ON THE MECHANISM OF THE ONE-POT CONVERSION OF 4-CARBOMETHOXY-5-HYDROXYIMIDAZOLES INTO 5-AMINO-4-CARBAMOYLIMIDAZOLES

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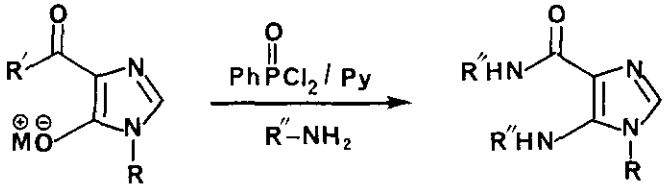
Abstract — A mechanism is proposed for the one-pot conversion of 4-carbomethoxy-5-hydroxyimidazoles into the corresponding 5-*amino*-4-*carbamoylimidazoles*.

We have recently reported[1] the synthesis and properties of several ammonium salts of 1-substituted 4-carbomethoxy-5-hydroxyimidazoles (1; R=H or alkyl, R'-OMe, M=RNH_3) which bear significance as metabolites in the biological degradation of xanthine to N-(iminomethyl)glycine[2,3] and as analogues of the naturally occurring potent antiviral nucleoside, *bredinin* (1; R=β-D-ribofuranosyl, R'=NH_2, M=H).[4] We have also reported[1] their one-pot conversion into 5-amino-4-carbamoylimidazoles (2) which are important as precursors to the ubiquitous natural products xanthine, guanine, hypoxanthine and their derivatives. We now wish to propose a mechanism for this conversion based on the gathered experimental evidence. The key reagent in this transformation is phenylphosphonic dichloride and the representative conversions that were carried out[1] are from 1a(R=CH_2Ph, R'=OMe and M=$PhCH_2NH_3$) to 2a(R=R''=CH_2Ph) and from 1b(R=CH_3, R'=OMe and M=CH_3NH_3) to 2b(R=CH_3, R''=CH_2Ph). Thus, the reaction of 1a or 1b (1 milliequiv.) with phenylphosphonic dichloride (1-2 milliequiv.) in pyridine (5 mL) at 115-130°C under N_2 for 15-20 minutes, followed by treatment of the resultant dark brown solution with benzylamine gave 2a and 2b, respectively.

An attempt to elucidate the mechanism of the above conversion led to the following observations: (a) The reaction of 1a with primary amines, without the use of $PhP(O)Cl_2$, resulted in the recovery of the starting materials despite employing vigorous reaction conditions, e.g. heating at 160-180°C



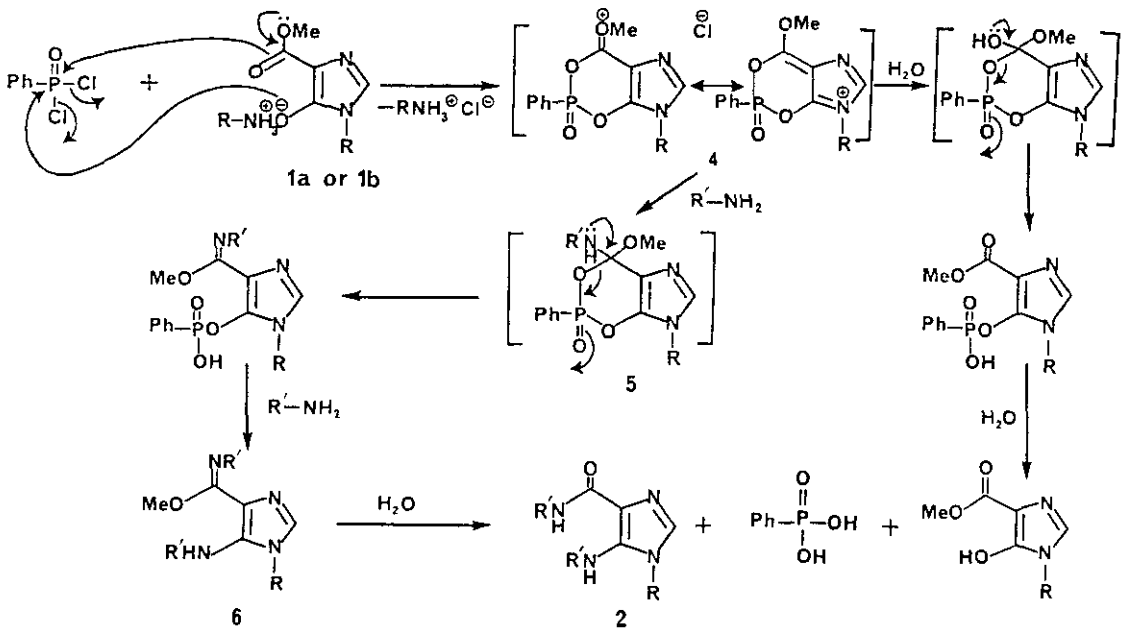
1 2

in a stainless steel bomb, (b) replacing $PhP(O)Cl_2$ with $POCl_3$ yielded an intractable mixture of products, (c) only one equivalent of the reagent need be employed for the reaction to proceed although an equivalent in excess had no adverse effect on the product yield, (d) a brief preheating of 1a with $PhP(O)Cl_2$ in pyridine at 115-130°C, before the addition of benzylamine, was crucial as the simple mixing and heating of all the reactants together provided only the product of the latter two reactants, i.e. phenylphosphonic di(N-benzyl)amide (3) $[PhP(O)(NHCH_2Ph)_2]$,[1] (e) separate reactions of 3 with 1a, under a variety of experimental conditions, failed to produce 2a indicating that 3 is not an intermediate in the above conversion, (f) the reactions of 1 salts (M=RNH_3, R'=OMe) with $PhP(O)Cl_2$/pyridine, followed by aqueous work-up afforded the corresponding parent hydroxy compounds (M=H, R'-OMe), (g) the conversion from 1 to 2 could also be effected by using the above parent compounds, in comparable yields.

Based on the above observations, we propose the following mechanism for the title conversion (see Scheme I): The nucleophilic displacement of 1a or 1b on $PhP(O)Cl_2$ yields the intermediate 4 which upon reaction with excess primary amine decomposes into the amino-imidate 6. Subsequent aqueous work-up yields the final amino-amide 2. Hydrolysis of 4 similarly yields the parent hydroxy-ester compounds.

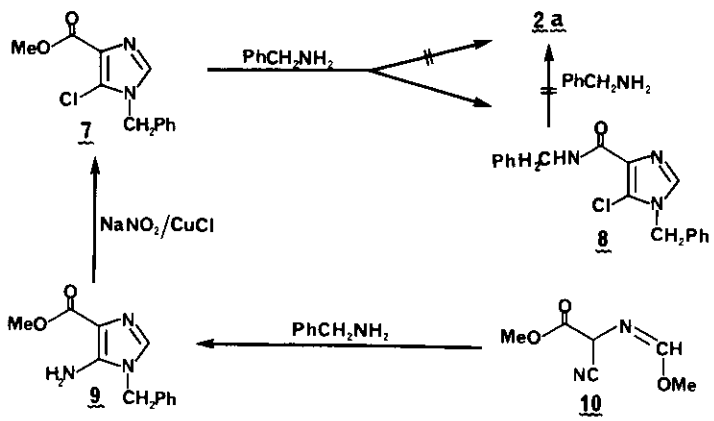
Since $PhP(O)Cl_2$ has been employed to replace a hydroxyl group by a chlorine atom in nitrogen heterocycles,[6] an alternative mechanism involving 1-benzyl-5-chloro-4-carbomethoxyimidazole (7) as

Scheme I



an intermediate was also considered. Therefore, compound 7 was prepared (Scheme II)[7] and subjected to reaction with benzylamine at reflux (b.p. 185°C) for several hours.

Scheme II



However, the only product that formed in this reaction was 1-benzyl-4-(N-benzyl)carbamoyl-5-chloroimidazole (8) [mp 137-138°C; ^{1}H NMR (Me_2SO-d_6) δ 4.38 (d, $J_{CH_2,NH}$ = 6.4 Hz, 2, side-chain CH_2), 5.26 (s, 2, ring CH_2), 7.4-7.27 (m, 10, two Ph), 8.05 (s, 1, imidazole CH), 8.5 (t, J_{NH,CH_2} = 6.4 Hz, 1, NH, exchangeable with D_2O); Anal.[5] C,H,N]. A separate reaction of 8 with benzylamine failed to produce 2a even after 14 hours at reflux.

The title conversion constitutes a facile general procedure for the preparation of various 1-substituted 5-(N-substituted)amino-4-(N-substituted)imidazole carboxamides which are the analogues of the de novo purine biosynthetic precursor AICAR: aminoimidazolecarboxamide ribotide (2; R=1-β-D-ribofuranosyl-5'-phosphate, R'=H).[8] The reaction also carries broad implications of versatility to other heterocyclic systems bearing vinylogous hydroxy-ester functions.

ACKNOWLEDGEMENTS

We express our thanks to a) the National Institutes of Health (Grant #CA 36154) and b) the Donors of the Petroleum Research Fund (Grant #14499-GB1), administered by the American Chemical Society, for the support of this research. We are indebted to Professor Patrick Callery of the University of Maryland at Baltimore for the mass spectral data.

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7. Compound 7 [mp 87-88°C; ^{1}H NMR (Me_2SO-d_6) δ 3.77 (s, 3, OMe), 5.30 (s, 2, CH_2), 7.35-7.26 (m, 5, Ph), 8.08 (s, 1, imidazole CH); mass spectrum (70 eV) m/e (relative intensity) 252 (M^++2, 4.68%), 250 (M^+, 15.24), 219 (M^+-OMe, 2.03), 91 ($^+CH_2Ph$, 100); Anal.[5] C,H,N] was prepared in 46% yield from the reaction of 5-amino-1-benzyl-4-carbomethoxyimidazole (9) with $NaNO_2$/CuCl, employing the procedure reported for the corresponding ethyl ester.[9] Compound 9 [mp 164-165°C; ^{1}H NMR (Me_2SO-d_6) δ 3.67 (s, 3, OMe), 5.10 (s, 2, CH_2), 6.07 (br, 2, NH_2, exchangeable with D_2O), 7.35-7.21 (m, 6, Ph+imidazole CH); Anal.[5] C,H,N], in turn, was analogously prepared[9] in 40% yield from the reaction of benzylamine with the reagent, methyl N-(α-carbomethoxy-α-cyano)methylmethanimidate (10) [distilled in a Kügelröhr apparatus at 105°C (oven temperature/ 0.15 mm/Hg; ^{1}H NMR (Me_2SO-d_6) δ 8.01 (s, 1, imidate CH), 5.62 (s, 1, CH), 3.80 (s, 3, ester OMe), 3.72 (s, 3, imidate OMe)], prepared from the reaction of methyl α-amino-α-cyanoacetate[10] with trimethyl orthoformate.

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Received, 17th June, 1985