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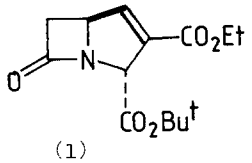
O- VERSUS N-METHANESULPHONYLATION AND N-(METHANESULPHONYL)-METHANESULPHONYLATION WITH METHANESULPHONYL CHLORIDE

Richard J. Stoodley* and Andrew Whiting

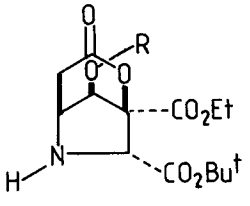
Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU

Summary: Depending upon the experimental conditions, t-butyl (1SR,5SR,7RS,8RS)-1-ethoxycarbonyl-8-hydroxy-2-oxa-6-azabicyclo[3.2.0]octane-7-carboxylate (2a) reacts with methanesulphonyl chloride to give predominantly the O-methanesulphonyl derivative (2b), the N-methanesulphonyl derivative (3a), or the N-(methanesulphonyl)methanesulphonyl derivative (6a).

Recently, we reported[1] that the carbapenem (1) (as a racemate) was converted into the oxazabicyclo-octane (2a) by the action of osmium (VIII) oxide. In the course of chemical studies, the reaction of the compound (2a) with methanesulphonyl chloride was examined. The results, which are now presented, reveal that considerable selection can be achieved in the O- versus N-methanesulphonylation of this compound; furthermore, predominant N-(methanesulphonyl)methanesulphonylation can also be effected.



(1)



(2)

a; R = H

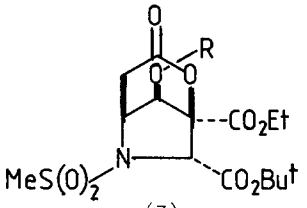
b; R = $S(O)_2Me$

c; R = $S(O)_2CH_2S(O)_2Me$

When treated in dichloromethane at 0°C with methanesulphonyl chloride (2 mol. equiv.) followed by triethylamine (2 mol. equiv.), the oxazabicyclo-octane (2a) was converted mainly into two products which were separated by silica-gel chromatography. The minor product (6% yield after recrystallisation, m.p. 122-123°C, was designated compound A. The major product (51% yield after recrystallisation), m.p. 122-124°C, was a methanesulphonyl derivative on the basis of its analytical and spectroscopic properties.

An unambiguous assignment of the structure of the last-cited compound, i.e. (2b) or (3a), was not feasible by 360 MHz ^{1}H-n.m.r. spectroscopy [δ ($CDCl_3$) inter alia 3.29 (3 H, s), 3.87

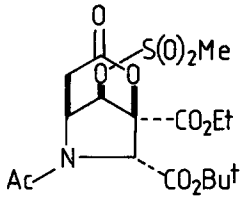
(1 H, s), 4.39 - 4.44 (1 H, m), and 5.37 (1 H, d, J 5.5 Hz)]. However, the material was converted (Ac_2O-pyridine) into an acetyl derivative (53% yield after SiO_2 chromatography and recrystallisation), m.p. 148-152°C (decomp.), which showed an amide absorption [$\nu_{max.}$ (KBr) 1 650 cm^{-1}] in the i.r. region. Clearly, the product was the acetamide (4) and therefore the precursor was the methanesulphonate (2b). In accord with this formulation, the methanesulphonate reacted with lead(IV) acetate in dichloromethane to give the oxazabicyclo-octene (5a) (47% yield after recrystallisation), m.p. 137°C. The last-mentioned compound was also obtained (84% yield after SiO_2 chromatography) from the previously described oxazabicyclo-octene (5b)[1] by the action of methanesulphonyl chloride and triethylamine in dichloromethane at 0°C.



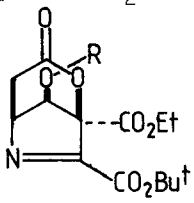
(3)

a; R = H

b; R = $S(O)_2Me$



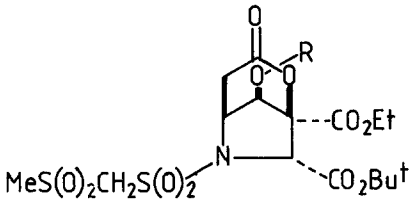
(4)



(5)

a; R = $S(O)_2Me$

b; R = H



(6)

a; R = H

b; R = Ac

c; R = $S(O)_2Me$

When treated in pyridine at 0°C with methanesulphonyl chloride (5 mol. equiv.), the oxazabicyclo-octane (2a) was converted into the methanesulphonamide (3a) (48% yield after recrystallisation), m.p. 145-147°C [δ (360 MHz, $CDCl_3$) 2.99 (3 H, s), 3.76br (1 H, s), 4.41 (1 H, s), 4.76 (1 H, dt, J, 9, 9, and 7 Hz), and 5.47 (1 H, d, J 9 Hz)]. The transformation of the methanesulphonamide (3a) into the bis(methanesulphonyl) derivative (3b) (57% yield after recrystallisation), m.p. 124-126°C, was accomplished by the action of methanesulphonyl chloride and triethylamine in dichloromethane.

Two compounds were produced when methanesulphonyl chloride (2 mol. equiv.) was added to a solution of the oxazabicyclo-octane (2a) in a 1 : 1 mixture of dichloromethane and triethylamine. The minor material, designated compound B, precipitated as a crystalline solid, m.p. 165-167°C,

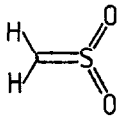
in 15% yield when chloroform was added to the crude product. Following silica-gel purification of the mother liquor, a further quantity of compound B (5% yield) was isolated together with the major component (46% yield), which was identical with the methanesulphonate (2b).

Compound B possessed the constitution $C_{16}H_{25}NO_{11}S_2$, requiring the addition of $C_2H_4O_4S_2$ to the precursor (2a). On the basis of its spectroscopic properties, compound B was formulated as the sulphonate (2c) or the sulphonamide (6a). In particular, 360 MHz ^{1}H-n.m.r. spectroscopy ($CDCl_3$) showed a three-proton singlet at δ 3.22 and two one-proton doublets (J 15 Hz) at δ 4.65 and 4.85 for the $MeS(O)_2CH_2S(O)_2$ moiety and a broad one-proton singlet at δ 3.74 (which disappeared in the presence of D_2O) for the OH or NH proton. Compound B reacted with acetic anhydride in pyridine to give an acetyl derivative (37% yield after recrystallisation), m.p. 112-114°C, which lacked an amide absorption in the i.r. region. Clearly, the product was the acetate (6b) and compound B was the sulphonamide (6a).

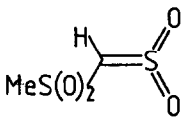
On the basis of its spectroscopic properties, compound A was considered to possess the structure (6c). In particular, the 360 MHz ^{1}H-n.m.r. spectrum ($CDCl_3$) showed signals at δ 3.18 (3 H, s) and 4.85 and 4.96 (each 1 H, d, J 15 Hz) for the $MeS(O)_2CH_2S(O)_2$ moiety and at δ 3.29 (3 H, s) and 5.47 (1 H, d, J 6 Hz) for the $MeS(O)_2OCH$ group. This formulation was corroborated by the finding that compound A was also produced (55% yield after recrystallisation) when the sulphonamide (6a) was treated in dichloromethane with triethylamine and methanesulphonyl chloride.

The aforecited results are of interest in a number of respects. Although *O*-[2] and *N*-methanesulphonylations[3] with methanesulphonyl chloride are well established, we are unaware of any studies in which differentiation between alcohols and amines[4] has been reported. Presumably in the presence of dichloromethane and triethylamine (conditions devised by Crossland and Servis[5]), sulphene (7) is the reactive species whereas, in pyridine, methanesulphonyl chloride is implicated.

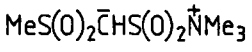
The conversions of the oxazabicyclo-octane (2a) into the sulphonamides (6a) and (6c) represent rare examples of (methanesulphonyl)methanesulphonylations induced by methanesulphonyl chloride and triethylamine. Opitz and his co-workers[6] provided the first examples of this reaction. Thus simple amines and *p*-nitrophenol, when introduced into a mixture ("aged" for 1 h) prepared by the addition of methanesulphonyl chloride (2 mol. equiv.) to a solution of triethylamine (3 mol. equiv.) in acetonitrile at -40°C, were transformed into their (methanesulphonyl)-methanesulphonyl derivatives. The German workers provided evidence for the involvement of the sulphene (8) and indeed were able to isolate a crystalline trimethylamine complex which, presumably, possessed the betaine structure (9).



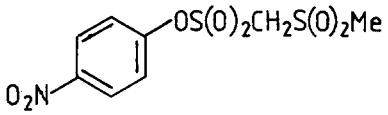
(7)



(8)



(9)



(10)

When subjected to Opitz'z conditions, the oxazabicyclo-octene (2a) was converted into the sulphonamide (6a) (37% yield after recrystallisation). Presumably, the sulphene (8) is implicated in the formation of the compounds (6a) and (6c). A consequence of this interpretation is that the species (7) and (8) discriminate between the alcohol and amino functions of the oxazabicyclo-octene (2a) in an opposite manner. In principle, the (methanesulphonyl)methanesulphonylation of the alcohol function of the compound (2a) is reversible. However, since the oxazabicyclo-octane (2a) was recovered unchanged when left in dichloromethane with the sulphonate (10) and triethylamine, we consider that the reactions leading to the compounds (6a) and (6c) are under kinetic control. Evidently, the alcohol function of the compound (2a) reacts more readily with sulphene (7) whereas its amino group preferentially attacks the sulphene (8).

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References and Footnotes

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