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CLEAVAGE REACTIONS USING BASIC HYDROGEN PEROXIDE. A METHOD FOR DEBLOCKING *p*-NITROBENZYL PROTECTED BASES AND PHENOLS

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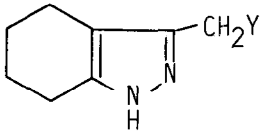
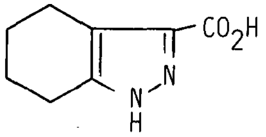
The hydrolysis of certain nitriles with basic hydrogen peroxide is accompanied by an oxidative cleavage reaction giving the lower homologue carboxylic acid. Under the same conditions, *p*-nitrobenzylated bases and phenols yield the corresponding N-H base or phenol respectively.

We report that an attempt to hydrolyse the nitrile (1) to the corresponding amide (2), using 30% H_2O_2 in 6N aqueous ethanolic sodium hydroxide at 50° for six hours[1,2] (the Radziszewski reaction), afforded the chain shortened acid (3) as the major product.



(1) Y= C≡N

(2) Y= CONH$_2$



(3)

Although there are isolated reports of peroxide induced C-C bond cleavage,[3] the reaction does not appear to be a recognised complication in the nitrile hydrolysis procedure.[1,2] The conversion of (1) into (3) therefore prompted an investigation of other compounds. We found that, under comparable conditions, butyronitrile hydrolysed smoothly to the amide but a repeat of the literature[1] hydrolysis of phenylacetonitrile gave not only the amide but also some benzoic acid (10%). For *p*-nitrophenylacetonitrile the oxidation reaction becomes more important, giving as much as 32% *p*-nitrobenzoic acid. Separate experiments with both nitriles established that the oxidation is not brought about by H_2O_2 or the basic medium alone.[4]

Further studies showed that the cleavage reaction is not restricted simply to nitriles. Thus *p*-nitrophenylacetic acid, ethyl *p*-nitrophenylacetate and *p*-nitrobenzylamine were each oxidised to *p*-nitrobenzoic acid in 52%, 72%, and

Table: Oxidative Cleavage of *p*-Nitrobenzylated Bases and Phenols

Starting Material	Product
1-*p*-nitrobenzylbenzimidazole	benzimidazole, 72%
5-chloro-1-*p*-nitrobenzylindazole	5-chloroindazole, 60%
N-methyl-N-*p*-nitrobenzylaniline	N-methylaniline, 44%
O-*p*-nitrobenzylphenol	phenol, 48%
O-*p*-nitrobenzyl-1-naphthol	1-naphthol, 39%

48% yield respectively. However, no benzoic acid was recovered from reactions with phenylacetic acid or its ethyl ester. Other results suggest the reaction may prove useful for deblocking *p*-nitrobenzyl protected functionalities. Thus various N-*p*-nitrobenzylated bases and O-*p*-nitrobenzylated phenols, Table, were cleaved satisfactorily to give *p*-nitrobenzoic acid and the corresponding N-H base or phenol. Yields, at present moderate, have yet to be optimised.

The mechanism of the cleavage reaction is unclear and may well vary with the class of compound involved. Oxidations of phenylacetic acid with basic hypochlorite[7] and with tetrabutylammonium periodate[8] to give benzaldehyde are thought to proceed via the α-hydroxylated compound. It is feasible that some of the products in the present work are formed via similar intermediates, a mechanistic analogy between a hypochlorite/base oxidation and a peroxide/base oxidation being an attractive one.

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4. Nitriles are cleaved oxidatively by *t*-BuOK/oxygen.[5] Phenylacetonitrile itself is reported to be oxidised in NaOMe/MeOH under oxygen at 30 psi.[6] *p*-Nitrophenylacetonitrile is unstable in 6N NaOH.
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