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THE CHEMISTRY OF CEPHAMYCINS. IV. ACYLATION OF AMIDES IN THE PRESENCE OF NEUTRAL ACID SCAVENGERS

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The art of amide acylation advanced very little in this century. The statement of Titherly[1] in 1904, "No single method has even approximately the character of a general method," probably still holds. Over the years, the reaction of primary amides was subject to numerous studies while secondary amides received only marginal attention[2]. We were interested in acylating sensitive cephalosporin derivatives with base sensitive acid chlorides under mild conditions. High temperature[1,3], strong acid catalyzed[4] and base catalyzed[1,5] reactions commonly used, were unsuitable for our purposes. The mild conditions required for the reaction of silylamides with acid chlorides[6] were attractive, but this method also failed in our case[7]. Consequently, we undertook the development of a new method suitable for the mild acylation of acid and base sensitive amides. In an earlier publication we have reported the use of this method for the transacylation of cephamycin derivatives[7]. In this paper we present the scope of this acylation reaction.

It is not generally known that acid chlorides react with secondary amides in non-polar solvents at a moderate rate under mild conditions. The initial reaction, however, is halted by the accumulation of HCl which protonates the amide and gives rise to cleavage reactions 2→1 and 2→3 or excessive degradation when sensitive amides are employed.

$$\underset{\underline{1}}{\text{RCONHR'}} + \text{R''COCl} \underset{\text{HCl}}{\rightleftharpoons} \underset{\underline{2}}{\overset{\text{R'}}{\text{RCONCOR''}}} \overset{\text{HCl}}{\rightleftharpoons} \underset{\underline{3}}{\text{R''CONHR'}}$$

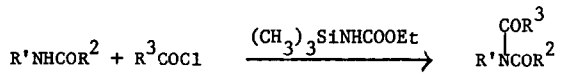
When the generated HCl is removed by a neutral acid scavenger the reaction can be carried to completion under mild, essentially neutral conditions. We find that negatively substituted

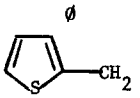
silyl amides and powdered molecular sieves are well suited as neutral acid acceptors. These substances, unlike the pyridine bases and tertiary amines, have no effect on the initial rate (ca. 5-10% of completion) but only affect the position of equilibrium.

Negatively substituted silyl amides react rapidly with HCl to form an amide (negatively substituted so as not to acylate competitively) and trimethylchlorosilane which is compatible with most acid sensitive functions. Secondary amides are acylated in good yield by overnight refluxing in methylene chloride with 2-4 molar excess of the acid chloride and trimethylsilyl trifluoroacetamide or trimethylsilyl urethane. As we previously demonstrated, the method is suitable for the selective acylation of β-lactam antibiotics with base sensitive acid chloride (e.g., thienylacetyl chloride) but the scope and limitations are best demonstrated on simple model compounds.

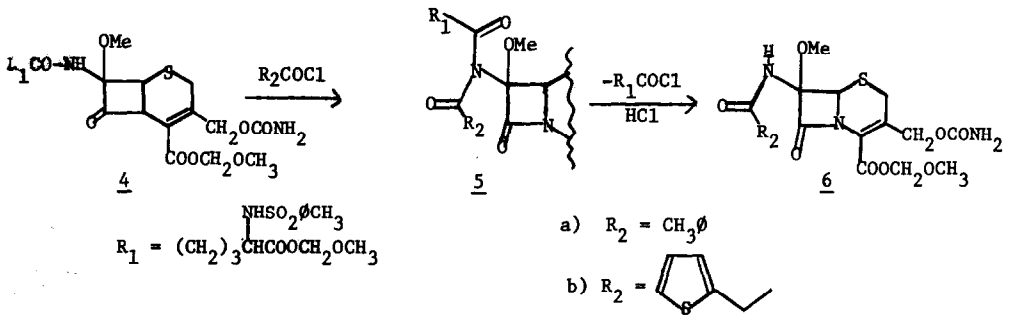
Table I shows that secondary aliphatic and aromatic amides or anilides can be readily acylated by either aliphatic or aromatic acid chlorides. The method is not applicable to primary amides which give poor yields of amides in competition with nitrile formation.

TABLE I



R^1	R^2	R^3	Yield (%)
i-pr	CH_3	ø	53
i-pr	ø	CH_3	96
ø	CH_3	CH_3	77
ø	CH_3	ø	95
i-pr	CH_3		55
R^1-R^2 = $-(CH_2)_5-$		ø	90

An important feature of this reaction is its selectivity. Negatively substituted amides such as trifluoroacetylamides, tosylamides of urethanes react very slowly in comparison with normal secondary amides. These groups therefore can be used as nitrogen protecting groups as illustrated by conversion 4→5.



Cephamycin derivative 4 was converted cleanly to imide 5a by reaction in dichloroethane for 20 hours. The product after quick chromatography[9] showed nmr ($CDCl_2$) δ 1.7 (br.s., $COCH_2$-CH_2-CH_2), 2.4 (br.s., O=C-CH_2-CH_2 and $CH_3\phi$), 3.3 (s, CH_2-OCH_3), 3.5 (m, -OCH_3, and S-CH_2), 3.7 (s, CH_2OCH_3), 5.0 (br.s. CH_2OCH_3 and CH_2OCONH_2), 5.2 (s, C_6H), 5.4 (br.s. CH_2OCH_3 and $CONH_2$), 5.9 (d.J = 8 H_2, -NH-TOS), 7.2-8.1 two A_2B_2 systems of aromatic protons) Cleavage with 0.01N HCl in EtOAc and MeOH for 16 hr at 65° afforded 6a nmr ($CDCl_3$) 3.5 (s and d C_7-OCH_3 and S-CH_2), 3.6 (s, CH_2OCH_3), 4.95 (br.d., CH_2OCO), 5.18 (s, C_6-H), 5.4 (s, CH_2OCH_3) 7.2-8.0 (A_2B_2 system of aromatic protons.

Similar reaction with thienylacetyl chloride afforded imide 5b which exhibited nmr spectrum similar to that of 5a except δ 4.15 (s, C_4H_3S-CH_2), 7.0 and 7.3 (m, C_4H_3S). Cleavage of this imide with 0.01N HCl at 65° for three hours afforded equal proportions of 4 and the methoxymethyl ester of cefoxitin (6b)[8].

In contrast to these clean conversions of 4→5, acylations using collidine as an HCl acceptor gave a tarry complex mixture of products resulting from non-selective acylation of the nitrogen functions accompanied by extensive Δ3→Δ2 double-bond isomerization. In absence of an acid acceptor complete destruction of 4 resulted.

An alternate method for the removal of HCl in these acylations involves the use of powdered typa 4A Molecular Sieves (600 mesh). Since the pore size of this substance is ca. 4Å it is capable of absorbing and neutralizing HCl but is completely without effect on the base sensitive amide 4 and arylacetyl chlorides. Thus reaction of 4 at 60° for nine hours in ethylene dichloride with four molar equivalents of thienylacetyl chloride in presence of 4.5 g powdered type 4A Molecular Sieve per mmole of 4 produces the imide 5b in 90% yield.

When partially hydrated Molecular Sieves were used (17% H_2O, 700 mg/mole of 4a), the same reaction yielded 6b directly in over 60% yield. In this case, the generated HCl is only partially absorbed and the equilibrium between the components results in the direct transacylation of 4 to 6b.

Previously Molecular Sieves found use in affecting equilibrium reactions where water (10) and methanol (11) were removed. To our knowledge this is the first application of Molecular Sieves in displacing an equilibrium reaction by absorption of HCl.

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