Deacylation of Amides: Removal of the Acyl Side-chain from Cephamycin Derivatives

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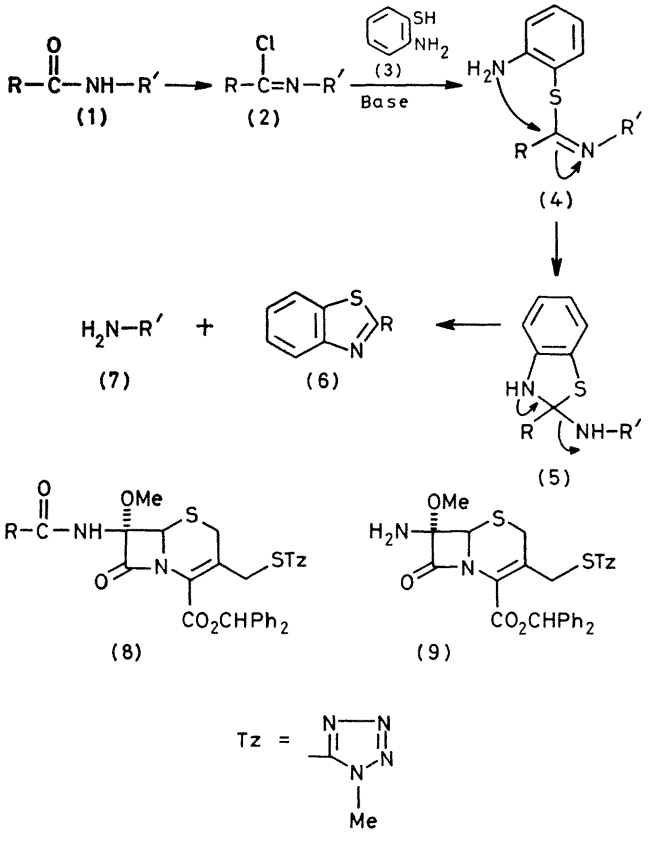
Summary Diphenylmethyl (6*R*,7*S*)-7-amino-7-methoxy-3-{[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl}-Δ^3-cephem-4-carboxylate (**9**) is obtained from a cephamycin C derivative by treatment of an imino chloride intermediate with *o*-aminobenzenethiol

APPLICATION to cephamycin derivatives of methodology that is well established for removal of the *N*-acyl side-chain at C-6(7) in penicillins (cephalosporins), *i e* imino chloride solvolysis, results in epimerization at C-7,[1] although a recent report in the patent literature claims that this epimerization is reduced substantially when the solvolysis is performed at temperatures near -70 °C [2] The imino chloride–methyl cuprate method of Karady *et al* [3] maintains the chirality at C-7 but is accompanied by Δ^3–Δ^2 isomerization The oxalyl chloride method, mentioned only briefly in an application to penicillins[4] but applied by Shiozaki *et al* [5] to cephamycins, is the only one that avoids both epimerization and isomerization We now report a novel method for deacylation of cephamycin derivatives that proceeds without epimerization at C-7 or Δ^3-Δ^2 isomerization



a; R = Pr^n
b; R = $Ph_2CHO_2CCH(NHCO_2Bu^t)[CH_2]_3$

It was reasoned that reaction of an imino chloride (**2**), derived from the corresponding amide, with *o*-aminobenzenethiol (**3**) in the presence of a suitable base should give an imino sulphide (**4**) that could undergo cyclization to the benzothiazoline (**5**). Subsequent base-catalysed elimination would provide the 2-substituted benzothiazole (**6**) and the desired amine (**7**).

Treatment of the *N*-butyramide (**8a**) sequentially with phosgene–pyridine in CH_2Cl_2 (3 h; room temp.) and aqueous $NaHCO_3$ provided, after drying and solvent removal, the corresponding imino chloride [>90%; $CDCl_3$ δ 2·75 (2H, t, $-CH_2-CCl=N$), 3·58 (3H, s, OMe), and 5·03 (1H, s, C-6)]. Reaction of this product in CH_2Cl_2 with 2 equiv. each of (**3**) and pyridine (1·5 h; room temp.) followed by work-up with aqueous $NaHCO_3$ and preparative t.l.c. on silica gel (Quantum PQ1F or Whatman PK1F) using CH_2Cl_2–EtOAc (9 : 1) afforded the 7α-methoxy amine (**9**)[6] (15%), the benzothiazole (**6a**)[7] (45%), and (**8a**) (23%).† Similar treatment of the cephamycin derivative (**8b**)[8] provided the corresponding isolated imino chloride [>90%, CD_2Cl_2 δ 2·73 (2H, t, $-CH_2-CCl=N-$), 3·48 (3H, s, OMe), and 5·00 (1H, s, C-6)] and subsequently (**9**) (20—25%) and (**6b**) {30—35%, m.p. 113—114 °C, $[\alpha]_D$ +4° (*c* 0·205, $CHCl_3$)}. In both examples, no products derived by epimerization at C-7 or isomerization of the Δ^3 double bond were observed. Substitution of *o*-aminophenol or *o*-phenylenediamine for (**3**) provided little, if any, of the desired products.

This sequence represents a novel, alternative method for *N*-deacylation of cephamycin derivatives. The yields given here do not represent optimized ones for these reactions.

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† Compounds (**6a**) and (**9**) were identified by comparisons (^1H n.m.r., i.r., t.l.c.) with authentic samples.

‡ Compound (**6b**) gave satisfactory spectral data and elemental analysis.

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