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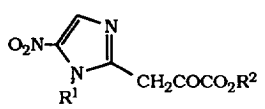
A Novel Decarbonylation of Heterocyclic Pyruvic Acid Derivatives using Sodium Perborate

Christopher A. Ramsden,[a]* Bruce J. Sargent[b] and Christiaan D. Wallett[a]

[a]Department of Chemistry, Keele University, Keele, Staffordshire ST5 5BG.
[b]Knoll Pharmaceuticals Research Department, Pennyfoot Street, Nottingham NG2 3AA.

Abstract: Decarbonylation of imidazo-2-yl and pyrid-2-ylpyruvic acids giving the corresponding acetic acids has been achieved using aqueous sodium perborate at room temperature. It is proposed that intramolecular hydrogen bonding, which inhibits conventional decarbonylation, facilitates epoxidation and subsequent decarboxylation of the enol tautomers.

5-Nitroimidazoles are useful precursors for the synthesis of a variety of molecules of biological interest.[1] Recently we specifically required an efficient synthesis of the unknown imidazo-2-ylacetic acids **3** for use as precursors to amides of pharmaceutical interest. For various reasons, including intramolecular hydrogen bonding to heterocyclic nitrogen, traditional routes to these and related acids are not viable. In this Letter we report a new route to sensitive heterocyclic acetic acids using a novel oxidative decarbonylation of the corresponding pyruvic acids, e.g. **1** (R^2=H) and **4** (R=H), by sodium perborate tetrahydrate (SPB) in water.



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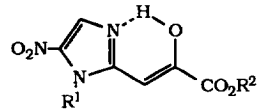

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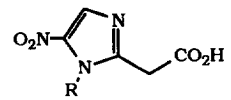

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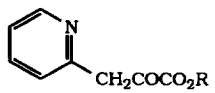

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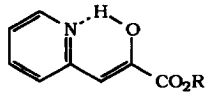

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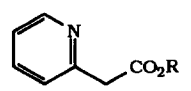

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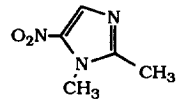
2-Methyl-5-nitroimidazoles are readily available[2] and for these studies we have used 1,2-dimethyl-5-nitroimidazole **7** (dimetridazole) as a model compound. The acidity of the 2-methyl substituents provides a convenient route to ethyl pyruvates, e.g. **1** (R^1=Me, R^2=Et), using ethyl oxalyl chloride:[3] similar reactions using ethyl chloroformate do not give the corresponding ethyl acetates but aroyl chlorides give the ketones **8** (X=O).[3,4]



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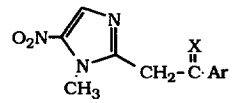

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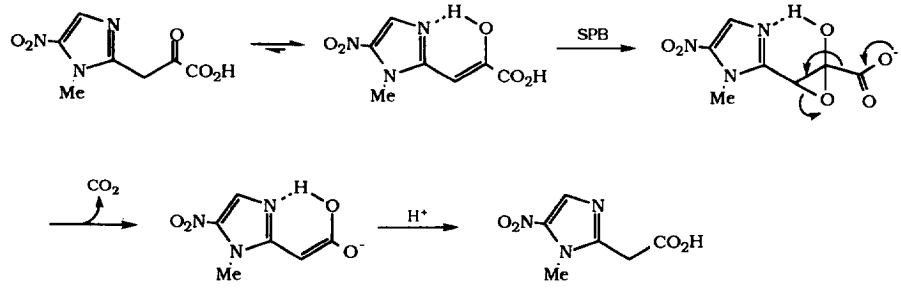
Conventional thermal (Fe, ground glass)[5] decarbonylation of the pyruvate ester **1** (R^1=Me, R^2=Et) was not achieved. This result is consistent with the observation that pyrid-2-ylpyruvates **4** also resist decarbonylation.[6] In both cases lack of reactivity is probably because intramolecular hydrogen bonding strongly favours the enolic form (i.e. **2**[3] and **5**[6]). We attempted to circumvent this problem by oxidising the free acid **1** (R^1=Me, R^2=H) but initial attempts using reagents such as H_2O_2/NaOH[7] and $Ca(OCl)_2$[8] were unsuccessful. McKillop and others have shown sodium perborate tetrahydrate (SPB) to be a versatile oxidising agent.[9] Prompted by our recent observation of a novel oxidative rearrangement of imines using SPB,[10] we investigated the reaction of the acid **1** (R^1=Me, R^2=H) with this reagent. Initial studies using SPB/TFA and SPB/AcOH were unsuccessful. However, in the latter case, our observation of the formation of dimetridazole **7** (*ca* 35%), which we concluded was formed by acid catalysed decarboxylation of the desired product **3** (R=Me), encouraged us to use SPB in aqueous solution. Using these conditions[11] at room temperature the acid **3** (R=Me) was obtained in good yield (81%) as a stable product that recrystallised from MeOH without decarboxylation. Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) showed that the acid **3** (R=Me) rapidly and cleanly decomposes with loss of CO_2 at *ca* 110 °C to form dimetridazole **7** (m.p. 138-9 °C).



Scheme 1

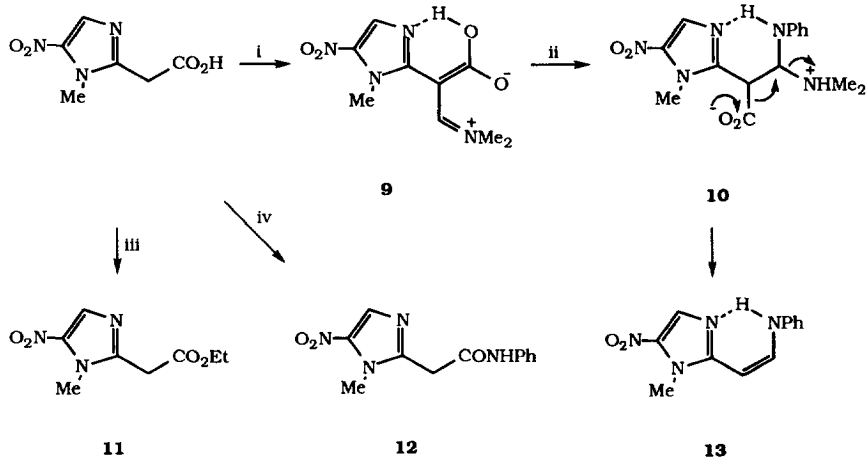
To investigate the generality of this reaction we have also transformed pyrid-2-ylpyruvic acid **4** (R=H)[12] into pyrid-2-ylacetic acid **6** (R=H). In this case the acid **6** (R=H) was not isolated but was readily transformed into its ethyl ester (91%) *in situ* by treatment with EtOH/HCl. Under identical reaction conditions,

no decarbonylation of phenylpyruvic acid ($PhCH_2CO.CO_2H$) was observed and this leads us to conclude that intramolecular hydrogen bonding to the heterocyclic substituent is essential for this oxidative decarbonylation.

We propose a mechanism in which epoxidation of the enol precedes decarboxylation (Scheme 1). It is interesting that the same intramolecular hydrogen bonding inhibits conventional decarbonylation[6] and the method that we report here therefore complements existing methodology. The mildness of the conditions is particularly attractive since further decarboxylation of sensitive heterocyclic acetic acid derivatives is avoided.

Subsequent transformations of the acid **3** (R=Me) to amides and esters were not straightforward and we attribute this problem to the acidity of the 2-methylene protons and the opportunity for intramolecular hydrogen bonding. Reaction with Vilsmeier's reagent (Me_2N^+=CHCl) followed by treatment with aniline gave the hydrogen bonded *cis*-alkene **13** (31%)(J_{CHCH} 8 Hz, δ_{NH} 10.47), m.p. 144-8 °C.[13] We rationalise the formation of this enamine **13** in terms of reaction of the reagent at carbon to give the hydrogen bonded intermediate **9** (Scheme 2). Treatment with aniline then gives the betaine **10** which can undergo elimination of CO_2 and Me_2NH. As far as we are aware, this is a novel mode of reaction of Vilsmeier's reagent which usually gives vinylamidinium salts with arylacetic acids.[14]

In an attempt to avoid reaction at carbon we investigated the use of a sterically hindered coupling agent. When the acid was treated with BOP-Cl[15] followed by aniline the desired amide **12** (56%), m.p. 141-3 °C, was obtained, and shown to be identical to a sample prepared by Beckmann rearrangement of the oxime **8** (X=NOH, Ar=Ph).[4] Other amines, including aliphatic amines, also condense in good yield and a similar procedure gives the ethyl ester (**11**)(95%), m.p. 42-6 °C.



Reagents: i, $(COCl)_2$/DMF/MeCN; ii, $PhNH_2/C_5H_5N$/MeCN; iii, BOP-Cl/Et_3N/EtOH/CH_2Cl_2; iv, BOP-Cl/$Et_3N/PhNH_2$/THF

Scheme2

In conclusion we have established an efficient and mild route to the carboxylic acids **3** using SPB. These acids, which can now be made in large batches, are versatile intermediates for the synthesis of heterocyclic molecules of potential biological interest.

Acknowledgements

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11. Preparation of **3** (R=Me). A solution of compound **1** (85.0g, 0.34mol) in water (500ml) was stirred at room temperature (15min) and sodium perborate tetrahydrate (48.9g, 0.34mol) was added gradually. After the initial evolution of gas and further stirring (72h), the fawn precipitate was collected, dried and identified as the acid **3** (R=Me)(51.0g, 81%): υ_{max}(KBr)/cm^{-1} 3432, 3146, 2404, 1706, 1548, 1480, 1380, 1250 and 1182; δ_H(270 MHz, $CDCl_3$), 13.01 (1H, br s, exchangeable OH), 8.04 (1H, s, 4-H), 3.98 (2H, s, 2-CH_2), 3.84 (3H, s, N-CH_3); *m/z* 185 (M^+); Found: C, 38.9; H, 3.7; N, 22.6. $C_6H_7N_3O_4$ requires C, 38.9; H, 3.8; N, 22.7%).
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13. Compound **13**: υ_{max}(KBr)/cm^{-1} 3012, 1635, 1598, 1464, 1354, 1290, 1204 and 1178; λ_{max}(EtOH)/nm 238 (ε 8731), 303 (ε 9761), 314 (ε 10846) and 427 (ε 10791); δ_H(270 MHz,$CDCl_3$ + d_6-DMSO), 10.47 (1H, d, *J* 11, NHPh), 8.05 (1H, s, 4-H), 7.41 (1H, pseudo-t, *J* 8 and 11, C=CH-N), 6.85-7.25 (5H, C_6H_5), 5.14 (1H, d, *J* 8, -CH=C) and 3.91 (3H, s, N-CH_3); *m/z* 244 (M^+); Found: C, 58.75; H, 4.70. $C_{12}H_{12}N_4O_2$ requires C, 59.01; H, 4.92%).
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