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Synthetic Methods

Straightforward Synthesis of Ethers: Metal-Free Reductive Coupling of Tosylhydrazones with Alcohols or Phenols**

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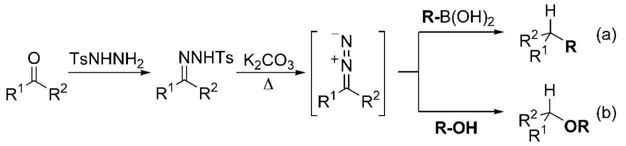
One approach to the design of sustainable synthetic routes is to develop advantageous, alternative reactions to well-established chemical transformations. Catalytic reactions are generally preferred in the context of sustainable chemistry;[1,2] however, metal-catalyzed reactions may also present problems associated with the high cost of precious metals and ligands, and the need to dispose of and eliminate the sometimes toxic metals once the reaction has been completed. For this reason, metal-free reactions that could exhibit the same levels of efficiency and selectivity as metal-catalyzed reactions are highly desirable.

The Williamson synthesis is the most typical method for the preparation of ethers.[3] However, this reaction is limited in that it requires hard bases, which reduces the functional group tolerance of the method. Moreover, the scope of the reaction is restricted by the need for good leaving groups, and importantly, the sensitivity to steric bulk; therefore, the synthesis of ethers derived from secondary and tertiary alcohols is still a challenging problem. One alternative to the Williamson ether synthesis is the condensation of alcohols catalyzed by Brønsted or Lewis acids; however, this approach is generally limited to the preparation of symmetrical ethers. Selective methods have been developed, but require specific combinations of alcohols, such as primary alcohols with benzylic or allylic alcohols, to avoid the formation of undesired symmetrical systems.[4] Among the methods for the synthesis of ethers based on S_N2 displacement reactions, the Mitsunobo reaction is a powerful and widely employed procedure for the synthesis of aryl alkyl ethers;[5] however, it is not atom economical and is environmentally unfriendly because of the need to use stoichiometric amounts of an azodicarboxylate and a phosphine.[6] For all these reasons, the development of general methodologies for the preparation of ethers is still challenging.[7]

A less popular approach for the synthesis of ethers is the reductive coupling of carbonyl compounds. Most of these methods involve the reaction of carbonyl or acetal groups with silyl ethers in the presence of a hydride source and a Lewis acid catalyst.[8] This type of chemistry could be suitable for the preparation of unsymmetrical ethers not easily available through the above-mentioned methods.

We have recently reported a new metal-free carbon–carbon bond-forming reaction between tosylhydrazones and boronic acids (Scheme 1 a).[9] This reaction can be envisioned as a very simple way to carry out a reductive coupling of a carbonyl compound, a transformation of high synthetic relevance. In continuing with our interest in metal-free processes employing tosylhydrazones, the synthesis of ethers by reductive etherification with alcohols or phenols emerged as an attractive transformation to study (Scheme 1 b). The combination of the diazo compound generated from the tosylhydrazone[10] with a hydroxylic compound would result in the formation of an ether, through an insertion reaction of the incipient carbene into the O−H bond.[11]



Scheme 1. a) Metal-free reductive coupling of tosylhydrazones and boronic acids. b) Metal-free reductive etherification of tosylhydrazones discussed in this work. Ts = tosyl.

Although many O−H insertion processes with phenols have been reported before, most of the examples involve diazo compounds stabilized by electron-withdrawing groups such as diazo ketones or diazo esters.[12,13] Moreover, the majority of the transformations are acid-[14] or transition-metal-catalyzed reactions,[15] as well as photochemical transformations.[16] Additionally, the thermal decomposition of diazo compounds in the presence of alcohols is extremely rare.[17–19]

Taking all these aspects into consideration, we decided to study in detail the reaction of tosylhydrazones with phenols and alcohols for the purpose of developing a new, useful, metal-free reductive etherification starting from carbonyl compounds. First of all, we focused on the reactions with phenols, which would lead to a new method for the synthesis of aryl ethers, a structural motif present in a variety of compounds having pharmaceutical activity.[20] To explore the reactivity of the *N*-tosylhydrazones towards phenols we selected the model reaction between the hydrazone derived from *p*-tolyl methyl ketone (**1a**) and *p*-bromophenol (**2a**; Table 1, entries 1–4).

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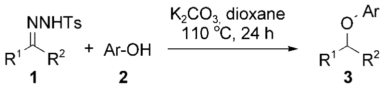
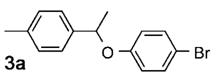
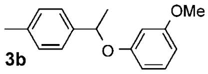
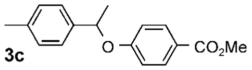
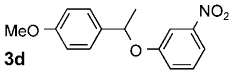
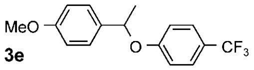
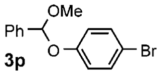
Table 1: Reductive coupling between tosylhydrazones **1** and phenols **2** by conventional heating.[a]



Entry	Ether 3	Yield [%][b]
1	 **3a**	32[c]
2		55[d]
3		55[e]
4		74
5		83[f]
6	 **3b**	70
7[g]	 **3c**	71
8	 **3d**	72
9	 **3e**	70
10[g]	 **3p**	81

[a] Reaction conditions: Tosylhydrazone **1** (0.3 mmol), phenol **2** (0.6 mmol), K_2CO_3 (3.5 equiv), dioxane (1 mL), 110 °C, 24 h. [b] Yield of isolated product. [c] Dioxane (2 mL), 110 °C, 12 h. [d] Mesitylene (2 mL) 140 °C, 12 h. [e] Dioxane (2 mL) 110 °C, 24 h. [f] Reaction was carried out on a 25 mmol scale. [g] 1.2 mL of dioxane employed.

The first attempts gave encouraging results. The reaction run in the presence of K_2CO_3 and using dioxane as the solvent at 110 °C afforded the aryl ether **3a** in 32 % yield (Table 1, entry 1). Upon heating the reaction mixture at 140 °C in mesitylene an important increase in the yield from 32 to 55 % was observed (Table 1, entry 2). A similar yield was obtained at 110 °C when dioxane was used as the solvent and the reaction time was doubled from 12 to 24 hours (Table 1, entry 3). Finally, it was found that with 1 mL of solvent, the reaction proceeded with substantially higher yield (Table 1, entry 4).

The reaction conditions used for entry 4 of Table 1 were applied to a series of phenols giving rise to the corresponding aryl ethers **3** in good yields, regardless of the electronic nature of the substituents on the phenol (Table 1, entries 6–9). Interestingly, under these conditions the reaction can be scaled up very efficiently. For instance, when the synthesis of **3a** was conducted on a 25 mmol scale, the aryl ether was obtained in an excellent yield of 83 % (Table 1, entry 5). Moreover, it should be highlighted that the use of a hydrazonate derived from methyl benzoate ($R^1 = Ph$, $R^2 = OCH_3$)[21] furnished the mixed acetal **3p**, which is difficult to synthesize by other methods (Table 1, entry 10).

At this point, because of the high temperatures and long reaction times required for the thermally induced O–H insertion, we decided to examine microwave (MW) irradiation as an energy source to facilitate this chemical reaction.

As a first attempt, treatment of the hydrazone **1a** with the phenol **2a** in dioxane at 140 °C for one hour gave ether **3a** in 63 % yield, whereas performing the reaction at 155 °C resulted in an increased yield of 72 %. A screen of solvents and bases (Table 2) revealed that K_2CO_3 was the best base to achieve the desired reaction (Table 2, entry 4). Moreover, we were pleased to find that experiments performed in dioxane, THF, or PhF proceeded with acceptable conversions and yields (Table 2, entries 4, 5, and 7). The influence of the temperature was also investigated and it was confirmed that reactions run at 155 °C gave the best results. These optimization studies concluded that the transformation could be best achieved by employing the reaction conditions listed in entry 7 of Table 2. Importantly, as in the conventionally heated reactions, a 2:1 excess of phenol was found to deliver the highest level of conversion. The MW-promoted reactions are advantageous in this particular transformation when compared to the reaction run using conventional heating: the higher reaction temperature allowed the processes to take place much faster, and in general, with slightly higher yields (Table 1, entries 4, and 6–9 versus Table 3, entries 1–5).

Table 2: Influence of solvents and bases in the MW-promoted synthesis of **3a** by reductive coupling between hydrazone **1a** and phenol **2a**.[a]

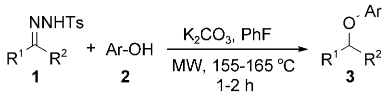
Entry	Base	Solvent	Volume [mL]	Yield [%][b]
1	K_3PO_4	dioxane	1.5	65
2	NaOH	dioxane	1.5	38
3	LiO*t*Bu	dioxane	1.5	–
4	$\mathbf{K_2CO_3}$	**dioxane**	**1.5**	**72**
5	K_2CO_3	THF	1.5	68
6	K_2CO_3	PhF	1.2	64
7	$\mathbf{K_2CO_3}$	**PhF**	**1.5**	**78**

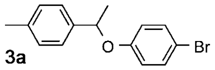
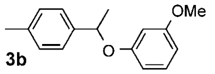
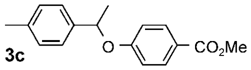
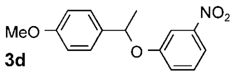
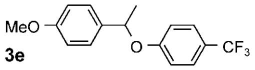
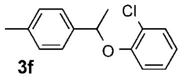
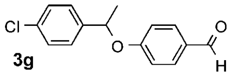
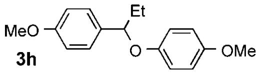
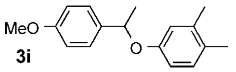
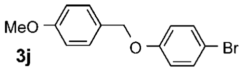
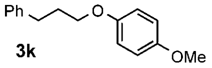
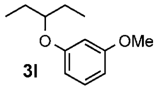
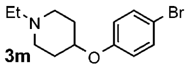
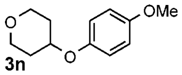
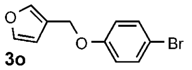
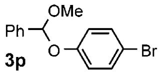
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), base (3.5 equiv), 155 °C, 1 h. The reactions were carried out in a Biotage Initiator synthesizer at constant temperature. [b] Yield of the isolated ether **3a**.

The scope of the process was studied under the optimized reaction conditions. The transformation proceeds very efficiently with a wide range of tosylhydrazones derived from aldehydes and ketones (Table 3). Therefore, hydrazones conjugated with aromatic systems undergo reaction to afford the desired products in high yields, regardless of their steric or electronic nature (Table 3, entries 1, 7, 9, 10, and 15). In the case of aliphatic substrates, the ethers are again formed in good yields (Table 3, entries 11 and 12). Furthermore, the transformation proceeds with cyclic hydrazones (Table 3, entries 13 and 14). Moreover, the mixed acetal **3p** could be also prepared by using the MW procedure. We next evaluated the diversity of substituted phenols that could be employed in the reaction and found the reaction to be extremely general. Both electron-withdrawing (Table 3, entries 1, 3, 4, and 5) and electron-donating substituents (Table 3, entries 2 and 9), as well as *ortho*-, *meta*-, and *para*-substitution patterns are well tolerated (Table 3, entries 6, 2, and 3, respectively).

As expected, halogen-substituted phenols proved to be suitable substrates, which lead to products that can undergo additional transformations by metal-catalyzed cross-couplings (Table 3, entries 1 and 6). The functional group tolerance is noteworthy given that potentially sensitive groups such as ester, aldehyde, nitro, and CF_3 groups are unaffected under the reactions conditions (Table 3, entries 3, 7, 4, and 5, respectively).

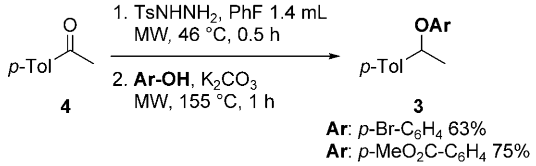
Table 3: Microwave-promoted reductive coupling between tosylhydrazones **1** and phenols **2**.[a]



Entry	*t* [h]	*T* [°C]	Vol. [mL]	Ether **3**	Yield [%][b]
1	1	155	1.5	 **3a**	78
2	1	155	1.4	 **3b**	82
3	1	160	1.4	 **3c**	80
4	2	160	1.4	 **3d**	78
5	1	155	1.2	 **3e**	52
6	2	165	1.4	 **3f**	80
7	1	160	1.4	 **3g**	40
8	2	155	1.4	 **3h**	52
9	2	155	1.4	 **3i**	81
10[c]	2	155	1.2	 **3j**	73
11	2	155	1.4	 **3k**	52
12[c]	2	155	1	 **3l**	70
13[c]	1	155	1.2	 **3m**	67
14	1	155	1.4	 **3n**	44
15	1	155	1.2	 **3o**	70
16	1	155	1.2	 **3p**	81

[a] Reaction conditions: Tosylhydrazone **1** (0.3 mmol), phenol **2** (0.6 mmol), K_2CO_3 (3.5 equiv), PhF (1–1.6 mL), 155–165 °C, 1–2 h. [b] Yield of isolated product. [c] Reaction conditions: Tosylhydrazone **1** (0.6 mmol), phenol **2** (0.3 mmol).

Tosylhydrazones are easily prepared by simply mixing the tosylhydrazide and the carbonyl compound. Therefore, we examined the possibility of synthesizing the hydrazones in situ to develop a one-pot procedure for the insertion process. Therefore, after the carbonyl compound **4** and the hydrazide had been heated for 30 minutes at 46 °C, the base and the phenol were added, and the mixture was then subjected to the reaction conditions of the reductive coupling. The ether **3** was isolated, although with a slight decrease in the yield (Scheme 2).



Scheme 2. MW-promoted one-pot reductive coupling.

At this point, we decided to investigate the alcohols as suitable substrates for this transformation. Delightfully, the reductive etherification could be also performed, although it was necessary to slightly modify the reaction conditions. Whereas an excess of the hydroxy source was necessary for the insertion of phenols, for the insertion of alcohols the best results were obtained with a 2:1 excess of the hydrazone.

As presented in Table 4, the reaction seems to be general with regard to the structure of the alcohol, because primary, secondary, tertiary, benzylic, and allylic systems led to the corresponding products. Again, the unusual and appealing mixed acetal **6 f** (Table 4, entry 6) was obtained by this simple reaction from the hydrazonate of methyl benzoate.

In summary, we have described a new procedure for the synthesis of ethers by a formal reductive etherification of carbonyl compounds. This metal-free C–O bond-forming reaction proceeds through the base-promoted decomposition of tosylhydrazones in the presence of phenols or alcohols, and results in the insertion reaction of the carbene into the O–H bond. Notably, the starting materials are readily available and stable; tosylhydrazones are readily synthesized from carbonyl compounds and carbonyl substrates can be directly employed in a one-pot fashion to generate the tosylhydrazone in situ. Furthermore, the operational simplicity of the process and the high functional group tolerance are remarkable. Taking into account that the ether functionality is present in a number of organic compounds, we believe that this methodology may become a very useful tool in organic synthesis.

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Keywords: alcohols · ethers · ketones · phenols · tosylhydrazones

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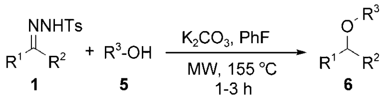
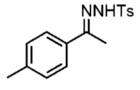
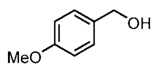
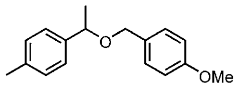
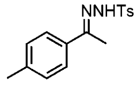
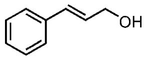
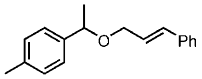
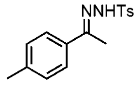
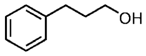
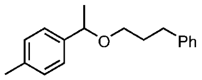
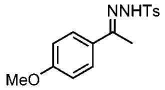
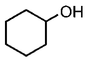
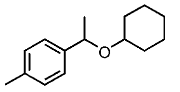
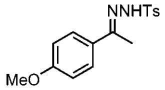
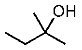
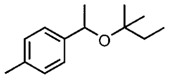
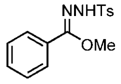
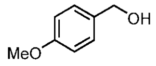
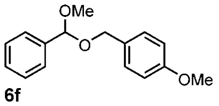
[1] P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**, p. 30.
[2] R. A. Sheldon, I. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, **2007**.
[3] a) J. March, *March's Advanced Organic Chemistry, Reaction, Mechanisms and Structure*, 5th ed., Wiley, New York, **2001**, pp. 477–478; b) L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, Burlington, **2005**, pp. 484–485, and references therein.

Table 4: Reductive coupling between tosylhydrazones **1** and alcohols **5**.[a]



Entry	Hydrazone **1**	Alcohol **5**	t [h]	Ether **6**	Yield [%][b]
1	 **1a**	 **5a**	2	 **6a**	66
2	 **1a**	 **5b**	2	 **6b**	61
3	 **1a**	 **5c**	2	 **6c**	74
4	 **1b**	 **5d**	2	 **6d**	66
5	 **1b**	 **5e**	3	 **6e**	57
6	 **1c**	 **5a**	1	 **6f**	61

[a] Reaction conditions: Tosylhydrazone **1** (0.6 mmol), alcohol **5** (0.3 mmol), K_2CO_3 (3.5 equiv), PhF (1.2 mL), 155 °C, 1–3 h. [b] Yield of isolated product.

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