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A Novel Deprotection / Functionalisation Sequence using 2,4-Dinitrobenzenesulfonamide : Part 1

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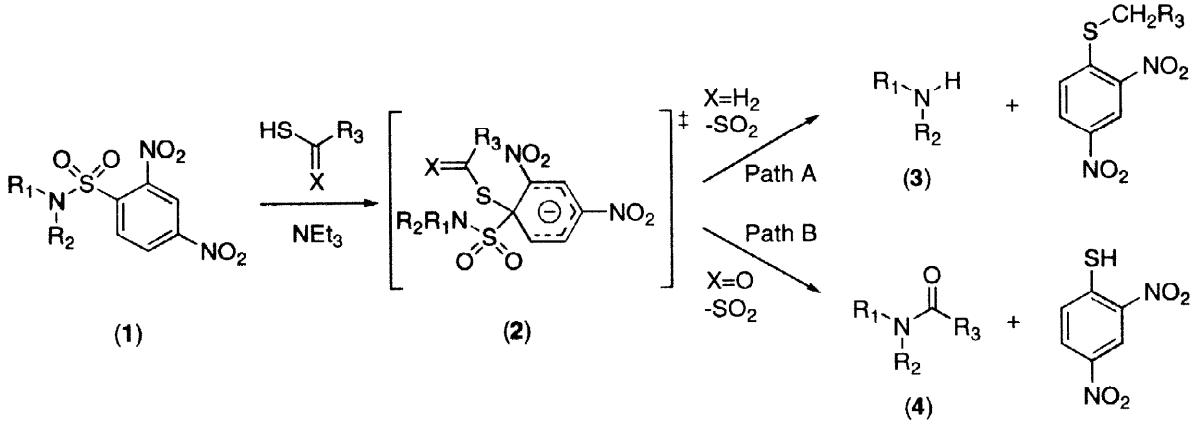
Abstract: Treatment of a series of 2,4-dinitrobenzenesulfonamides with various thioacids in the presence of cesium carbonate leads directly to the corresponding amides.

The recent introduction of the 2- and 4-nitrobenzenesulfonyl protecting group for amines by Fukuyama and co-workers[2] has generated much interest since its initial publication.[3] The related 2,4-dinitrobenzenesulfonyl derivative (**1**), has found much use in our laboratories both in solution and on solid-phase due to its robustness to a variety of reaction conditions, the ease with which it can be functionalised, and the mildness with which it can be removed with thiols or amines.[4]

The mechanism for the deprotection reaction with a thiol involves *ipso* attack of a thio nucleophile to form an initial Meisenheimer type complex (**2**), which, after loss of sulfur dioxide gives a free amine (**3**) (Scheme 1, Path A). We were intrigued by the possibility that introducing a carbonyl group α to the thio nucleophile would generate an acylating agent that could react directly with the amine produced to form an amide (**4**) (Scheme 1, Path B). Herein we report our findings in this area and the scope and limitations of this novel deprotection / functionalisation sequence.



Scheme 1

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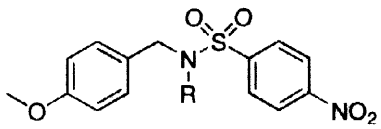
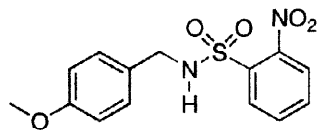
It is well documented that dinitrophenyl esters are highly reactive acylating agents for the formation of amides and esters,[5] thio derivatives being more reactive than their corresponding oxygen analogues.[6] With this in mind we initially investigated the use of thiolacetic acid in our proposed sequence, the starting materials being prepared *via* standard procedures similar to those used by Fukuyama.[2,4] After scanning a number of solvents and bases we found treatment of a solution of sulfonamide (**1a**) in DMF at room temperature with two equivalents of cesium carbonate and thiolacetic acid for 30 minutes led to the corresponding amide (**4a**) in 95% yield after purification (Table 1, entry1).[7]

Encouraged by these initial results a series of other thioacids and sulfonamides were examined (Table 1).[8] The reaction appears to be general with aliphatic and aromatic thioacids reacting in high yields with both mono- (entries 4-6) and di-substituted (entries 2-3) sulfonamides. Reaction of the aniline derived sulfonamides (**1g** and **1h**), although slower, still proceeded at room temperature, to give the corresponding amides (entries 7-8) in excellent yield.

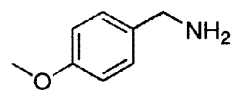
Reaction of the 2- and 4-mononitrobenzenesulfonamides (**5a, b**) and (**6**) under standard conditions, even at elevated temperatures, afforded either the amine (**7**) or recovered starting material (Figure 1). Similarly the use of benzoic or acetic acid instead of a thioacid led to the recovery of starting material. Thus for the reaction to proceed it is necessary to use both a dinitrobenzenesulfonamide and a thioacid.



(**5a**) R = H
(**5b**) R = CH_2CH_2OMe



(**6**)

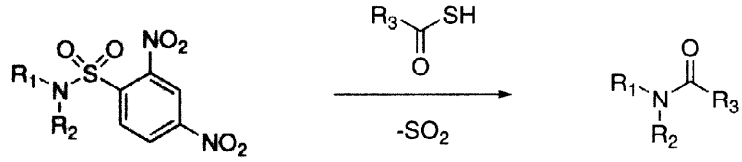


(**7**)

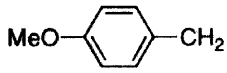
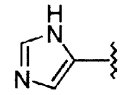
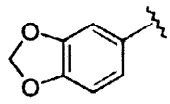
Figure 1

Typical experimental procedure: To a stirred solution of thiobenzoic acid (0.134mL, 1.08mmol, 2eq.) in anhydrous DMF (5.4mL) under nitrogen was added cesium carbonate (176mg, 1.08mmol, 2eq.), followed by *N*-[(4-methoxyphenyl)methyl]-2,4-dinitrobenzenesulfonamide (**1d**) (200mg, 0.54mmol) and stirring was continued for a further 30 minutes. The reaction mixture was separated between saturated ammonium chloride solution (10mL) and ethyl acetate (10mL). The aqueous phase was extracted with more ethyl acetate (2x10mL) and the combined organics were washed with brine, dried over magnesium sulfate, treated with activated carbon, filtered and reduced. Purification of the crude product on silica eluting with 20-30% ethyl acetate/hexanes gave *N*-[(4-methoxyphenyl)methyl]-benzamide (**4d**) (118mg, 90%) as a pale yellow solid; mp 87-88°C. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.72(2H, dd, J = 7.2, 2.2Hz), 7.44-7.35(3H, m), 7.23(2H, dd, J = 6.7, 2.1Hz), 6.83(2H, dd, J = 6.7, 2.1Hz), 6.28(1H, bs), 4.54(2H, d, J = 5.5Hz), 3.75(3H, s). ^{13}C NMR (100MHz, $CDCl_3$) δ 167.29, 159.14, 134.67, 131.52, 130.27, 129.33, 128.59, 126.56, 114.18, 55.32, 43.64. (Found C,74.4; H,6.4; N,5.7; m/z 242.1. $C_{15}H_{15}N_1O_2$ requires C,74.7; H,6.3; N,5.8; M+[H^+] 242.1).

Table 1. Reaction of sulfonamides with thioacids.



(1a-h) (4a-h)

Entry	Sulfonamide	R_1	R_2	R_3	Time hr.	% Yield
1	1a		H	Me	0.5	95
2	1b	"	CH_2CH_2OMe	Ph	0.5	90
3	1c	"	Allyl	CF_3	0.5	87
4	1d	"	H	Ph	0.5	90
5	1e	"	H	^{t}Bu	0.5	95
6[a]	1f	"	H		1	81
7	1g		H	^{t}Bu	4	94
8	1h	"	CH_2CH_2OMe	Ph	4	96

[a] Three equivalents of cesium carbonate were used.

In summary, we have found a novel, high yielding, one step transformation of protected amines to mono- and di-substituted amides. Despite the fact that there are a limited number of commercially available thioacids, there are several known procedures by which they can be prepared.[9] Thus, by starting from readily accessible 2,4-dinitrobenzenesulfonamides, which may be functionalised by either the Mitsunobu reaction[10] or alkylation,[11] this sequence should prove to be a useful alternative to the standard two step deprotection / coupling protocol often employed in the synthesis amides.[12] In the following paper of this issue the extension of this methodology to the synthesis of ureas, thioureas and thioamides is presented.

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8. All compounds were characterised by ^{1}H NMR, ^{13}C NMR, and MS or elemental analysis.
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