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Cyclopentyl Methyl Ether-NH$_4$X: a Solvent/ Catalyst System for Low Impact Acetalization Reactions

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Ugo Azzena,[a,*] Massimo Carraro,[a] Ashenafi Damtew Mamuye,[a,‡] Irene Murgia[a] and Luisa Pisano[a], Giuseppe Zedde[a]

Cyclopentyl methyl ether, a low impact ether forming a positive azeotrope with water, was successfully employed as a solvent in the synthesis of 1,3-dioxanes and 1,3-dioxolanes carried out under Dean-Stark conditions by the acetalization of aliphatic and aromatic aldehydes or ketones, employing ammonium salts as environmentally friendly acidic catalysts.

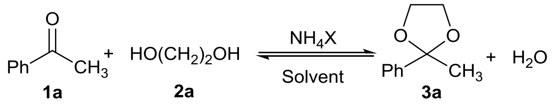
Acetals are a fundamental class of substrates in organic chemistry usually employed in the protection of carbonyl groups during multistep synthesis,[1] as well as intermediates in the monoprotection of diols.[2] Additionally, they found applications as fragrances[3] or profragrances[4] in everyday life. Typically, acetals are synthesized starting from aldehydes or ketones with alcohols or polyols under azeotropic distillation conditions in the presence of an acid catalyst. The system commonly employed uses toluene as a solvent and *p*-toluenesulfonic acid (*p*-TSA) as a catalyst, often in the presence of large excess of alcohol. Within this field, most green approaches concern the employment of heterogeneous acidic catalysts, due to their ease of separation and recovery from reaction mixtures.[5]

Cyclopentyl methyl ether (CPME) is emerging as a green alternative to ethereal solvents such as tetrahydrofuran, dioxane and diethyl ether. This solvent, industrially produced via a 100% atom economical reaction, is characterized by low toxicity, high boiling point, resistance to peroxide formation, stability towards acids and bases, low heat of vaporization, and a narrow explosion range. Although a note of caution is due to its relatively low auto ignition temperature (180 °C), it forms a positive azeotrope with H_2O (bp 83 °C, azeotropic composition: CPME/H_2O = 83.7:16.3 w/w) thus resulting easy to recover and dry, due to its high hydrophobicity.[6]

These characteristics prompted us to evaluate its employment as an alternative to solvents with a higher environmental impact, such as toluene,[7] in reactions run under azeotropic distillation conditions, for instance the acetalization reaction.

We found it advantageous, from the green chemistry standpoint, to keep the excess of alcohols to a low level and to substitute *p*-toluenesulfonic acid (*p*-TSA) with inorganic solid acids, such as ammonium salts. Indeed, compounds such as ammonium chloride, bromide and hydrogensulfate are cheap, easily available and relatively mild acids[8] and, due to their smaller formula weight, give rise to a low amount of generated wastes. Additionally, it is worth noting that these salts do not need any kind of activation as required, for example, by other acidic solid catalysts such as zeolites or clays.

Table 1. Synthesis of dioxolane **3a**.[a]



Entry	Diol (equiv)	Solvent	NH$_4$X	**3a** (%)[b]
1	1.1	CPME	NH$_4$HSO$_4$	90[c]
2	1.5	CPME	NH$_4$HSO$_4$	95
3	2.0	CPME	NH$_4$HSO$_4$	98
4	1.1	CPME	NH$_4$Br	79[d]
5	1.1	CPME	NH$_4$Cl	65[d]
6	1.1	Toluene	NH$_4$HSO$_4$	80
7	1.1	2-MeTHF	NH$_4$HSO$_4$	31

[a] All reactions were run at reflux during 6 h in the presence of the catalyst (3 mol % of **1a**). [b] As determined by ^{1}H-NMR analyses of crude reaction mixtures; no other product was detected besides **1a**. [c] Comparable results were obtained recycling 4 times the recovered catalyst. [d] Comparable results were observed recycling twice the recovered catalyst.

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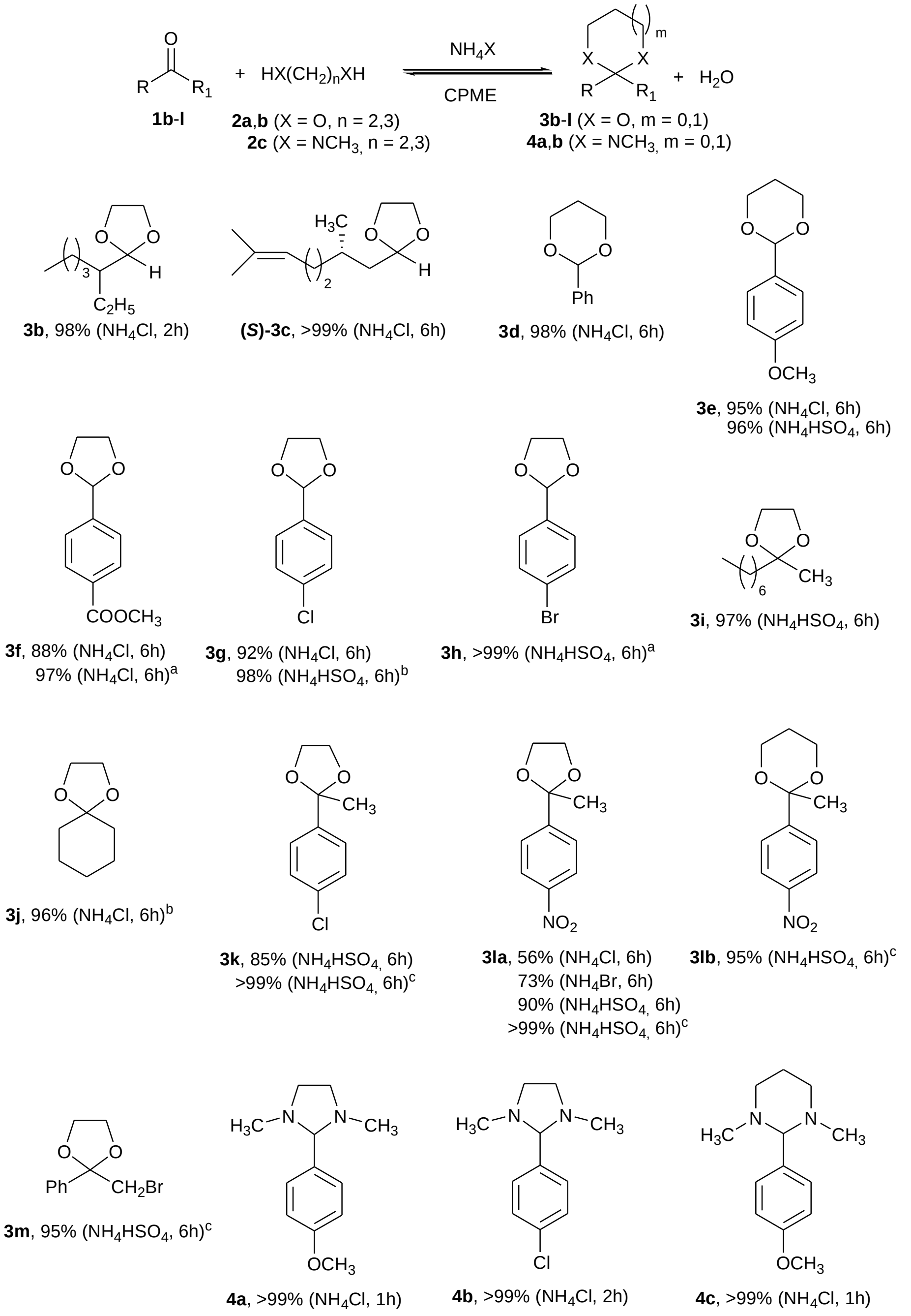
Taking acetophenone, **1a**, as a model compound, we investigated its conversion into the corresponding 1,3-dioxolane, **3a**, by refluxing a 4M solution of the ketone with 1,2-ethandiol, **2a**, under Dean-Stark conditions in the presence of the acidic catalysts (3 mol% of **1a**). For comparison purposes, few reactions were run employing as a solvent either toluene or an alternative low impact ether, i.e., 2-MeTHF,[9] under otherwise identical reaction conditions (Table 1).



Scheme 1 Synthesis of acetals in CPME. Reaction conditions: 4M solution of **1** in CPME, 1.1 equiv of **2a-c** (unless otherwise indicated), 3 mol% of NH_4X (with respect to **1**), reflux (Dean-Stark conditions); NH_4X = NH_4Cl, NH_4Br or NH_4HSO_4; percentages represent conversion of the starting materials as determined by ^{1}H-NMR; no other product, besides starting material, was detected. [a]In the presence of 1.4 equiv of diol; [b]A comparable result was obtained recycling the recovered catalyst. [c]In the presence of 2.0 equiv of diol.

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As expected, ammonium salts proved insoluble in the organic solvents, thus allowing both their recovery and a successive easy work up of the reaction mixtures. Indeed, after decantation of the catalyst, the resulting solution was neutralized over K_2CO_3, followed by evaporation of the solvent in vacuo (see Electronic Supplementary Information). Concerning reactions run in CPME, our results show that NH_4HSO_4, the most acidic between the chosen ammonium salts, resulted more effective than NH_4Br and NH_4Cl as a catalyst (Table 1, entry 1 vs. entries 4 and 5). A moderate increase in the amount of the diol (2.0 equivs of 2a) was sufficient to achieve an almost quantitative conversion of the starting material within the allotted reaction time (Table 1, entry 3).[10] Additionally, NH_4HSO_4 was efficiently recycled 4 times (Table 1, entry 1), whilst both NH_4Br and NH_4Cl were recycled twice (Table 1, entries 4 and 5, respectively) without observing any decrease of their catalytic activities.

Interestingly, no improvement was observed employing toluene as a solvent and NH_4HSO_4 as a catalyst (Table 1, entry 6); finally, a very low conversion of the starting material was observed running a similar reaction in 2-MeTHF (Table 1, entry 7), probably due to the relatively low boiling point of its azeotrope with H_2O.

The above described procedure was successfully extended to the synthesis of a series of 1,3-dioxolanes (including **3b**, a known fragrance,[11] enantiomerically pure **3c**, and the biologically active compounds **3k** and **3la**[12]), 1,3-dioxanes (including **3e**, an intermediate in the synthesis of a monoprotected 1,3-propandiol,[13] and the biologically active compounds **3lb**[12]), 1,3-dimethylimidazolidines **4a**,**b** and the hexahydropyrimidine **4c**, as diagrammatically illustrated in Scheme 1.

Taken as a whole, our results show that the ammonium salts efficiently catalyzed the almost quantitative conversion of aliphatic as well as aromatic aldehydes, **1b**-**h**, into the corresponding dioxolanes and dioxanes, **3**, and aminals, **4**, in the presence of minor excesses of the required dinucleophiles (1.1 to 1.4 equivs), and similar results were obtained with ketones **1i** and **1j**.

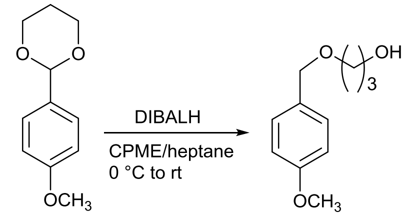
As already observed with **1a**, slightly lower reactivities were observed in the case of aromatic ketones **1k-m**, as expected on the basis of their relatively low electrophilicities; indeed, up to 2.0 equivs of the diol and the employment of NH_4HSO_4 as a catalyst were necessary to drive their conversions up to ≥ 95%, as evidenced in the case of dioxolanes **3k-3la**.[14]

Besides what already reported in Table 1, the efficiency of NH_4HSO_4 as a catalyst in the acetalization of aromatic ketones is outlined in comparative experiments related to the synthesis of compound **3la** (Scheme 1).

Additionally, the recovery and reuse of the acidic catalysts was effectively applied to the synthesis of dioxolanes **3g** (NH_4HSO_4) and **3j** (NH_4Cl).

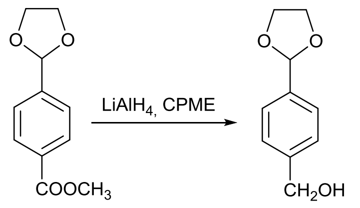
It is also interesting to observe that aminals **4a-c** were obtained with higher yields and shorter reaction times compared to those necessary to obtain the corresponding cyclic acetals **3e** and **3g**, respectively, likely due to the higher nucleophilicity of the nitrogen vs. oxygen dinucleophiles.

To further assess the usefulness of our protocol, few crude acetals synthesized as described above were further elaborated employing CPME as a solvent (or a co-solvent), as depicted in equations 3-5. Accordingly, the monoprotection of 1,3-propandiol as the corresponding 3-(4-methoxybenzyloxy)-1-propanol, **5a**, was efficiently realized by submitting crude acetal **3e** to reduction with DIBAL-H (equation 1); reduction of crude (4-carboxymethylphenyl)-1,3-dioxolane, **3f**, with $LiAlH_4$ afforded the corresponding benzyl alcohol, **5b**, in 70% overall yield (equation 2); finally, ring opening of crude α-brominated dioxolane **3m** was realized in 85% overall yield via a SET reduction run with 1,2-disodiotetraphenylethane[15] (equation 3).



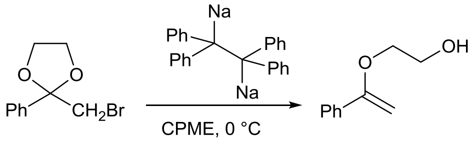
(1)

3e **5a**, 72% isolated yield



(2)

3f **5b**, 70% isolated yield



(3)

3m **5c**, 85% isolated yield

As the generation of peroxides is a major security concern for reactions run in ethereal solvents, we next investigated the stability of CPME towards the formation of peroxides under the above reported reaction conditions. To this end, we employed a commercially available kit (Quantofix®, measuring range 0.5 – 25 mg/L H_2O_2) allowing a semi-quantitative evaluation of these dangerous by-products in non-aqueous solvents. According to the reported resistance of CPME to autoxidation,[16] we found it possible to run our reactions with the commercially available solvent (stabilized with 50 ppm of BHT) exposed to air through a $CaCl_2$ tube, without observing any formation of peroxides.

Finally, it is worth mentioning that it was possible to realize an 85% mass recovery of CPME by submitting the solvent, collected by evaporation of reaction mixtures, to filtration over acidic alumina followed by drying over KOH and distillation (see Electronic Supplementary Information). From this point of view, it is worth mentioning that recovery of CPME by distillation is economically favourable due to its relatively low latent heat of vaporization.[6a]

Conclusions

As a conclusion, we were able to demonstrate the capability of CPME to promote the acetalization of aldehydes and ketones employing ammonium salts as acidic catalysts, thus representing an efficient green alternative to toluene/*p*-TSA. Accordingly, our results disclose an environmentally sustainable approach to the synthesis of a particularly important class of organic compounds as well as an alternative approach to reactions run under Dean-Stark conditions. Additionally, besides underlying the possibility of an easy and efficient recovery of CPME, it is worth noting that the employment as acidic catalysts of low impact, highly economical, recyclable and non soluble ammonium salts allowed the set up of a particularly simple and efficient work up with a reduced production of wastes.

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[a] *Dipartimento di Chimica e Farmacia, Università di Sassari, via Vienna 2, 07100 – Sassari (Italy)*
‡Current Address: Department of Pharmaceutical Chemistry, University of Vienna, Althanstrasse 14, Vienna, Austria

Electronic Supplementary Information (ESI) available: General method, synthetic procedures, characterization data of all compounds including copies of ^1H and ^{13}C NMR of previously not completely described compounds. See DOI: 10.1039/c000000x/

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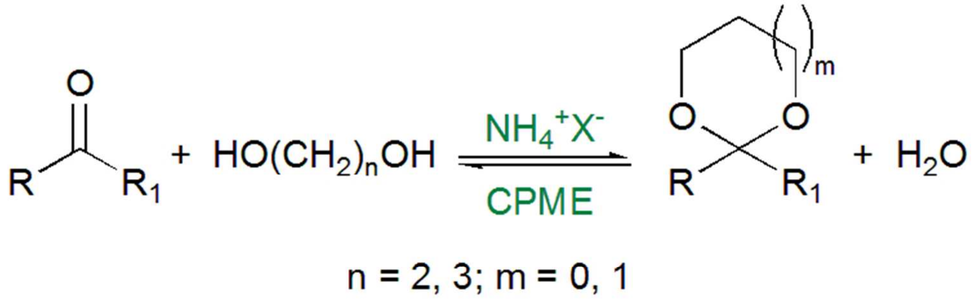

Cyclopentyl methyl ether and ammonium salts provide an environmentally friendly reaction medium for the synthesis of acetals

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