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A catalytic symmetrical etherification

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A novel, catalytic, thermal etherification produces minimal waste and can be carried out under almost neutral conditions.

Most methods for etherification use either strongly acidic or basic conditions.[1–3] Their disadvantages have been summarised by Lemaire and co-workers, who explored hydrogenolysis of hemiacetals as an alternative.[4] The long-established Williamson synthesis[5] is still the most common procedure. It involves substitution of an alkyl halide (RX) by a strongly basic alkoxide or phenoxide (*e.g.* KOR or NaOR) and so is unsuitable if base catalysed elimination of HX from RX can compete.[6,7] A stoichiometric amount of waste salt (KX or NaX) is also produced. Importantly, inorganic salts account for the bulk of industrial chemical wastes.[7] Besides polluting soil and ground water, salts can lower the pH of atmospheric moisture and have been implicated in the formation of acid-dew.[8] Hence, their minimisation is essential.

Our research is directed toward technologies and methodologies for environmentally benign organic chemistry.[6,9] We now report a catalytic etherification that produces minimal organic waste and that can be carried out without the addition of acid or base.[10]

For a symmetrical ether, an excess of alcohol (ROH) and a catalytic amount of RX are heated. A solvolytic displacement reaction[11a] between RX and ROH affords R_2O along with HX or its elements [hereafter referred to as HX; eqn. (1)]. The liberated HX reacts with another molecule of ROH to form water and to regenerate RX [eqn. (2)]. If the rates of these forward reactions are comparable, the concentration of HX will be low throughout and that of RX will remain relatively constant. Although HX and RX are stoichiometric reactants or products in eqn. (1) and (2), they do not appear in the sum [eqn. (3)]. The net process involves condensation of two molecules of ROH to give R_2O plus water.

$$\mathrm{RX} + \mathrm{ROH} \rightleftharpoons \mathrm{R_2O} + \mathrm{HX} \qquad (1)$$

$$\mathrm{HX} + \mathrm{ROH} \rightleftharpoons \mathrm{RX} + \mathrm{H_2O} \qquad (2)$$

$$2\,\mathrm{ROH} \rightleftharpoons \mathrm{R_2O} + \mathrm{H_2O} \qquad (3)$$

A widely accepted mechanism of etherification catalysed by strong acids (commonly, sulfuric acid is used) involves protonation of the hydroxy function of an alcohol to give the corresponding oxonium ion as a better leaving group.[1,2] The reaction then can proceed through substitution by another molecule of the alcohol or by elimination of water, followed by acid-catalysed addition of the alcohol to the resulting olefin. Although the overall reaction is also satisfied by eqn. (3), the solution would remain acidic throughout.

By contrast, the present process requires participation by the counterion X^- and utilises ostensibly neutral conditions. For it to operate efficiently, X^- should be a good leaving group [to satisfy eqn. (1)], an effective nucleophile [to accommodate eqn. (2)] and a weak base to minimise competing elimination reactions.[12] Bromide and iodide possess these properties.[13] To the best of our knowledge, a critical participatory role for the counterion of the acid has not previously been envisaged or recognised.

The examples presented in Table 1 were obtained by heating the reactants in glass-lined pressure vessels without water removal. Conversions rather than yields have been quoted, owing to the catalytic nature of the systems, and by-product formation was negligible in all cases. Neat Bu^nOH was unreactive at 200 °C (entry 1), but in the presence of a catalytic amount of Bu^nBr it afforded $Bu^n{}_2O$ without significant consumption of the haloalkane (entry 2). A comparable result was obtained with $PhCH_2CH_2OH$ at 220 °C (entries 4 and 5). Styrene or 1-phenylethyl derivatives, that might have been anticipated through mechanisms involving elimination, were not detected. Cyclopropylmethanol, although highly acid-labile,[14] was stable at reflux (entry 6), but in the presence of a catalytic amount of cyclopropylmethyl bromide, it condensed to form bis(cyclopropylmethyl) ether, without significant depletion of the bromide or rearrangement (entry 7), until the conversion was approximately 50%. This result indicated that the concentration of acid was not sufficiently high to affect the cyclopropylmethyl group.

As the reaction further progressed though, phase separation occurred and HBr accumulated in the aqueous medium. Consequently, the rate of etherification slowed and the unreacted alcohol and the product ether were decomposed by the acid to give cyclobutyl and homoallyl alcohols along with mixtures of ethers containing cyclopropyl, cyclobutyl and homoallyl functionalities.[14]

Nonetheless, the examples in Table 1 demonstrated the process, its applicability for base- or acid-labile compounds (entries 5 and 7, respectively) and the catalytic role of RX.

Table 1 Example reactions and conditions

Entry	Starting material(s)	*T* /°C	*t*/h	Major product(s)	Conversion(%)
1	Bu^nOH	200	2	no reaction	—
2	Bu^nOH (10 ml) + Bu^nBr (1 mol)	200	1	$Bu^n{}_2O$	26
3[a]	Bu^nOH (10 mol) + Bu^nBr (1 mol) + LiBr (1 mol	200	1	$Bu^n{}_2O$	54
4	$PhCH_2CH_2OH$	220	22	$(PhCH_2CH_2)_2O$	< 1
5[a]	$PhCH_2CH_2OH$ (10 mol) + $PhCH_2CH_2Br$ (1 mol)	220	21	$(PhCH_2CH_2)_2O$	76
6	Cyclopropylmethanol	120	24	no reaction	
7[a,b]	Cyclopropylmethanol (10 mol) + cyclopropylmethyl bromide (0.9 mol)	115	24	bis(cyclopropylmethyl) ether	51
8[a,c,d,e]	Bu^sOH (10 mol) +Bu^sBr (1 mol)	150	5	$Bu^s{}_2O$(1 : 1 mixture of diastereoisomers)	8
9[a,c,d,e]	Bu^sOH (10 mol) +Bu^sBr (1 mol) +LiBr (1 mol)	150	5	$Bu^s{}_2O$(1 : 1 mixture of diastereoisomers)	18

[a] Concentration of bromo derivative essentially unchanged after the reaction. [b] Extended heating led to acid catalysed decomposition. See text. [c] Optically pure Bu^sOH also afforded a 1 : 1 mixture of diastereoisomers, suggestive of an S_N1 mechanism. [d] Prolonged heating led to some evolution of gas. [e] Neat Bu^sOH did not react at 150 °C for 5 h.

The pathway was investigated by heating $PhCH_2CH_2OH$ with Bu_4NBr (not entered in Table 1). After 20 h at 200 °C, $(PhCH_2CH_2)_2O$ was not detected (but $PhCH_2CH_2OBu^n$ was produced by Hoffmann degradation, in low conversion). $PhCH_2CH_2Br$ and $(PhCH_2CH_2)_2O$ formed only after a few drops of acid (HOAc) were added to the reaction mixture, followed by further heating. This experiment indicated that the presence of X^- was insufficient to drive the reaction and that HX was required. We have also found that the process can be started from eqn. (2). In an example, HBr (9 mol%) was heated with $PhCH_2CH_2OH$ at 200 °C. After 3 h, the product mixture was no longer acidic and contained $PhCH_2CH_2Br$ (9%) and $(PhCH_2CH_2)_2O$ (6%) along with unreacted $PhCH_2CH_2OH$. These results were all consistent with the pathway in eqn. (1)–(3) and indicated that mechanisms proposed for acid-catalysed etherification[1,2] may in some cases need to accommodate possible participatory roles of the counterion.

As mentioned above, although hydroxy and alkoxy functions are not readily displaced from carbon atoms, protonation in strong acid greatly facilitates their leaving.[1,2] Indeed, HBr and HI have been employed as cleavage agents for ethers for well over a century.[15] Conversely, the rate of solvolytic displacement of alkyl halides by alcohols [the forward reaction in eqn. (1)] can be accelerated by a small amount of water.[11b] However, excess water would shift unfavourably the position of equilibrium in eqn. (2) and promote the reverse reaction in eqn. (3). These opposing factors indicate that, for etherification, depletion of water should be beneficial but complete removal may be detrimental. Also, when the concentration of alcohol is 10–50 times larger than that of RX, the first order rate constant of eqn. (1) can rise considerably.[16] Thus the rate and extent of reaction in eqn. (1) will depend on the relative concentrations of RX and ROH as well as on the concentration of water present. Entries 3 and 9 were consistent with reports that the addition of alkaline metal salts also can accelerate solvolytic processes,[17] including the rate of ionisation of RX.[18] Our results and published data[11,16–18] indicate that the catalytic process would operate most effectively at low to moderate conversions and should be amenable to continuous processing. This aspect and the preparation of unsymmetrical and polyethers will be discussed elsewhere.

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