Facile and Mild Displacement of Nitrite Ions in Electron-Deficient Nitroarenes by Alkyl or Aryl Thiols in the Presence of Magnesium Methoxide as a Solid Base Catalyst

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Abstract: The nucleophilic aromatic substitution reaction (S_NAr) between nitroarenes (having electron-withdrawing groups in the *ortho* or *para* position), and alkyl- or arylthiols using magnesium methoxide as a solid base catalyst is described. This method leads to the creation of a series of valuable compounds from arylsulfides via nucleophilic displacement of the nitro group with the sulfanyl moiety. This facile method is a synthetically useful process, and it is significant that the nucleophile is promoted effectively by magnesium methoxide as a base in *N*,*N*-dimethylformamide. The displacement of then nitrite ion occurred in the presence of a variety of functional groups that caused an electron-deficient ring such as aldehyde, ketone, ester, cyano, and nitro groups.

Key words: nitroarene, thiol, magnesium methoxide, aryl thioether

A large amount of information is available on nucleophilic aromatic substitution (S_NAr) reactions where the nitro group enables nucleophilic substitutions in the benzene ring, thus altering the *ortho* and *para* positions of the nitro group.[1] In all of these reactions, the presence of nitro and other electron-withdrawing groups on the benzene ring activates other substituents, even nitro groups, at the *ortho* and *para* positions for displacement with nucleophiles.[2] Thus, this can result in the removal of a nitro group by a nucleophile.[3] Nucleophilic displacement of a nitro group from a benzene ring carrying only one activating group has rarely been observed.[4] This is no doubt due to the fact that it also has a very strong activating effect toward nucleophilic displacement of other substituents on an aromatic nucleus. Baumann has shown that sodium α-toluene thiolate reacts with methyl *p*-nitrobenzoate to form methyl *p*-(benzylthio)benzoate, resulting in the loss of nitrite.[5]

Beck et al.[6] have shown that, when a dipolar aprotic solvent (DMF) is employed, the displacement of a nitro group by thiolates occurs readily at room temperature. As previously reported, it has been found that 4,4′-dinitrobenzophenone readily undergoes replacement of the nitro group by sodium phenoxide in dipolar aprotic solvents.[7] Kornblum et al. reported the synthesis of aromatic sulfides via displacement of a nitro group with sodium thiolates in the presence of hexamethylphosphoramide (HMPA).[8] However, in all of these procedures, nucleophiles must be pre-prepared as sodium salts and this can lead to side reactions such as oxidation of the thiolate anion to sulfinate, nucleophilic attack on the functional group, or reduction of the nitro substituent.[5]

This study reports an improved method for S_NAr reactions of activated nitroarenes with thiols. The present reaction is high-yielding and is a facile procedure compared with similar reactions, and should prove to be an extremely useful tool for formation of an sp^2 carbon–sulfur covalent bond.[9]

We began our study by investigating the base and solvent required for this reaction. The reaction of 2-nitrobenzaldehyde (**1a**) with thiophenol (**2a**) was chosen as a model reaction. To our satisfaction an initial attempt in which a mixture of substrates **1a** and **2a** was added to freshly prepared solid magnesium methoxide in dimethyl sulfoxide (Table 1, entry 8) provided a good yield of the desired coupling product.

In order to determine the appropriate base for this reaction, several metal alkoxides and other organic and inorganic bases were applied (Table 1, entries 2–7). When sodium methoxide was used as a base the yield of **3a** was very low due to side reactions resulting from nucleophilic attack of the methoxide (Table 1, entry 4). As can be seen in Table 1, magnesium methoxide proved to be most efficient among bases tested. This effect may be due to the high basicity of magnesium methoxide in DMF. The use of potassium carbonate and sodium carbonate resulted in lower yields, and organic bases such as triethylamine were far less effective (Table 1, entries 5–7).

Screening different solvents indicated that *N*,*N*-dimethylformamide and dimethyl sulfoxide were the best choices, although these solvents generally provided a lower yield of adduct at room temperature; however, the reaction in DMF was accelerated sixfold by increasing the temperature to 80 °C (Table 1, entries 1 and 9).

While a stoichiometric amount (0.5 mol) of magnesium methoxide should be sufficient to achieve quantitative conversion, using 1 mol of magnesium methoxide yielded 2-phenylthiobenzaldehyde in 87% yield. Substoichiometric amounts of the base resulted in poor conversions even with prolonged reaction times.

Encouraged by the ease of this reaction, we next focused on expanding the scope of the methodology. Table 2 highlights the broad range of the various electron-deficient substrates that can be used to ease the S_NAr reaction, in-

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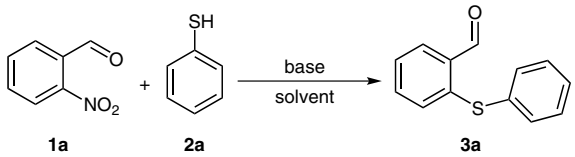
Table 1 Optimization Study of the Reaction[a]



1a 2a 3a

Entry	Base	Solvent	Time (°C)	Time (h)	Yield (%)[b]
1	$Mg(OMe)_2$	DMF	80	4	87
2	$Mg(OEt)_2$	DMF	80	5	72
3	$Ca(OMe)_2$	DMF	80	7	45
4	$Na(OMe)_2$	DMF	80	4	40[c]
5	K_2CO_3	DMF	80	4	13
6	Na_2CO_3	DMF	80	4	7
7	Et_3N	DMF	80	4	<3
8	$Mg(OMe)_2$	DMSO	80	5	71
9	$Mg(OMe)_2$	DMF	r.t.	25	80
10	$Mg(OMe)_2$	THF	65	10	14
11	$Mg(OMe)_2$	MeOH	60	10	15
12	$Mg(OMe)_2$	EtOH	65	10	11

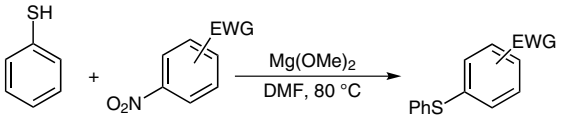
[a] Reaction conditions: starting materials (2 mmol) were added to solid magnesium methoxide (2 mmol) in related solvents (8 mL).
[b] Isolated yields.
[c] Moreover, a product yield of 32% including displacement of the methoxide ion was obtained.

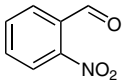
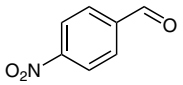
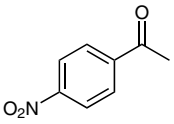
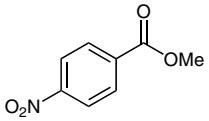
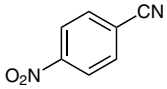
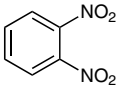
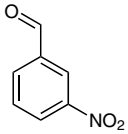
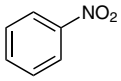
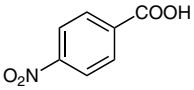
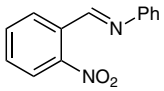
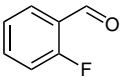
cluding a formyl group and other electron-withdrawing groups such as ketone, nitro, and cyano groups (Table 2, entries 3–6). It is worth noting that the S_NAr reaction of 4-nitromethylbenzoate occurred without any byproducts resulting from cleavage of the methyl ester linkage (Table 2, entry 4). The reaction of nitrobenzene and 3-nitrobenzaldehyde with **2a** failed to afford the corresponding product even at an elevated temperature (Table 2, entries 7 and 8).

The reaction of 2-fluorobenzaldehyde with thiophenol provided 2-phenylthiobenzaldehyde after 12 hours in only 14% yield, with 83% of 2-fluorobenzaldehyde recovered (Table 2, entry 11). Substrates containing carboxylic acid and imine moieties as electron-withdrawing groups did not provide the desired coupling products (Table 2, entries 9 and 10).

Finally, we investigated the S_NAr reaction of some nitro substrates with 1,3-propanedithiol (Table 3) and 3-mercaptopropanoic acid (Table 4) under the same reaction conditions and in the presence of 2.5 equivalents of $Mg(OMe)_2$ as a solid base. However, the reaction of 1,3-propanedithiol and 3-mercaptopropanoic acid with some nitroarenes and magnesium methoxide led to related compounds in high yield.

Table 2 S_NAr Reaction of Thiophenol with Electron-Deficient Rings[a]



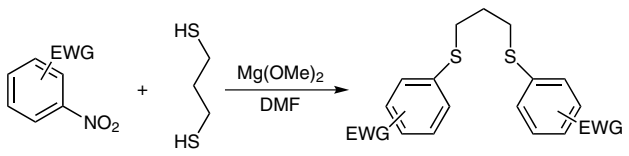
Entry	Substrate	Time (h)	Yield (%)[b]
1		4	87
2		4	88
3		5	84
4		6	85
5		6	78
6		5	81
7		15	–
8		15	–
9		20	<3
10		20	–
11		12	14

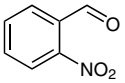
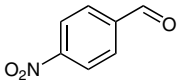
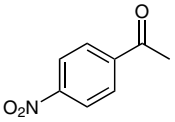
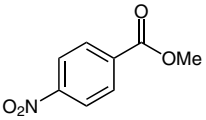
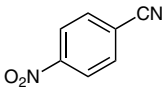
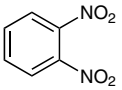
[a] Reaction conditions: starting materials (2 mmol) were added to magnesium methoxide (2 mmol) in DMF (8 mL) as solvent.
[b] Isolated yield.

As illustrated in Table 4, the S_NAr reaction 3-mercaptopropanoic acid led to the corresponding adducts, although with a longer reaction time (Table 4, entries 1–4).

In conclusion, we have successfully demonstrated that the nucleophilic aromatic substitution reaction between electron-deficient nitroarens and thiol derivatives can be effi-

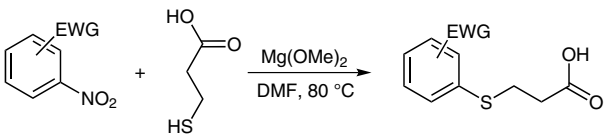
Table 3 S_NAr Reaction of Nitro Substrates with 1,3-Propanedithiol[a]

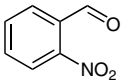
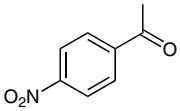
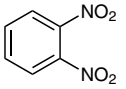
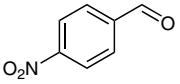


Entry	Nitro substrate	Time (h)	Yield (%)[b]
1		7	81
2		7	85
3		8	77
4		8	78
5		9	71
6		8	76

[a] Reaction conditions: 1,3-propanedithiol (2.0 mmol) and nitro substrate (4.0 mmol) were added to magnesium methoxide (5.0 mmol) in DMF (10 mL).
[b] Isolated yield.

Table 4 S_NAr Reaction with 3-Mercaptopropanoic Acid[a]



Entry	Nitro substrate	Time (h)	Yield (%)[b]
1		10	80
2		10	73
3		10	71
4		10	82

[a] Reaction conditions: 3-mercaptopropanoic acid (2.0 mmol) and nitro substrate (2.0 mmol) were added to magnesium methoxide (5.0 mmol) in DMF (10 mL).
[b] Isolated yield.

ciently performed via deprotonation using magnesium methoxide as the base. This novel C–S bond-formation reaction provides moderate to excellent yields of the corresponding thioether adducts under mild conditions and short reaction times. The versatility of this reaction allowed us to efficiently prepare novel thioether compounds, which are subsequently evaluated as novel xenobiotics.

Representative Procedure
Freshly prepared $Mg(OMe)_2$ (see Supporting Information; 0.18 g, 2 mmol) was placed in a 20 mL reaction flask. DMF (8 mL), 2-nitrobenzaldehyde (0.30 g, 2 mmol), and thiophenol (0.22 g, 2 mmol) were added and stirred at 80 °C for 4 h, and the progress of the reaction was monitored by TLC. After completion of the reaction, H_2O (50 mL) was added, and the aqueous solution was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure to produce a yellow oil that was purified by chromatography on silica gel to afford 2-phenylthiobenzaldehyde (0.37 g 87% yield).

2-(Phenylthio)benzaldehyde (Table 2, Entry 1)
Yellow oil. IR (thin film): 3060 (HAr), 2846, 2738 (HCO), 1686 (C=O), 1584, 1445 (C=C, Ar), 1392, 1299, 1195, 751, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.38 (s, 1 H, HC=O), 7.88 (s, 1 H, Ar), 7.26–7.43 (m, 7 H, Ar), 7.10 (s, 1 H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 126.3, 128.4, 129.7, 130.3, 131.9, 133.1, 133.2, 133.7, 134.1, 141.5, 191.4. MS: *m/z* (%) = 215 (1.5) $[M + 1]^+$, 215 (12) $[M^+]$, 185 (45), 109 (74), 105 (23), 76 (100). Anal. Calcd for $C_{13}H_{10}OS$ (214.28): C, 72.8; H, 4.7. Found: C, 72.7; H, 4.6.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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