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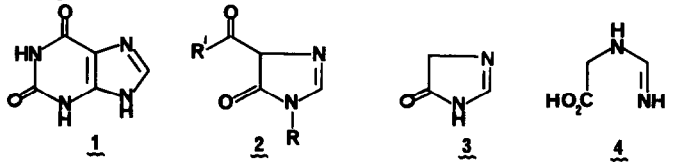
A GENERAL METHOD FOR THE SYNTHESIS OF 1-SUBSTITUTED (OR UNSUBSTITUTED)-4-CARBOMETHOXY-2-IMIDAZOLIN-5-ONES

Ramachandra S. Hosmane* and Benjamin B. Lim

Laboratory for Chemical Dynamics
Department of Chemistry, University of Maryland Baltimore County
Catonsville, Maryland 21228

A general method for the synthesis of the title compounds by employing the reagent methyl N-(dicarbomethoxymethyl)methanimidate is described. The preparation, properties and reactions of the reagent are also reported.

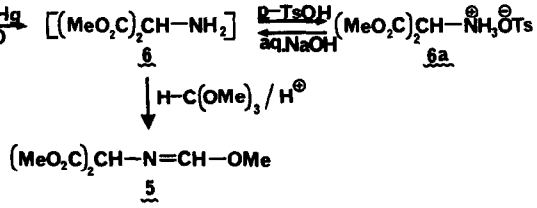
The proposed pathway for the biological degradation of xanthine (1) to *N*-(iminomethyl)glycine (4) involves the intermediacy of 2-imidazolin-4(5)-one (3).[1,2] Imidazolinones bearing the general structure 2 are important as a) intermediate catabolites between 1 and 3 in the above pathway, b) labile entities in the microbial degradation of a variety of imidazole derivatives,[3] and c) analogues of the naturally occurring potent antiviral/antitumor nucleoside, bredinin (2, R=β-D-ribofuranosyl, R'=NH_2).[4] Surprisingly, however, little has been reported on the synthesis



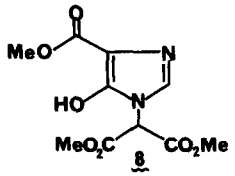
and reactions of imidazolinones. For example, the laboratory synthesis of 3 has been achieved only recently,[5] and the only known synthesis of 2(R=H, R'=OEt) is reported to occur in poor yield and is not general.[6] We report here a general procedure for the synthesis of a variety of 1-substituted 4-carbomethoxy-2-imidazolin-5-ones (2; R=H or alkyl, R'=OMe) by exploring the use of an imidic acid ester. This is a further demonstration of the versatility of this class of reagents for organic/bio-organic syntheses.[7]

The desired reagent methyl *N*-(dicarbomethoxymethyl)methanimidate (5), which would permit the incorporation of a synthetic fragment C-N-C(CO_2Me)-CO- onto nucleophiles in a single step, was prepared by the slow dropwise addition of dimethyl aminomalonate (6) to a large excess of refluxing trimethyl orthoformate, containing catalytic amounts of trifluoroacetic acid. The amine (6), in turn, was obtained from dimethyl isonitrosomalonate (7) by convenient reduction with aluminum-amalgam instead of the reported catalytic hydrogenation at 1800 psi.[8] Since 6 is unstable, it was stored as a stable, crystalline salt of *p*-toluenesulfonic acid (6a) and was regenerated, as necessary, upon treatment with aqueous sodium hydroxide. The reagent 5 was distilled as a colorless liquid from a Kügelrohr apparatus [85°-95°C (oven temp)/(0.5 mm Hg] in 51% yield, and was stable

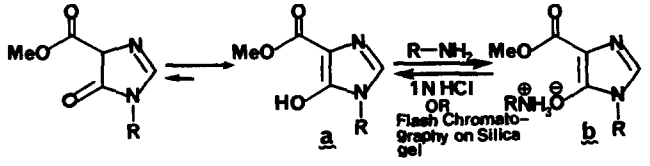
in a refrigerator, free of moisture, for several months; ^{1}H NMR (DMSO-d_6) δ 3.68 (s, 3, imidate CH_3), 3.71 (s, 6, two ester CH_3), 4.99 (s, 1, malonate CH), 7.91 (s, 1, imine CH); IR (Neat) 3000 (=CH), 1770-1740 (C=O) cm^{-1}; mass spectrum (70 e*V*) *m/e* 174 (M^+-CH_3), 130 (M^+-CO_2CH_3); *Anal.*[9a] C, H, N.



The mode of addition of the reactants played a crucial role in the formation of the reagent 5. A simple mixing and heating of 6, the ortho ester and the acid resulted in a product whose spectroscopic and microanalytical data were consistent with the structure 8 [46%, mp 177-178°C; ^{1}H NMR (DMSO-d_6) δ 3.65 (s, 3, 4-CO_2Me), 3.77 (s, 6, two malonate CO_2Me), 5.88 (s, 1, malonate CH), 8.39 (s, 1, imidate CH); mass spectrum (70 e*V*) *m/e* 272 (M^+), 240 (M^+-CH_3OH), 213 (M^+-CO_2Me); *Anal.*[9b] C, H, N]. Compound 8 apparently arose through condensation of the pre-formed 5 with the unreacted 6.



The reagent 5 was reacted with six primary amines: ammonia, methyl-, benzyl-, propyl-, butyl-, and cyclohexylamine, at room temperature. The respective imidazolinones 9-14 were isolated as their hydroxy tautomers, as detected by ^{1}H NMR, either in the parent forms (a) or



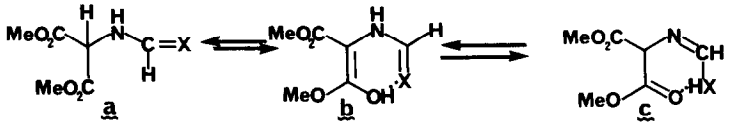
COMPD.	R
9;	H
10;	CH_3
11;	$CH_2C_6H_5$
12;	$(CH_2)_2CH_3$
13;	$(CH_2)_3CH_3$
14;	Cyclohexyl

as the ammonium (alkylammonium) salts (b), or both. The formation of a or b was dependent upon whether the exact or excess amounts of the amines were employed in the ring-closure reactions. The two forms could be conveniently interconverted: a → b by treatment with excess amine, and b → a by hydrochloric acid or with flash chromatography on silica gel. The physical data for the compounds 9 to 14 are as follows: 9b [67%; mp 191-192°C (dec.); ^{1}H NMR (DMSO-d_6) δ 3.59 (s, 3, CH_3), 5.87 (br, 4, NH_4^+, exchangeable with D_2O), 7.19 (s, 1, CH); mass spectrum (70 e*V*) *m/e* 142 (M^+-NH_3), 110 (M^+-NH_3-CH_3OH), 83 (M^+-NH_3-CO_2Me)]; 10a [90%, mp 147-148°C (dec.); ^{1}H NMR (DMSO-d_6) δ 3.20 (s, 3, N-CH_3), 3.62 (s, 3, OCH_3), 8.09 (s, 1, CH); mass spectrum (70 e*V*) *m/e* 156 (M^+), 124 (M^+-CH_3OH), 96 (M^+-CH_3OH-CO); *Anal.*[9b] C, H, N]; 10b [90%; mp 160-162°C (dec.); ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3, salt N-CH_3), 3.07 (s, 3, ring N-CH_3), 3.52 (s, 3, OCH_3), 6.3 (br, 3, NH_3^+, exchangeable with D_2O), 6.97 (s, 1, CH); mass spectrum (70 e*V*) *m/e* 156 (M^+-CH_3NH_2),

124 (M^+-CH_3NH_2-CH_3OH), 96 (M^+-CH_3NH_2-CH_3OH-CO)]; 11a [70%; mp 180°C (dec.); ^{1}H NMR (DMSO-d_6) δ 3.63 (s, 3, CH_3), 4.87 (s, 2, CH_2), 7.31 (s, 5, Ph), 8.31 (s, 1, CH); mass spectrum (70 e*V*) *m/e* 232 (M^+), 200 (M^+-CH_3OH); *Anal.*[9b] C, H, N]; 11b [78%; mp 144-146°C (dec.); ^{1}H NMR (DMSO-d_6) δ 3.55 (s, 3, CH_3), 3.94 (s, 2, salt N-CH_2), 4.74 (s, 2, ring N-CH_2), 7.19 (s, 1, CH), 7.38-7.25 (m, 10, 2 Ph); mass spectrum (70 e*V*) *m/e* 232 (M^+-$C_6H_5CH_2NH_2$), 200 (M^+-$C_6H_5CH_2NH_2$-CH_3OH); *Anal.*[9b] C, H, N]; 12a [65%; mp 152-154°C (dec.); ^{1}H NMR (DMSO-d_6) δ 0.83 (t, *J*=7.1 Hz, 3, C-CH_3), 1.63 (M, *J*=7.1 Hz, 2, C-CH_2-C), 3.62 (t, *J*=7.1 Hz, 2, N-CH_2-C), 3.62 (s, 3, OCH_3), 8.2 (s, 1, CH); mass spectrum (70 e*V*) *m/e* 184 (M^+), 152 (M^+-CH_3OH), 124 (M^+-CH_3OH-CO); *Anal.*[9b] C, H, N]; 13a [58%; mp 177-179°C (dec.); ^{1}H NMR (DMSO-d_6) δ 0.87 (t, *J*=7.1 Hz, 3, C-CH_3), 1.06-1.79 (m, 4, 2 C-CH_2-C), 3.64 (t *J*=7.1 Hz, 3, N-CH_2C), 3.64 (s, 3, OCH_3), 8.22 (s, 1, CH); mass spectrum (70 e*V*) *m/e* 198 (M^+), 166 (M^+-CH_3OH), 138 (M^+-CH_3OH-CO); *Anal.*[9b] C, H, N]; 14a [44%, mp 200-202°C (dec.); ^{1}H NMR (DMSO-d_6) δ 1-2 (br, 11, cyclohexyl H's), 3.63 (s, 3, CH_3), 8.27 (s, 1, CH); mass spectrum (70 e*V*) *m/e* 224 (M^+), 192 (M^+-CH_3OH), 164 (M^+-CH_3OH-CO); *Anal.*[9b] C, H, N]; 14b [77%, mp 144-146°C (dec.); ^{1}H NMR (DMSO-d_6) δ 1-2 (br, 22, cyclohexyl H's), 3.53 (s, 3, CH_3), 6.92 (br, 3, NH_3^+, exchangeable with D_2O), 7.12 (s, 1, CH)].

In general, the proton NMR resonances of both the ester methyls and the imidazole CH's showed upfield shifts of ∿0.1 and 1 ppm, respectively in salts (b) as compared with those in the parent compounds (a). The mass spectra of 9-14 exhibited a characteristic fragmentation pattern: an initial loss of methanol from the parent ion, followed by loss of carbon monoxide.

The reagent 5 was also tested against oxygen and sulfur nucleophiles. Thus, treatment with water resulted in 15 [mp 79-80°C (lit.[10] mp 85.5°C); ^{1}H NMR (DMSO-d_6) δ 3.63, 3.75 (two s, 6, 2 CH_3), 5.18 (d , *J*=7.06 Hz, 1, malonate CH), 8.3 (s, 1, amide CH), 9.03 (br, 1, NH, exchangeable with D_2O); IR (KBr) 3300 (NH), 1750, 1660 (C=O) cm^{-1}; mass spectrum (70 e*V*) *m/e* 147 (M^+-CO), 132 (M^+-NHCO), 116 (M^+-CO_2Me); *Anal.*[9b] C, H, N]; and the reaction with sodium hydrosulfide hydrate (NaSH. x H_2O) gave 16 [78%, mp 74°C (lit.[11] 71-72°C); ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 6, 2 CH_3), 5.76 (s, 1, malonate CH), 9.39 (s, 1, thioamide CH), 11.04 (br, 1, SH, exchangeable with D_2O); IR (KBr) 3225 (NH), 1750 (C=O) cm^{-1}; mass spectrum (70 e*V*) *m/e* 191 (M^+), 159 (M^+-CH_3OH), 131 (M^+-NH-CH=S); *Anal.*[9b] C, H, N].

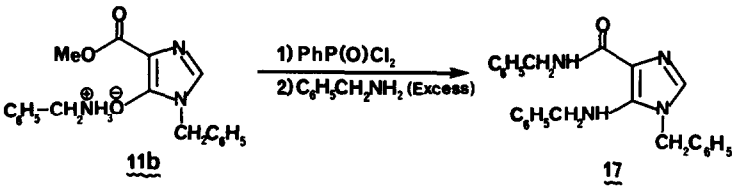


15, X=O
16, X=S

While compound 15 existed in variable tautomeric forms (a-c), depending upon solvent and concentration, only form c was detected for 16 by ^{1}H NMR, under the same conditions.

In view of the biological significance of 5-amino-4-carbamoylimidazoles as precursors to the ubiquitous natural purine derivatives such as xanthine, guanine and hypoxanthine,[12] conversion of the above hydroxy/ester imidazoles (9-14) into their amino/amide counterparts was of interest. An exemplary conversion was achieved, in a one-pot reaction, using compound 11b. The reaction of the latter with phenylphosphonic dichloride in pyridine at 110-115°C, followed

by treatment with benzylamine afforded 1-benzyl-5-benzylamino-4-(*N*-benzyl)carbamoylimidazole (17) [53%; mp 140°C; ^{1}H NMR (DMSO-d_6) δ 4.74 (s, 2, NCH_2), 4.82-5.13 (br, 5, two $NHCH_2$ + one NH), 7.11 (s, 1 imidazole CH), 7.28 (s, 15, 3 Ph); mass spectrum (70 e*V*) *m/e* 396 (M^+), 305 (M^+-CH_2Ph); *Anal.*[9b] C, H, N]. Since the simple mixing and heating of phenylphosphonic dichloride, benzylamine and 11b only led to the product of the first two reactants *i.e.*, phenylphosphonic di-(*N*-benzyl)-amide[9b] which in a separate reaction with 11b failed to produce 17, the initial heating of 11b with the phosphorus reagent, before the addition of the amine, was crucial in the above reaction. The study of the detailed mechanism and generality of this reaction is currently in progress.



11b 17

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