Regiospecific Substitution of Pyridine by Trialkylalkynylborates in the Presence of Acetyl Chloride

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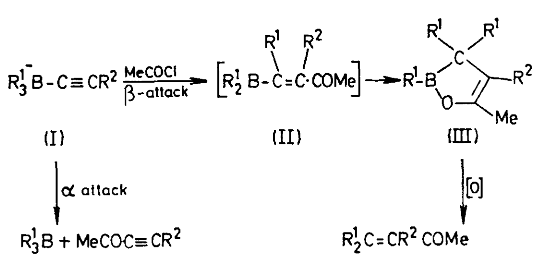
Summary An outline is given of a novel, versatile, and gentle process which involves trialkylalkynylborates and leads specifically to 4-substituted dihydropyridines.

Whilst the protonation and alkylation of trialkylalkynylborates (I) have been shown to be versatile and high-yield routes to many types of ketone and olefin,[1] the reaction of such salts with acetyl chloride remains an unsatisfactory synthetic procedure.[2,3] Reaction may proceed by either α- or β-attack on the salt and the product from the latter route undergoes a cyclisation reminiscent of the cyanoborate process[4] leading to (III), which on oxidation gives αβ-unsaturated ketones in yields of 30—40% (Scheme 1).

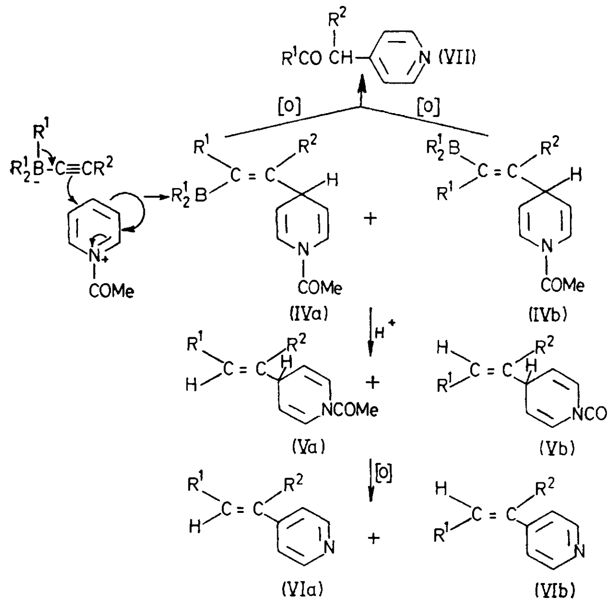
It had previously been remarked that the once-migrated intermediate (II) could be isolated as the pyridine adduct, though no details of the characterisation were given.[2] As (II) is a vinylogous α-oxoborane it seemed important to us, both on theoretical grounds and because of the synthetic possibilities, to isolate and characterise the product from this reaction.

The procedure followed was to prepare the salts (I) in hexane, pump off the volatile material, and add pyridine followed by acetyl chloride at −78°. The mixture was allowed to warm to room temperature over 10—15 min and then either oxidised with acetate-buffered hydrogen peroxide or hydrolysed with an organic acid, normally acetic acid, and then oxidised.



Scheme 1

We were intrigued to find that the reaction had in fact followed an entirely different course from that previously supposed. The acylpyridinium species had undergone nucleophilic attack on the heterocyclic ring, a known class of reaction,[5] in a completely regiospecific fashion to give 4-substituted dihydropyridines (IV) (Scheme 2).



Scheme 2

Hydrolysis of these compounds gives the intermediates (Va) and (Vb) which may be isolated and characterised and were shown to be oxidised by air in *ca.* 20 h to the olefins (VIa) and (VIb). Alternatively hydrolysis was followed directly by buffered peroxide oxidation to give the olefins (VIa) and (VIb) in a ratio of 65:35. The olefins may be separated by column chromatography and independently characterised. Direct oxidation of the mixture (IVa) and (IVb) leads to the ketone (VII), yields being shown in the Table.

Table

The 4-substitution of pyridine by $R^1_3\bar{B}C{\equiv}CR_2$[a]

R^1	R^2	Yields of ketone (VII)[b]	Yields of olefins (VIa) + (VIb)
(i) n-Hexyl	Bu^n	76	72
(ii) ,, ...	n-Hexyl	72	68
(iii) Cyclopentyl ..	Bu^n	74	78[c]
(iv) Cyclohexyl ..	n-Hexyl	68	71[d]
(v) n-Hexyl	Ph	—	66

[a] All yields are of isolated purified product. [b] All products characterised by mass, n.m.r., and i.r. spectra, and by elemental analysis of picrate derivatives of representative samples. [c] Hydrolysed by acetic acid at 55° in 20 h. [d] Hydrolysed by isobutyric acid at 65° in 17 h.

No trace of 2-substitution could be found, though such products were sought. The reaction is thus a great contrast to the reaction of silver acetylides with pyridine which gives only α-substitution.[6] To our knowledge this is the first example of attack by a borate salt on a heterocyclic system and extensions of the reaction to other heteroaromatic bases are under investigation. As it stands it is a smooth, high-yield route to 4-substituted pyridines which should lead readily to many derivatives. In this connection it is noteworthy that buffered oxidation of (III,v) (R^1 = n-hexyl, R^2 = Ph) gives the required product (VII,v) (56%, contaminated with some hydrolysis product) but oxidation in the presence of sodium hydroxide can produce 4-benzoylpyridine directly.

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