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A MILD OXIDATIVE NEF REACTION

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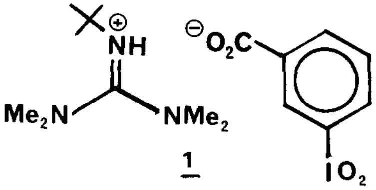
Summary : m-Iodoxybenzoic acid, in presence of an excess of N, N, N', N'-tetramethyl-N"-t-butylguanidine, is a mild and efficient reagent for the conversion of secondary nitro compounds to ketones.

The conversion of a nitro group into a carbonyl (the Nef Reaction) is of considerable synthetic value and many reagents have been developed for effecting this transformation[1-4]. Oxidative cleavage of the nitronate anion may yield the corresponding carbonyl derivative but the oxidizing agents usually employed (e.g. $KMnO_4$[5]; $K_2S_2O_8$[6]; O_3[7]; $^1O_2$[8]; H_2O_2[9] etc.) are often incompatible with sensitive functionality. We have therefore sought to develop a mild oxidative system tolerant of other easily oxidizable functional groups.

The salt (1), simply obtained by mixing N,N,N',N'-tetramethyl-N"-t-butyl-guanidine[10] (2) and m-iodoxybenzoic acid, is a soluble reagent capable of cleaving glycols under extremely mild conditions[11]. We envisaged that, in the presence of an excess of the guanidine base (2), the nitronate would be formed and oxidised *in situ* leading ultimately to the carbonyl derivative (Scheme 1).



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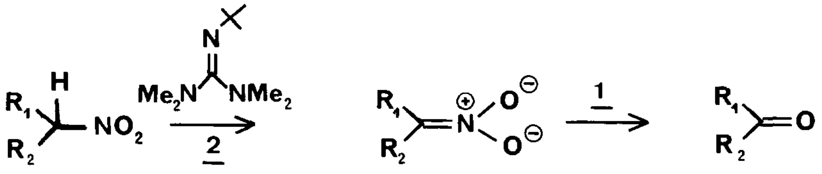
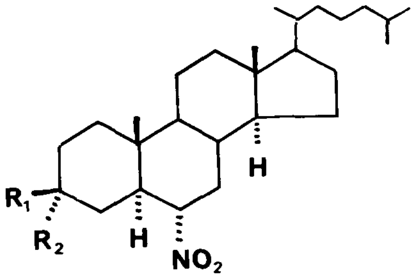


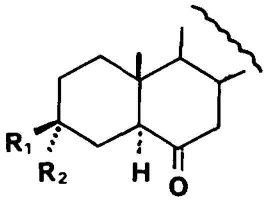
SCHEME 1

Indeed when 3β-acetoxy-6α-nitrocholestane (3) was treated with m-iodoxybenzoic acid and an excess of the guanidine base (2) in dichloromethane at room temperature, a smooth reaction took place and the 6-keto steroid (4) was obtained in 95% yield. Triethylamine was not satisfactory as base, whereas DBU gave similar results, although the reaction was slower.

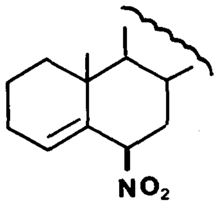
Secondary nitro compounds afforded in general good yields of ketones (Table). Of particular interest is example (7) which gave the corresponding ketone (8) in excellent yield. The survival of the easily oxidized dithiolane moiety demonstrates the mildness of the reagent.



3 : R_1 = OAc , R_2 = H
5 : R_1 , R_2 = O
7 : R_1 , R_2 = $\left[\begin{smallmatrix}S-\\S-\end{smallmatrix}\right.$



4 : R_1 = OAc , R_2 = H
6 : R_1 , R_2 = O
8 : R_1 , R_2 = $\left[\begin{smallmatrix}S-\\S-\end{smallmatrix}\right.$



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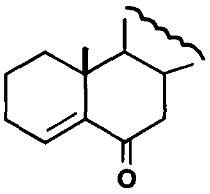

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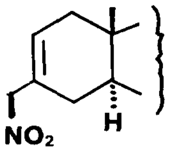

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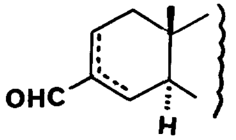

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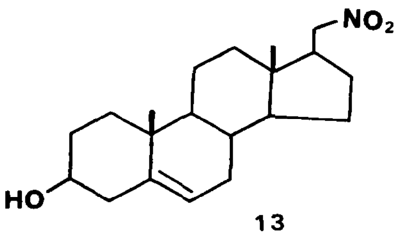

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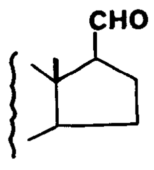

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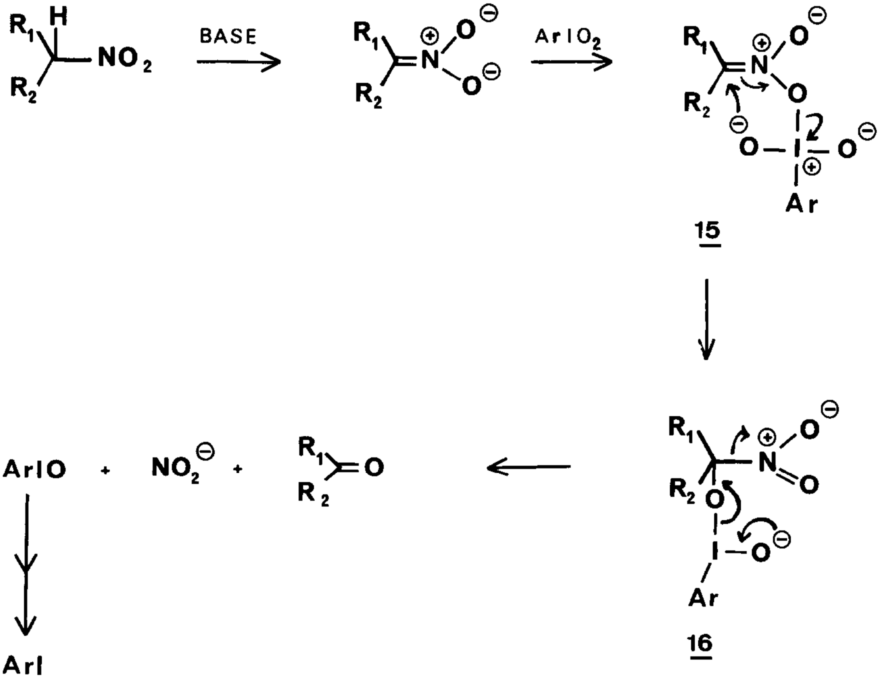
Table

Nitro Compounds	Product	Yield (%)
(**3**)	(**4**)	95
(**5**)	(**6**)	78
(**7**)	(**8**)	89
(**9**)	(**10**)	58
(**11**)	(**12**)	33*
(**13**)	(**14**)	41

* Characterised as 2,4-dinitrophenylhydrazone.

Compounds with a primary nitro group gave only moderate to low yields of aldehydes. Aldehyde (**12**) was obtained as a mixture of double bond isomers (8:2).

A plausible mechanism for this oxidation is shown in Scheme 2. The nitronate anion reacts with *m*-iodoxybenzoic acid to give the intermediate (**15**) which collapses via (**16**) to the carbonyl compound, nitrous acid and *m*-iodoso benzoic acid. The presence of nitrite in the reaction mixture was detected by a diazo coupling[12]. The *m*-iodosobenzoic acid formed may also act as an oxidant towards the nitronate. Indeed, iodosobenzene under similar conditions converted the nitro steroid (**3**) into the ketone (**4**) in 57% yield.



SCHEME 2

A typical experimental procedure is as follows :

To a mixture of 3β-acetoxy-6α-nitrocholestane (**3**) (250 mg) and *m*-iodoxy benzoic acid (400 mg) in dichloromethane (7 ml) is added the guanidine base (0.4 ml). After stirring at room temperature for 4-5 hours, the reaction mixture is poured into 0.5 N NaOH and the organic layer separated and washed with dilute HCl, water and dried (Na_2SO_4). Filtration through a silica plug and evaporation gave the 6-ketosteroid (**5**) as a white cristalline solid (227 mg, 95%), identical with an authentic sample.

When operating on a small scale, the work-up is reduced to a simple filtration of the reaction mixture through a short column of silica. All reagent derived side products being very polar remain adsorbed on the silica. Moreover, the *m*-iodobenzoic acid formed is easily separated by base extraction and recycled to *m*-iodoxybenzoic acid by oxidation with commercial sodium hypochlorite[13].

In conclusion, this simple and mild oxidative variation of the Nef Reaction is a useful addition to existing methods.

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