Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 7337–7339

Tetrahedron Letters

Imidazole based solid-supported catalysts for the benzoin condensation

John M. D. Storey* and Craig Williamson

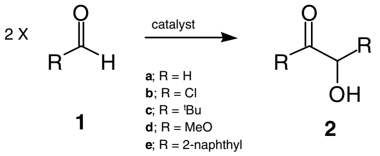
Department of Chemistry, University of Aberdeen, Meston Building, Meston Walk, Old Aberdeen AB24 3UE, UK

Received 8 June 2005; revised 28 July 2005; accepted 25 August 2005
Available online 13 September 2005

Abstract—New polymer-supported imidazolium salts have been synthesised, and their utility as pre-catalysts in the benzoin reaction has been demonstrated.

N-Heterocyclic carbenes have received much attention recently for the catalysis of organic reactions due to their ability to form acyl-anion equivalents.[1] This feature has been successfully exploited in numerous catalytic reactions. Notable examples include the Stetter reaction,[2] the acylation/trans-esterification of alcohols,[3] and the synthesis of γ-butyrolactones.[4] Our interest in their use focuses upon the benzoin condensation.

The benzoin condensation provides a convenient and powerful method for the formation of C–C bonds from aldehyde starting materials (Scheme 1). In its traditional form, only aromatic aldehydes or glyoxals could be coupled using cyanide anion as a catalyst.[5] Several nucleophilic carbenes derived from heterocyclic systems including triazoles[6] and thiazoles[7] have also found application as catalysts, which has increased the scope of the reaction allowing aliphatic aldehydes to be coupled. Unfortunately, these systems generally rely on high catalyst loadings (10–30 mol %), and frequently need long reaction times, often leading to catalyst decomposition under the basic conditions required.



Scheme 1.

Imidazole derived heterocycles have also been used as active catalysts in the benzoin condensation for some time,[8] although they have been mainly overlooked due to their comparatively low C2 acidity. A number of recent reports however, have described efficient imidazole based carbene catalysts with the advantage of trivial catalyst synthesis, and increased stability over other heterocyclic systems.[9]

Despite these developments, cyanide anion still remains a serious contender for practical synthesis of symmetrical acyloins, as evidenced by recent reports.[10] Indeed, the development of novel cyanide ion catalytic systems has recently been reported.[11] It became apparent that there was a need for an efficient catalytic system, which would ease handling, and reduce reaction times to minutes rather than hours or days. In addition, easy removal of the catalyst from the reaction mixture was a desirable design feature.

We describe here the synthesis and use of three easily prepared polymer-bound imidazolium salt carbene precursors, and their subsequent application in the benzoin condensation of a range of aromatic aldehydes. The use of a polymer support appeared to be an attractive proposition, since we believed that this should alleviate the handling problems associated with free salts of imidazoles, which tend to form viscous room temperature ionic liquids.

Previously there have been numerous examples of immobilisation of imidazolium derived carbene-containing

---

Keywords: Benzoin condensation; Solid-supported imidazolium catalysts.

* Corresponding author. Tel.: +44 01224 272926; fax: +44 01224 272921; e-mail: j.storey@abdn.ac.uk

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.08.141

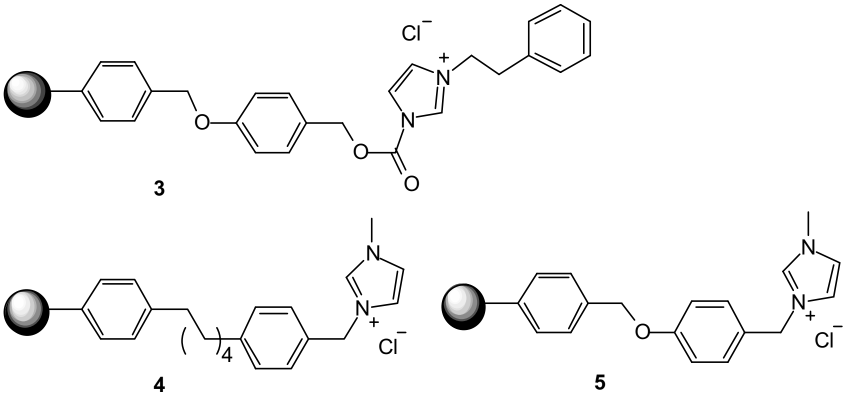


Figure 1. Solid-supported imidazolium catalysts.

catalysts onto polymers, although these all tend to be based on metal centred catalysts using one or more carbene ligands as a covalent linker.[12] However, it would appear that this communication represents the first attempt to immobilise imidazolylidenes onto a solid phase to act as catalysts, in the absence of a metal.

Three different, commercially available, functionalised polystyrene beads were modified to produce quaternary salts (Fig. 1). Imidazole carbamate resin was quaternised with (2-chloroethyl)benzene to give **3**. [(4-Chloromethyl)-5-phenyl] pentylstyrene and chlorinated Wang resin were quaternised with *N*-methylimidazole to give salts **4** and **5**, respectively. All quaternisations were performed in refluxing toluene with a 10-fold excess of modifying agent. After filtration to isolate the supported salts, and washing with toluene, the catalysts were stored under vacuum (15 mmHg) at 25 °C to remove all residual solvent.

The loading of the resins was determined by averaging three microanalyses for each. For **3**, the loading was found to be 0.62 mmol/g, **4** had a loading of 0.89 mmol/g and **5** had a loading of 1.32 mmol/g.

The activity of these solid-supported catalysts was then investigated for the condensation of a range of substi-

Table 1. Yield of benzoins using solid-supported catalysis[a]

Entry	Catalyst	Amount of catalyst (mol %)	Reactant	Time	Isolated yield (%)
a	3	1.25	**1a**	5 min	37
b	3	0.5	**1a**	60 min	66
c	3	0.5	**1b**	10 min	39
d	3	0.5	**1c**	5 h	20
e	3	0.5	**1d**	48 h	7
f	4[b]	1.0	**1a**	10 min	77
g	4[b]	0.7	**1a**	5 min	54
h	4[b]	0.3	**1a**	5 min	35
i	4[b]	0.09	**1a**	30 min	30
j	4[b]	0.7	**1b**	10 min	30
k	4[b]	0.7	**1c**	15 min	29
l	4[b]	3.5	**1d**	90 min	41
m	4[b]	0.7	**1e**	30 min	56
n	4[c]	0.7	**1a**	25 h	62
o	4[d]	0.7	**1a**	40 h	34
p	5	1.0	**1a**	15 min	72
q	4[e]	1.4	**1a**	1 h	57
r	Unmodified beads	0.7	**1a**	48 h	0

[a] Typical procedure for benzoin condensation: A two-necked flask was charged with the catalyst, THF (50 cm^3), and the appropriate aldehyde. The reaction mixture was heated to reflux with vigorous stirring, and base (0.5 cm^3 50% aq NaOH) was added in one portion via a syringe. When the reaction mixture solidified, the solvent was removed, and the resulting solid dissolved in water, and extracted with DCM (3×50 cm^3). The combined organic extracts were filtered to remove the catalyst, dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc) followed by recrystallisation from EtOH. Benzoins were characterised by comparison with the literature data.

[b] THF as solvent.

[c] Acetonitrile as solvent.

[d] Methanol as solvent.

[e] NaH as base, where NaH was used as base, it was first washed with dry petrol, and suspended in dry THF. The polymer-supported pre-catalyst and aldehyde were then added to the suspension at room temperature. If heat was required it was applied after all components had been combined. After reaction, the beads were filtered and washed with MeOH. Removal of solvent from the filtrate produced a residue, which was washed with water before purification.

tuted aromatic aldehydes (Table 1). In most cases, the reaction times were short, with moderate to good yields, which follow the previously observed trend of electron-deficient aldehydes reacting more rapidly than electron-rich aldehydes in benzoin condensation reactions.

Entry i clearly shows that less than 0.1 mol % of catalyst is needed for reasonable conversion to the benzoin product after just 30 min.

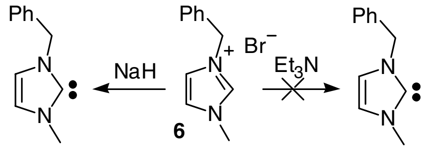
Solvent effects were briefly investigated (entries g, n and o). THF proved to be a far superior solvent with respect to the rate of benzoin formation of those tested. The relative swelling of polystyrene could explain this, since methanol and acetonitrile do not swell the polystyrene to the same degree as THF.[13] Greater swelling assists diffusion of reactants and products to and from the active sites within the beads.[14]

Since diffusion is a relevant factor in solid-phase catalysis, the limit of the catalysts with regard to substrate size was also investigated. 2-Naphthaldehyde **1e** was rapidly coupled in moderate yield (entry m), thus indicating substrates are not limited to monocyclic aldehydes.

Variation of the base required for formation of the carbene was also investigated. As previously described,[9] excess aqueous NaOH is effective in deprotonating imidazolium salts, however NaOH has a tendency to cause the benzoins formed in the reaction to precipitate as their sodium salts, which solidifies the reaction medium and tends to retard any further reaction. Triethylamine is a commonly employed base for benzoin reactions, but was shown to be completely inactive in this case. The ^{1}H NMR spectrum of structurally similar, non-tethered salt **6** (Scheme 2) in the presence of excess triethylamine, showed no evidence of C2 deprotonation after a prolonged time, even at temperatures close to that of refluxing THF, confirming that Et_3N is insufficiently basic to initiate this reaction.

A similar NMR experiment using sodium hydride as base showed, as expected, that deprotonation occurred rapidly at room temperature. It was found that using stoichiometric NaH (1 equiv per equivalent of active catalytic site) in a catalytic reaction produced similar yields of benzoin to reactions conducted using NaOH as the base, and the benzoin formed remained in solution (entry q).

Entry r indicates that the polymer is not responsible for the catalytic activity, since as expected none of the benzoin product was produced during this reaction, and starting material was recovered in near quantitative yield.



Scheme 2.

Regeneration of the catalyst after each cycle was also possible simply by treatment with acid. This was demonstrated using catalyst **4**, which was used in three successive benzoin condensations, albeit with approximately 10% lower yield in each cycle. We believe that this is the first reported re-use of an imidazole based catalyst in benzoin reactions.

In summary, the first polymer-supported imidazolium salt pre-catalysts have been reported and their utility for the benzoin reaction has been demonstrated. Moreover, these catalysts are easy to handle, can be used at lower catalyst loading than previously reported non-polymer-supported catalysts, reaction times are cut from many hours or days to minutes, and they can be regenerated for re-use.

Acknowledgments

We gratefully thank EPSRC for financial support. In addition, we would like to thank the EPSRC National Mass Spectrometry Centre at the University of Wales, Swansea, for providing accurate mass measurements.

References and notes

1. Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326–1328.
2. Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–712.
3. Grasa, G. A.; Kissling, R. A.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583–3586.
4. Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371; Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205–6208.
5. Studinger, H. *Ber. Dtsch. Chem. Ges.* **1913**, *46*, 3535–3538; Ide, W. S.; Buck, J. S. *Org. React.* **1948**, *4*, 269–304.
6. Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743–1745; Enders, D.; Breuer, K.; Kallfass, U.; Balensiefer, T. *Synthesis* **2003**, *8*, 1292–1295.
7. Knight, R. L.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3611–3614; Dvorak, C. A.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 2925–2928; Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891–1893.
8. Lappert, M. F.; Maskell, R. K. *J. Chem. Soc., Chem. Commun.* **1982**, 580–581.
9. Gao, G.; Xiao, R.; Yuan, Y.; Zhou, C.; You, J.; Xie, R. J. *Chem. Res. (S)* **2002**, 262–263; Orlandi, S.; Caporale, M.; Benaglia, M.; Annunziata, R. *Tetrahedron: Asymmetry* **2003**, *14*, 3827–3830.
10. Ohnishi, H.; Kozaki, M.; Okada, K. *Synth. Met.* **2003**, *135*, 85–86; Faghihi, K.; Zamani, K.; Mallakpour, S. *Iran. Polym. J.* **2002**, *11*, 339–347; Tarasolli, A.; Shushizadeh, M. R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 803–809.
11. Bausch, C. C.; Johnson, J. S. *J. Org. Chem.* **2004**, *69*, 4283–4285; Demir, A. S.; Reis, O. *Tetrahedron* **2004**, *60*, 3803–3811.
12. Nieczypor, P.; Buchowicz, W.; Meester, W.; Rutjes, F.; Mol, J. *Tetrahedron Lett.* **2001**, *42*, 7103–7105; Nguyen, S. T.; Grubbs, R. H. *J. Organomet. Chem.* **1995**, *497*, 195–200; Ahmed, M.; Barrett, A. G. M.; Braddock, D. C.; Cramp, S. M.; Procopiou, P. A. *Tetrahedron Lett.* **1999**, *40*, 8657–8662.
13. Keifer, P. A.; Baltusis, L.; Rice, D. M.; Tymiak, A. A.; Shoolery, J. N. *J. Magn. Reson., Ser. A* **1996**, *119*, 65–75.
14. Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2157.