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# A PROTECTING GROUP FOR THE PYRROLE NITROGEN

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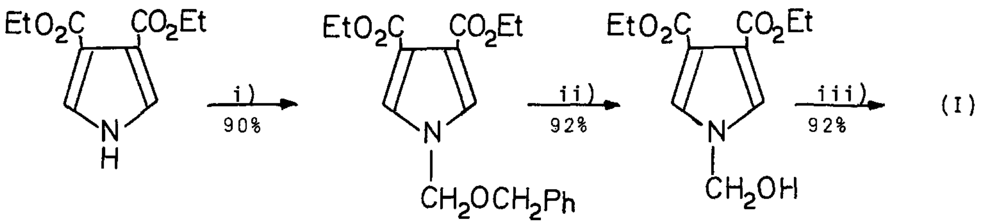
Pyrrole has a pKa of 16.5, similar to that of methanol. Electron withdrawing substituents further increase the acidity of the 1-proton as a consequence of the enhanced stability which they confer upon the pyrrolyl anion.[1] The resulting ease of proton removal is frequently a source of inconvenience. For example, metal hydride reductions of pyrrolecarboxylic acid derivatives proceed beyond the hydroxymethyl stage as a result of 1-proton abstraction.[2] Methylation of pyrrolecarboxylic acids with diazomethane can result in concurrent N-methylation.[3] Carbanionic reagents abstract the 1-proton thereby reducing the reactivity of ring carbonyl substituents to a level which often prevents further reaction.[4] Remers et al have recently examined 1-acetyl, 1-benzoyl, 1-benzenesulfonyl and 1-benzyl substituents for their suitability as protecting groups for the pyrrole nitrogen.[4] Only the 1-benzyl substituent is base stable and since this is removed by sodium-liquid ammonia its utility is restricted to compounds compatible with such vigorous reductive cleavage. Catalytic hydrogenolysis of the 1-benzyl substituent has previously been shown to be difficult.[5]

During work upon some 3.4-substituted pyrroles we have found an N-benzyloxymethyl substituent[6] to be of considerable use. It was introduced onto the diester (I) via the sodium pyrrole to afford (II). The group satisfactorily survived various reactions at the ester functions. It is, for example, stable to 4M hydrochloric acid, to refluxing acetic anhydride, to refluxing 10% aqueous ethanolic potassium hydroxide and to dimethylcadmium.



(I) (II) (III)

i) NaH/THF; 2h reflux
$PhCH_2OCH_2Cl$; 12h 25°

ii) $H_2$/10% Pd-C
1 atm, 6h 25°

iii) $PhCH_2NMe_3OH$
$H_2O$-THF; 3h reflux

Hydrogenolysis of (II) at palladium on carbon affords the corresponding 1-hydroxymethylpyrrole (III). This is fairly stable in aqueous acid but readily eliminates formaldehyde, upon heating under reflux in aqueous-THF containing a catalytic amount of Triton B, to afford the N-unsubstituted pyrrole.

## Acknowledgement

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