Synthesis of thioethers *via* metal-free reductive coupling of tosylhydrazones with thiols†

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A metal-free procedure for the synthesis of thioethers is described *via* the base-promoted reductive coupling of tosylhydrazones with thiols through an insertion of a carbene into the S–H bond.

Thioethers are essential building blocks for organosulfur chemistry,[1] and they also play important roles in materials science, biology and chemistry.[2] There are several commonly used methods for the synthesis of thioethers. The classical method involves the conversion of thiols to thioethers by the alkylation of thiols with organic halides under strong base conditions.[3] The second method is transition metal-catalyzed (including Pd, Cu, Co, Ni, Fe and other metal catalysts) hetero-cross-coupling (C–S) between aryl or alkyl halides and thiols.[4] In general, this method involves a ligand other than a metal salt catalyst, a base and a solvent. Moreover, the high cost and toxicity of some metal catalysts and ligands restrict their applications in large-scale processes. The third method involves the addition of a thiol to an alkene.[5] Although some of these methods have proven to be highly effective in such coupling reactions, the development of alternative routes to thioethers is still desirable. In fact, a few base- or metal-free processes have also been reported, such as the S-alkylation of aromatic and aliphatic thiols with alkyl halides promoted by silica,[6a] and the ionic liquid ([pmIm]Br)-catalyzed coupling of alkyl halides with thiols.[6b]

Tosylhydrazones have attracted extensive attention for a long time because of their various useful applications in organic synthesis. In particular, they have been used widely as precursors of diazo compounds and carbenes.[7] Carbenes can undergo insertion into X–H (X=C, O, S, N, *etc.*) bonds.[7] For example, Aggarwal *et al.* have reported the application of tosylhydrazone sodium slats in the sulfur-mediated asymmetric epoxidation of carbonyl compounds.[7a] Wang and co-workers have reported the synthesis of di- and tri-substituted olefins by the Pd-catalyzed oxidative cross-coupling of tosylhydrazones with arylboronic acids[7c] and benzyl halides ($ArCH_2X$).[7d]

Recently, metal-free reactions have shown the same levels of efficiency as metal-catalyzed reactions.[8] Barluenga *et al.* have developed a novel metal-free carbon–carbon bond-forming reaction between tosylhydrazones and boronic acids.[9a] Subsequently, Barluenga *et al.* reported the synthesis of ethers *via* the metal-free reductive coupling of tosylhydrazones with alcohols or phenols in the presence of base,[9b] and the procedure inserted a carbene into the O–H bond.[10] On the other hand, many transition metal-catalyzed S–H insertion processes with thiols have also been reported, usually involved diazo compounds stabilized by electron withdrawing groups such as diazo esters and diazo ketones.[11] Prompted by these results, and our efforts in metal-free reactions[12] and C–S bond-forming reactions,[13] we believe that this metal-free reaction may be applied for the synthesis of thioethers *via* a combination of a thiol with a diazo compound generated from the tosylhydrazone.

To verify the practicability of the projected route we selected a model reaction between tosylhydrazone **1a**, generated from *p*-methoxyphenyl methyl ketone and benzenethiol (**2a**); the results are shown in Table 1. In an initial experiment, we observed the formation of the desired product, **3a** (38% yield), when the reaction was performed in the presence of $NaHCO_3$ in DMSO at 110 °C (Table 1, entry 1). Further screening of bases revealed that the yield could be dramatically improved when DBU was utilized in the reaction (Table 1, entry 2). A better result was obtained when the base was changed to K_2CO_3 (Table 1, entry 7). However, inferior results were displayed when other bases were used in the reaction. Subsequently, we examined the effect of different solvents (Table 1, entries 8–11), and the results show that experiments proceeded smoothly in DMF, dioxane or pyridine to afford the desired product, **3a**, in excellent yields (Table 1, entries 8, 9 and 11). Further studies showed that decreasing the amount of base or thiol decreased the yield (Table 1, entries 12–14). The probable factor for the latter observation is that thiols are prone to undergo oxidative S–S coupling reactions, and some undesired disulfides were detected. Decreasing the reaction temperature retarded the reaction and produced product **3a** in only moderate yield (Table 1, entry 15). The optimized conditions [K_2CO_3 (3.0 equiv), dioxane, 110 °C] are similar to the Barluenga's conditions for the synthesis of ethers.[9b]

To demonstrate the generality of this method, the scope of the reaction was investigated under the optimized conditions, and the results are summarized in Table 2. As seen in Table 2, we found that the conditions proved useful for a wide range of thiols and tosylhydrazones derived from ketones. It was found that most reactions proceeded smoothly to afford the desired products, **3**, in moderate to good yields. Additionally, the reaction of tosylhydrazone **1a** with thiols was found to tolerate a range of different groups, regardless of their electronic or steric nature (Table 2, entries 1–5). For instance, tosylhydrazone **1a** reacted with 4-methylbenzenethiol (**2b**), leading to thioether **3b** in 77% yield (Table 2, entry 2). When 4-chlorobenzenethiol (**2c**) was employed in the reaction, the corresponding product, **3c**, was

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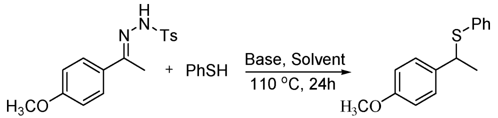
Table 1 Conditions screened for the reductive coupling between tosylhydrazone **1a** and benzenethiol (**2a**)[a]



1a **2a** **3a**

Entry	Base	Solvent	Yield (%)[b]
1	$NaHCO_3$	DMSO	38
2	DBU	DMSO	78
3	Et_3N	DMSO	Trace
4	DABCO	DMSO	Trace
5	KOH	DMSO	66
6	Na_2CO_3	DMSO	58
7	K_2CO_3	DMSO	80
8	K_2CO_3	DMF	92
9	K_2CO_3	Dioxane	93
10	K_2CO_3	Toluene	78
11	K_2CO_3	Pyridine	91
12[c]	K_2CO_3	Dioxane	80
13[d]	K_2CO_3	Dioxane	84
14[e]	K_2CO_3	Dioxane	58
15[f]	K_2CO_3	Dioxane	41

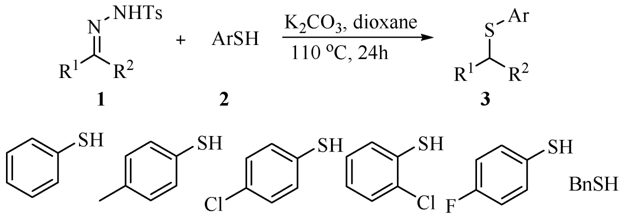
[a] Reaction conditions: tosylhydrazone **1a** (0.3 mmol), benzenethiol (**2a**; 2.0 equiv.), base (3.0 equiv.), solvent (3 mL), 110 °C, 24 h. [b] Isolated yield based on tosylhydrazone **1a**. [c] K_2CO_3 (1.0 equiv.). [d] K_2CO_3 (2.0 equiv.). [e] **1a** with **2a** in a 1 : 1.1 ratio. [f] 80 °C, 48 h.

generated in 90% yield (Table 2, entry 3). The reaction of tosylhydrazone **1a** with sterically-hindered 2-chlorobenzenethiol (**2d**) gave rise to thioether **3d** in 85% yield (Table 2, entry 4). Unfortunately, in the case of aliphatic substrate **2f**, none of the desired product was detected (Table 2, entry 6). With respect to other tosylhydrazones, both electron-neutral and electron-poor tosylhydrazones were examined in this reaction (Table 2, entries 7–16). When substrates **1b**, **1c**, **1d** and **1e** were employed in the reaction, the desired products were isolated in moderate to good yield (Table 2, entries 7–16). Comparing the results obtained, better yields were displayed when substrates with an electron-donating group attached to the aromatic ring were employed in the reaction. Unfortunately, when the tosylhydrazone of pentan-2-one, **1f**, reacted with thiol **2a**, none of the desired product, **3q**, was detected (Table 2, entry 17).

To broaden the scope of substrates, we further investigated the metal-free reductive coupling reaction of thiols with tosylhydrazones derived from aldehydes. We found that the reactions could also be carried out by the same procedure, and a wide range of structurally varied tosylhydrazones (**1g**, **1h** and **1i**) and thiols (**2a**, **2b** and **2c**) underwent reaction smoothly to provide the corresponding benzylic thioethers **3** in moderate to good yields (Table 2, entries 18–25). However, in the case of tosylhydrazone **1j**, derived from an aliphatic aldehyde, it remained inert (Table 2, entry 26).

Finally, we investigated a cascade one-pot reaction starting from tosylhydrazide and a carbonyl compound. A solution of tosylhydrazide and 4-methoxybenzaldehyde in dioxane was stirred at room temperature for 2 h. Subsequently, thiol **2a** and K_2CO_3 were added, and the mixture stirred for 24 h. The result showed that the isolated yield (73%) of product **3r** slightly decreased (Scheme 1).

Table 2 Reductive coupling between tosylhydrazones **1** and thiols **2**[a] [14]



2a **2b** **2c** **2d** **2e** **2f**

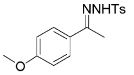
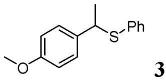
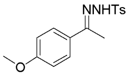
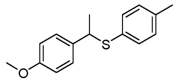
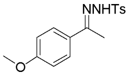
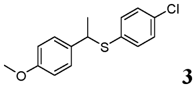
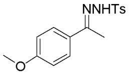
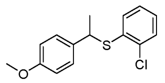
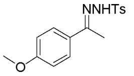
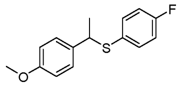
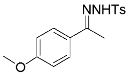
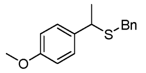
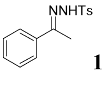
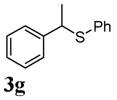
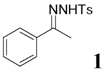
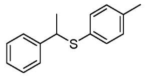
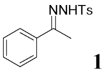
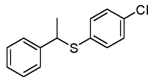
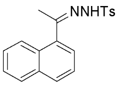
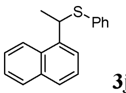
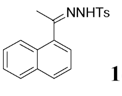
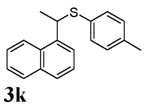
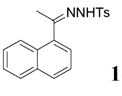
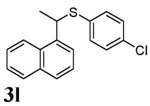
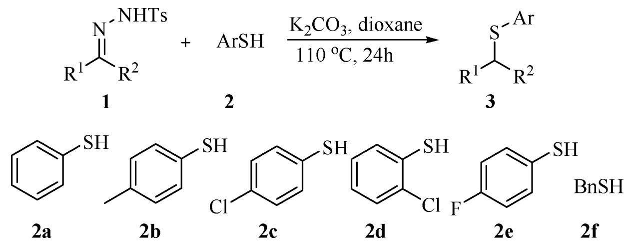
Entry	Tosylhydrazone 1	Thiol 2	Thioether 3	Yield (%)[b]
1	 **1a**	**2a**	 **3a**	93
2	 **1a**	**2b**	 **3b**	77
3	 **1a**	**2c**	 **3c**	90
4	 **1a**	**2d**	 **3d**	85
5	 **1a**	**2e**	 **3e**	88
6	 **1a**	**2f**	 **3f**	—
7	 **1b**	**2a**	 **3g**	68
8	 **1b**	**2b**	 **3h**	61
9	 **1b**	**2c**	 **3i**	60
10	 **1c**	**2a**	 **3j**	50
11	 **1c**	**2b**	 **3k**	45
12	 **1c**	**2c**	 **3l**	67

Table 2 *(Contd.)*



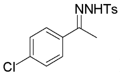
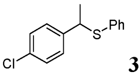
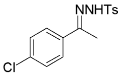
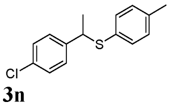
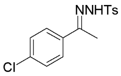
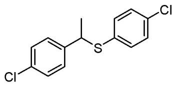
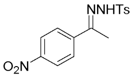
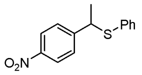
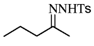
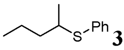
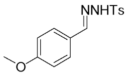
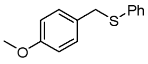
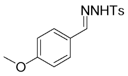
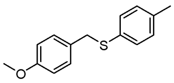
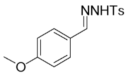
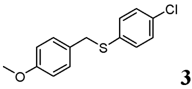
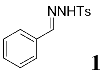
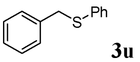
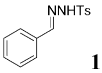
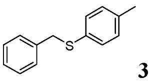
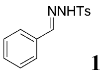
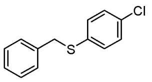
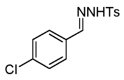
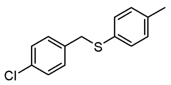
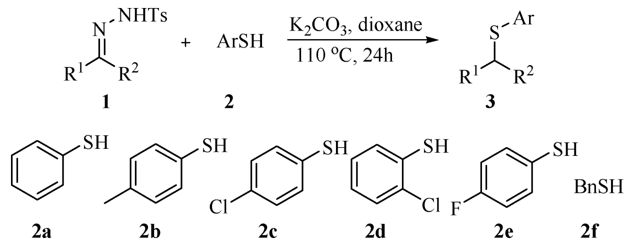
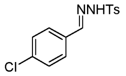
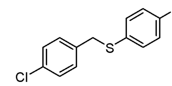
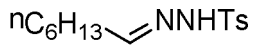
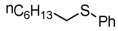
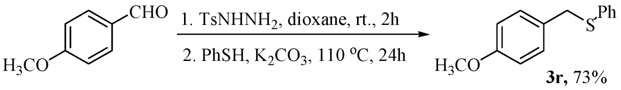
Entry	Tosylhydrazone **1**	Thiol **2**	Thioether **3**	Yield (%)[b]
13	 **1d**	**2a**	 **3m**	53
14	 **1d**	**2b**	 **3n**	76
15	 **1d**	**2c**	 **3o**	70
16	 **1e**	**2a**	 **3p**	53
17	 **1f**	**2a**	 **3q**	—
18	 **1g**	**2a**	 **3r**	75
19	 **1g**	**2b**	 **3s**	85
20	 **1g**	**2c**	 **3t**	72
21	 **1h**	**2a**	 **3u**	70
22	 **1h**	**2b**	 **3v**	52
23	 **1h**	**2c**	 **3w**	61
24	 **1i**	**2b**	 **3x**	58

Table 2 *(Contd.)*



Entry	Tosylhydrazone **1**	Thiol **2**	Thioether **3**	Yield (%)[b]
25	 **1i**	**2c**	 **3y**	48
26	 **1j**	**2a**	 **3z**	—

[a] Reaction conditions: tosylhydrazone **1** (0.3 mmol), thiol **2** (2.0 equiv.), K_2CO_3 (3.0 equiv.), dioxane (3 mL), 110 °C, 24 h. [b] Isolated yield based on tosylhydrazone **1**.



Scheme 1 Base-promoted one-pot reductive coupling.

The proposed reductive coupling mechanism is generally explained by the initial generation of an intermediate carbene *via* the base-promoted thermal decomposition of the tosylhydrazone,[9b] then resulting in the insertion reaction of the incipient carbene into the S–H bond of the thiol, giving rise to the corresponding unsymmetrical benzylic thioether.

In conclusion, the reaction of thiols with tosylhydrazones in the presence of K_2CO_3 represents a general, operationally simple, inexpensive and efficient approach to the synthesis of thioethers. A variety of unsymmetrical benzylic thioethers were synthesized in moderate to good yields *via* a metal-free reductive coupling procedure. It is noteworthy that the transformation can be carried out in a one-pot fashion starting from a carbonyl compound. We believe that the metal-free conditions make the procedure a better alternative to existing methods[3,4,5] for the synthesis of thioethers.

Acknowledgements

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14 General procedure for the metal-free reductive coupling reaction of tosylhydrazones **1** with thiols **2**: a mixture of tosylhydrazone **1** (0.3 mmol), thiol **2** (0.6 mmol, 2.0 equiv.) and K_2CO_3 (0.9 mmol, 3.0 equiv.) in dioxane (3.0 mL) is stirred at 110 °C for 24 h under N_2. After completion of the reaction, as indicated by TLC, the mixture is cooled to room temperature. After adding ethyl acetate (10 mL), the organic phase is washed with saturated brine, dried with $MgSO_4$ and concentrated under a vacuum. The residue is then purified by flash chromatography on silica gel to afford product **3** (for details, please see the ESI†).