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A NEW APPROACH TO THE SYNTHESIS OF AMINO IMIDAZOLES APPLICATION TO THE CEPHALOSPORIN SERIES

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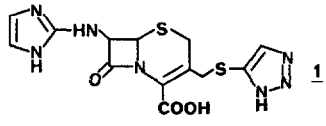
Summary : A new, mild approach to amino imidazole 10 starting from the silylated carbodiimide 9 and weakly basic amine 12 is described.

In the course of our work on cephalosporins with novel C-7 heterocyclic substituents, we discovered that the amino imidazole substituent led to compounds possessing particularly interesting biological properties[1]. Cephalosporin 1, a potent, β-lactamase stable, orally active compound, was thus selected for extensive biological studies.



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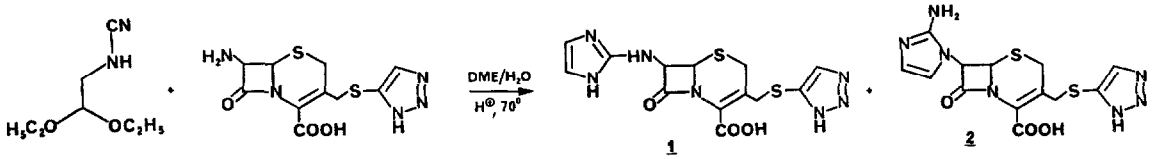
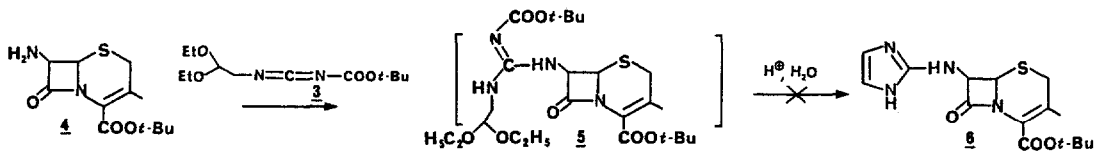
A number of approaches to 2-amino imidazoles are known in the literature[2] ; only two proved applicable in the cephalosporin series : the reaction of 2-fluoro imidazoles with 7-amino cephalosporanates, and the condensation of the cyanamide of amino acetaldehyde diethyl acetal with 7-ACA in acidic conditions. However both reactions gave only low yields of 1, the cyanamide approach leading in addition to significant amounts of the isomeric 2-amino imidazole 2[12] which proved difficult to separate from the desired 2-amino imidazole 1[12].

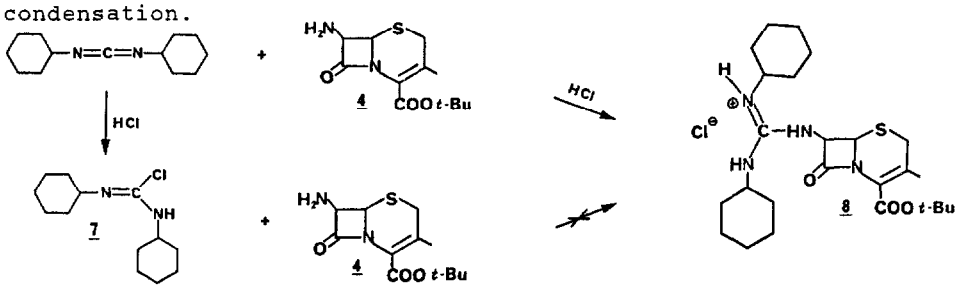


1 2

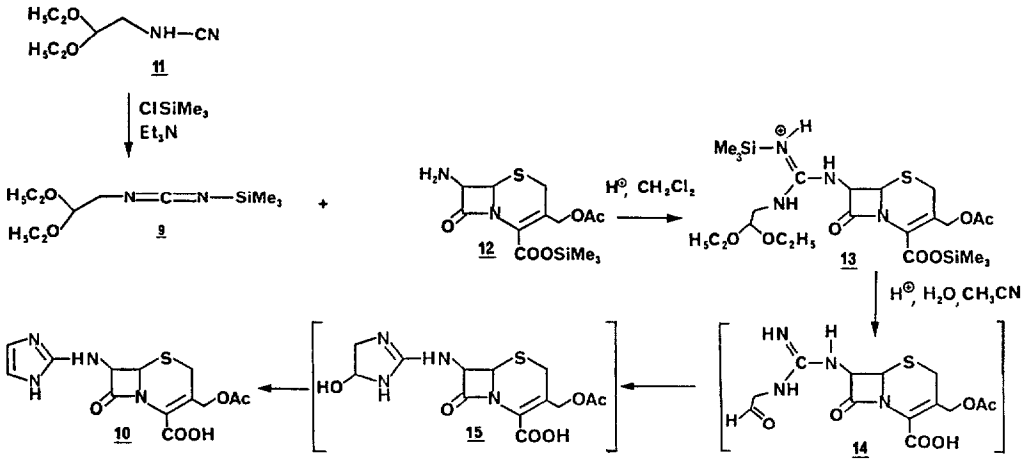
Carbodiimide chemistry was investigated next as a potentially useful approach to these compounds. Carbodiimides substituted by electron withdrawing groups are known to be very reactive electrophiles[3]. We have synthesized *in situ* carbodiimide 3[3,10] and have found that it condenses easily with 7-amino cephalosporin ester 4 at 0°C in CH_2Cl_2, to give the open chain guanidine 5 which possesses all the required structural features for a later transformation into an amino imidazole group. Unfortunately this molecule proved unstable and could not be successfully deprotected in reasonable yield and cyclized to the amino imidazole 6.



In general, carbodiimides do not condense easily with amines except under vigorous conditions[4,5]. A few carbodiimidium salts are known, and, not surprisingly, they display a high reactivity towards nucleophiles[6]. It has also been reported that carbodiimides can be condensed, under acid catalysis, with amines of low pKa[7]. The reactive species here again is probably a charged carbodiimidium salt[7]. 7-Amino cephalosporanates, pKa = 4.5, fall into the category of weakly basic amines and might therefore condense with carbodiimides under similar conditions. In a model experiment we have indeed been able to condense DCCI with a 7-ACA ester 4 in the presence of hydrogen chloride in CH_2Cl_2 at R.T. to give 8[12]. Under these conditions hydrogen chloride can add to DCCI to give the chloroformamidine 7[11] which can react fairly easily with primary and secondary amines to give the corresponding guanidine[8]. We have also been able to show that this putative intermediate 7, prepared independently[11], is in fact not an intermediate in the condensation, since no reaction between 7 and 4 occurs under these conditions. Not surprisingly in the absence of acid, no reaction occurs between 4 and DCCI. The protonated carbodiimide is therefore most probably the reactive intermediate in the condensation.



We then turned our attention to the silylated carbodiimide 9 which is the ideal intermediate towards the synthesis of amino imidazole 10. In fact, the silylated carbodiimide 9[12] is a stable, distillable (Bp 70° / 0.03 mm Hg) liquid, which was easily prepared from cyanamide 11 by reaction with trimethylsilyl chloride in THF in the presence of triethylamine[4,9]. As with DCCI, it can be condensed with the silylated ester of 7-ACA 12 in the presence of a strong acid (CF_3SO_3H, H_2SO_4, etc.) in anhydrous CH_2Cl_2 to give the silylated open chain guanidine 13[12]. Treatment of this intermediate with concentrated HCl (12 N) 1 eq., at R.T. for 4 hours in CH_3CN gives the amino imidazole 10[12] probably via the intermediates 14 and 15 which have not been isolated.



In conclusion, the above process provides for an efficient (>60% yield), one pot synthesis of 10[1], a key intermediate for the development compound 1 on an industrial scale. We also believe that other amino imidazoles should be easily accessible from weakly basic amines by this procedure.

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(1) - Biological properties of these compounds will be published elsewhere, see also the preceding paper.

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(10) - 3 was obtained from the corresponding thiourea by reaction with yellow mercuric chloride, sulfur, in acetonitrile, in the presence of 4 to give directly the fairly unstable cephalosporin 5.
^{1}H-NMR, 90 MHz, $CDCl_3$, δ ppm : 1.1, t (J = 7.2 Hz), 6H ; 1.4, s, 18H ; 2.04, s, 3H ; 3.1-3.8, m, 8H ; 4.34, d (J = 4 Hz), 1H ; 4.6, dd (J = 4 Hz, 7.7 Hz), 1H ; 4.86, t (J = 6 Hz), 1H. IR, KBr : 1770, 1720, 1620 cm^{-1}.

(11) - Obtained by addition of one equivalent of HCl to a solution of DCCI in $CHCl_3$ at R.T.

(12) 1 Anal. C, H, N, S. ^{1}H-NMR, 90 MHz, DMSO d_6, TFA d, δ ppm : 3.51, 3.74, AB (J = 18.5 Hz), 2H ; 3.88, 4.08, AB (J = 12.8 Hz), 2H ; 5.1, 5.5, AB (J = 4.3 Hz) ; 7.08, s, 2H ; 7.87, s, 1H. IR, KBr : 1770, 1680 cm^{-1}.

2 ^{1}H-NMR, 90 MHz, DMSO d_6, CD_3COOD, δ ppm : 3.43, 3.8, AB (J = 19.2 Hz), 2H ; 3.95, 4.2, AB (J = 13.6 Hz), 2H ; 5.17, 6.05, AB (J = 4.6 Hz), 2H ; 6.7, 6.8, AB (J = 2.7 Hz), 2H ; 7.8, s, 1H.

8 ^{1}H-NMR, 90 MHz, DMSO d_6, TFA d, δ ppm : 0.7-2, m, 20H ; 1.45, s, 9H ; 1.95, s, 3H ; 3.2-3.8, m, 4H ; 5.15, 5.65, AB (J = 4.5 Hz), 2H. IR, KBr : 1760, 1720, 1635, 1610 cm^{-1}.

9 ^{1}H-NMR, 90 MHz, $CDCl_3$, δ ppm : 0.2, s, 9H ; 1.2, t (J = 7 Hz), 6H ; 3.24, d (J = 5 Hz), 2H ; 3.4-3.8, m, 4H ; 4.5, t (J = 5 Hz), 1H. IR, CH_2Cl_2 : 2170 cm^{-1}.

10 Anal. C, H, N, S. ^{1}H-NMR, 90 MHz, DMSO d_6, TFA d, δ ppm : 2.0, s, 3H ; 3.45, 3.65, AB (J = 19.2 Hz), 2H ; 4.74, 5.06, AB (J = 12.8 Hz), 2H ; 5.2, 5.6, AB (J = 4.4 Hz), 2H ; 7.04, s, 2H. IR, KBr : 1780, 1735, 1660 cm^{-1}.

13 ^{1}H-NMR, 90 MHz, $CDCl_3$, δ ppm : 0, s, 9H ; 0.25, s, 9H ; 1.05, t (J = 6.4 Hz), 6H ; 1.95, s, 3H ; 3.0-3.8, m, 8H ; 4.45, t (J = 3.8 Hz), 1H ; 4.8, 5.15, AB (J = 14 Hz), 2H ; 5.15, d (J = 4.5 Hz), 1H ; 5.5, dd (J = 4.5 Hz, 7.7 Hz), 1H. IR, CH_2Cl_2 : 1785, 1735, 1700, 1670 cm^{-1}.

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