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Rapid and efficient protic ionic liquid-mediated pinacol rearrangements under microwave irradiation†

Luke C. Henderson*[a] **and Nolene Byrne***[b]

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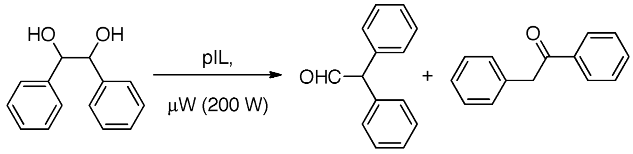
Several protic ionic liquids were tested as potential mediators for pinacol rearrangements employing microwave irradiation. Using hydrobenzoin as a model substrate, the optimal conditions were found to be heating at 80 °C for 5 min using H_2SO_4:triethylamine as the ionic liquid. A key feature of this reaction was to keep the microwave power low (20 W) to avoid ionic liquid degradation. Application of these conditions to triphenylethylene glycol gave rearrangement products in high yield and purity, while phenylethylene glycol and styrene oxide gave pinacol products that underwent a cascade aldol condensation. These conditions represent an efficient means by which pinacol rearrangements can be carried out while avoiding the use of strong Brønsted acids, high temperatures and extended reaction times.

The pinacol–pinacolone[1] (and related) rearrangement has had a major impact on synthetic organic chemistry.[2] This transformation involves the dehydration of *vic*-diols, resulting in a carbocation intermediate that is stabilised *via* an alkyl (or hydride) migration.[3] The pinacol rearrangement has been used to great effect in natural product synthesis,[4] for example D,L-marcfortine C, which possesses antiparasitic activity.[5] Typically, pinacol rearrangements require the use of very strong Brønsted acids (typically H_2SO_4, Cl_3CCO_2H, triflic acid), with H_2SO_4 being the most common. Several alternatives to these acids have been reported, including solid-supported catalysts[6] and antimony-based ionic liquids.[7] Never-the-less, these alternative catalysts still require the use of harsh reaction conditions, and an efficient, mild and safe means of carrying out pinacol rearrangements is desirable.

Protic ionic liquids (pILs) are a class of ionic liquids that are formed by mixing strictly equimolar amounts (1 : 1) of Brønsted acids and bases. The strength of the acid/base combination determines the degree to which the acidic proton is transferred—the proton activity. This tuneable parameter has been used previously to probe the suitability of pILs to carry out organic transformations.[8] The pinacol rearrangement is an ideal candidate for the application of pILs as several reaction features, such as the strength of the acid (or in this case the proton activity), the reaction duration and the temperature, are considered crucial for a successful transformation.[3a] Here, we demonstrate the use of a pIL as a mediator for pinacol rearrangements to complement the previously mentioned alternatives to acid catalysis. This methodology gives products rapidly (5 min) and in high yield (> 90%) under microwave irradiation. Additionally, the ionic liquid can be removed by filtration through silica; a safe and simple work-up compared to the neutralisation of strong acids.

Results and discussion

We chose hydrobenzoin as our model compound for preliminary studies as it is commercially available, and the pinacol rearrangement products are both well known and characterized (see Scheme 1). Four pILs were investigated for their ability to carry out the desired rearrangement. Each of the pILs have varying degrees of acidity, depending largely on the choice of anion. This was considered prudent as the strength of acid is widely regarded as the most important reaction parameter for pinacol rearrangements.



1 **2** **3**

Scheme 1 Hydrobenzoin pinacol rearrangements.[9]

Our initial attempts to effect this transformation employed triethylamine:methane sulfonic acid (TeaMs) (Table 1, entry 1). We were encouraged to see spots on the TLC corresponding to the pinacol products but an intense absorbance correlating

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[a] *School of Life and Environmental Sciences, Deakin University, Pigdons Road, Waurn Ponds, Victoria, Australia, 3217. E-mail: luke.henderson@deakin.edu.au; Fax: +61 3 5227 1040; Tel: +61 3 52271416*

[b] *Institute for Research Innovation and Technology, Deakin University, Pigdons Road, Waurn Ponds, Victoria, Australia, 3217. E-mail: nolene.byrne@deakin.edu.au; Fax: +61 3 5227 1040; Tel: +61 3 522 72609*

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Table 1 Preliminary investigations into suitable pILs

Entry	pIL	*T*/°C	Time/min	Ratio **2** : **3**	Conversion (%)
1	TeaMs	120	20	2 : 1	14
2[a]	TeaMs	120	20	—	0
3	TeaTFA	120	20	2 : 1	9
4	TeaTFA	120	40	0 : 1	12
5	TeaTFA	180	20	—	0[b]
6	TeaH$_2$SO$_4$	120	20	2 : 1	100[c]
7	TeaTfOH	120	20	—	0

[a] 20% v/v water added. [b] Compound and pIL degradation products were observed. [c] Combined isolated yield of **1** and **2** was 31%

to hydrobenzoin **1** suggested a poor conversion. This was confirmed by ^{1}H NMR, which showed only a 14% conversion to desired products **2** and **3**.

The reaction was repeated in TeaMs using 20% v/v H$_2$O (Table 1, entry 2) to solubilize **1**, but this appeared to inhibit the reaction. Similarly, using triethylamine trifluoroacetic acid (TeaTFA) at 120 °C for both 20 (Table 1, entry 4) and 40 (Table 1, entry 5) min gave only traces of the desired products. In an attempt to encourage reaction conversion, a higher temperature was employed (Table 1, entry 6), which resulted in only pIL and compound degradation products. Employing TeaH$_2$SO$_4$, the pIL with strongest proton activity, we were delighted to see the complete consumption of the starting material to the desired products.[10] Diphenyl aldehyde **2** was formed in preference to ketone **3** in an approximately 2 : 1 ratio (respectively), though in a moderate yield of 31%. Finally, trifluoromethanesulfonic acid (TfOH)Tea (Table 1, entry 7) returned only traces of the desired products. With a suitable pIL in hand, our attention turned to increasing the yield of this reaction. Though the reaction proceeded quickly, we considered the 31% yield obtained from our preliminary investigations not synthetically useful.

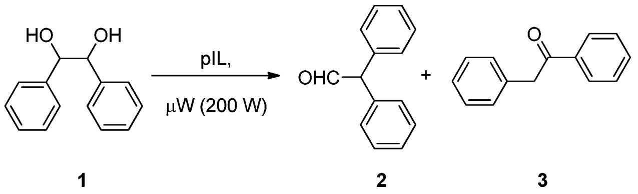
It was noted that after microwave irradiation of TeaH$_2$SO$_4$, the reaction mixture was severely discoloured and liberated a distinct odour (SO$_3$), suggesting degradation of the pIL. It was thought that the reaction could be proceeding very rapidly, and as such the 20 min timescale may be leading to both ionic liquid, and subsequently product, degradation. In an effort to minimise this effect, the reaction was repeated under identical conditions but reducing the duration.

Reacting **1** at 120 °C for 10 and 5 min (Table 2, entries 1 and 2) increased the yield, supporting the hypothesis of compound degradation. However, even at reaction rates as short as 1 min (Table 2, entry 4), pIL degradation was still evident. Lowering the reaction temperature to 80 °C (Table 2, entry 5) significantly increased the yield to 67%, but unfortunately pIL degradation seemed to still be occurring, albeit inconsistently (*i.e.* pIL degradation and subsequently lower yields occurred in 2 out of every 4 repeat reactions at 80 °C). Examination of the reaction temperature/wattage profile for all of the above examples showed a large temperature spike in the initial stages of the reaction corresponding to a large pulse of microwave irradiation (200 W). This large amount of energy elevated the reaction temperature to well in excess of the set value (typically 30–40 °C over the desired temperature), leading to pIL degradation and low yields. Due to the very high polarity of pILs they efficiently convert microwave energy to heat. To avoid this effect, the maximum wattage was decreased from 200 W to 20 W, giving much better control over the reaction temperature (see the ESI for a comparison of reaction profiles†).

Table 2 Optimisation of the reaction conditions

Entry	Time/min	Power/W	*T*/°C	Ratio **2** : **3**	Yield (%)[a]
1	10	200	120	74 : 26	47
2	5	200	120	67 : 33	40
3	2	200	120	46 : 54	36
4	1	200	120	31 : 69	21
5	5	200	80	82 : 18	67
6[b]	5	20	120	84 : 16	82
7[b]	5	20	80	83 : 17	91
8[c]	5	n/a	80	nd	0

[a] Yield taken as the combined yield of **1** and **2**. [b] Maximum 20 W of microwave energy. [c] Reaction heated under conventional thermal conditions (oil bath).

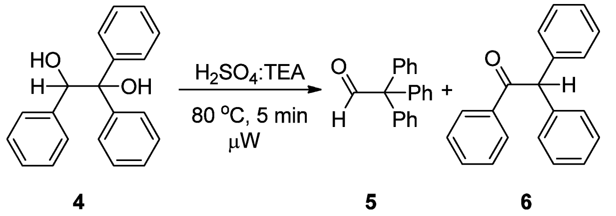


Scheme 2 Optimisation of reaction duration, temperature and yield.

Repeating the reaction at both 120 °C and 80 °C (Table 2, entries 6 and 7) utilising the lower microwave power gave much higher yields, with 80 °C being optimal and no pIL degradation being evident in either case. Microwave irradiation is also known to increase reaction rates;[11] therefore, to determine any microwave specific effects, the successful reaction conditions (Table 2, entry 7) were repeated using oil bath heating (Table 2, entry 8). Under thermal heating conditions, the reaction did not proceed at all, showing no trace of either pinacol products **1** or **2**.

With an optimal set of conditions in hand, our attention turned to the application of these reaction conditions to another *vic*-diol commonly used to evaluate pinacol reaction conditions. Triphenyldiol **4** was subjected to the optimised reaction conditions, giving 100% conversion to the desired products in a yield of 91%. Analysis by ^{1}H NMR of the key resonances showed a preference for ketone **6** formation over aldehyde **5** in a ratio of 3 : 1, respectively.

Though it cannot be unequivocally determined, one would assume that during the reaction, the more stable dibenzylic cation is formed in preference to the alternative monobenzylic cation. The two products observed from this intermediate arise from hydride migration (leading to ketone **6**) or phenyl migration

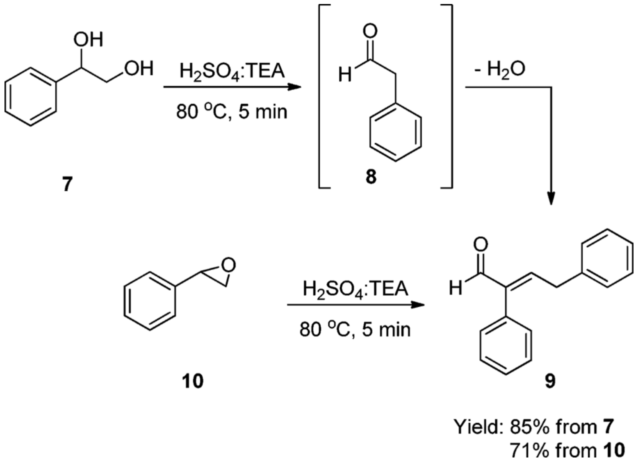


Scheme 3 Pinacol rearrangement of 1,2,2-triphenylethane-1,2-diol (**4**).

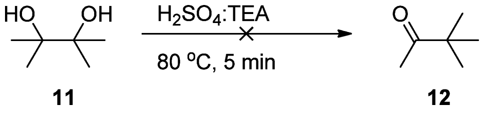
(leading to aldehyde **5**). Although phenyl groups are reported to migrate in preference to most other alkyl/hydride groups,[3] in this case, there is a severe steric demand on the aldehyde α-carbon, and thus the hydride is observed to migrate in preference. Interestingly, scaling up this reaction (5 fold) while incorporating the same volume of ionic liquid (0.25 mL) gave a very similar result under the specified conditions (yield 86%, product ratio 1 : 3 **5** : **6**, respectively), thus demonstrating the suitability of this methodology for the large scale synthesis of synthetically useful synthons.

Though pinacol rearrangements are not usually carried out with monosubstituted glycols due to potential side reactions, we applied these conditions to phenyl-1,2-ethanediol (**7**). Complete consumption of the starting material was observed within the 5 min timeframe, but analysis by ^{1}H NMR of the crude material showed a mixture of products, within which the desired aldehyde **8** was the minor product (< 10%). The major constituent of the reaction mixture was found to be unsaturated aldehyde **9**, isolated in an excellent yield of 85%. The formation of this product was attributed to a rapid pinacol rearrangement followed by aldol condensation.

In an attempt to diminish the formation of **9**, a semi-pinacol reaction using epoxide **10** was carried out under identical reaction conditions. Similarly to the previous reaction, the crude material was a mixture of products, in which unsaturated aldehyde **9** was, again, the principle component. Chromatographic separation gave aldehyde **9** in a good 71% isolated yield. Obtaining unsaturated aldehyde **9** from both **7** and **10**, though, disappointed our attempts to obtain aldehyde **8**. Scheme 4 highlights the potential application of protic ionic liquids to facilitate aldol reactions. This area of investigation is currently under way in our laboratory and the results will be reported in due course. Finally, to expand the generality of this methodology, we wished to employ a non-phenyl bearing substrate to account for carbocation stabilisation. A typical example is 2,3-dimethyl-2,3-butanediol (**11**, pinacol), which involves only methyl migration to effect the successful transformation. Application of our optimal conditions to pinacol **12** (Scheme 5) resulted in complete compound degradation with no identifiable compound being isolated from the reaction work-up.



Scheme 4 Rearrangement of 1-phenylethyleneglycol (**7**).



Scheme 5 Attempted rearrangement of pinacol (**11**).

This result, while not optimal, has been observed in other pinacol methodology studies, whereby it is presumed that the present α-hydrogens to the carbocationic species preferentially undergo elimination reactions. Never-the-less, this has clearly demonstrated the suitability of ionic liquid-mediated pinacol rearrangements to either di- or tri-phenyl-bearing glycols, as is observed with compounds **1** and **4**.

Conclusions

We have demonstrated the suitability of the protic ionic liquid $TeaH_2SO_4$ as a mediator for pinacol rearrangements employing either di- or tri-phenyl glycols. Complete consumption of the starting materials and high yields can be obtained from this system in 5 min and at a mild temperature of 80 °C under microwave irradiation. It was found that microwave irradiation power was important in controlling pIL degradation and for furnishing products in excellent yield. This reaction system removes the requirement of highly corrosive and dangerous acids. In all of the reactions undertaken in this manuscript, removal of the ionic liquid was carried out by filtration through a silica plug to give analytically-pure pinacol products.

Acknowledgements

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9 Experimental procedure: The diol (50 mg) was placed into a microwave reactor vessel charged with TeaH$_2$SO$_4$ (0.25 mL). The vessel was then heated to the specified temperature for the desired time. The crude product mixture was diluted with CH$_2$Cl$_2$ (10 mL) and examined by TLC (ethyl acetate : pet. spirit 1 : 2). The crude mixture was then filtered through a silica pad and washed thoroughly with CH$_2$Cl$_2$ (30 mL). The filtrate was then concentrated *in vacuo*.

10 Note, in the case of TeaH$_2$SO$_4$, the anionic portion of this pIL (HSO$_4^-$) is still acidic in character, and as such may contribute to the high level of activity observed in this system.

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