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A practical and selective reduction of nitroarenes using elemental sulfur and mild base

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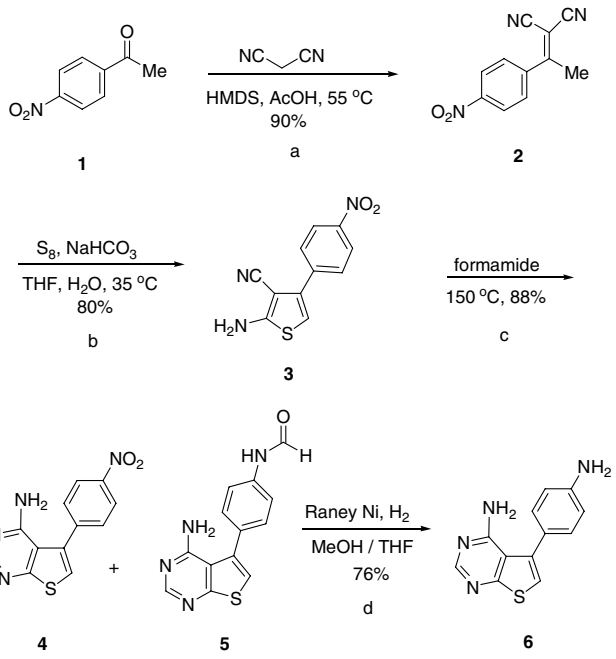
Abstract—A method was developed to reduce aromatic nitro compounds to the corresponding anilines using sulfur and base. The method tolerates a range of functional groups on the benzene ring, avoids the use of hydrogen and transition metals and provides the anilines in moderate to high yields.

Aromatic amines find applicability in diverse fields including pharmaceuticals, agrochemicals, dyes, and photographic materials. One route for their preparation is by reduction of nitroarenes. Numerous methods have been developed to accomplish this transformation including catalytic hydrogenation,[1] iron, tin, or zinc,[2] sodium borohydride/catalyst,[3] and hydrazine/catalyst.[4] Nitroarenes may also be reduced by sulfides, polysulfides, or elemental sulfur.[5]

In 1950, Hirao used elemental sulfur (S_8) in refluxing aqueous sodium hydroxide to reduce nitroarenes.[6] This method, however, was not applicable to substituted arenes. Related methods have been developed which use sulfur with alumina supported NaOH[7] in neat nitroarene or with amine base or ammonia as solvent.[8] Herein, we report the development of a general and practical reduction of nitroarenes using S_8.

Thienopyrimidine **6** was identified as an intermediate in the synthesis of a multitargeted kinase inhibitor (Scheme 1).[9] This core was prepared by Knoevenagel condensation of 4-nitroacetophenone (**1**) with malononitrile followed by a modified Gewald reaction using S_8 and sodium bicarbonate. The resulting thiophene (**3**) was heated at 150 °C in formamide to yield thienopyrimidine **4** along with up to 20% of formylated aniline **5**. Further investigation indicated that the reduction resulted from the presence of residual sulfur carried through from the Gewald reaction (reaction b). The addition of triphenylphosphine as a sulfur scavenger to the pyrimidine forming reaction suppressed this reduction. Finally, a Raney nickel reduction of thienopyrimidine **4** yielded 76% aniline **6** along with N-alkylated and S-extruded byproducts. The presence of these byproducts along with the observed nitro reduction by S_8 suggested the potential for investigating sulfur as a nitroarene reductant.



Scheme 1. Synthesis of thienopyrimidine **6**.

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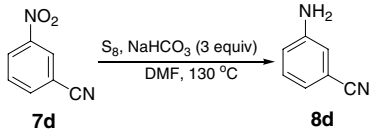
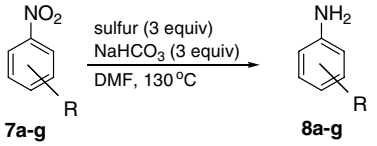


7d 8d (1)

Further study of the reduction showed that sulfur might be used to reduce a variety of nitro arenes to the corresponding anilines. The influence of base, solvent and reagent equivalents was investigated to determine standard conditions for the reduction. A screen of amine and inorganic bases including propylamine, $NaHCO_3$, Na_2CO_3, NaOH, and K_2HPO_4 with sulfur in formamide at 100 °C showed $NaHCO_3$ to provide the best conversion while minimizing side product formation. A product mixture containing aniline and formylated aniline byproducts, however, complicated these reactions. Attempts to drive the reaction completely to the formylated product by extending the reaction time were unsuccessful, but a change of solvent from formamide to dimethylformamide eliminated this side product formation. Next, it was shown that 3 equiv each of S_8 and $NaHCO_3$ gave the best conversion to product. Using 3-nitrobenzonitrile (**7d**, Eq. 1), the conversion at 2 h was 96%[10] with 3 equiv of S_8 versus 64% with 2 equiv, and 40% with 1 equiv. Investigation of the reaction temperature showed that elevated temperatures (130 °C) were typically required for the reduction. Therefore, optimal conditions were the nitroarene (1 equiv), sulfur (3 equiv), and $NaHCO_3$ (3 equiv) in DMF at 130 °C.

The scope of the reaction was examined using various substituted nitroarenes (Table 1). The reaction was found to tolerate a range of functionalities on the aromatic ring including nitrile, ester, amide, and chloride substituents. However, attempts to reduce both 3- and 4-bromo-nitrobenzene resulted in significant decomposition. The yield of these latter reactions was not improved at 100 °C. Finally, reduction of nitropyrimidine **4** (Eq. 2) proceeded cleanly under these conditions to afford aniline **6** in 93% yield. The higher yield relative to the reaction run under previous conditions (76%) is attributed to the absence of N-alkylated and S-extruded byproducts formed during the Raney nickel reduction.[9]

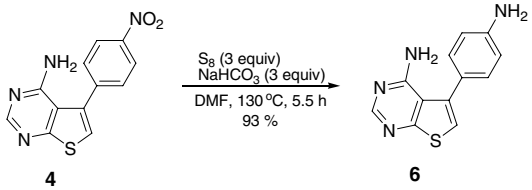
Table 1. S_8 Reduction of functionalized nitroarenes



7a-g 8a-g

Substrate	R	Time (h)	Yield[a] (**8a**–**g**) (%)
7a	2-Phenyl	18	88
7b	3-CF_3	18	73
7c	4-OEt	3	64
7d	3-CN	2	87
7e	3-Cl	6	96
7f	3-CO_2Et	1	72
7g	3-Morpholine carboxamide	2	87

[a] Isolated yield of purified product.



4 6 (2)

With the optimized reaction conditions in hand, the effect of the nature of the base was revisited. Using 2-nitrobiphenyl (**7a**) and 3 equiv of sulfur in DMF we found that a variety of bases provided clean conversion to 2-aminobiphenyl (**8a**). Primary, secondary, and tertiary amine bases (benzylamine,[11] morpholine and Hunig's base) all showed good conversion, with Hunig's base proving optimal (96% conversion by HPLC area %). Other inorganic bases also provided comparable results to $NaHCO_3$. The reaction showed similar conversion with K_2CO_3 and a faster reaction with NaOH. Unfortunately, as with $NaHCO_3$, Hunig's base did not cleanly provide a reduced product when attempted on 3-bromo-nitrobenzene.

In conclusion, we report a method for the conversion of functionalized nitroarenes to the corresponding anilines with sulfur and base in moderate to high yields. This method does not require the use of transition metals or hydrogen gas and highlights the capacity of sulfur as an inexpensive 2-electron reductant.[12] The conditions are also notable for their compatibility with a range of functional groups and use of a mild base.

General method for synthesis of substituted anilines. Biphenyl-2-amine (8a). To a flask equipped with reflux condenser were added 2-nitrobiphenyl (2.0 g, 10.0 mmol), sulfur (0.96 g, 30.1 mmol), $NaHCO_3$ (2.53 g, 30.1 mmol) and DMF (20 mL) and the suspension was heated to 130 °C. (*Note*: Reaction shows gas evolution.) The reaction was stirred for 18 h and cooled to room temperature. The dark brown reaction mixture was partitioned between MTBE (50 mL) and water (50 mL) and the aq extracted with MTBE (50 mL). The combined organics were washed with water (50 mL) and brine (25 mL), dried over Na_2SO_4, and concentrated to 1.8 g yellow oil. The crude material was chromatographed with 10% isopropyl acetate/heptane and dried in vacuo at room temperature overnight to yield 1.5 g (88%) yellow solid **8a**. Mp = 53–54 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.73 (s, 2H), 6.63 (td, $J = 7.34$, 1.23 Hz, 1H), 6.75 (dd, $J = 8.03$, 1.17 Hz, 1H), 6.97 (dd, $J = 7.48$, 1.58 Hz, 1H), 7.04 (ddd, $J = 7.99$, 7.24, 1.65 Hz, 1H), 7.30–7.35 (m, 1H), 7.38–7.46 (m, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 114.8, 116.3, 125.6, 126.2, 127.7, 128.1, 128.2, 129.5, 139.1, 144.3 ppm; MS (DCI+) m/z 170.0 (M+1). Anal. Calcd for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found C, 85.01; H, 6.78; N, 8.24.

Supplementary data

Isolation details and characterization for compounds **8b–g** and **6**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.079.

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10. HPLC area % ratio at 225 nm.
11. Although the reaction with benzylamine showed 89% conversion by HPLC area % ratio, the assay was complicated by the presence of benzylamine by-products.
12. The mechanism of the reduction of nitroarenes in propylamine solvent has been proposed to proceed through a nitroaromatic radical anion by a single electron transfer mechanism (see Ref. 8).