Mild General Synthesis of 4-Substituted Piperidines†

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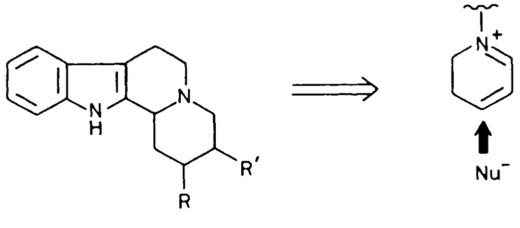
4-Substituted piperidines are easily accessible in high yield *via* a Lewis acid-catalysed addition of silyl enol ethers to 2-cyano-1,2,5,6-tetrahydropyridines.



Scheme 1

A vexed question in various attempted syntheses of indole alkaloids has been the introduction of suitable functionalized alkyl substituents to the 4-position of a piperidine unit.[1] Most methods to effect the desired transformation have involved dihydropyridines as synthetic intermediates (*cf.* Scheme 1).[2] Their use, however, generally leads to a number of difficulties; dihydropyridines are often unstable and their reactivity usually drastically limits the choice of nucleophiles. As Grierson and Husson have shown,[2] the 2-cyano-1,2,5,6-tetrahydropyridines (**1**) offer a versatile alternative to direct exploitation of dihydropyridines. However, even their use

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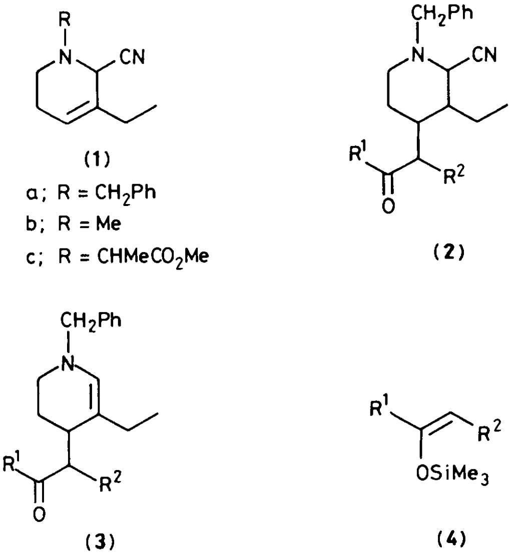
† For Part 5 of the series 'Novel Applications of the Modified Polonovski Reaction,' see ref. 3.



(1)
a; R = CH$_2$Ph
b; R = Me
c; R = CHMeCO$_2$Me

(2)

(3)

(4)

Scheme 2. Preparation of the aminonitriles (**2**) from (**1a**) and the silyl enol ethers (**4**).

For (2)—(4)	R^1	R^2	% Yield of (2)^a
a	H	Et	94
b	Et	Me	95
c	Ph	H	80
d	–[CH$_2$]$_4$–		98
e	OMe	CO$_2$Me	90

[a] Yield of purified product.

has been limited to reactions with metal enolates as the nucleophilic reagents, and frequently an expensive silver salt is used to enhance the leaving potential of the cyano group. Recently, Zn halides have also been suggested as the required Lewis acid catalysts[3,4] but often they cannot be used owing to the concomitant appearance of both the aminonitrile (**2**) and the corresponding enamine (**3**) in product mixtures.

Preformed iminium ions have recently gained considerable attention in the 'modern' Mannich reaction with metal,[5] silyl,[6] and boron[7] enolates as nucleophiles. This new methodology has been recommended[8] because of the good yields commonly obtained and because the modern methods of enolate formation are amenable to nearly complete regiocontrol.[9] We report now a new and general method for the introduction of various functionalized alkyl groups to the 4-position of a piperidine unit employing silyl enol ethers as nucleophiles. Typically, addition of the aminonitrile (**1a**) to a cooled (−78 °C) solution of the silyl enol ether (**4a**) and $BF_3 \cdot Et_2O$ in tetrahydrofuran (THF) under an argon atmosphere and stirring the reaction mixture overnight gave, after normal extractive work-up, the aminonitrile (**2a**) in 94% yield. Scheme 2 presents examples with representative aldehyde and ketone silyl enol ethers.‡ As starting materials, the 2-cyano-1,2,5,6-tetrahydropyridines (**1**) are easily available *via* a route employing the modified Polonovski reaction.[2,10]

The mild conditions required for the reaction, the high degree of regioselectivity in both reaction partners (silyl enolate and unsaturated aminonitrile), the ease of operation, and high yields combine to make this a superior method for the introduction of functionalized alkyl groups at the 4-position of piperidines.

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‡ All compounds were fully characterised by the usual physical methods.