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# Ionic liquid-supported TEMPO as catalyst in the oxidation of alcohols to aldehydes and ketones

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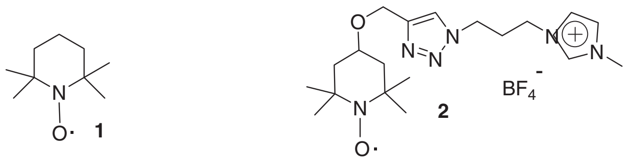
ABSTRACT

We describe an efficient synthesis of an ionic liquid-supported TEMPO which was used for the oxidation of alcohols to aldehydes and ketones. The predictable solubility of ionic liquids allows an easy separation of the oxidation products from reagents. Furthermore, the oxidation can be carried out using an ionic liquid as the solvent instead of dichloromethane; and the IL-supported TEMPO can be recycled and used several times without the loss of efficiency.

The oxidation of alcohols into the corresponding aldehydes or ketones is a process of major importance in organic synthesis.[1] Protocols for this transformation include the use of environmentally hazardous oxidizing agents in stoichiometric amount.[2] Over the past decades, new oxidation methods have been developed which tried to circumvent the use of toxic reagents in accordance with the increasing environmental consciousness of both academic and industrial research.[3] Recently, stable-free nitroxyl radicals, such as 2,2,6,6-tetramethylpiperidine-1-oxyl or TEMPO **1** (Fig. 1), have emerged as metal-free catalysts for selective oxidation of organic compounds.[4] The procedure includes the use of 1 mol % of TEMPO and a stoichiometric amount of a terminal oxidant. Piancatelli and co-workers[4e] demonstrated that commercially available bis(acetoxy)iodobenzene (BAIB) could be used as the terminal oxidant in combination with TEMPO. The oxidative process is very mild and compatible with many functional and protecting groups. However, TEMPO is a rather expensive chemical agent, and efficient recycling is highly desirable. This has led to the synthesis of several immobilized TEMPO moieties.[5] Herein, we report the synthesis and use of **2** (Fig. 1), a TEMPO-derived task-specific ionic liquid (TSIL).

Ionic liquids (ILs) have received much attention in recent years from the scientific community, mainly as environmentally benign reaction media.[6] Their unique properties such as high thermal and chemical stability, negligible vapor pressure, non-flammability, high loading capacity, and easy recyclability make them appealing for an organic chemist. The solubility of the ionic liquids can be tuned readily by modifying the structure of the cation or the anion, so that they can phase separate from organic as well as aqueous media, rendering purifications much easier. Ionic liquid-supported TEMPO **2** was prepared via the synthetic route shown in Scheme 1.

Commercially available chloropropanol **3** reacted with sodium azide to give 98% of azide **4** which was easily converted into iodide **5**.[7] Reaction of iodide **5** with *N*-methyl-imidazole **6** afforded ionic liquid **7** in 95% yield. Anion exchange using $NaBF_4$ afforded ionic liquid **8** in 99% yield, setting the stage for the click chemistry reaction,[8] which occurred uneventfully to give almost quantitatively ionic liquid-supported TEMPO **2**,[9] hereafter designated as 'IL-CLICK-TEMPO' **2**. The $^1H$ NMR spectrum of **2** in $CDCl_3$ gave broad lines and after running the spectrum in $CD_3COCD_3$ and varying the concentration we managed to get a decent $^1H$ NMR of **2**, shown in Figure 2.



TEMPO

IL supported TEMPO

Figure 1.

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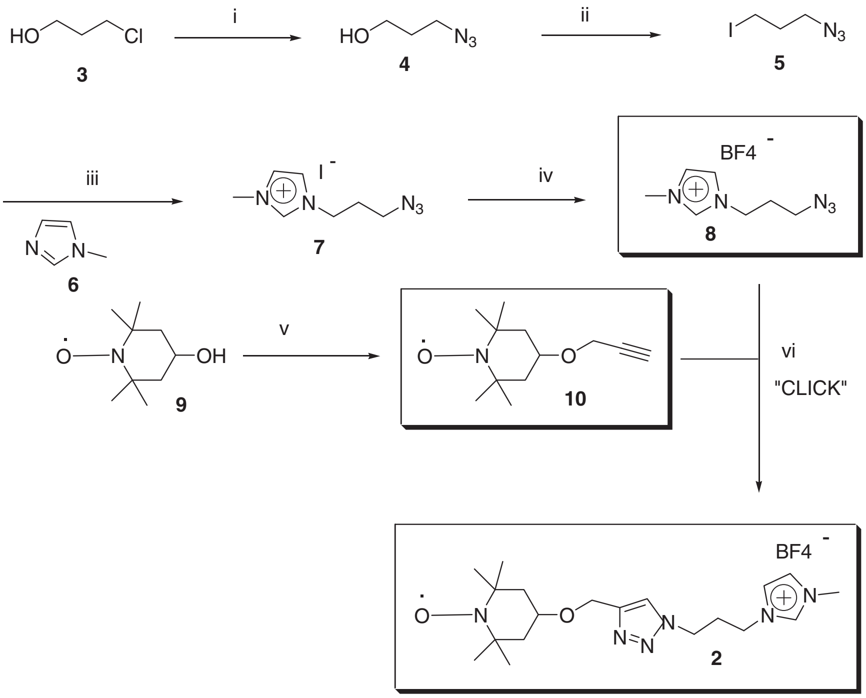


**Scheme 1.** Reagents and conditions: (i) $NaN_3$, $H_2O$, reflux (98%); (ii) $I_2$, $PPh_3$, imidazole, THF (79%); (iii) **6**, rt (95%); (iv) $NaBF_4$, $CH_3CN$, 60 °C (99%); (v) propargyl bromide, NaH, DMF (60%); (vi) $CuSO_4 \cdot 5H_2O$, Na-ascorbate, $^t$BuOH/$H_2O$ (99%).

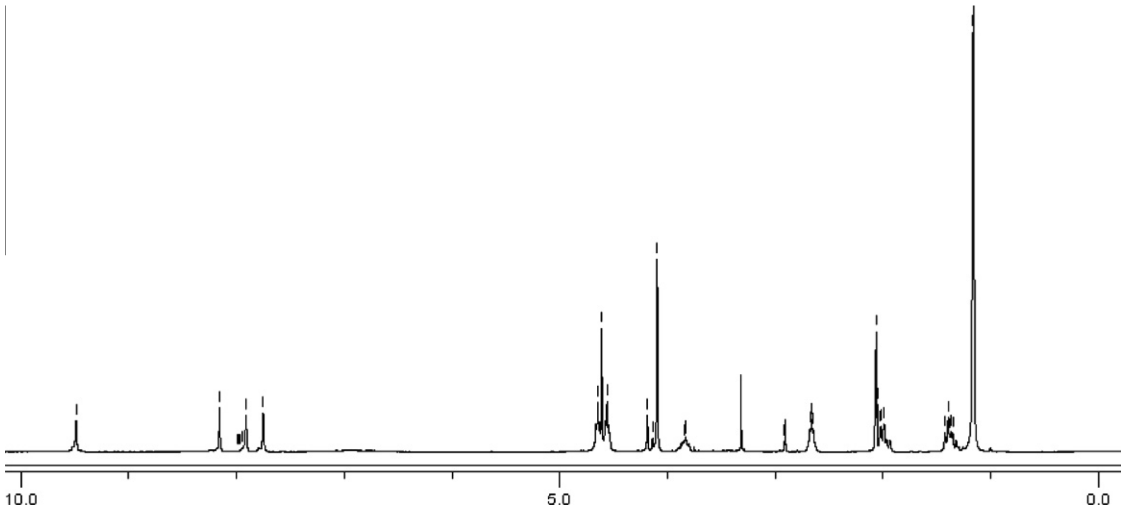


**Figure 2.** $^1$H NMR of 'IL-CLICK-TEMPO' **2**.

By anchoring TEMPO to an ionic liquid moiety we expected to facilitate the separation of the catalyst from the desired product and to be able to reuse the rather expensive TEMPO.

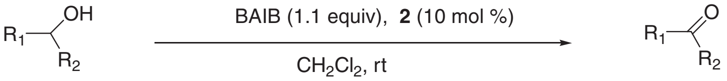
The reactivity and the scope of IL-CLICK-TEMPO **2** were investigated under Piancatelli and co-workers' conditions[4e] using BAIB as the terminal oxidant and the results are summarized in Table 1.

Under these conditions, a variety of alcohols were oxidized into the corresponding carbonyl compounds in excellent yields. Primary alcohols were rapidly oxidized, while secondary alcohols required longer reaction times. The carbonyl compounds were easily separated from the IL-supported TEMPO as follows: after completion of the reaction (tlc), the dichoromethane was rotatory evaporated and the residue was taken up with ether. In this solvent, IL-CLICK-TEMPO **2** was not soluble and was recovered by decantation, ready for another run. The ether phase containing the carbonyl derivative was concentrated and the residue was chromatographed on silica gel. The recovered catalyst **2** could be reused several times without loss in yields (Table 2).

In order to further enlarge the scope of our method we wondered if we could avoid the use of a toxic volatile organic compound (VOC) such as dichloromethane as the reaction solvent by carrying out the reaction in an ionic liquid medium. Accordingly the reaction was run under the same conditions as mentioned above but using different ILs as the solvent instead of dichloro-

**Table 1**

IL-CLICK-TEMPO **2** oxidation of alcohols to carbonyl derivatives



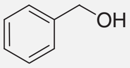
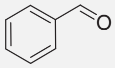
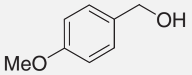
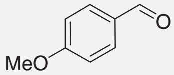
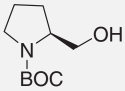
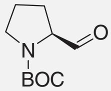
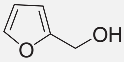
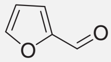
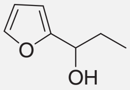
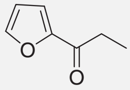
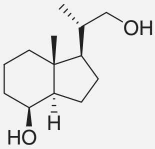
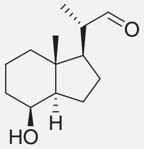
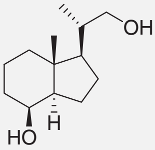
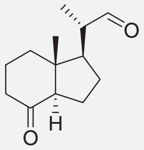
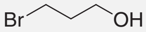
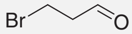
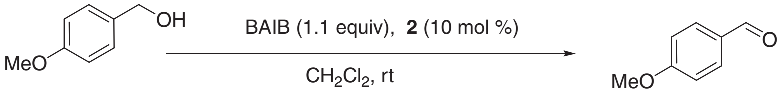
| Entry | Alcohol | Product | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 |  |  | 5 | 99 |
| 2 |  |  | 30 | 95 |
| 3 |  |  | 10 | 98 |
| 4 |  |  | 3 | 86 |
| 5 |  |  | 3 | 94 |
| 6 |  |  | 15 | 99 |
| 7 |  |  | 120 | 92 |
| 8 |  |  | 3 | 98 |

**Table 2**

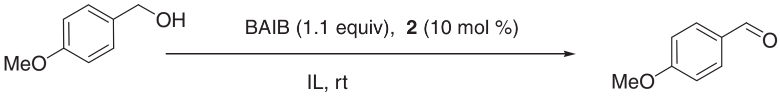
Recycling of IL-CLICK-TEMPO **2:** oxidation of *p*-methoxybenzyl alcohol in $CH_2Cl_2$



| Run | Time (min) | Yield (%) |
|---|---|---|
| 1 | 30 | 95 |
| 2 | 30 | 95 |
| 3 | 30 | 95 |
| 4 | 30 | 95 |
| 5 | 30 | 95 |

**Table 3**

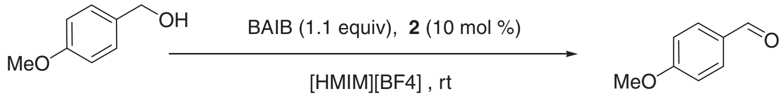
Oxidation of *p*-methoxybenzyl alcohol in ionic liquid medium



| Run | IL | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | [HMIM][$BF_4$] | 1 | 94 |
| 2 | [HMIM][Cl] | 1 | 89 |
| 3 | [BMIM][$BF_4$] | 1 | 67 |
| 4 | [OMIM][Cl] | 1 | 40 |

**Table 4**

Recycling of IL-CLICK-TEMPO **2:** oxidation of *p*-methoxybenzyl alcohol in [HMIM][$BF_4$]



| Run | Time (h) | Yield (%) |
|---|---|---|
| 1 | 1 | 94 |
| 2 | 1 | 94 |
| 3 | 1.25 | 92 |
| 4 | 12 | 88 |
| 5 | 48 | 36 |

methane. We were delighted to see that the reaction did proceed in an ionic liquid medium to give good yields although the reaction times were a bit longer (Table 3).

[HMIM][$BF_4$] proved to be the solvent of choice for this reaction and was used to run the recycling experiments (Table 4).

Typical experimental procedure: To a solution of *p*-methoxybenzyl alcohol (90 µl, 0.7 mmol) in [HMIM][$BF_4$] (1 ml) were added BAIB (262 mg, 0.8 mmol, 1.1 equiv) and catalyst **2** (34 mg, 0.07 mmol, 0.1 equiv). The mixture was stirred at room temperature for 1 h (tlc), then $Et_2O$ (4 ml) was added and the ionic liquid-phase was separated by decantation. The organic phase was rotatory evaporated and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate 7/3) to afford *p*-methoxybenzylaldehyde (0.9 g, 94%). To the ionic liquid-phase containing catalyst **2** were added the same quantities of BAIB and of *p*-methoxybenzyl alcohol as mentioned above, to carry out the next run. From the results of Table 4, IL-CLICK-TEMPO **2** can be reused up to four times.

In conclusion, we have shown that the ionic liquid-supported TEMPO **2** could be easily prepared via click chemistry and that **2** could be used in oxidation reactions in an ionic liquid medium, affording excellent yields of carbonyl compounds. Additional advantages of IL-CLICK-TEMPO **2** over free TEMPO are: simplified workup procedure and easy recovery and recycling.

## Acknowledgments

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9. *Selected spectral data for* **2**: mp: 44 °C; $^1$H NMR (acetone, 300 MHz) $\delta$: 9.48 (1H, s, CH); 8.15, 7.98, 7.75 (1H, 3s, CH); 4.64 (2H, s, O–$CH_2$); 4.60, 3.83, 1.39 (N–$CH_2$–$CH_2$–$CH_2$–N); 4.13 (3H, s, N–$CH_3$); 2.64–2.67 (1H, m, CH); 1.92–2.07 (2H, m, *trans*-3,5-H, $CH_2$); 1.36–1.42 (2H, m, *cis*-3,5-H, $CH_2$); 1.16, 1.17 (12H, 2s, *cis*-, *trans*-2,6-$CH_3$); $^{13}$C NMR (acetone) $\delta$: 145.38 ($CH_2$–*C*(N)=CH); 124.00 (C(N)=CH–N); 61.48 (O–*C*$H_2$); 44.60; 44.44 (2 × $CH_2$–N); 30.85 ($CH_2$–$CH_2$–$CH_2$); 137.38 (C-5); 123.63 (C-3); 122.76 (C-2); 36.26 ($CH_3$); 54.83 (*tert*-C); 48.98 (CH); 47.00; 46.68 (2 × $CH_2$); 29.62; 20.09 (*cis*, *trans*-2,6-$CH_3$); IR-($CDCl_3$, $\nu$($cm^{-1}$)): 3419, 2938, 1571 (C=C), 1457, 1363, 1172, 1079, 752, 620; MS (FAB$^+$) [*m*/*z*, (%)]: 377 ([M+1]$^+$ (63), 252 (66), 222 (34), 212 ([$C_{13}H_{24}O_2$]$^+$ (100%).