condensation of the title isocyanates with olefins and subsequent dissolving-metal reduction (sulphonyl derivatives) or chromatography on Florisil (trifluoroacetyl derivatives) gave several *N*-unsubstituted β-lactams including two 8-aza-2-oxabicyclo[4.2.0]octan-7-one derivatives.

Chlorosulphonyl isocyanate (CSI) has been widely used for the preparation of β-lactams by reaction with olefins followed by mildly reductive dechlorosulphonylation.[1] For example, the synthetically versatile[2] 4-acetoxyazetidin-2-one is thus readily available from vinyl acetate albeit in modest yield.[3] However, CSI has several limitations including the failure to convert vinyl ethers directly into 4-alkoxyazetidin-2-ones.[4] Such a transformation would be of use in the concise synthesis of oxacephems and related systems. Recently, Ganem has reported a novel β-lactam synthesis which involved the halogen-mediated cyclisation of *N*-toluene-4-sulphonyl- and *N*-2,2,2-trichloroethoxysulphonyl-but-3-enamides.[5] In con-

Table 1

Entry[a]	Isocyanate	Olefin	β-Lactam (%, m.p.)	Other product (%, m.p.)	Deprotection step[b] β-Lactam (%, m.p.)	Deprotection step[b] Other product (%, m.p.)
1	(**1a**)	(**2a**)	—	(**3**) (63, 95 °C)	—	—
2	(**1b**)	(**2a**)	—	(**4a**) (87, 123—125 °C)	—	—
3	(**1c**)	(**2a**)	—	(**4b**) (78, 132—133 °C)	—	—
4	(**1a**)	(**2b**)	(**5d**)[c]	—	(**5a**) (61, 45—48 °C)	—
5	(**1a**)	(**2c**)	(**5e**)[c]	—	(**5b**) (40, 95—99 °C)	—
6	(**1b**)	(**6a**)	(**8a**) (89, 135 °C)	—	(**8c**) (22, oil)	(**11**) (71, 146—148 °C)
7	(**1c**)	(**6a**)	(**8b**) (99, 137 °C)	—	(**8c**) (29, oil)	(**11**) (9)
8	(**1c**)	(**6b**)	(**10a**) (67, 149—151 °C)	—	(**10b**) (42, 155—157 °C)	—
9	(**1c**)	(**7**)	(**9a**) (60, 102—104 °C)	—	(**9b**) (98, 105 °C)	—

[a] The isocyanate olefin condensations were carried out at room temperature in chloroform (entries 1—6), carbon tetrachloride (7), diethyl ether (8), or diethyl ether at reflux (9). [b] The deprotection reactions were carried out using Florisil and diethyl ether (entries 4,5); zinc dust and ammonium chloride in aqueous tetrahydrofuran (THF) (6,7) or zinc–copper couple in dry THF (8,9). [c] The intermediate β-lactams were not isolated but directly deprotected.

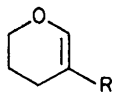


(**1**)

a; X = CF_3CO

b; X = $CCl_3CH_2SO_2$

c; X = $CCl_3CH_2OSO_2$

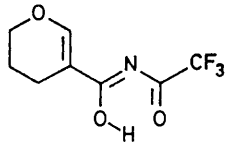


(**2**)

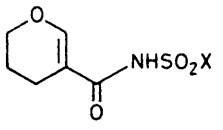
a; R = H

b; R = Me

c; R = $PhCH_2$



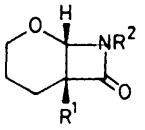
(**3**)



(**4**)

a; X = CCl_3CH_2

b; X = CCl_3CH_2O



(**5**)

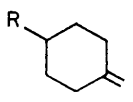
a; R^1 = Me, R^2 = H

b; R^1 = $PhCH_2$, R^2 = H

c; R^1 = H, R^2 = Ts

d; R^1 = Me, R^2 = CF_3CO

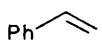
e; R^1 = $PhCH_2$, R^2 = CF_3CO



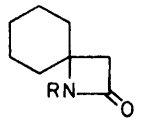
(**6**)

a; R = H

b; R = Ph



(**7**)

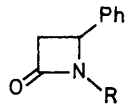


(**8**)

a; R = $CCl_3CH_2SO_2$

b; R = $CCl_3CH_2OSO_2$

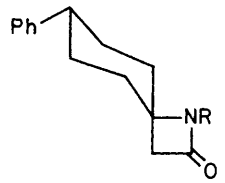
c; R = H



(**9**)

a; R = $CCl_3CH_2OSO_2$

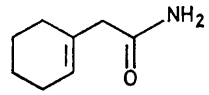
b; R = H



(**10**)

a; R = $CCl_3CH_2OSO_2$

b; R = H



(**11**)

nection with the design of CSI surrogates we have had occasion to study the preparation and reactions of 1-(2,2,2-trichloroethoxysulphonyl)azetidin-2-one derivatives and related β-lactams. Herein we report our preliminary observations.

Isocyanates that are used for β-lactam synthesis must satisfy two criteria: the *N*-substituent must be electron-withdrawing to permit cycloaddition[1,6] and also must be readily removable under mild conditions. In this context we have examined the condensation reactions of trifluoroacetyl,[7] 2,2,2-trichloroethylsulphonyl, and 2,2,2-trichloroethoxysulphonyl[8] isocyanates (**1a**, **b**, and **c**) with olefins. We considered that after cycloaddition the *N*-substituent should be readily removable using Florisil[9] for the β-lactams derived from (**1a**) or by dissolving metal reduction for those from (**1b** or **c**).

The hitherto unknown isocyanate (**1b**)† was prepared from *N*-2,2,2-trichloroethylsulphonamide[10] by reaction with n-butyl isocyanate and aluminium chloride in nitrobenzene followed by phosgene in chlorobenzene at 120 °C (56%). The isocyanates (**1a**, **b**, and **c**) were condensed with several olefins (Table 1). Dihydropyran (**2a**) reacted with (**1a**, **b**, and **c**) to give the α,β-unsaturated amides (**3**) and (**4a** and **b**);[11] no β-lactam was isolated. However, the substituted dihydropyrans (**2b** and **c**) reacted smoothly with trifluoroacetyl isocyanate to give, after chromatography of the reaction mixture on Florisil in diethyl ether solution, the required β-lactams (**5a** and **b**). Although toluene-4-sulphonyl isocyanate has previously been condensed with dihydropyran (**2a**) giving the bicyclic β-lactam (**5c**)[12] *N*-deprotection could not be achieved. In contrast, trifluoroacetyl isocyanate provides a convenient entry to the *N*-unsubstituted 8-aza-2-oxabicyclo[4.2.0]octan-7-one (**5**, R^2 = H) system.

The isocyanates (**1b** and **c**) condensed cleanly and in good yield with methylenecyclohexane (**6a**), 4-phenylmethylenecyclohexane (**6b**), and styrene (**7**) to give the β-lactams (**8a** and **b**), (**9a**), and (**10a**). Reduction of these using either zinc dust or zinc–copper couple gave the desulphonylated β-lactams (**8c**),[13] (**9b**),[14] and (**10b**), albeit in modest yields (Table 1). The β,γ-

† All new compounds were fully characterised by spectral data and microanalyses. The isocyanate (**1b**) was microanalysed as *N*-methoxycarbonyl-*N*-2,2,2-trichloroethylsulphonamide, m.p. 108 °C, produced from (**1b**) and methanol (99%).

unsaturated amide (**11**) was formed in addition to (**8c**) on the reduction of both β-lactams (**8a** and **b**).

Clearly, trifluoroacetyl isocyanate (**1a**) and the sulphonyl isocyanates (**1b** and **c**) are convenient reagents for β-lactam synthesis. The isocyanate (**1a**) is especially useful for the preparation of the sensitive products (**5a** and **b**). We have yet to apply this reagent (**1a**) for the synthesis of β-lactams from acyclic vinyl ethers.

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