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2,4-Dinitrobenzenesulfonamides: A Simple and Practical Method for the Preparation of a Variety of Secondary Amines and Diamines.

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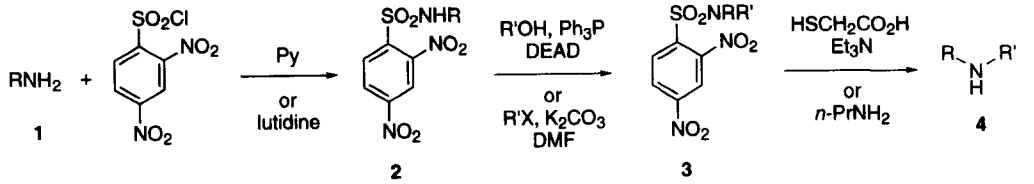
Abstract: 2,4-Dinitrobenzenesulfonamides, readily prepared from primary amines and 2,4-dinitrobenzenesulfonyl chloride, can be alkylated by the Mitsunobu reaction or by the conventional methods to give *N,N*-disubstituted sulfonamides in excellent yields. Since 2,4-dinitrobenzenesulfonamides can be removed without deprotecting 2-nitrobenzenesulfonamides, a wide variety of diamines could be prepared by the combined use of these protecting/activating groups. © 1997 Elsevier Science Ltd.

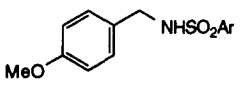
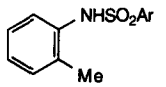
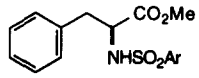
Although transformation of primary amines to the corresponding secondary amines have been extensively studied over the decades, there appear to be only a few practical and versatile methods available.[1] Recently, we have reported the novel use of 2- and 4-nitrobenzenesulfonamides that provides an efficient way for the synthesis of secondary amines.[2] In light of the mild reaction conditions employed for the deprotection of these sulfonamides, we were encouraged to search for sulfonamides that could be deprotected under even milder conditions. Herein we report 2,4-dinitrobenzenesulfonamides which undergo exceptionally facile and selective deprotection in the presence of 2-nitrobenzenesulfonamides.

Scheme 1



N-Monosubstituted 2,4-dinitrobenzenesulfonamides **2**, readily prepared from 2,4-dinitrobenzenesulfonyl chloride and the corresponding primary amines **1**, can be alkylated efficiently under the Mitsunobu conditions[3] (R'OH, DEAD, PPh_3, benzene, 23 °C) or under the conventional conditions (R'X, K_2CO_3, DMF, 23 °C) to give *N,N*-disubstituted 2,4-dinitrobenzenesulfonamide **3** in excellent yields (Scheme 1). Facile deprotection of **3** was achieved by treatment with excess *n*-propylamine[4] (20 eq) in CH_2Cl_2 at 23 °C for 10 min to give the desired secondary amines **4** in near quantitative yields. Alternatively, **3** can be deprotected upon treatment with $HSCH_2CO_2H$ (1.3 eq) and Et_3N (2 eq) in CH_2Cl_2 at 23 °C for 5 min. The latter procedure is more convenient in that the by-product, 2,4-dinitrophenylthioacetic acid, can be easily removed by washing the ethereal layer with an aqueous $NaHCO_3$ solution. Practically pure amines can thus be obtained without chromatographic separation. These results are summarized in Table 1.

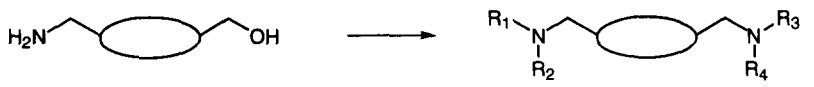
Table 1. Alkylation and Deprotection of 2,4-Dinitrobenzenesulfonamides.

R'X or R'OH	 **2a**			 **2b**			 **2c**		
	Alkylation[a] **3**[b] (% yield)	Deprotection[c] **4**[b,d] % yield		Alkylation[a] **3**[b] (% yield)	Deprotection[c] **4**[b,d] % yield		Alkylation[a] **3**[b] (% yield)	Deprotection[c] **4**[b,d] % yield	
		PA	MA		PA	MA		PA	MA
	20 min (87)	91	91	1 hr (97)	90	92	4 hr (95)	90	98
	20 min (97)	91	94	1 hr (97)	92	98	7 hr (99)	88	97
	2 hr (89)	91	97	7 hr (96)	89	95	12 hr (87)	94	98
	24 hr (48)[e]								
	20 min (99)	91	97	20 min (99)	90	96	20 min (94)	89	97
	20 min (96)	92	94	20 min (97)	93	98	20 min (97)	93	91

[a]For alkyl halides: R'X (1.5 eq), K_2CO_3 (5 eq), DMF, 23 °C. For *n*-PrBr: R'X (2 eq), K_2CO_3 (8 eq), DMF, 23 °C. For alcohols: R'OH (2 eq), DEAD (2 eq), PPh_3 (2 eq), benzene, 23 °C, 20 min. [b]Satisfactory spectroscopic data were obtained on all new compounds. [c]PA: *n*-$PrNH_2$ (20 eq), CH_2Cl_2, 23 °C, 10 min. MA: $HSCH_2COOH$ (1.3 eq), Et_3N (2 eq), CH_2Cl_2, 23 °C, 5 min. [d]Separated by silica gel chromatography after partitioning between Et_2O and an aqueous $NaHCO_3$ solution. [e]Poor alkylating agent such as *n*-PrBr gave moderate yields due to the decomposition of **2** when exposed to K_2CO_3 for a prolonged period.[5]

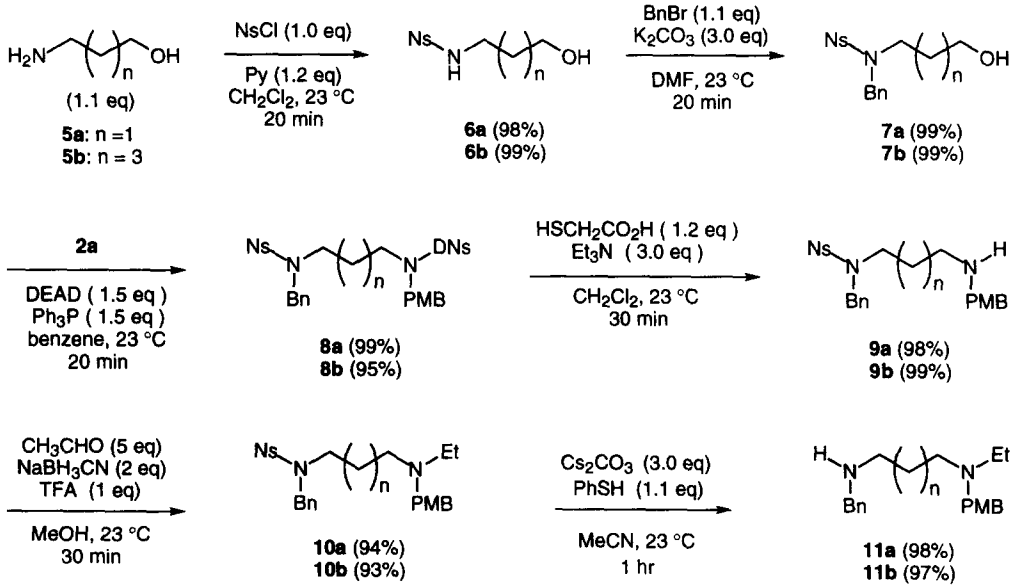
Since both 2-nitro- and 2,4-dinitrobenzenesulfonamides, derived from primary amines, can be easily *N*-alkylated by the Mitsunobu reaction or by the conventional methods, a combination of these sulfonamides may be used for the preparation of a wide variety of diamines as illustrated in Scheme 2. To demonstrate the general applicability of our protocol, 3-amino-1-propanol (**5a**) and 5-amino-1-pentanol (**5b**) were chosen as the starting materials (Scheme 3). Thus, the readily available amino alcohols **5** were converted to 2-nitrobenzenesulfonamides **6** by treatment with 2-nitrobenzenesulfonyl chloride (NsCl) and pyridine in CH_2Cl_2. Selective

Scheme 2



alkylation of **6** with benzyl bromide and K_2CO_3 in DMF furnished N,N-dialkyl-2-nitrobenzenesulfonamides **7** in almost quantitative yields. The second amino functionality was introduced to **7** by means of the Mitsunobu reaction (DEAD, Ph_3P, benzene) with *N*-*p*-methoxybenzyl-2,4-dinitrobenzenesulfonamide **2a**, which was easily prepared from *p*-methoxybenzylamine ($PMBNH_2$) and 2,4-dinitrobenzenesulfonyl chloride (DNsCl). Selective deprotection of 2,4-dinitrobenzenesulfonamides **8** was performed by treatment with $HSCH_2CO_2H$ and Et_3N in CH_2Cl_2 to give the desired amines **9** in near quantitative yields. The secondary amines **9** can either be alkylated or acylated at this stage. As examples, **9** were subjected to reductive alkylation (CH_3CHO, $NaBH_3CN$, TFA, MeOH) to give the tertiary amines **10** in high yields. Finally, the 2-nitrobenzenesulfonamides **10** were deprotected with PhSH and Cs_2CO_3 in CH_3CN to give the amines **11** in high yields, which, once again, can either be alkylated or acylated with a wide variety of reagents.

Scheme 3



Ns = 2-nitrobenzenesulfonyl, DNs = 2,4-dinitrobenzenesulfonyl

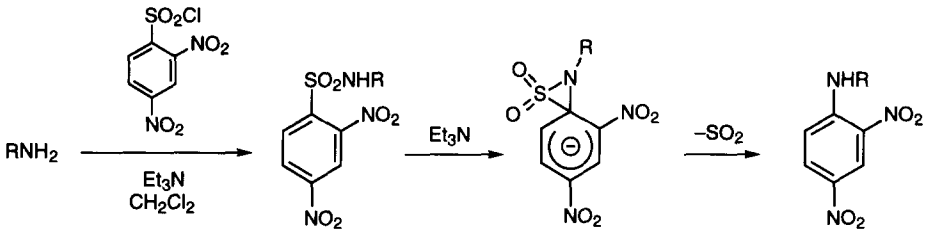
Because of the extreme ease of the entire procedure, we believe that the use of 2,4-dinitrobenzenesulfonamides in conjunction with 2- and 4-nitrobenzenesulfonamides serves as a method of choice for the preparation of a wide variety of secondary amines just like the Gabriel synthesis for primary amines. As illustrated in Scheme 2, our protocol seems particularly suited for preparation of the combinatorial library of diamine derivatives which may find widespread use in pharmaceutical industries. In addition, these nitrobenzenesulfonamides proved to be quite amenable to the solid-state synthesis of secondary amines for

peptide synthesis and/or combinatorial chemistry.[6] Application of our protocol to the synthesis of primary amines is currently underway and the results will be disclosed in due course.

Acknowledgment. Financial assistance from Japan Science and Technology Corporation (JST) and the National Institutes of Health (Grant CA28119) is gratefully acknowledged.

References and Notes

1. For a general synthesis of amines, see: Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*, 2nd ed.; Academic, New York, 1983; Chapter 13.
2. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373-6374.
3. (a) Mitsunobu, O. *Synthesis* **1981**, 1-28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335-656.
4. While a variety of amine and thiol nucleophiles can be used for the deprotection of 2,4-dinitrobenzenesulfonamides, *n*-propylamine was chosen because it is easy to remove (b.p. 48 °C) and inexpensive.
5. Somewhat lower yields of sulfonamides **2** were obtained using triethylamine as a base because of the concomitant decomposition of **2** via the intramolecular Meisenheimer complex.



2
Major product

Minor product

6. (a) Wipf, P.; Henninger, T. C. *J. Org. Chem.* **1997**, *62*, 1586-1587. (b) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301-2302. (c) Private communications from Drs. John Nuss (Chiron) and Lihu Yang (Merck).

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