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Unexpected nuclear formylation and acetylation of some nitroanilines with dimethyl sulfoxide in the presence of a strong base

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Abstract

When treated with a strong base such as KO^{t}Bu or NaH in dimethyl sulfoxide at room temperature, 2,4-dinitro-, 2-cyano-4-nitro- and 4-cyano-2-nitroanilines were found to undergo regiospecific acylation at the 3-position to afford the corresponding 3-formyl or 3-acetyl derivatives in fair to moderate yields.

Keywords: acylation; sulfoxides; nitro compounds; arenes; carbanions.

Due to the inherent importance of carbonyl compounds as starting materials in organic synthesis, the Friedel–Crafts type acylation has been widely employed as a tool for introducing the carbonyl function into aromatic systems.[1] This reaction proceeds via the electrophilic pathway involving the acylium ion or its complex as the attacking species, so it fails when the substrates bear electron-withdrawing substituent groups. This is the reason why nitrobenzene is sometimes used as a reaction medium for the Friedel–Crafts reaction. In the last two decades, however, several indirect methods have been developed for the introduction of the formyl group into nitroarenes, which are based on the vicarious nucleophilic substitution of hydrogen with anions of tris(phenylthio)methane,[2] haloforms,[3] chloromethyl phenyl sulfone[4] and tris(benzotriazol-1-yl)methane.[5] In the present paper, we wish to report the direct formylation and acetylation of some nitroanilines with dimethyl sulfoxide (DMSO) in the presence of a strong base at room temperature.

During the course of our ongoing program on the nucleophilic displacement reaction of nitroarenes,[6] we have come across an unusual acylation that took place at the most crowded site of nitroanilines **1**, when they were treated with potassium *tert*-butoxide or sodium hydride in DMSO at room temperature. Thus, 2,4-dinitroaniline **1a** underwent formylation at the 3-position

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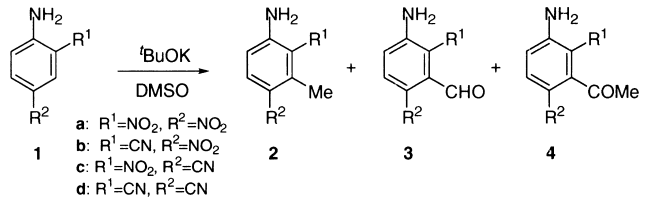
to give the corresponding aldehyde **3a**. The product distribution was similar irrespective of the bases employed. The acylation was always accompanied by methylation to a considerable extent under the conditions employed (Scheme 1).



Scheme 1.

When 2,4-dinitroaniline **1a** and potassium *tert*-butoxide were dissolved in DMSO in a ratio of 1:4 and stirred for 6 h under ambient conditions, 3-methyl-2,4-dinitroaniline **2a** was obtained in 86% yield, as expected.[7] Quenching of the reaction mixture with heavy water led to partial deuteration of the methyl group, ruling out the possible operation of a free radical mechanism. In anticipation of promoting the rate of methylation as well as the product yield, we carried out the reaction under an atmosphere of oxygen.[8] To our surprise, however, 3-amino-2,6-dinitrobenzaldehyde **3a** was isolated in 20% yield in addition to the expected **2a**. Previously, Russell et al. reported that nitrobenzene reacts with methylsulfinylmethyl anion under atmospheric conditions to produce *o*- and *p*-nitrobenzoic acids.[9] The observed discrepancy may be ascribed to steric crowdedness around the reaction site, which would suppress oxidation of the initially formed aldehyde **3a**. With this assumption in mind, we next chose less crowded 2-cyano-4-nitroaniline **1b** and 4-cyano-2-nitroaniline **1c** as the substrates. To our great surprise, these compounds were found to undergo acetylation at the 3-position to give 3-acetyl-2-cyano-4-nitroaniline **4b** and 3-acetyl-4-cyano-2-nitroaniline **4c** in 42 and 32% yields, respectively, in addition to the corresponding methylation products **2b** and **2c** (Table 1). When the reaction of **1b** was carried out under oxygen, the yields of **2b** and **4b** were 23 and 44%, respectively. Under argon, they were obtained in 26 and 38% yields, respectively. 2,4-Dinitroanisole and *N*,*N*-dimethyl-2,4-dinitroaniline failed to behave similarly, while 2,4-dicyanoaniline **1d** and 2,4-dinitrophenol resulted in the recovery of the starting materials. When the *N*-acetyl derivative of

Table 1
Reaction of nitroanilines and related compounds with methylsulfinylmethyl anion

Substrate	R^1	R^2	Yield (%)[a]		
1			**2**	**3**	**4**
1a[b]	NO_2	NO_2	42	20	–
1b	CN	NO_2	27	–	42
1c	NO_2	CN	20	–	32
1d[c]	CN	CN	–	–	–

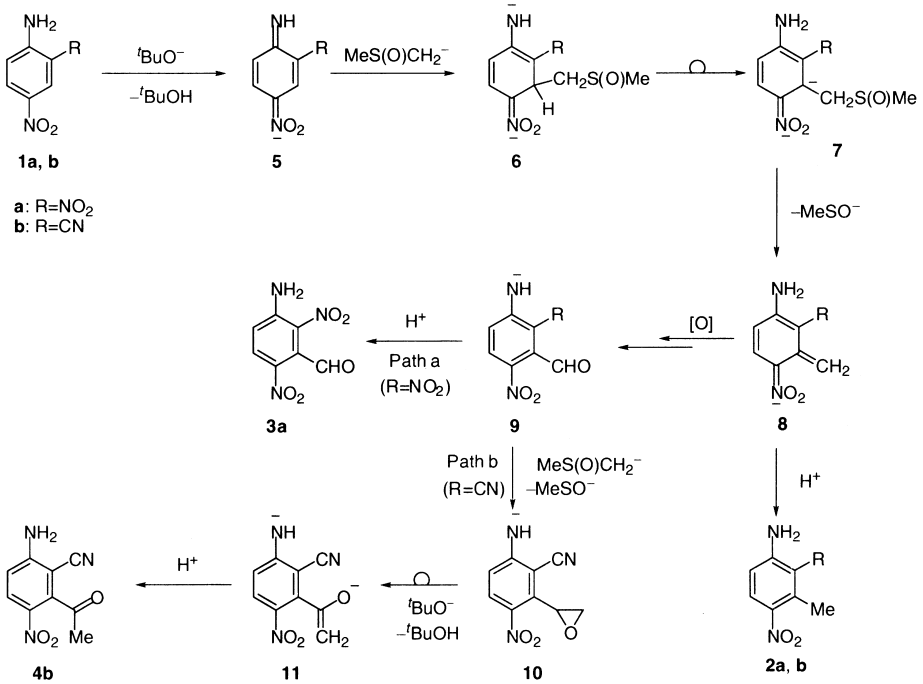
[a] Isolated yield. For reaction conditions, see the text. Products were characterized by ^{1}H NMR, IR and MS spectra and elemental analysis.

[b] The reaction was carried out under oxygen.

[c] Starting material was recovered almost unchanged.

nitroaniline **1a** was subjected to the action of potassium *tert*-butoxide under similar conditions, there resulted a complex mixture of products as a tarry matter. Therefore, the effective operation of a push–pull electronic interaction, the presence of strongly electron-withdrawing substituent groups close to the reaction site, and ease of formation of anilino anion seem to be crucial for the present unusual acylation of nitroanilines with DMSO.

Based on the existing information, a possible mechanistic pathway to the unusual acylation products **3** and **4** is illustrated in Scheme 2. Nitroaniline **1** first deprotonates on the nitrogen to generate the stabilized anion **5**, which combines with methylsulfinylmethyl anion at the most electropositive ring site to form the adduct ion **6**. This ion undergoes isomerization to **7**, followed by the release of methylsulfinyl anion to afford the nitronate **8**, which is protonated to give the methylation product **2**. Under an atmosphere of oxygen, the anion **8** would be oxidized to the aldehyde anion **9**.[10] The formation of **9** is the common starting point for the following two different pathways a and b. When the substituent R at the 2-position of **9** is a nitro group, steric congestion would disturb further transformation of the aldehyde function (path a). However, when R is a cyano group, the second attack by methylsulfinylmethyl anion would take place at the carbonyl function of **9** to produce the epoxide **10**,[12] which, in the presence of a strong base, would undergo a Wittig-type rearrangement to give methyl ketone **4b** via the enolate **11** (path b).[13] The progress of the reaction was monitored by ^{1}H NMR, but we failed to observe any intermediate stages definitely. We reserve a discussion of the acylation mechanism for future publication.



Scheme 2.

The representative procedure for the acylation of nitroanilines **1** is as follows. A mixture of 2-cyano-4-nitroaniline (**1b**; 0.20 g, 1.2 mmol), potassium *tert*-butoxide (0.60 g, 5.4 mmol) and

DMSO (5 ml) was stirred at room temperature under air. After 6 h, the colored solution was diluted with 1 M HCl (30 ml) and the organic phase was extracted with CH_2Cl_2 (3×30 ml). The combined extracts were evaporated to leave a solid residue, which was chromatographed on silica gel using a mixture of hexane–AcOEt as the solvent to elute 2-cyano-3-methyl-4-nitroaniline (**2b**; 59 mg, 0.33 mmol) and 3-acetyl-2-cyano-4-nitroaniline (**4b**; 0.11 g, 0.52 mmol) in this order.[14]

In summary, some nitroanilines of an extended capto-dative electronic structure have been found to undergo direct formylation or acetylation at a crowded ring site by the action of a strong base in DMSO at room temperature. Apparently limited in scope, the present reaction offers a novel type of nucleophilic aromatic substitution that takes place in DMSO under strongly basic conditions.[15]

References

1. For details of Friedel–Crafts acylation, see: Olah, G. A. *Friedel–Crafts and Related Reactions*, Vols. 1 and 3. Wiley: New York, 1963–64.
2. (a) Makosza, M.; Winiarski, J. *Chem. Lett*. **1984**, 1623. (b) Grobel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.
3. Makosza, M.; Owczarczyk, Z. *J. Org. Chem*. **1989**, *54*, 5094; *Tetrahedron Lett*. **1987**, *28*, 3021.
4. (a) Wulf, J. P.; Sienkiewicz, K.; Makosza, M.; Schmitz, E. *Liebigs Ann. Chem*. **1991**, 537. (b) Makosza, M.; Golinski, J.; Baran, J. *J. Org. Chem*. **1984**, *49*, 1488.
5. Katritzky, A. R.; Xie, L. *Tetrahedron Lett*. **1996**, *37*, 347.
6. Kawakami, T.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1259, and papers cited therein.
7. Argabright, P. A.; Hofmann, J. E.; Schriesheim, A. *J. Org. Chem*. **1965**, *30*, 3233.
8. It appears that some oxygen is required, since under conditions where oxygen was excluded, the reaction was sluggish and incomplete.
9. Russell, G. A.; Weiner, S. A. *J. Org. Chem*. **1966**, *31*, 248.
10. The decomposition of sulfoxide **6** to aldehyde **9** has formal analogy to the thermal decomposition of benzyl methyl sulfoxide to benzaldehyde and methanethiol, which has been explained to proceed by way of benzyl methylsulfenate.[11]
11. Carruthers, W.; Entwistle, I. D.; Johnstone, R. A. W.; Millard, B. J. *Chem. Ind*. **1966**, 342.
12. Chaykovsky, M.; Corey, E. J. *J. Org. Chem*. **1963**, *28*, 254.
13. For a review of the Wittig rearrangement, see: Marshall, J. A. In *Comprehensive Organic Chemistry*, Vol. 3; Trost, B. M., Ed.; Pergamon: Oxford, 1991; p. 975.
14. Compound **2b**. Mp 203–204°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 2.82 (s, 3H, Ar–CH_3), 5.02 (br, 2H, Ar–NH_2), 6.65 (d, 1H, J=9.0, Ar–*H*), 8.11 (d, 1H, J=9.0, Ar–*H*), MS (EI, 70 eV): m/z 177 [M$^+$] (83%), 160 (100%); IR (KBr; ν, cm^{-1}): 2226 (CN), 1647 (C=O), 1590, 1350 (NO_2). Found: C, 54.07; H, 3.96; N, 23.54%. $C_8H_7N_3O_2$ requires: C, 54.24; H, 3.98; N, 23.72%. Compound **4b**. Mp 158–159°C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ (ppm) 2.63 (s, 3H, CO–CH_3), 7.08 (d, 1H, J=9.7, Ar–*H*), 7.69 (d, 1H, J=9.7, Ar–*H*), 7.08 (br, 2H, Ar–NH_2); MS (EI, 70 eV): m/z 205 [M$^+$] (51%), 190 (100%), 176 (55%); IR (KBr; ν, cm^{-1}): 2207 (CN), 1655 (C=O), 1526, 1332 (NO_2). Found: C, 52.99; H, 3.51; N, 20.25%. $C_9H_7N_3O_3$ requires: C, 52.69; H, 3.41; N, 20.48%.
15. For leading monographs on nucleophilic aromatic substitution of nitroarenes, see: (a) Churakhin, O.; Charushin, V.; van der Plas, H. C. *Nucleophilic Aromatic Substitution of Hydrogen*; Academic: New York, 1994. (b) Terrier, F. *Nucleophilic Aromatic Displacement*; VCH: New York, 1991.