Henry reactions catalysed by modified Mg–Al hydrotalcite:

an efficient reusable solid base for selective synthesis of β-nitroalkanols†

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Summary

Henry reactions have been performed for the first time with suitably activated Mg–Al hydrotalcite as catalyst in quantitative yields in the liquid phase under mild reaction conditions and with low reaction times. Exclusive synthesis of β-nitroalkanols (**3**) is realised by the compatible basic Brönsted hydroxy sites of the modified hydrotalcite. Reusability with consistent activity and selectivity for a number of cycles is established indicating that the hydrated hydrotalcite employed here is a potentially eco-friendly catalyst which can replace soluble bases in commercial synthesis.

Introduction

The design and development of environment-friendly solid base catalysts to replace soluble bases for C–C bond formation in organic transformations widely employed in the bulk and fine chemical industries in order to achieve atomic selectivity of the desired product and reduce the salts formed as a result of neutralisation of soluble bases is of intense research activity.[1–3] 2-Nitroalkanols, the products of the Henry reaction and important representatives of C–C bond formation, are ubiquitous materials extensively used in many important syntheses.[4] The greatest challenge in the selective synthesis of 2-nitroalkanols among the multiple product options such as polymerization, aldol olefins and Cannizzaro products, is the selection of the appropriate base to achieve the most sensitive operation in the organic synthesis. Further, 2-nitroalkanols formed from aryl aldehydes tend to eliminate water to form nitroalkenes[5] which readily polymerise. The classical methods for this important transformation involving the use of bases such as alkali metal hydroxides, carbonates, bicarbonates, alkoxides, barium and calcium hydroxide, magnesium and aluminium ethoxides, a rhodium complex, potassium exchanged zirconium phosphate and also organic bases such as primary, secondary and tertiary amines predominantly give dehydrated products.[4] Thus, careful control of the basicity of the reaction medium is crucial to achieve better yields of β-nitroalcohols. Such efforts require longer reaction times but only give moderate yields.[6,7]

Heterogeneous catalysis induced by solid catalysts such as basic alumina,[8] alumina-KF,[9] amberlyst[6] and phase transfer catalysis with surfactants[10] are the two divergent approaches applied in an attempt to obtain improved selectivity. The former approach requires longer reaction times and in some cases affords condensed olefins.[5,11] Although good selectivity has been achieved in phase transfer reactions, the reaction still requires a soluble base, which tends to give salts upon neutralisation at the end of the reaction.[10] With this background, we envisaged the use of solid bases in the form of layered double hydroxides (LDHs) or hydrotalcite like compounds (HTLCs) in view of their potential usefulness as adsorbents, anion-exchangers and most importantly as basic catalysts.[3,12] LDHs upon thermal decomposition at *ca.* 450 °C give highly active homogeneous mixed oxides, which are potential basic catalysts used for a variety of organic transformations.[13–17] Recently, we reported a modified method[2] for the activation of a hydrotalcite catalyst the basicity of which was tuned for base catalysed aldol, Knoevenagel and Michael reactions[18,19] in the liquid phase under very mild reaction conditions. The significance of 2-nitroalkanols in organic synthesis[4] and our continued interest involving hydrotalcites prompted us to explore the Henry reaction.

Green Context

The Henry reaction is an important class of C–C bond forming reaction. It operates under base catalysis conditions to give β-nitro alkanols, important intermediates for a variety of useful compounds such as amino alcohols. Difficulties which lead to poor selectivity and thus waste include dehydration (and possible subsequent reaction of the nitroalkene formed) and Cannizzaro reaction of the aldehydic component. This paper describes the application of Mg–Al hydrotalcites to the Henry reaction. Hydrotalcites are mixed oxides, in some ways similar to clays, but basic rather than acidic, and have found uses as medium strength base catalysts in recent years. They are readily prepared, and catalyse several reactions selectively. In the cases described here, they produce a selective and clean reaction under mild conditions. Catalyst reuse is also demonstrated. A fully optimised procedure would require further optimisation of the solvent used to wash the catalyst, and recovery and recycling of the excess nitroalkane. *DJM*

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Experimental

Here, we report a convenient and selective synthesis of 2-nitroalkanols *via* the Henry reaction,[20] Scheme 1, affording 100% selectivity to β-nitroalcohols (**3**) in quantitative yields using modified Mg–Al hydrotalcite.[18] Modified Mg–Al hydrotalcite (Mg/Al ratio = 2.5) was synthesized as follows: an aqueous solution (0.221 l) containing $Mg(NO_3)_2 \cdot 6H_2O$ (0.2213 mol) (Aldrich) and $Al(NO_3)_3 \cdot 9H_2O$ (0.0885 mol) (Aldrich) was added slowly to a second solution (0.221 l) containing NaOH (0.7162 mol) and Na_2CO_3 (0.2084 mol) in a 1.0 l round-bottom flask under vigorous stirring. The addition took nearly 3 h. Then the contents were heated to 338 K for 16 h. The precipitate formed was filtered off and washed with hot distilled water until the pH of the filtrate was 7. The precipitate was dried in an oven at 353 K for 15 h. The XRD pattern shows the presence of pure hydrotalcite, with lattice parameters corresponding to those reported in the literature.[3]
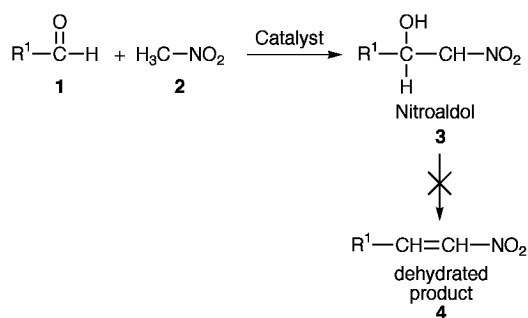
Scheme 1 Henry reactions between nitromethane and various substituted aromatic and aliphatic aldehydes.

Table 1 Henry reactions of various substituted aromatic and aliphatic aldehydes with nitromethane catalysed by MHT

Entry	R^1	Time/h	Yield (%)[a]
1	phenyl	0.5	95[b]
2	O_2N-phenyl	0.5	100
3	methylfuran	1.0	92
4	MeO-phenyl	1.5	54
5	phenyl-OMe	1.0	98 (97)[c]
6	MeO-phenyl	1.5	93
7	(MeO)₃-phenyl	2.0	88
8	Cl-phenyl	1.0	95
9	Et	1.0	100
10	Me₂CHCH₂	1.0	100

[a] Determined by ^1H NMR, based on starting aldehyde.
[b] Isolated pure product. [c] Yield after fifth cycle.

The synthesised Mg–Al hydrotalcite catalyst was first activated by calcination at to 723 K in a flow of air. The temperature was raised at a rate of 10 K min^{−1} to 723 K and maintained at this temperature for 8 h. The solid was then cooled in dry nitrogen and rehydrated at room temperature under a flow of nitrogen gas (6 l h[−1]) saturated with water vapour for *ca.* 6 h before use in reactions.

Results and discussion

Results of Henry aldol product synthesis are compiled in Table 1 with modified hydrotalcites showing the best catalytic performance. No dehydrated product (**4**) was observed even after continuing the reaction for prolonged periods when we deliberately chose aryl aldehydes as one of the reactants. The reused catalyst exhibited consistent activity and selectivity.

Taking the Henry reaction of benzaldehyde with nitromethane as a model reaction we compared the activity and selectivity of the modified Mg–Al hydrotalcite catalyst with a variety of soluble and solid bases such as sodium hydroxide, neutral aluminium oxide, magnesium oxide and diamino-functionalised MCM-41[21] under similar reaction conditions (Table 2). The reaction of benz-

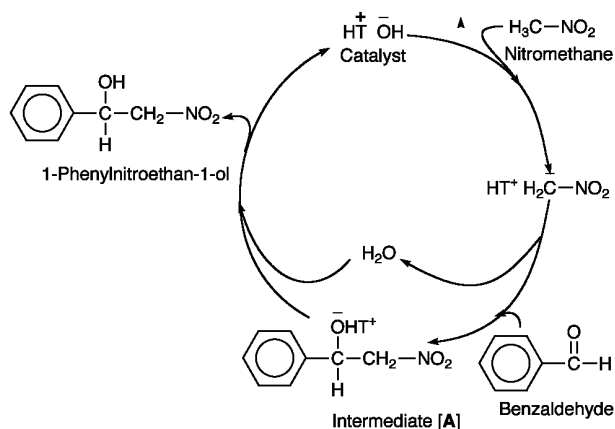**Table 2** Henry reaction between benzaldehyde and nitromethane using various base catalysts

Entry	Catalyst	t/h	Yield (%)[a]
1	Modified Mg–Al hydrotalcite	0.5	95[b]
2	Aluminium oxide	12.0	37
3	Magnesium oxide	8.0	51
4	Sodium hydroxide with PTC	2.0	70[c]
5	Diamino-functionalised MCM-41	3.0	97[d]

[a] Determined by ^1H NMR, based on starting aldehyde, unless otherwise stated. [b] Isolated pure product. [c] Isolated yield, using sodium hydroxide with surfactant.[10] [d] Using diamino-functionalised MCM-41, nitroalkene is the sole product.[21]

aldehyde with nitromethane using magnesium oxide or neutral aluminium oxide catalyst required longer reaction times and gave poor yields, while the reaction with diamino-functionalised MCM-41 yields the nitroalkene as the sole reaction product. The Henry reaction was slightly sluggish under phase transfer conditions[10] using sodium hydroxide as a soluble base. In summary, the results show that the modified Mg–Al hydrotalcite catalyst is more active and selective than the other catalysts.

The Henry reaction usually requires Brönsted hydroxy sites to abstract a proton from an active methylene group of the nitro compound. X-Ray diffraction studies of the activated hydrotalcite show that the layered structure is removed upon calcination but is restored by rehydration and a meixnerite-like structure is formed in which OH^{−} are the compensating anions. These anions are mobile and therefore basic and catalyse several reactions proceeding through basic mechanisms such as aldolisation,[2,22,23] Knoevenagel[18] or Michael reactions.[19] From their catalytic properties it is usually accepted that LDH has a pK_b of *ca.* 11.4–12 and therefore is a base of moderate strength comparable to piperidine.[23] The lack of activity of calcined hydrotalcites reiterates that the reaction of Henry requires Brönsted bases of mild strength.

The classical mechanism of the Henry reaction[6] can therefore be applied here. The abstraction of a proton from the active methylene group of the nitro compound gives a carbanion which can be stabilised by the cationic charge of aluminium in the lattice of hydrotalcite as suggested in Scheme 2. In this scheme it is sug-

Scheme 2 A plausible mechanism for the Henry reaction between nitromethane and benzaldehyde catalysed by modified Mg–Al hydrotalcite.

gested that this carbanion further adds to the carbonyl compound to form an intermediate **A** which, in turn, removes a proton from water to give the final nitro aldol product. It is of interest that this aldolisation reaction is very specific towards the nature of the Brönsted base.[2,23] In spite of the large number of basic sites determined by calorimetric adsorption of CO_2, decarbonated hydrotalcites are not active, as they do not have any Brönsted hydroxy groups.

Conclusion

Compatible Brönsted basic hydroxy sites present in the modified hydrotalcite give rise to selective nitroaldol reactions in excellent yields over short times more efficiently than methodologies described earlier. The following advantages are: (a) high catalytic activity under very mild liquid phase conditions, (b) easy separation of the catalyst by simple filtration, (c) excellent yields and 100% selectivity of β-nitroalkanols at high rates of reaction, (d) use of non-toxic and inexpensive materials, (e) recycling of the catalyst and (f) zero emission of pollutants. The present catalytic system is thus a potential alternative to soluble bases.

Acknowledgements

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20 *Representative procedure*: To a mixture of nitromethane (10 mmol) and benzaldehyde (2 mmol), 0.2 g of catalyst was added at room temperature and stirring was continued until completion of the reaction, as monitored by TLC. The catalyst was filtered off, washed with dichloromethane (10 ml × 3) and the filtrate concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 60–120 mesh; hexane–ethyl acetate 98 : 2 v/v) to give $PhCH(OH)CH_2NO_2$ (0.317 g, 95% yield). The product was characterised by comparison of its NMR and IR spectra with those reported in the literature.[10]
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