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

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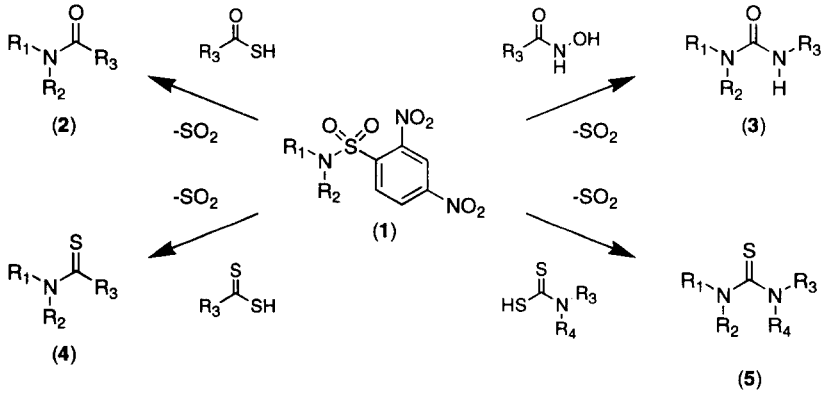
Abstract: Treatment of a series of 2,4-dinitrobenzenesulfonamides with either hydroxamic acids, dithioacids, or dithiocarbamic acids leads directly to the corresponding ureas, thioamides and thioureas respectively. © 1998 Elsevier Science Ltd. All rights reserved.

With the rapidly developing field of combinatorial chemistry, and the ever increasing rate at which large diverse sets of compounds can be synthesised and screened in high throughput biological assays, the need for new ways to rapidly elaborate a simple framework in order to pursue and optimise biological leads is becoming more apparent.[2]

In the preceding paper of this issue we showed that treatment of a series of 2,4-dinitrobenzenesulfonamides (**1**) with thioacids, in the presence of cesium carbonate led directly to the corresponding amide (**2**) (Scheme 1).[3] By considering the mechanism of this transformation we found it reasonable that the reaction may also proceed with other related dual nucleophiles / electrophiles. In this communication we present the extension of this methodology to the synthesis of ureas (**3**), thioamides (**4**) and thioureas (**5**).



Scheme 1

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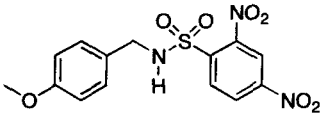
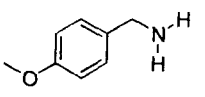
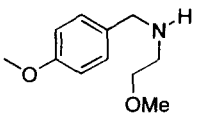


(1a)



(6)

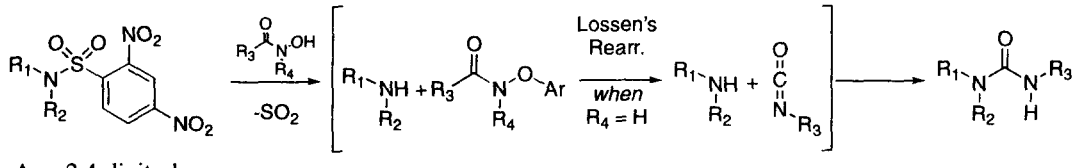


(7)

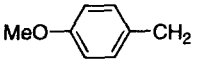
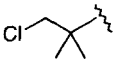
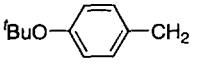
Figure 1

The Lossen rearrangement has received widespread attention in the synthesis of isocyanates and amines,[4] and we reasoned that hydroxamic acids should be ideal precursors for the *in situ* synthesis of ureas. Indeed, treatment of the sulfonamide (**1a**) (Figure 1) with benzene hydroxamic acid and cesium carbonate in DMF at room temperature for four hours led to the desired urea in 79% yield (Table 1, entry 1). The reaction appears to proceed *via* the anticipated isocyanate intermediate, since reaction of an *N*-substituted hydroxamic acid (entry 6) resulted in formation of the amine (**6**). The scope of this reaction appears to be similar to that of the Lossen rearrangement, with aryl (entry 1, 2), benzyl (entry 4) and tertiary alkyl groups (entry 3) leading to the expected ureas, whereas primary alkyl groups (entry 5), with a lower propensity for migration, led to the free amine (**7**). The ease with which hydroxamic acids can be prepared[5] suggests that this should prove to be a useful alternative to the use of either phosgene,[6] or isocyanates.[7]

Table 1. Reaction of sulfonamides with hydroxamic acids.[a]



Ar = 2,4-dinitrobenzene

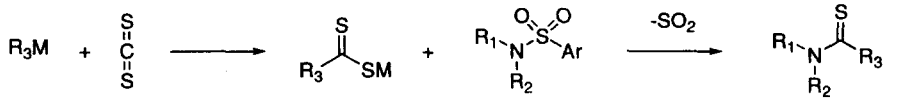
Entry	R_1	R_2	R_3	R_4	% Yield
1		H	Ph	H	79
2	"	CH_2CH_2OMe	Ph	H	86
3	"	H		H	78
4	"	H		H	82
5	"	CH_2CH_2OMe	Me	H	N.A.
6	"	H	Ph	Bn	N.A.

[a]All reactions were carried out as a 1M DMF solution, in the presence of 2 equivalents of hydroxamic acid and cesium carbonate.

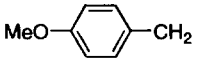
We next turned our attention to the synthesis of thioamides and thioureas. There are a limited number of commercially available dithioacids and dithiocarbamic acids, so we sought to develop a one pot procedure for

their synthesis[8] that allowed for *in situ* reaction with a dinitrosulfonamide. The results obtained are shown in Tables 2 and 3.

Table 2. Reaction of sulfonamides with carbon disulfide / organometallic adduct.[a]



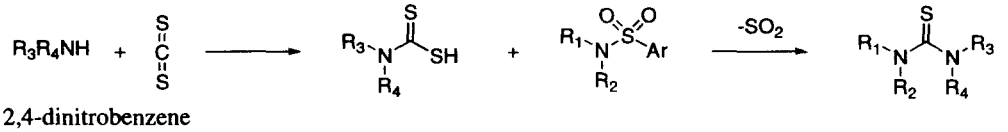
Ar = 2,4-dinitrobenzene

Entry	R_1	R_2	R_3	M	Temp. (°C)	% Yield
1		H	Ph	MgBr	68	73
2	"	H	Ph	MgBr	80	88
3	"	H	*p*-ClPh	MgBr	80	90
4	"	CH_2CH_2OMe	^iPr	Li	80	86
5	"	CH_2CH_2OMe		Li	80	77

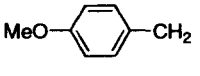
[a] All reactions carried out as a 1M solution in the presence of 2 equivalents of dithioacid.

Treatment of a THF solution of carbondisulfide with phenylmagnesium bromide for 30 minutes at 0°C followed by addition of sulfonamide (**1a**) and heating the resulting solution at reflux for 18 hours gave the expected thioamide in 73% yield (Table 2, entry 1). A shorter reaction time (4 hours) and higher yield (88%) was obtained by removal of the THF from the solution containing the Grignard adduct and resuspending in DMF before addition of the sulfonamide and heating at 80°C (entry 2). A series of other Grignards and alkyl lithiums also led to high yields of thioamides with functionality amenable to further transformations (Table 2, entries 3-5).

Table 3. Reaction of sulfonamide with carbon disulfide / amine adduct.[a]



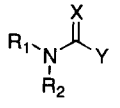
Ar = 2,4-dinitrobenzene

Entry	R_1	R_2	R_3	R_4	Temp. (°C)	% Yield
1		H	Me	Me	80	68
2	"	H	H	Ph	80	65
3	"	H	Me	Bn	80	74
4	"	CH_2CH_2OMe	Me	Bn	80	76

[a] Reactions were carried out as a 1M DMF solution, in the presence of 2 equivalents of cesium carbonate and dithiocarbamic acid.

Similar success was also observed with the synthesis of di-, tri-, and tetra-substituted thioureas (Table 3). For the formation of dithiocarbamic acids with carbon disulfide, best results were obtained by reacting the appropriate amine with carbon disulfide in dichloromethane in the presence of one equivalent of dry pyridine, followed by aqueous workup and isolation. Addition of DMF, cesium carbonate and a sulfonamide to the crude dithioamide, followed by heating at 80°C for 12 hours gave the desired thioureas in good yield (Table 3, entries 1-4). This provides access to di- and tri-substituted thioureas without having to use the highly toxic thiophosgene,[6] or phosphorous triamides,[9] and unsymmetrical tetra-substituted thioureas, which have been synthesised before in one pot from a free amine,[10] albeit in lower yields than presented here.

In summary, we have extended the methodology presented in the previous paper to the synthesis of ureas, thioamides and thioureas. This methodology provides a useful alternative to the known procedures used in the functionalisation of amines, and will be useful in the production of a diverse combinatorial library based around the scaffold shown in Figure 2. We are unaware of any similar protocols to this where a protecting group is converted to an activated species upon cleavage and subsequently goes on to react with the cleavage product in a predictable manner.



R_1 = Alkyl, Aryl
R_2 = H, Alkyl
X = O, S
Y = Alkyl, Aryl, NR_3R_4

Figure 2

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References and Notes

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