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Communications

Hydroxylation of Nitroarenes with Alkyl Hydroperoxide Anions via Vicarious Nucleophilic Substitution of Hydrogen[1]

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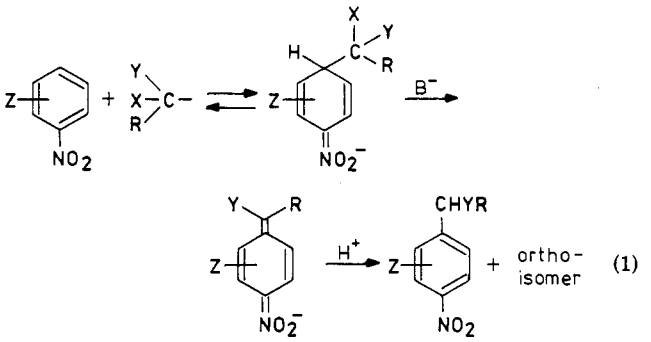
Summary: *tert*-Butyl and cumyl hydroperoxides in strongly basic media react with a variety of nitroarenes to produce *o*- and/or *p*-nitrophenols. The reaction proceeds via an addition–base-induced β-elimination pathway analogous to that of vicarious nucleophilic substitution.

The replacement of hydrogen on aromatic rings with a variety of substituents via electrophilic aromatic substitution is one of the most important processes in organic chemistry.[2] In contrast, the nucleophilic aromatic substitution of hydrogen was not well-recognized until recently.[3] Some years ago, we introduced the new concept of nucleophilic substitution of hydrogen on aromatic nitro compounds with functionalized alkyl groups, and we named it vicarious nucleophilic substitution (VNS).[4] It is represented by the reaction of nitroarenes with carbanions that contain α-leaving groups, as shown in eq 1, and is quite general with respect to both the carbanion and the nitroarene reactants. For example, both carbo- and heterocyclic nitroarenes may be employed. VNS can be considered to be a nucleophilic alkylation.[5,6]



(1)

The stoichiometry of this reaction is identical with that of the Friedel–Crafts reaction, which is an electrophilic alkylation. However, it proceeds with the inverse polarity, so one can consider it to be an Umpolung of the Friedel–Crafts reaction.[5] Following this reasoning, one can expect that other substitutents can also replace hydrogen on nitroaromatic rings via initial nucleophilic attachment. Indeed, the amination of nitroarenes with hydroxylamine[7] and, much more efficiently, with 4-amino-1,2,4-triazole[8] in basic media proceeds undoubtedly via a mechanism similar to VNS.

Taking into account the high nucleophilicity of hydroperoxy anions and the weakness of the O–O bond, we expected that they should react with nitroarenes according to the VNS mechanism to produce nitrophenols. Indeed, *tert*-butyl hydroperoxide and cumyl hydroperoxide reacted in strongly basic media with many nitroarenes, affording products of hydroxylation in the ortho or para positions.[9]

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Scheme I

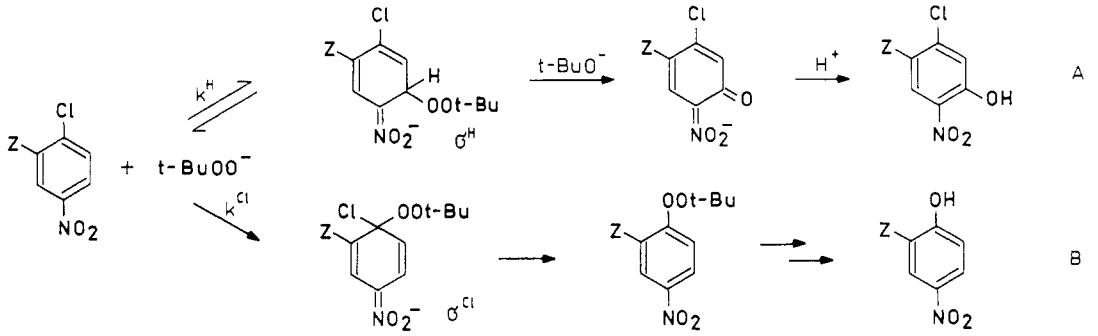
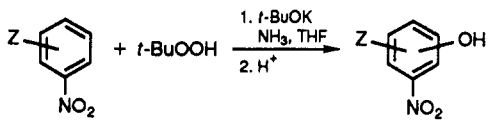


Table I



n	Z	product[a]	% yield[b]
1	H	4-OH	45[c]
		2-OH	traces
2	4-F	4-OH[d]	75
3	4-CF_3	2-OH-4-CF_3	80
4	3-F	4-OH-3-F	76
		2-OH-3-F	7
5	3-Cl	4-OH-3-Cl	79
		2-OH-3-Cl	3
		6-OH-3-Cl	1
6	3-CN	4-OH-3-CN	87[f]
7	3-CF_3	4-OH-3-CF_3[e]	86
8	3-NO_2	4-OH-3-NO_2	96
9	1-NO_2-naphthalene	2-OH-1-NO_2Nph	87, traces[f]
		4-OH-1-NO_2Nph	traces, 89[f]
10	2-NO_2-thiophene	3-OH-2-NO_2Thp	72[g] (>90)[h]

[a] Position of substituents in relation to the NO_2 group, all products were identical to those describe (mp, NMR). [b] Isolated products. [c] Cumyl hydroperoxide was used. [d] Product of S_NAr of halogen. [e] Previously was not reported: mp 105–108 °C, ^1H NMR, δ 7.32 (d, J = 9.1 Hz, 1 H), 8.38 (dd, J = 9.1 and 2.8 Hz, 1 H), 8.42 (d, J = 9.8 Hz, 1 H). Anal. ($C_7H_4F_3NO_3$) C, H, N. [f] NaOH instead of t-BuOK was used. [g] Previously was not reported, ^1H NMR δ 6.90 (d, J = 5.9 Hz, 1 H), 7.87 (d, J = 5.9 Hz, 1 H). Due to instability was not obtained in pure state. [h] Stable tetrabutylammonium salt isolated according to the ion pair extraction procedure: mp 123 °C; ^1H NMR δ 0.97–1.80 (m, 28 H), 2.97–3.23 (m, 8 H), 6.10 (d, J = 6 Hz, 1 H), 7.00 (d, J = 6 Hz, 1 H). Anal. ($C_{20}H_{38}N_2O_3S$) C, H, N, S.

Results of the VNS hydroxylation with *tert*-butyl hydroperoxide are given in Tables I and II. The typical procedure is as follows: To a solution of t-BuOK (0.84 g 7.5 mmol) in liquid ammonia (10 mL) was added dropwise a solution of $ArNO_2$ (3 mmol) and t-BuOOH (0.3 g 3.3 mmol) in tetrahydrofuran (THF) (3 mL). After 15 min ammonium chloride was added, the ammonia was evaporated, and the product was isolated and purified by column chromatography.

Since peroxides and hydroperoxides are strong oxidants, the hydroxylation could conceivably proceed via an alternative pathway: by oxidation of the σ-adducts. Such oxidative hydroxylation processes have been known for many years but have no general applicability.[10] Thus, one of the major questions is whether these *tert*-alkyl hydroperoxide hydroxylations proceed along the same mechanistic pathway as the VNS—namely, nucleophilic attachment followed by base-induced β-elimination.[5,11]

Table II. Reactions of *tert*-Butyl Hydroperoxide with *p*-Chloronitrobenzene and with 2,4-Dinitrochlorobenzene (Scheme I)

	Z = H		Z = NO_2	
t-BuOK:t-BuOOH	% A	% B	% A	% B
1:1	traces	52	50	20
2:1	27	27	93	traces
5:1	47	16		
5:1[a]	73	7		

[a] $PhCMe_2OOH$ instead of t-BuOOH.

In this respect, results of the reactions with halonitrobenzenes are instructive. For example, in the reaction of *p*-chloronitrobenzene and 2,4-dinitrochlorobenzene with *tert*-butyl hydroperoxide, products of hydroxylation (A) and of S_NAr replacement of halogen (B)[12] are formed (Table II). The ratio of A:B is governed by the concentration of base, hydroxylation being favored by higher base concentration.

Since neither the rate constant ratio, k^H/k^{Cl}, nor the rate of further transformation of the anionic σ^{Cl} adducts should be affected by base concentration, it is reasonable to conclude that the rate of the conversion of σ^H adduct is accelerated by the high base concentration. This behavior supports a mechanistic pathway analogous to the VNS.

Surprisingly, 2,4-dinitrochlorobenzene exhibits a much stronger tendency for VNS hydroxylation than *p*-chloronitrobenzene. Formation of 2,4-dinitro-5-chlorophenol was the predominant process even when the reaction with *tert*-butyl hydroperoxide was carried out with low base concentration. Under such conditions, S_NAr of halogen should be favored. Nevertheless, VNS hydroxylation was the main reaction, and a portion of the chlorodinitrobenzene was recovered.

Thus, similarly to carbanions and OH^- anions,[10b] hydroperoxide anions attach to nitroaromatic rings faster at positions bearing hydrogen than at those bearing halogen.

Interestingly, orientation of the hydroxylation of 1-nitronaphthalene can be efficiently controlled by the conditions. In the presence of sodium hydroxide it occurs at position 4 whereas the use of potassium *tert*-butoxide assures selective hydroxylation at position 2 (Table I, entry 9). These differences are apparently due to the limited solubility of NaOH in liquid ammonia. Since a high concentration of strong base favors 2-hydroxylation, whereas

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a weaker base in lower concentration promotes 4-hydroxylation, one can suppose that the former process is kinetically controlled. Orientation in substituted nitrobenzenes is much less sensitive to changes in the conditions and so far cannot be efficiently controlled.

The selected examples presented in Table I show the generality of this reaction. Since this simple process proceeds under mild conditions giving a variety of substituted nitrophenols in high yields, it can be of substantial value even in a large-scale synthesis. Moreover, some phenols which are not available by traditional methods, as, for example, 2-nitro-3-hyroxythiophene, can be readily prepared via direct VNS hydroxylation (entry 10).

The generality of the vicarious nucleophilic substitution of hydrogen with carbon, amino, and hydroxy substituents and the known nucleophilic replacements of hydrogen via oxidative pathways,[10,13] lead to the conclusion that there is a set of reactions by which hydrogen on electrophilic arenes can be replaced via nucleophilic attack. Due to their similarity in stoichiometry, these reactions can be considered to be a mirror reflection of electrophilic aromatic substitution.[14] There is also a similarity between these processes with respect to ipso substitution. Electrophilic replacement of substituents other than hydrogen on aromatic rings—ipso substitution—is possible, but the substitution of hydrogen is usually much faster.[15] Similarly, nucleophilic substitution of hydrogen on halonitroarenes via VNS, under properly selected conditions, proceeds much faster than conventional S_NAr of halogen (ipso substitution), making the latter a secondary process.[16]

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Regioselective Aza-Cope Rearrangement of α-Halogenated and Nonhalogenated Imines

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Summary: The 3-aza-Cope rearrangement of α-halogenated and nonhalogenated ketimines by deprotonation of the corresponding iminium salts was found to be an especially facile and regioselective process. Deuterium labeling studies supported the proposed mechanism which required the rearrangement to be highly concerted.

The regioselective deprotonation of ketimines is an important reaction for the formation of new carbon–carbon double bonds via alkylation or via aldol-type addition to carbonyl groups.[1a] Dialkyl ketimines are generally deprotonated with high regioselectivity anti to the *N*-alkyl substituent. Highly diastereoselective alkylations of ketimine and aldimine anions have also been observed with optically active N-substituents capable of internally chelating the metal counterion of the 1-azaenolate.[1b,c]

Less work has been reported on the regioselective functionalization of halogenated imines or the stereoselectivity of the alkylation of haloazaenolates.[2] 2-Fluorocyclohexanone can be regiospecifically functionalized using the corresponding pyrrolidine enamine, without stereochemical control.[3] Recently we have shown that the fluoroacetone imine of valinol *O*-methyl ether and the 2-fluorocyclohexanone imine of phenylalaninol *O*-methyl ether can be regioselectively deprotonated and diastereoselectively alkylated to form optically enriched 3-fluoroalkanones and 2-fluoro-2-alkylcyclohexanones[3,4] in modest to good enantiomeric excess.[4]

Stereochemical control in the substitution of imines can also be achieved using the Cope or Claisen rearrangements.[5-11] The 3-aza-Cope rearrangement in particular has been used to form quaternary centers[12-14] or has been employed in natural products synthesis.[15,16] Unfortunately, the conditions for the rearrangement of these *N*-allylenamines are quite rigorous, often requiring high temperatures.[12,17-20] It has been reported that both

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