C. R. Chimie 16 (2013) 634–639

Contents lists available at SciVerse ScienceDirect

Comptes Rendus Chimie

www.sciencedirect.com

Preliminary communication/Communication

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

Luke C. Henderson [a,b,*], Megan T. Thornton [b], Nolene Byrne [a], Bronwyn L. Fox [a], Kelsey D. Waugh [b], Jennifer S. Squire [b], Linden Servinis [b], Joshua P. Delaney [b], Hannah L. Brozinski [b], Luke M. Andrighetto [b], Jarrad M. Altimari [b]

[a] *Institute for Frontier Materials, Deakin University, Waurn Ponds Campus, Geelong, 3216, Victoria, Australia*
[b] *Strategic Research Center for Chemistry and Biotechnology, Deakin University, Pigdons Road, Waurn Ponds Campus, Geelong, 3216, Victoria, Australia*

ARTICLE INFO

Article history:
Received 28 November 2012
Accepted after revision 3 April 2013
Available online 6 May 2013

Keywords:
Protic ionic liquid
Thioether
Thiol
Microwave irradiation

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.

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.

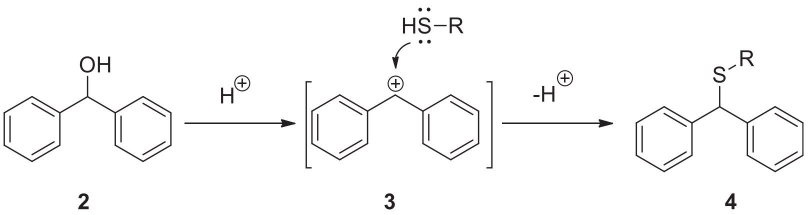
The formation of DPM thioethers typically uses diphenylmethanol **2** and employs strong Brønsted acids and the desired thiol [5d,7], or conversely, the use of diphenylmethylene halides and the corresponding thiolate anion [8]. There have been recent examples of both $ZrCl_4$ and $HClO_4$-supported on 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

---

* Corresponding author. Institute for Frontier Materials, Deakin University, Waurn Ponds Campus, Geelong, 3216, Victoria, Australia.
E-mail address: luke.henderson@deakin.edu.au (L.C. Henderson).

1631-0748/$ – see front matter © 2013 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.crci.2013.04.002



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 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,

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.

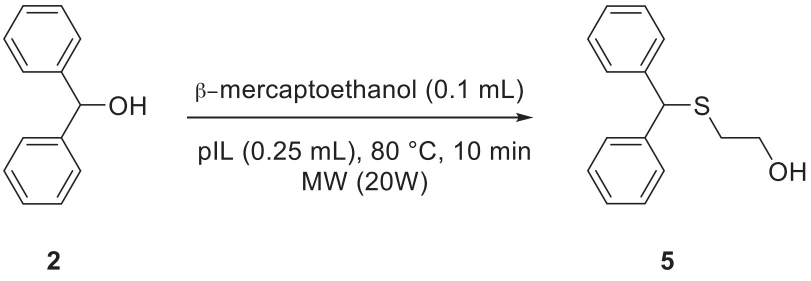
[b] Does not take into account heating and cooling times.

[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**.



Scheme 2. Thioether formation using β-mercaptoethanol.