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# Direct coupling of nucleophiles with nitroaromatic compounds via fluoride-promoted oxidative nucleophilic aromatic substitution for hydrogen

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**Abstract**—Useful yields are achieved in the regioselective direct coupling of amines, amides, and ketones with *m*-dinitrobenzene, 1-nitronaphthalene, and 1,3-dinitronaphthalene, through oxidatively activated nucleophilic aromatic substitution for hydrogen promoted by fluoride anions. © 2001 Elsevier Science Ltd. All rights reserved.

Nucleophilic aromatic substitution is one of the most widely used approaches for the functionalization of aromatics and forms the backbone of numerous important synthesis of pharmaceuticals and potential drugs. However, new atomically efficient chemical reactions, designed to avoid the use of chlorinated aromatics, are required, mainly due to environmental reasons. In this sense, we have focused our attention on nucleophilic aromatic substitution for hydrogen reactions (NASH)[1] as a means of generating functionalized aromatics without the need for halogenated materials or intermediates.[2,3] NASH reactions formally require the replacement of a hydride ion and they occur 'spontaneously', consuming part of the starting material in the oxidation of the anionic σ-complex, or they are promoted by the addition of external oxidants. Low yields (with few exceptions)[4] and lack of generality are the main drawbacks of the first approach.[1] We have recently shown[2] that the use of UV irradiation (to help the redox step) and fluoride anions (to activate the nucleophile in an essentially neutral medium)[5] furnishes useful yields of *N*-alkyl and *N*-acyl anilines,[2a] and *C*-arylated ketones, esters and nitriles[2b] could be also be furnished.

The second approach, oxidative nucleophilic substitution of hydrogen (ONASH), is brought about by the addition of an external oxidant. Although many examples of this transformation have been reported,[6] it suffers from significant limitations.[6d] The most important of these is the sensitivity of the nucleophilic agents (and the anions of the substitution products) towards oxidation. This, in connection with the often unfavorable position of the addition equilibrium and, hence, low concentration of the $\sigma^H$ adducts and high concentration of the nucleophiles, leads to undesired oxidation of nucleophiles and suppression of the ONASH reaction. Therefore, the ONASH process only proceeds satisfactorily with simple nucleophiles, such as $OH^-$ or $CN^-$, resistant to oxidation, or with very stabilized anions, such as the 2-phenylpropionitrile carbanion.[7] Very recently, we have described a successful oxidative electrochemical approach to the cyanation of nitroarenes.[3]

The removal of a proton and two electrons from σ-complexes has been shown to be facilitated in a class of reaction referred to as vicarious nucleophilic substitution (VNS).[8] These reactions require a good leaving group, usually a halide, in a position α to the nucleophile such that decomposition of the corresponding σ-complex results in β-elimination of HX. While this class of reaction has provided useful mechanistic insight and a significant synthetic utility, the requirement for an auxiliary leaving group still persists.

Here, we describe how nucleophile activation by fluoride anions can overcome many of the drawbacks associated with oxidation of the nucleophile (or of the anion of the final substitution product) in ONASH reactions, thus broadening the synthetic scope of the reaction. The fluoride anion is not easily oxidized ($E° =$ 2.4 V versus NHE in acetonitrile),[9] and its activity as a nucleophile activating agent in aprotic solvents is not due to anion generation (HF $pK_a = 15$ in DMSO)[10] but

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is due to its ability to form very strong hydrogen bonds, even with hydrogens bonded to carbon.[5] Activation of the nucleophile is due to partial negative charge transfer upon hydrogen-bond formation, and the tendency of the hydrogen-bonded-complex to undergo oxidation will probably be lower than the one of the free anion. Therefore, we have explored the viability of ONASH reactions of different nitroaromatic substrates with oxidizable nucleophiles, activated by fluoride anions.

In Table 1 (Scheme 1) reactions of *m*-dinitrobenzene (*m*-DNB), 1-nitronaphthalene, and 1,3-dinitronaphthalene with different nucleophiles in the presence of $KMnO_4$, as oxidant, and fluoride anions, as the nucleophile activating agent, are described. Thus, in experiments 1 and 2, excellent yields of regioselective hydrogen substitution by amines are obtained. The reactions with amides also give fair to good yields of substitution products, and it is important to notice that these experiments constitute a formal 'chlorine free' new route to 2,4-dinitroaniline through hydrolysis of the obtained amides (or treatment of the amides with methanolic ammonia).[11] Recently, we have described a photochemical alternative that eludes the use of an external oxidant and that gives similar results.[2b] In experiments 5–7, carbon nucleophiles are used with different results. Thus, ketones give rise to hydrogen-substitution products in fair yields but acetonitrile fails to do so.

The experiments with 1-nitronaphthalene and 1,3-dinitronaphthalene (Table 1, exp. 8–11) are very significant and they help to understand the limits of the scope of the reaction. Thus, electron-rich 1-nitronaphthalene (when compared with *m*-DNB) reacts with a relatively acidic nucleophile, such as acetone ($pK_a = 26.5$ in DMSO),[10] but fails (the starting material is recovered) with a much less acidic nucleophile, such as *n*-butylamine ($pK_a > 35$ in DMSO). This indicates that the activation of the nucleophile through hydrogen-bond formation with fluoride anions is very much dependent on the acidity of the active hydrogens and, in each case, a threshold exists that depends on the balance between the electrophilicity[12] of the aromatic compound and the

**Table 1.** Reactions of nitroaromatic compounds with nucleophiles in the presence of $KMnO_4$ and fluoride anions (TBAF)

| Exp. | Substrate | Nucleophile | Conditions[a] | Product | Yield(%)[b] |
|---|---|---|---|---|---|
| 1 | *m*-Dinitrobenzene | $CH_3(CH_2)_3NH_2$ | DMF, 1.5 h, rt | **1a** | 63[c] |
| 2 | *m*-Dinitrobenzene | $PhNH_2$ | DMF, 1 h, rt | **1b** | 75[d] |
| 3 | *m*-Dinitrobenzene | $CH_3CONH_2$ | DMF, 1 h, rt | **1c** | 35[d] |
| 4 | *m*-Dinitrobenzene | $PhCONH_2$ | DMF, 0.75 h, rt | **1d** | 61[d] |
| 5 | *m*-Dinitrobenzene | $CH_3COCH_2CH_3$ | 1 h, rt | **1e**[e] | 42 |
| 6 | *m*-Dinitrobenzene | $CH_3CN$ | 1 h, rt | **1f** | Traces |
| 7 | *m*-Dinitrobenzene | $CH_3COCH_3$ | 20 min, rt | **1g** | 44 |
| 8 | 1-Nitronaphthalene | $CH_3(CH_2)_3NH_2$ | DMF, 1 h, rt | **2a** | [f] |
| 9 | 1-Nitronaphthalene | $CH_3COCH_3$ | 1.5 h, rt | **2g** | 29[g] |
| 10 | 1,3-Dinitronaphthalene | $CH_3(CH_2)_3NH_2$ | DMF, 4.5 h, rt | **3a** | 34[h] |
| 11 | 1,3-Dinitronaphthalene | $CH_3COCH_2CH_3$ | 1.5 h, rt | **3e** | [i] |

[a] Molar ratio of substrate/$KMnO_4$ = 1:1. An excess of nucleophile (5 equiv.) was used in the reactions in DMF; in the others the nucleophile was used as the solvent. 5 equiv. of FTBA·$3H_2O$.

[b] Preparative yields of isolated products. For selected data of new compounds, see Ref. 14.

[c] *N*-(2,4-Dinitrophenyl)butyramide (8% yield) was also obtained.

[d] 2,4-Dinitrophenol was also obtained in 22, 23 and 13% yield in experiments 2–4, respectively.

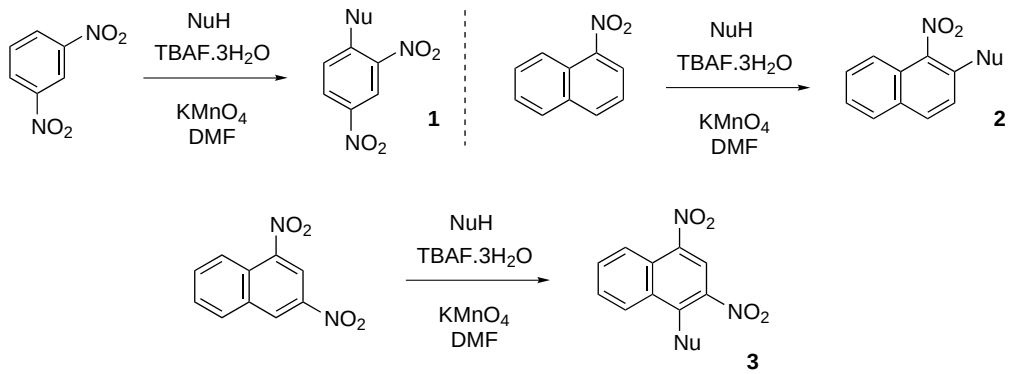
[e] Compound **1e** is a mixture of 1-(2,4-dinitrophenyl)butan-2-one and 3-(2,4-dinitrophenyl)butan-2-one.

[f] The starting material 1-nitronaphthalene was fully recovered.

[g] A small amount of the isomer 1-(4-nitronaphthalen-1-yl)acetone was also obtained.

[h] 53% of starting material was recovered.

[i] Extensive degradation of the reaction mixture was observed.




**Scheme 1.**

activity of the nucleophile (directly related to the acidity).

On the other hand, the experiments with 1,3-dinitronaphthalene afford information about the existence of two additional thresholds in our reactions. Thus, this substrate is more electrophilic than 1-nitronaphthalene and *m*-DNB,[12] and, in this case, the substitution with a ketone (butanone, exp. 11, Table 1) fails but the starting material is not recovered and extensive degradation is observed. This is very similar to what occurs in experiment 6 (Table 1) with *m*-DNB when acetonitrile is used as the nucleophile. We attribute this behavior to the acidity of the final substitution products, that would not be stable in the reaction mixture, undergoing oxidation in the presence of $KMnO_4$. In experiment 10, another interesting feature of these reactions can be established. Thus, even though 1,3-dinitronaphthelene is the most electrophilic substrate among the three studied, and that the reaction with *n*-butylamine is very clean, it is rather slow (only 66% conversion after 4.5 h). This behavior is attributed to the fact that the σ-adduct intermediate in the case of 1,3-dinitronaphthalene has a high redox potential, practically at the limit of the oxidizing power of $KMnO_4$ in DMF.[13]

The results reported in Scheme 1 and Table 1 broaden considerably the usefulness of the ONASH reaction, allowing the introduction of typical carbon and nitrogen nucleophiles in aromatic rings in a very simple way.

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12. A simple ordering of electrophilicity can be achieved by considering the energies of the LUMO orbitals of the nitroaromatic compounds calculated using the semi-empirical AM1 method implemented in the MOPAC package: 1,3-dinitronaphthalene, $E_{LUMO}=-2.06$ eV; *m*-dinitrobenzene, $E_{LUMO}=-1.91$ eV; 1-nitronaphthalene, $E_{LUMO}=-1.30$ eV.
13. $E°(MnO_4^-)=-0.6$ V (versus SCE in DMF), see: Bock, H.; Jaculi, D. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 305. Using cyclic voltammetry we have measured $E_{pc}=0.8$ V (versus SCE) for σ-adducts of 1,3-dinitronaphthalene and $E_{pc}=0.6$ V (versus SCE) for σ-adducts of *m*-DNB, with amines.
14. Selected data for 1-(1-nitronaphthalen-2-yl)acetone, **2g**: $\delta_H$ (250 MHz, $CDCl_3$): 2.24 (s, 3H), 3.88 (s, 2H), 7.30 (dd, *J* 8.5, 1.0, 1H), 7.56 (m, 2H), 7.85 (m, 3H); $\delta_C$ (62.5 MHz): 29.77, 46.51, 121.78, 124.68, 125.03, 127.30, 127.87, 128.04, 128.79, 131.18, 133.04, 147.72, 203.28; IR: *v* 1714, 1519, 1344, 1316 $cm^{-1}$; mp 75–76°C. Anal. calcd for $C_{12}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.18; H, 4.84; N, 6.01. Selected data for *N*-butyl-(2,4-dinitronaphthalen-1-yl)amine, **3a**: $\delta_H$ (250 MHz, $CDCl_3$): 0.95 (t, *J* 7.3, 3H), 1.47 (m, 2H), 3.89 (q, *J* 6.8, 2H), 7.56 (t, *J* 7.2, 1H), 7.80 (t, *J* 7.2, 1H), 8.32 (dd, *J* 8.6, 0.7, 1H), 8.75 (dd, *J* 8.6, 0.7, 1H), 9.16 (s, 1H), 9.73 (broad s, 1H); $\delta_C$ (62.5 MHz): 13.59, 19.87, 33.50, 50.93, 123.68, 124.48, 124.87, 126.09, 126.21, 128.33, 129.92, 132.77, 135.34, 152.14; IR: *v* 1587, 1548, 1402 $cm^{-1}$; mp 74–76°C. Anal. calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.14; H, 5.28; N, 14.39.