A New Synthesis of Pyrroles from Nitroalkenes

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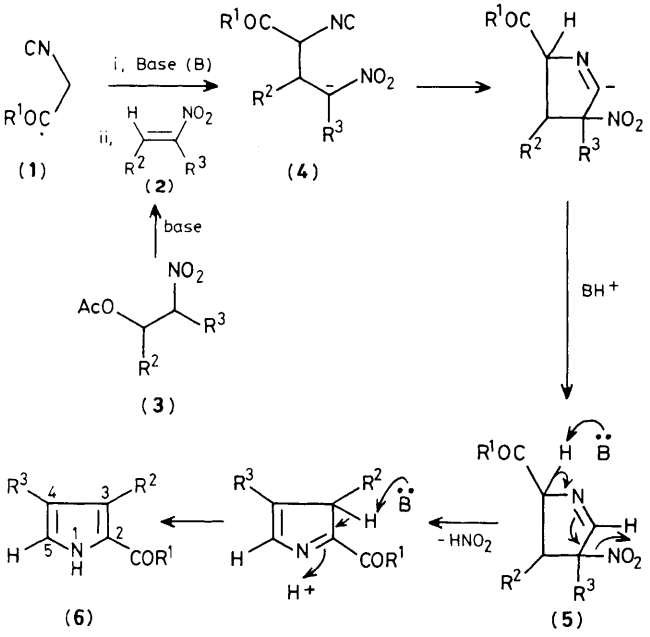
Nitroalkenes, or their β-acetoxynitro precursors, react with α-isocyanoacetate esters in the presence of base to give high yields of 5-unsubstituted pyrroles; some important pyrroles are easily synthesised by this method.

We have recently reported[1] a convenient method for the synthesis of pyrroles from nitroketones using diphenyl disulphide–tributylphosphine as reductant. We now report another new route to pyrroles unsubstituted in position 5 and, therefore, particularly relevant to the porphyrin field. Central to this method is the ability of the nitro group to depart as nitrite under certain conditions.[2] Thus base-catalysed Michael addition of an α-isocyanoacetate (**1**) to a nitroalkene (**2**) followed by cyclisation of the nitronate anion (**4**) onto the isocyano group would lead to the pyrroline (**5**) (Scheme 1). Similar isonitrile cyclisations have been used extensively by Schöllkopf, Van Leusen, and others for the preparation of various heterocycles.[3] Base-catalysed expulsion of nitrite from the pyrroline and double bond rearrangement would finally give the pyrrole (**6**) (Scheme 1).

This conception was easily reduced to practice. Thus, addition of the β-nitrostyrene derivative (**2a**) to a mixture of t-butyl α-isocyanoacetate (**1a**) and the guanidine base (**7**)[4] in tetrahydrofuran–propan-2-ol at room temperature resulted in a smooth reaction to give the expected pyrrole (**6a**) in 90%



Scheme 1

For (**1**):
a; R^1 = Bu^{t}O
b; R^1 = EtO
c; R^1 = MeO
d; R^1 = Me_2N

For (**2**):
a; R^2 = *p*-$MeOC_6H_4$, R^3 = Me
b; R^2 = *p*-$PhCH_2OC_6H_4$, R^3 = Me
c; R^2 = *p*-$MeOC_6H_4$, R^3 = H
d; R^2 = H, R^3 = Me

For (**3**):
a; R^2 = H, R^3 = Me
b; R^2 = R^3 = Et
c; R^2 = Me, R^3 = Et
d; R^2 = Et, R^3 = Me
e; R^2 = Me, R^3 = $CH_2CH_2CO_2Me$

For (**6**):
a; R^1 = Bu^{t}O, R^2 = *p*-$MeOC_6H_4$, R^3 = Me
b; R^1 = EtO, R^2 = *p*-$PhCH_2OC_6H_4$, R^3 = Me
c; R^1 = Bu^{t}O, R^2 = H, R^3 = Me
d; R^1 = MeO, R^3 = Me, R^2 = H
e; R^1 = Bu^{t}O, R^2 = R^3 = Et
f; R^1 = Bu^{t}O, R^2 = Me, R^3 = Et
g; R^1 = Bu^{t}O, R^2 = Et, R^3 = Me
h; R^1 = Bu^{t}O, R^2 = Me, R^3 = $CH_2CH_2CO_2Me$
i; R^1 = Me_2N, R^2 = Me, R^3 = Et

yield. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) could also be used as base, the reaction being somewhat slower (80% yield).

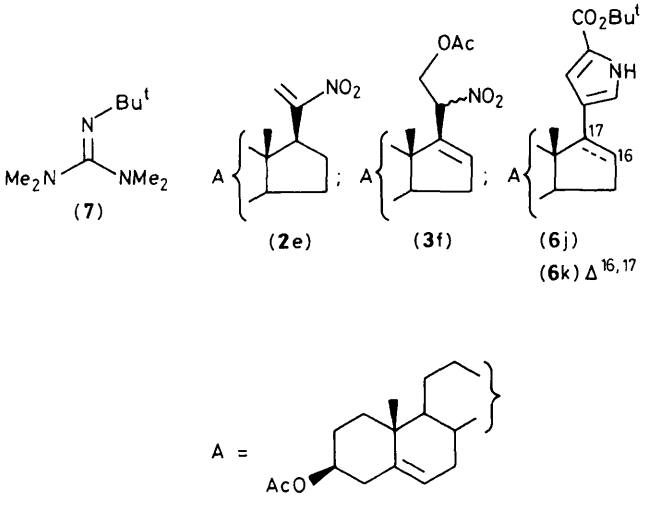
In the case of aliphatic nitroalkenes, we have found it more convenient to generate them *in situ* from the usually more accessible β-nitroacetoxy precursors (**3**); naturally an additional equivalent of base must be present (Scheme 1). This modification is epecially advantageous when the nitroalkene is very active and prone to base-catalysed polymerisation. For example, the pyrrole (**6c**) is produced in 70% yield from 1-acetoxy-2-nitropropane (**3a**). From nitropropene (**2d**) itself, the yield is only 48%. The methyl ester analogue (**6d**) can be similarly prepared in 60% yield using methyl α-isocyanoacetate (**1c**). This pyrrole is the trail marker pheromone of the Texas leaf-cutting ant, *Atta texana* (Buckley).[5]

A number of pyrroles substituted in the 3- and 4-positions with, among others, methyl, ethyl, and propionate groups were easily prepared in generally high yield (Table 1). In

Table 1.

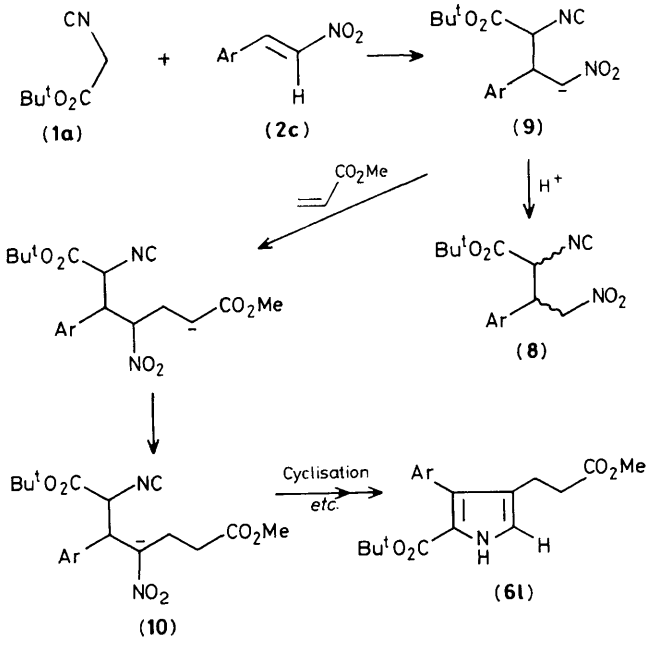
Isocyano-compound (**1**)	Nitro-compound (**2**) or (**3**)	Pyrrole produced	Yield (%) of isolated product
(**1a**)	(**2a**)	(**6a**)	90[a]
(**1b**)	(**2b**)	(**6b**)	91
(**1a**)	(**3a**)	(**6c**)	70[b]
(**1c**)	(**3a**)	(**6d**)	60[d]
(**1a**)	(**3b**)	(**6e**)	55
(**1a**)	(**3c**)	(**6f**)	95
(**1a**)	(**3d**)	(**6g**)	68
(**1a**)	(**3e**)	(**6h**)	97
(**1a**)	(**2e**)[c]	(**6j**)	91
(**1a**)	(**3f**)[c]	(**6k**)	85
(**1d**)	(**3c**)	(**6i**)	77

[a] Yield was 80% using DBU. [b] Yield is only 48% starting from nitropropene (**2d**). [c] Easily obtained from 3β-hydroxy-androst-5-en-17-one. See Ref. 8. [d] Bu^{t}OH–tetrahydrofuran (1 : 1) used as solvent.



addition, the pyrroles obtained have the 2-position conveniently protected with carboxy ester function (the t-butyl ester is particularly useful) allowing selective reaction at the 5-position. Such pyrroles constitute basic building blocks for various natural porphyrins and bile pigments and are only tediously obtained by more conventional approaches.[6] The ester function in the 2-position may be replaced with an amide simply by performing the condensation using, for instance, *N,N*-dimethyl-α-isocyanoacetamide (**1d**). Pyrroles of this type [*e.g.* (**6i**)] have proved extremely useful in the synthesis of porphyrins *via* the oxobilane route.[6]

In contrast to its homologue (**2a**), the nitrostyrene derivative (**2c**), lacking the β-methyl group, failed to give the corresponding pyrrole on reaction with the isocyanide (**1a**) under the usual conditions. If the condensation is conducted at −70 °C, however, a good yield of the adduct (**8**) (characterised spectroscopically) is obtained after quenching (Scheme 2). This indicated that cyclisation in the case of a primary nitronate [*e.g.* (**9**)] is not efficient. We took advantage of this observation to introduce in one step the important propionate side chain. Thus addition of methyl acrylate to the cold reaction mixture and warming to room temperature afforded (**6l**) directly in 60—65% yield. In this case Michael addition followed by proton shift gives a secondary nitronate (**10**) which now cyclises normally, providing an expedient access to complex pyrroles (Scheme 2).



Scheme 2. Ar = *p*-MeOC$_6$H$_4$.

This new synthesis of pyrroles proceeds under mild conditions and could, in principle, be geared for the preparation of labelled substrates useful for biosynthetic studies. The starting materials and reagents[7] are readily available. β-Nitroacetoxy derivatives are simply obtained by base-catalysed addition of nitroalkanes to aldehydes (the Henry reaction[2]) followed by acetylation. In some cases we have succeeded in simplifying this sequence into a one-pot procedure by using *N,N*-dimethylaminopyridine (DMAP) both as the base and acetylation catalyst.

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