Chemoselective Reduction of Nitroarenes in the Presence of Acid-Sensitive Functional Groups: Solid-Phase Syntheses of Amino Aryl Azides and Benzotriazoles

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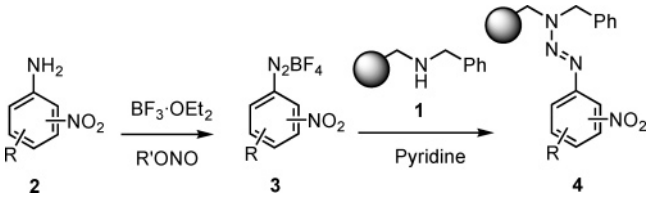
The reduction of nitroarenes is surely one of the most common reactions in functional group interconversion, since it allows access to anilines not accessible from arenes by direct electrophilic aromatic substitution, at least in a preparative scale. For combinatorial chemistry on solid supports, anilines are often incompatible with coupling conditions and are usually prepared from corresponding nitro compounds, which are commercially available in a wide range of desirable substitution patterns. Despite a very long list of possible reducing agents and an even larger variation of reaction conditions, most selective and powerful reducing media are either acidic (typically $SnCl_2$) or use heterogeneous methods (e.g., Fe/HCl). However, these methods are unsuitable for acid-labile molecules, on solid supports, or both.[1,2] Because most linkers for solid-phase syntheses are acid-labile,[3] there is a great need for methods for the chemoselective reduction of nitroarenes on solid supports under neutral or basic conditions.[4,5]

In the past, triazenes have been used not only as cheap protective groups for amines[6] but also as versatile multifunctional linkers for the solid-phase synthesis of many different chemical entities, in particular, benzoannelated nitrogen heterocycles.[7] The introduction of the amino group on triazene-linked arene moiety would provide broad access to further functionalization with large potential for diversification. Since triazenes are acid-sensitive functional groups with the ability to reduce to anilines, a chemoselective basic reduction method is needed. Herein, we describe the first chemoselective reduction of triazene-linked nitroarenes on solid supports.[8]

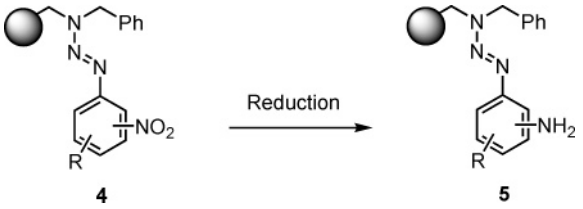
To our knowledge, the only example for a chemoselective reduction of this type has been reported by the Diederich group using palladium on charcoal.[9] Although this is a powerful method, it is not viable on solid supports. Hence, we were able to screen out a large variety of reducing media.

First, we prepared a large number (Figure 1) of nitroarenes on solid supports linked by a triazene moiety via standard and optimized procedures from anilines **2** (via corresponding diazonium salts **3**) and benzylaminomethyl polystyrene **1** (Scheme 1), which was available from chloromethylated polystyrene (1−2% cross-linked with divinyl benzene).[10,11]

Scheme 1. Synthesis of Nitroarenes on Solid Supports[11]



Scheme 2. Nitro Group Reduction on Solid Supports



To evaluate the influence of the triazene moiety and other functional groups (esters, halides, and ethers), different anilines, **2a**−**l**, were used as starting materials to prepare nitro resins **4a**−**l**. Nitro resin **4m** was synthesized via a nucleophilic substitution of a fluoride by an amine on a solid support.[12]

The assessment of the conversion was determined by cleavage from solid supports with 5% trifluoroacetic acid in the presence of trimethylsilylazide[13b] to yield nitroazides **6a**−**l** and aminoazides **7b**−**c** (Scheme 3). It was shown earlier[13] that this cleavage method proceeds quantitatively. This was confirmed here by determination of the yield after purification. For *ortho*-amino resins **5a**, **5d**−**l**, and **4m**, 1*H*-benzotriazoles **8a**, **8d**−**l**, and **8m** were formed (Figure 2) from the initially released *ortho*-amino-diazonium ions in a well-known[12] rapid cyclization reaction.

Reduction with $Na_2S_2O_4/K_2CO_3$ or Na_2S/K_2CO_3. In our initial screening, we used sodium dithionite (Table 1)[14] and sodium sulfide (Table 2) as mild reducing agents, applicable for the reduction of nitro groups in the presence of a triazene moiety. However, both reducing methods were not suitable for most resins used. The reduction with Na_2S/K_2CO_3 showed a strong dependency on the substitution pattern. While the para-substituted nitro groups in **4b** were completely reduced at 55 °C within 2 days (entry 5, Table 2), the ortho substitution in compound **4a** gave a sluggish reduction at 80 °C: after 7 days, only one-half of the nitro functionality was reduced to the amine (entry 2, Table 2). An additional electron-withdrawing group enhanced the reactivity (compare entries 6 and 4, Table 2). This influence was stronger with the mild reducing agent sodium dithionite. While the ester-derived nitroarene **4c** was being reduced at 40 °C within 5 days to 87% (entry 5,

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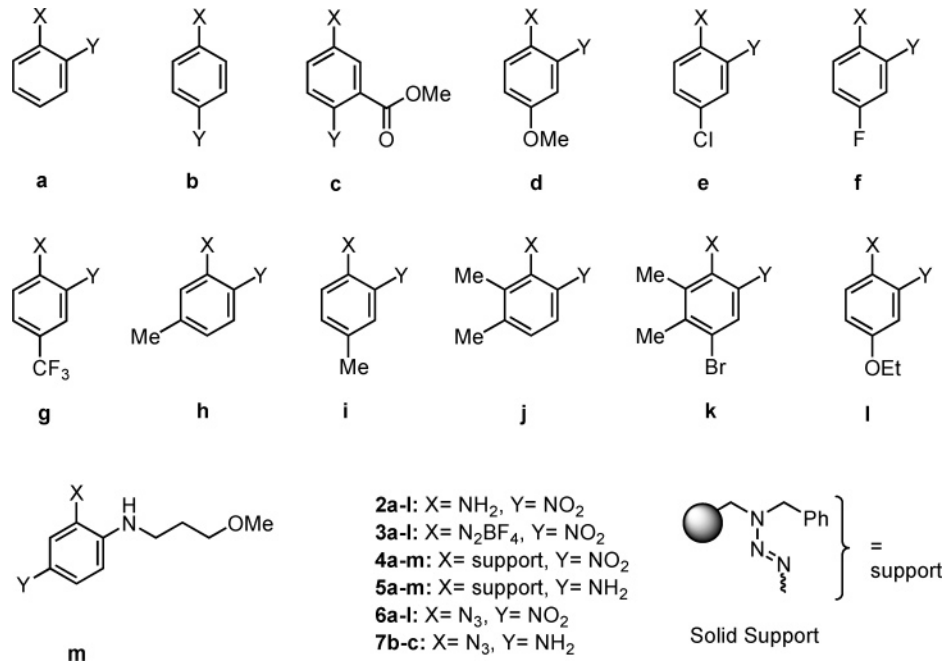

Figure 1. Substitution patterns of compounds **2**−**7**.

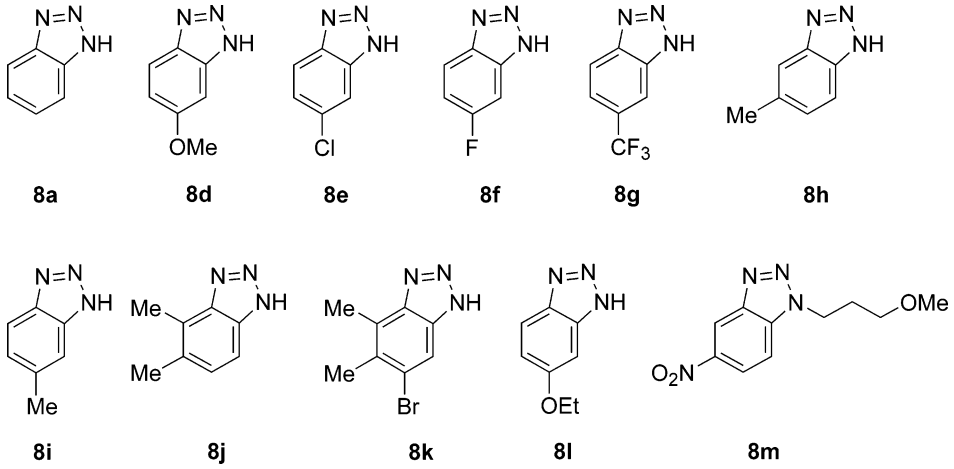

Figure 2. 1*H*-Benzotriazoles **8a**, **8d**−**l**, **8m**.

Scheme 3. Cleavage from Solid Supports

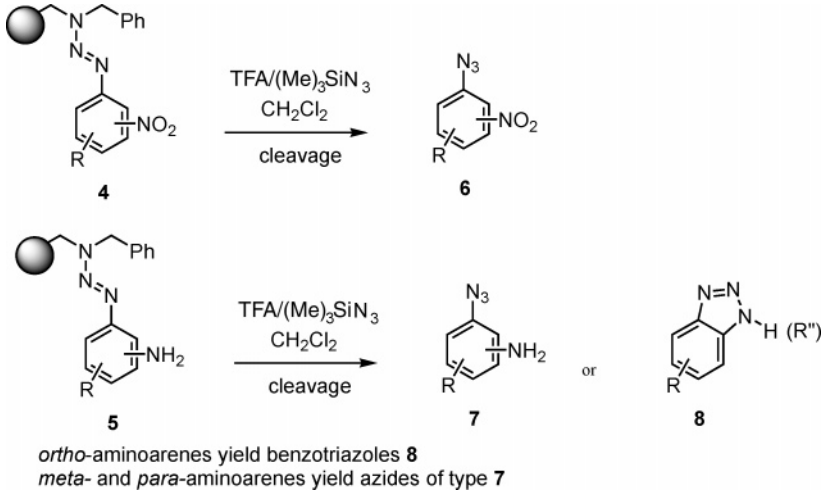

Table 1), the unsubstituted pendent **4b** was not reduced under these conditions (entries 1−2, Table 1). The solvent mixture proved to be crucial, and DMF was superior to THF (entry 4 vs entry 5, Table 1).

Table 1. Reduction of Nitro Resins **4** with $Na_2S_2O_4/K_2CO_3$

entry	nitroarene	product	reagents	temp	time	conversion[a]
1	**4b**	**5b**	12 equiv $Na_2S_2O_4$, 12 equiv K_2CO_3, DMF/H_2O (9:1)	25 °C	3 d	none
2	**4b**	**5b**	12 equiv $Na_2S_2O_4$, 12 equiv K_2CO_3, THF/H_2O (9:1)	40 °C	6 d	none
3	**4c**	**5c**	12 equiv $Na_2S_2O_4$, 12 equiv K_2CO_3, THF/MeOH/H_2O (5:1:1)	40 °C	2 d	29%
4	**4c**	**5c**	12 equiv $Na_2S_2O_4$, 12 equiv K_2CO_3, THF/MeOH/H_2O (5:1:1)	40 °C	5 d	58%
5	**4c**	**5c**	12 equiv $Na_2S_2O_4$, 12 equiv K_2CO_3, DMF/H_2O (9:1)	40 °C	5 d	87%

[a] Determined by ^{1}H NMR spectroscopy after cleavage.

Table 2. Reduction of Nitro Resins **4** with Na_2S/K_2CO_3

entry	nitroarene	product	reagents and solvent	temp	time	conversion[a]
1	**4a**	**5a**	16 equiv Na_2S, 16 equiv K_2CO_3, DMF/H_2O (9:1)	40 °C	3 d	none
2	**4a**	**5a**	10 equiv Na_2S, 10 equiv K_2CO_3, DMF/H_2O (9:1)	80 °C	7 d	52%
3	**4b**	**5b**	12 equiv Na_2S, 12 equiv K_2CO_3, DMF/H_2O (9:1)	25 °C	3 d	26%
4	**4b**	**5b**	12 equiv Na_2S, 12 equiv K_2CO_3, DMF/H_2O (9:1)	40 °C	3 d	87%
5	**4b**	**5b**	12 equiv Na_2S, 12 equiv K_2CO_3, DMF/H_2O (9:1)	55 °C	2 d	96%
6	**4c**	**5c**	12 equiv Na_2S, 12 equiv K_2CO_3, DMF/H_2O (9:1)	40 °C	2 d	99%

[a] Determined by ^{1}H NMR spectroscopy after cleavage.

Table 3. Reduction of Nitro Resins **4** with Sodium Sulfide under SET catalysis of **9**[a]

entry	nitroarene	product	time	conversion[b]
1	**4a**	**5a**	4 d	>95%
2	**4d**	**5d**	4 d	>95%
3	**4e**	**5e**	4 d	>95%
4	**4f**	**5f**	4 d	>95%
5	**4g**	**5g**	4 d	>95%
6	**4h**	**5h**	4 d	>95%
7	**4i**	**5i**	4 d	>95%
8	**4j**	**5j**	4 d	68%
9	**4k**	**5k**	4 d	81%
10	**4l**	**5l**	4 d	80%
11	**4m**	**5m**	3 d	none

[a] Reaction conditions: 10 equiv of Na_2S, 10 equiv of K_2CO_3, 0.1 equiv of **9**, DMF/H_2O (9:1), 80 °C. [b] Determined by ^{1}H NMR spectroscopy after cleavage.

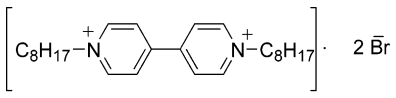

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Figure 3. Reduction catalyst *N*,*N*-dioctyl-4,4-bipyridinium dibromide (dioctyl viologen, **9**).

Reduction with Na_2S/K_2CO_3 with Single-Electron Transfer (SET) Catalysis. We also screened for additives. In the presence of a commercially available SET and phase-transfer catalyst, *N*,*N*-dioctyl-4,4-bipyridinium dibromide (dioctyl viologen, **9**, Figure 3) (10 mol %), the reduction with sodium sulfide proved to be faster.[15,16,17] This method was particularly suitable for *ortho*-nitro resins which were difficult to reduce under other conditions. This catalyst was soluble in both DMF and DMF/water mixtures. Although it has been suggested that the catalytic effect might be caused by the phase-transfer abilities of **9**, we are inclined to believe that electron transfer was involved because sodium sulfide showed great solubility in DMF and DMF/water mixtures without the catalyst. Additionally, for reactions without the catalyst, the strong dependence on the substitution pattern (ortho vs meta and para) suggests that diffusion to the solid support was not decisive but rather the differences in Volta potentials. The workup was especially easy and applicable therefore to automated synthesis. The yields were very high for both electron-poor and electron-rich nitroarenes (Table 3). Only the aminonitroarene **4m** was unsuitable for this method.

Reduction with Bartra Reagent $[HNEt_3]^+[Sn(SPh)_3]^-$. In addition to the conventional methods, we explored the Bartra reagent $[HNEt_3]^+[Sn(SPh)_3]^-$ in toluene.[18] The Bartra reagent reduced reliably unreactive *ortho*-nitroarene resins at ambient temperature (Table 4); however, the triazene moiety was susceptible to cleavage, and hence diminished functionalization was observed (35−65%). Another difficulty resulting from the hydrolysis of the reagent was the production of insoluble tin oxides, which were soluble after acidic treatment with trifluoroacetic acid; this made the workup quite cumbersome.

In summary, we have demonstrated the first chemoselective reduction of nitroarenes on solid supports in the presence of other reducible functional groups such as triazenes. A unique combination of a single-electron transfer reagent (viologen) with sodium sulfide proved to be convenient in terms of reducing the strength and for the workup. The relatively long reaction times appear justified, considering the possibilities for further diversification of yielded aminoarenes on solid supports.

Table 4. Reduction of Nitro Resins **4** with Bartra Reagent[a]

entry	nitroarene	product	reagents and solvent	time	conversion
1	**4a**	**5a**	15 equiv $[HNEt_3]^+[Sn(SPh)_3]^-$, toluene (absolute)	4 d	>95%[b]
2	**4b**	**5b**	12 equiv $[HNEt_3]^+[Sn(SAr)_3]^-$,[e] toluene (absolute)	14 h	>95%[b]
3	**4d**	**5d**	15 equiv $[HNEt_3]^+[Sn(SPh)_3]^-$, toluene (absolute)	4 d	>95%[b]
4	**4e**	**5e**	12 equiv $[HNEt_3]^+[Sn(SPh)_3]^-$, toluene (absolute)	6 d	>95%[c]
5	**4f**	**5f**	12 equiv $[HNEt_3]^+[Sn(SPh)_3]^-$, toluene (absolute)	6 d	>95%[c]
6	**4g**	**5g**	12 equiv $[HNEt_3]^+[Sn(SPh)_3]^-$, toluene (absolute)	6 d	>95%[c]
7	**4h**	**5h**	15 equiv $[HNEt_3]^+[Sn(SPh)_3]^-$, toluene (absolute)	7 d	74%[d]

[a] All reactions performed at 25 °C. [b] Determined by ^{1}H NMR after cleavage. [c] GC-MS. [d] GC. [e] HSAr = 2,4,5-trichlorothiophenol.

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Supporting Information Available. General methods and spectroscopic and analytical data for all products is not described in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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