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Protic ionic liquids as recyclable solvents for the acid catalysed synthesis of diphenylmethyl thioethers

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ABSTRACT

The acid catalysed formation of diphenylmethyl (DPM) thioethers was successfully achieved using the protic ionic liquid (pIL) triethylamine:methanesulfonic acid (TeaMs) as the reaction solvent under microwave irradiation. A slight excess of methanesulfonic acid (10% v/v) was required to facilitate the reaction, which was applied to a variety of thiols. Aliphatic, aromatic and heterocyclic aromatic thiols were converted to their corresponding DPM thioethers in high yields (63–99%), in short reaction times (5–20 min) and using mild temperatures (80–100 °C). Finally, the pIL (TeaMS) was recycled five times without loss of yield.

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1. Introduction

The application of thioethers in organic chemistry has been extremely varied; they are crucial to the generation of sulfur based heterocycles, are used in agrochemicals and pharmaceuticals, and have been utilised as a protecting group for thiols, all with great success [1,2]. Diphenylmethyl (DPM) thioether has been reported in several medicinal applications [3]; it features in the recent synthesis of novel benzothiazepines for the treatment of type II diabetes [4], and forms the central core of Modafinil, a compound used to treat narcolepsy [5].

Additionally, the oxidation of DPM thioethers to their corresponding sulfones, such as compound **1**, accesses reagents which have been successfully employed in the elaboration of both alkyl and olefinated triphenyl scaffolds, via Friedel–Crafts reactions and the use of Grignard reagents [6]. These are commonly derived from α-amidosulfones, and require the use of Lewis acids or proton sources through an additional Friedel–Crafts synthetic step to synthesise the sulfone product. Given their synthetic versatility, there is a constant demand for rapid, high yielding and clean methods for synthesising these intermediates.

The formation of DPM thioethers typically uses diphenylmethanol **2** and employs strong Brønsted acids and the desired thiol [5d,7], or conversely, the use of diphenylmethylene halides and the corresponding thiolate anion [8]. There have been recent examples of both $ZrCl_4$ and $HClO_4$-supported on silica [9] and Lewis acids [10] as catalysts for this transformation, as well as $AlPW_{12}O_{40}$ catalysts [11], which are able to be recycled. The use of a strong proton source takes the advantage of the rapid formation of the diphenylmethylene cationic species **3**, which is then scavenged by the highly nucleophilic thiol group (Scheme 1).

In our continuing search for reactions novel to the application of protic ionic liquid (pIL) solvents [12], our attention turned to the formation of DPM thioethers. pILs are a class of ionic liquids which are formed by mixing equimolar amounts of Brønsted acids and bases [13]. Due

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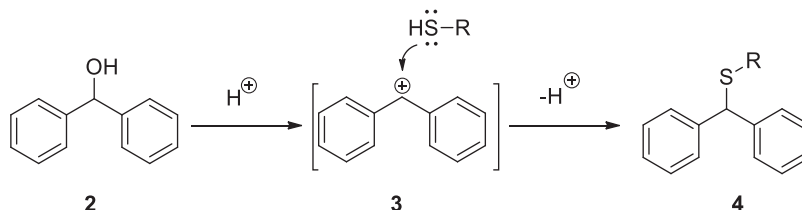
Scheme 1. Acid catalysed formation of DPM thioethers.

to their highly polar nature, they are excellent solvents for organic transformations facilitated by microwave irradiation. This manuscript presents an investigation into the formation of thioethers facilitated by pILs doped with a slight excess of methansulfonic acid (10% v/v). These reactions occur rapidly (10–20 min) at mild temperatures (80–100 °C), and demonstrate an excellent tolerance for alkyl, aryl and heteroaromatic thiols.

2. Results and discussion

We chose diphenylmethanol **2** and β-mercaptoethanol as our model reactants for optimisation, due to the synthesis of the bifunctional DPM thioether product **5**, which holds significant synthetic utility (as the alcohol moiety offers a range of versatile functional group inter-conversions). Additionally, this compound has been reliably synthesised in high yield by other groups and as such provides a literature reference for identification [5c,9]. Using triethylamine:methanesulfonic acid (TeaMs) at 80 °C for 20 min (Table 1, entry 1), we were surprised to see that there was no trace of the product observed in the crude reaction mixture. It is not uncommon that one pIL is optimal for a given transformation and as such, we tried a selection of other commonly employed pILs (triethylamine:formic acid (TeaFa), triethylamine:trifluoroacetic acid (TeaTFA) and triethylamine:sulfuric acid (TeaH$_2$SO$_4$) (Table 1, entries 2–4)), which showed no improvement in any case (Scheme 2).

As a result, we considered that in this instance, a catalytic amount of acid is required to facilitate this transformation, thus, we added a slight excess of methanesulfonic acid to TeaMS and repeated this reaction (Table 1, entry 5). We were pleased to observe, in the presence of acid catalyst (3% v/v), the formation of the desired compound **5** after 10 min at 80 °C, though in a moderate conversion (34%). Rather than increase reaction time to encourage further conversion, we increased the amount of methanesulfonic acid in the TeaMs solvent. The

Table 1
Optimisation of thioether formation[a].

Entry	Solvent	Acid (v/v%)	Time (min)[b]	Conv. (%)[c]
1	TeaMs	0	20	0
2	TeaFa	0	20	0
3	TeaTFA	0	20	0
4	TeaH$_2$SO$_4$	0	20	0
5	TeaMs	3	10	34
6	TeaMs	5	10	65
7	TeaMs	10	10	99
8	Emim	10	10	58
9	TeaMs	10	5	82
10	TeaMs	10	2	43[d]
11	TeaMs	10	1	39[d]
12	TeaFa	10	10	10
13	TeaTFA	10	10	Trace
14	CH$_2$Cl$_2$	10	10	0[e]
15	Et$_2$O	10	10	10[d]
16	Neat	0	10	0[f]

[a] Experimental procedure: DPM-OH **2** (100 mg) was placed into a microwave reactor vessel charged with thiol (0.1 mL) and treated with acid doped TeaMs (0.25 mL) with a stirrer bar. The vessel was then heated to the desired temperature for the desired time. The solution was then diluted with water and diethyl ether, 5 mL of NaOH (2 M solution) was added and the aqueous phase extracted three times with diethyl ether. The combined organic phases were then dried (MgSO$_4$), filtered and the filtrate removed in vacuo to give clear oil.
[b] Does not take into account heating and cooling times.
[c] Determined by integration of key peaks in the ^{1}H NMR spectrum.
[d] The remaining components of this mixture were starting material and dimerised **2**.
[e] A complex mixture of products was obtained from this reaction.
[f] The crude material from this reaction was only starting alcohol **2**.

samples were then doped with 5% and 10% (v/v) acid, respectively, and upon repeating the reaction, increased conversions within the 10 min reaction duration were noted (Table 1, entries 6 and 7), of 65% and 99%, respectively. Thus, we determined 10% v/v methanesulfonic acid to be optimal for this system.

Given these conditions, we set out to determine if there was any benefit of using the pIL in this system. Therefore,
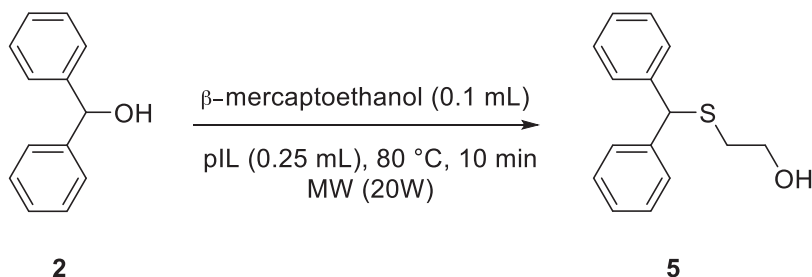
Scheme 2. Thioether formation using β-mercaptoethanol.
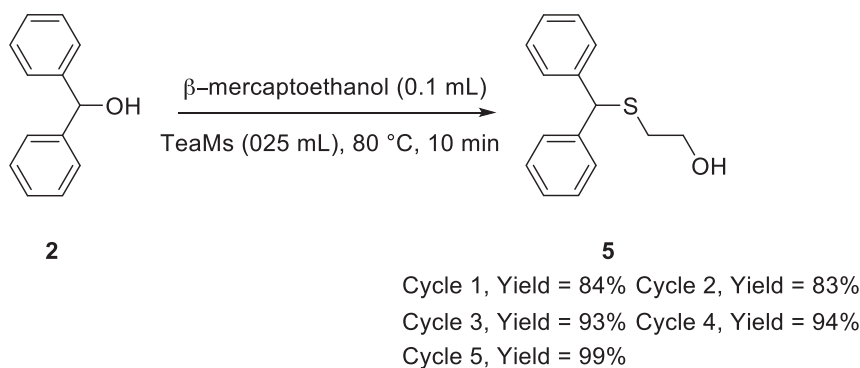
Scheme 3. Recycling protic ionic liquids and yields after five cycles.

the reaction was repeated in 1-ethyl-3-methylimidazo-lium methane sulfonate (EMimSO₄, an aprotic ionic liquid), with 10% v/v of methanesulfonic acid doped into the system (Table 1, entry 8). These conditions gave the desired product albeit with an inferior conversion (58%), suggesting that aprotic ionic liquids may be suitable for this transformation, though further optimisation would be required.

We considered the use of pIL solvents superior for this transformation as they have several advantages over imidazole-based ionic liquids:

- they are composed of reagents which are ubiquitous throughout organic chemistry laboratories;
- they are relatively cheap;
- pILs are the result of equimolar mixing rather than several synthetic steps which are required for the isolation of imidazole-based ILs.

Given the nucleophilic nature of thiols in comparison to alcohols, it was thought that the formation of the DPM thioether might be taking place much faster than the corresponding symmetric ether formation. Halving the reaction time to 5 min (Table 1, entry 9) gave a similar result to the previous entry, though in a reduced conversion (82%). Continuing along this line of investigation, further reductions in reaction duration to 2 and 1 min(s) (Table 1, entries 10 and 11) gave partial conversion to the desired thioether **5** (43% and 39%, respectively).

In light of these results for TeaMs, whereby a slight excess of acid component was required to facilitate this reaction, we returned to the previously investigated pILs, which proved unable to facilitate this reaction on their own. In each case, the acid component of the pIL was added to each neutral ionic liquid with the exception of Tea:H₂SO₄, as the aqueous portion of this acid can compete with the thiol in the etherification reaction. Applying the same reaction conditions elucidated earlier (Table 1, entry 7) to each of these now acid doped pILs, very little conversion to the desired product was observed (Table 1, entries 12 and 13). Finally, to verify that this reaction could not be performed in a standard organic solvent under the same reaction conditions, we repeated this methodology using dichloromethane and diethyl ether to replace the pIL solvent and found that in these instances, a complex mixture of products and starting material 2 were isolated in the crude reaction mixture in each case (Table 1, entries 14 and 15). Similarly, we repeated the reaction in neat thiol

(Table 1, entry 16) and found that the reaction did not proceed at all.

Therefore, the optimal reaction conditions were determined to be: 10 min, 80 °C, TeaMs with 10% methanesulfonic acid 10% v/v (Table 1, entry 7). This example offers not only extremely rapid and clean formation of the desired product, but also demonstrates selectivity of the formation of DPM thioether over the ether product.

Removal of the pIL from the reaction mixture can be carried out via a number of ways:
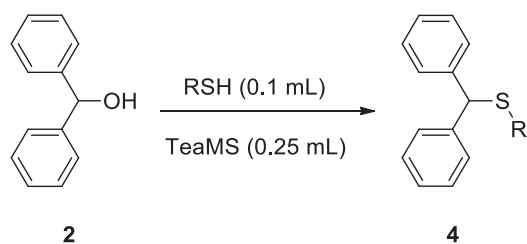
- aqueous work-up removes the polar pIL by placing the pIL into the water layer or;
- by filtration of the crude reaction mixture through a silica plug, giving the desired product in the presence of excess thiol.

Though these are very easy means to remove the pIL, it is quite wasteful and thus, our attention turned at investigating the recycling potential of the TeaMs reaction solvent.

To carry out this study (Scheme 3), we chose the same reactants that were used to optimise the reaction conditions (as comparison TLC and ¹H NMR spectra were at hand). To recycle TeaMs, the first reaction was carried out as per usual (10 min, 80 °C, TeaMs with 10% additional methanesulfonic acid v/v). The reaction mixture was then cooled to room temperature and the pIL was washed with diethyl ether twice. The ethereal layer was removed by pipette and reduced to dryness under vacuum, giving the desired product as clear oil. The starting reagents were added to the remaining pIL and the reaction cycle was repeated.

To our surprise, the reaction progression increased with each reuse of the pIL, culminating in progressive conversion increase from 84% (first use) to 99% (after fifth use)[1]. Though counter-intuitive, this result could be explained by

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[1] pIL recycling procedure: DPM-OH **2** (100 mg) was placed into a microwave reactor vessel charged with β-mercaptoethanol (0.1 mL) with a stirrer bar and treated with TeaMs (0.25 mL). The vessel was then heated to 80 °C for 10 min under microwave irradiation. The resulting clear solution was then washed with diethyl ether 2 × 5 mL) while being vigorously stirred. The combined diethylether layers were dried (MgSO₄) and solvent removed in vacuo to give clear oil. The remaining ionic liquid was then retreated with DPM-OH **2** (100 mg), β-mercaptoethanol (0.1 mL) and the reaction procedure repeated.

Scheme 4. Scope of thioether formation.

Fig. 1. Structures of Modafinil, an anti-narcoleptic agent, and a diphenylsulfone used in Friedel–Crafts reactions as derived from a DPM thioether.

the reaction "work-up" procedure; the β-mercaptoethanol is more polar than both starting material **2** and the desired product **5**. As such, the diethylether washes to remove both **2** and **5** may not remove all of the β-mercaptoethanol from the TeaMs layer. Therefore, after several recycles of the pIL, the residual amount of β-mercaptoethanol left behind from each previous use will accumulate in the pIL, resulting in a faster and more efficient reaction. Analysis by ^{1}H NMR of the TeaMs layer after the fifth use confirmed the presence of residual β-mercaptoethanol in the pIL. Our focus then turned to the scope of the reaction, by incorporating other thiols (Scheme 4).

Primary thiols 1-mercaptobutanol and benzyl-mercaptan proceeded under the optimised reaction conditions to give their corresponding DPM thioethers **4a** and **4b** in good to excellent yields (Table 2, entries 1 and 2), respectively. Our initial attempt employing methylthioglycolate under the same reaction conditions (Table 2, entry 3) gave very poor conversion (~5%); this was attributed to the deactivating effect of the methyl ester functionality. We considered this example extremely important, as it forms the structural backbone of Modafinil (Fig. 1). In an attempt to boost the reaction conversion, the reaction temperature was increased to 100 °C and the reaction time to 20 min (Table 1, entry 4) and we were pleased to see that under these slightly modified conditions, the conversion of methylglycolate to **4c** proceeded quantitatively. This also elucidated a set of reaction conditions which would be
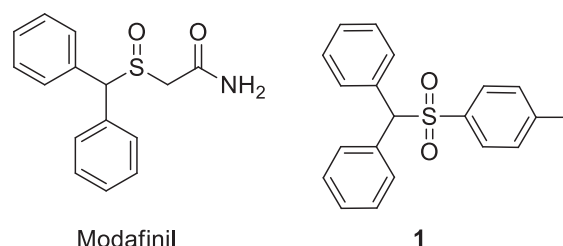
suitable for less reactive thiols. This important intermediate **4c** has been used in several studies on the development of Modafinil analogues, and as a substrate upon which chiral oxidations have been carried out to investigate the active stereochemistry of the pharmaceutical [14].

Isopropyl thiol and cyclohexanethiol (Table 2, entries 5 and 6) gave poor conversion to **4d** (11%) and **4e** (23%), respectively at 80 °C. We attributed this lower conversion to the increased steric bulk of these thiols as they were the first secondary thiols investigated in this series.

Applying the modified conditions used for methylthioglycolate (100 °C and 20 min) showed a substantial increase in reaction conversion (Table 2, entries 7 and 8) for each product, **4d** (77%) and **4e** (63%). Thioacetic acid also required an extended reaction time of 20 min (Table 2, entry 9) to get a synthetically viable yield (75%) of **4f**.

Next we examined a series of aromatic thiols, and considering their steric influence, we chose to only employ the longer reaction conditions (100 °C, 20 min) to these examples. Both aromatic thiols, 1-naphthalenethiol and 4-fluorothiophenol gave their corresponding DPM thioethers **4g** and **4h**, respectively, in very high yield (99%, Table 2, entries 10 and 11).

Our attention then turned to the use of heterocyclic scaffolds, which bear more than one heteroatom in their core, as complex small molecules of this nature feature heavily in naturally occurring compounds and in medicinal
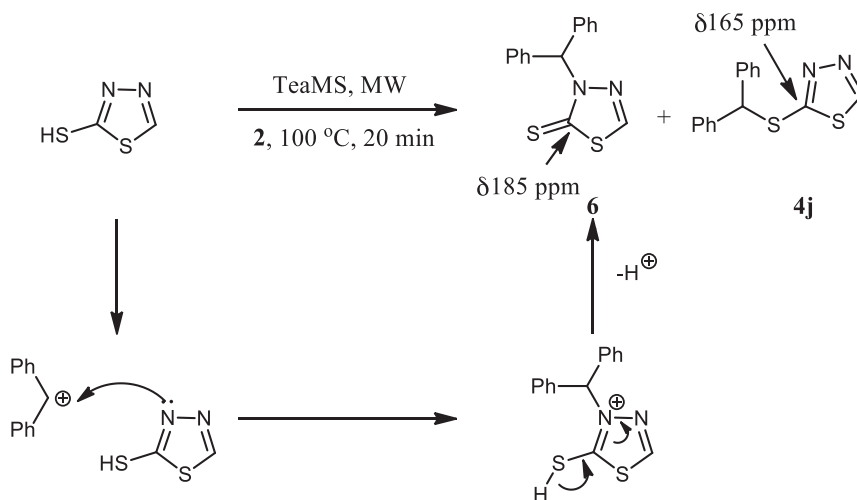
Scheme 5. Proposed mechanism of **6** formation including diagnostic shifts of the C2 carbon.

chemistry [15]. Employing 4-methyl-2-mercaptothiazole gave the desired product **4i** in excellent yield of 94% (Table 2, entry 12) and the application of these same conditions to 2-mercapto-1,3,4-thiadiazole consumed all of the starting DPM-OH **2** (Table 2, entry 13), though it gave two products. This mixture consisted of a 2:1 ratio of diphenyl-methylthioether **4j** to **6**, respectively, as determined by the integration of key peaks in the ^{1}H NMR spectrum. These compounds were separated chromatographically

and the analysis of **6** by ^{13}C NMR spectroscopy confirmed the identity of the thiocarbonyl (δ 185 ppm) of **6** when compared to the peak C2 of **4j** (δ 165 ppm). The formation of this compound is thought to arise via the interception of the benzhydryl cation by the nitrogen at the 3-position of the heterocycle, followed by collapsing of the thiol S–H bond to give the diagnostic thiocarbonyl (Scheme 5). The N-alkylated thiazole core of **6** is a central component to key compounds, which have been used to synthesise crown

Table 2
Reaction scope of thioether formation[a].

Entry	Thiol	Temp (°C)	Time (min)	Product	Yield (%)[b]
1	HO( )₂SH	80	5	**4a**	68
2	(benzyl) SH	80	5	**4b**	99
3	MeO–C(O)–SH	80	10	**4c**	5
4	MeO–C(O)–SH	100	20	**4c**	99
5	isopropyl SH	80	2	**4d**	11
6	cyclohexyl SH	80	5	**4e**	23
7	isopropyl SH	100	20	**4d**	77
8	cyclohexyl SH	100	20	**4e**	63
9	C(O)–SH	100	20	**4f**	75
10	naphthyl SH	100	20	**4g**	99
11	F–C₆H₄–SH	100	20	**4h**	99
12	4-methylthiazole HS	100	20	**4i**	94
13	thiadiazole HS	100	20	**4j**	96[c]

ethers and other heterocycles, which have demonstrated important properties, such as anti-microbial, anti-inflammatory and anti-cancer amongst others [16].

3. Conclusions

In this manuscript, we have described the use of pILs as a recyclable solvent to facilitate the acid catalysed formation of diphenylmethylthioethers. These reactions proceeded quickly, in high yields and were successfully applied to the etherification of a wide range of thiols. In addition, we have demonstrated the reusability of TeaMs in this protocol, which demonstrated an increase in reaction progression with each reuse.

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