

Oxidative nucleophilic substitution of hydrogen in nitroarenes with phenylacetic acid derivatives

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Dedicated to Professor V. I. Minkin on the occasion of his 70th birthday

Abstract—Oxidative nucleophilic substitution of hydrogen (ONSH) in nitroarenes with carbanion of isopropyl phenyl acetate gives various products depending on the conditions and oxidant. The reaction carried out in liquid ammonia and KMnO_4 oxidant gives *iso*-propyl α -hydroxy- α -nitroarylphenylacetates formed via hydroxylation of the initial ONSH products. In some cases additionally dimeric, trimeric and tetrameric products are formed. In THF and $\text{Bu}_4\text{N}^+\text{MnO}_4^-$ or DDQ oxidants simple ONSH products are formed whereas oxidation by dimethyl dioxirane (DMD) gave *iso*-propyl hydroxyaryl phenyl acetates. The dimeric and trimeric products are apparently formed via coupling of nitrobenzylic radicals generated in course of oxidation with nitrobenzylic carbanions of the ONSH products.
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1. Introduction

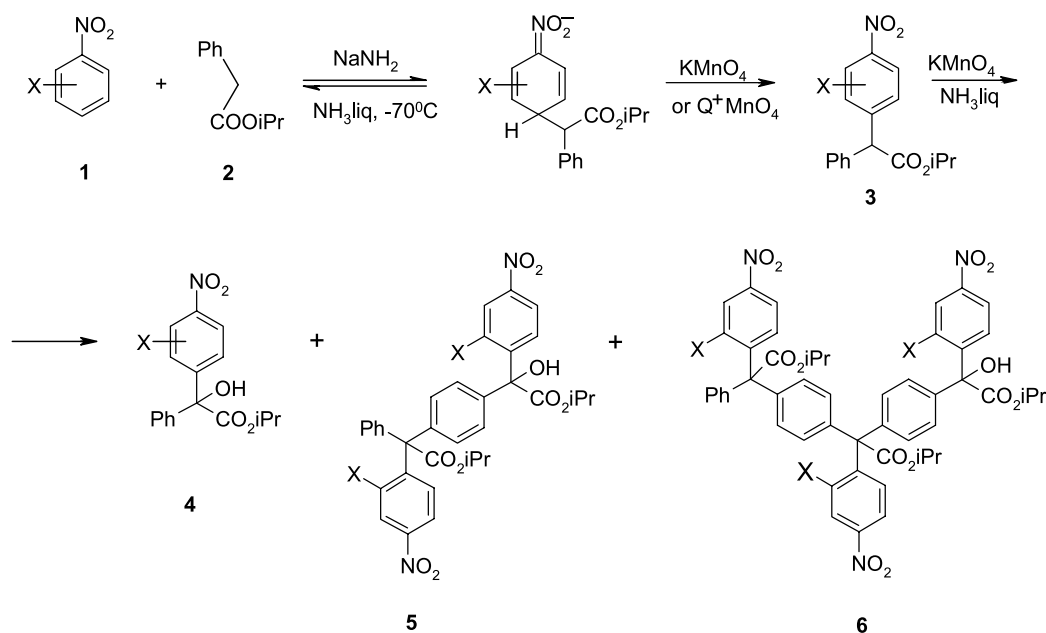
Oxidative nucleophilic substitution of hydrogen (ONSH), in nitroarenes and other electron deficient arenes is presently a well recognized process.^{1–6} Of particular interest and value is introduction of carbon substituents into nitroaromatic rings via oxidation of σ^{H} adducts of carbon nucleophiles such as Grignard reagents^{7–9} and carbanions¹⁰ to nitroarenes. In our recent studies we have shown that this reaction proceeds efficiently between nitroarenes and tertiary (methinic) carbanions generated from 2-phenylalkanenitriles¹¹ and esters of *iso*-butyric¹² and 2-phenylpropionic acids.¹³ Addition of these carbanions to nitroarenes proceeds mainly *para* to the nitro group and the produced σ^{H} adducts are oxidized by KMnO_4 ^{11–13} in liquid ammonia or DDQ in THF giving products of ONSH in *para* positions. It should be noted that oxidation with KMnO_4 is sensitive to steric hindrances, bulky substituents *ortho* to the addition site (*meta* to the nitro group) hinder or inhibit the oxidation process.¹¹ On the other hand, oxidation of these σ^{H} adducts with dimethyl dioxirane (DMD) in THF gives *para* substituted phenols.^{14,15} This oxidant reacts directly with negatively charged nitro group

of the σ^{H} adducts in a process analogous to the Nef reaction.¹⁵

Oxidation of σ^{H} adducts of secondary (methylenic) carbanions to nitroarenes is somewhat more complicated process because the addition can take place at *ortho* and *para* positions so isomeric σ^{H} adducts and subsequently ONSH products can be formed. Moreover the products in which hydrogen of the methylenic group is replaced with a nitroaromatic ring are much stronger CH acids than the carbanion precursors thus in the case the reaction media contain basis agents, the ONSH products could be deprotonated and further oxidized. The highly stabilized nitrobenzylic carbanions of the ONSH products are weak nucleophiles and do not form σ^{H} adducts with nitroarenes so disubstitution via ONSH is not observed. There are many reported examples of ONSH process with secondary carbanions in which atmospheric oxygen acted as the oxidant, usually in these cases the reaction requires excess of base.^{10,16,17} It is therefore supposed that σ^{H} adducts of such carbanions are further deprotonated before being oxidized with oxygen. The reaction of secondary carbanion of phenylacetone nitrile with nitrobenzene in liquid ammonia and KMnO_4 oxidant gave a mixture of *o*- and *p*-nitrobenzophenones.¹⁸ It seems that the initial ONSH products formed by oxidation of the σ^{H} adducts *ortho* and *para* to the nitro group were deprotonated and the produced carbanions oxidized to cyanohydrines that dissociated to benzophenones.

Keywords: Carbanions; Nitroarenes; σ -Adducts; Oxidation; Nucleophilic substitution.

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Scheme 1.

2. Results and discussion

The products of ONSH reaction in nitroarenes by carbanions of alkyl phenylacetates—esters of nitroaryl phenylacetic acids—upon deprotonation and further oxidation should form esters of α -hydroxy nitroaryl phenylacetic acids. Since such esters should be stable under these conditions we have studied ONSH reaction in a series of substituted nitrobenzenes **1a–o** with carbanion of *iso*-propyl phenylacetate **2**. The reactions were carried out in liquid ammonia, the carbanions generated by action of NaNH_2 and the intermediate σ^{H} adducts oxidized with KMnO_4 . Since the expected ONSH products **3a** should be strong CH acids the base was used in excess. The reaction of **2** with nitrobenzene **1a** in ratio 1:1 gave not a simple ONSH product **3a**, but *iso*-propyl 2-phenyl-2-*p*-nitrophenyl-2-hydroxypropionate **4a**, in moderate yield 40%. Obviously, the expected initially formed ONSH product was further deprotonated and oxidized in form of nitrobenzylic carbanion to the hydroxy ester. When nitrobenzene was used in an excess (2 equiv) yield of **4a** was much higher: 78%. It seems therefore that in the former case, due to moderate electrophilicity of **1a**, the addition equilibrium was not sufficiently shifted to the σ^{H} adducts, hence in further experiments nitroarenes were used in excess. It should be mentioned that under these conditions the ONSH reaction proceeded only *para* to the nitro group. Similar products were formed in the reaction of **2** with a series of nitroarenes **1b–m**.

The reaction of **2** with *m*-halonitrobenzenes **1c,e,g,h**, and **j** was more complicated. Besides of the expected α -hydroxyesters **4c,e,g,h,j**, produced via hydroxylation of the initial ONSH products, substantial quantities of products of higher molecular weight were isolated from the reaction mixtures. For instance the reaction of **2** with *m*-chloronitrobenzene **1e** gave expected hydroxyester **4e** 29% and two other products **5e** and **6e**. On the basis of detailed MS (EI and ESI experiments), ^1H and ^{13}C NMR analysis including

correlation spectra of the compounds **5e** and **6e** they were assigned dimeric and trimeric structures, respectively, as shown in Scheme 1. Detailed analyses of the NMR spectra of compounds **5** and **6** are presented at the end of the paper. Results of the reaction of **2** with nitroarenes and KMnO_4 oxidant are given in Table 1

Table 1. Oxidation of σ^{H} adducts of **2**[−] to nitroarenes by KMnO_4 in $\text{NH}_3(\text{liq})$ and by $\text{Bu}_4\text{N}^+\text{MnO}_4^-$ in THF (Scheme 1)

X	ArNO ₂ No.	Products, No. yields							
		KMnO ₄ /NH ₃ liq ^a				Q ⁺ MnO ₄ [−] / THF ^b			
H	1a	4a	78						
2-F	1b	4b	77				3b	45	
3-F	1c	4c	39	5c	27	6c	5	3c	20
2-Cl	1d	4d	57					3d	30
3-Cl	1e	4e	29	5e	39	6e	15	3e	69
2-Br	1f	4f	60					3f	26
3-Br	1g	4g	27	5g	48	6g	17	3g	73
3-I	1h	4h	22	5h	37	6h	13		
3-MeO	1j	4j	29	5j	19	6j	23 ^c		
2-CN	1k	4k	47						
2-NT ^d	1l	4l	26						
1-NN ^e	1m	4m	40						

^a Ratio ArNO₂: **2** = 2.

^b Ratio ArNO₂: **2** = 1.2.

^c Tetramer **6j**[†] was also isolated.

^d 2-Nitrothiophene.

^e 1-Nitronaphthalene.

It should be stressed that compounds **5** and **6** were formed only when the reacting nitroarene contained a substituent X located *meta* to the nitro group. It appears that this substituent affects the reaction course due to its steric, not electronic, effects because products **5** and **6** were formed also in the reaction of **2** with nitrobenzene substituted in *meta* position not only with halogens but also with electrodonating group (X=OMe), *m*-nitroanisole **1j**. It appears that hydroxy esters **3** and dimeric and trimeric products **5** and **6** are formed as a result of oxidation of

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