Isolute® Si-carbonate catalyzes the nitronate addition to both aldehydes and electron-poor alkenes under solvent-free conditions†

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It has been found that commercial ISOLUTE® Si-carbonate catalyzes both nitroaldol and Michael reactions, from nitroalkanes and under solvent-free conditions, allowing satisfactory to good yields of nitroalkanols and γ-nitro-functionalized carbonyl and cyano derivatives. In addition, a one-pot Henry–Michael reaction can be performed.

Introduction

In the 21st century we can expect the drive toward cleaner technologies brought about by public, legislative and corporate pressure to provide new and exciting opportunities for catalysis and catalytic processes.[1] In this context, the heterogeneous catalysis shows great potential for environmental pollution control.

The efficient use of a solid catalyst that stays in a separate phase from the organic compounds can go a long way to achieve important goals. In fact, product isolation is simplified and reactions often run under milder conditions and give higher selectivity. The atom efficiency of the reaction is improved, the process is facilitated, precious raw materials used in the manufacture of the catalyst have increased lifetime (through reuse), and the volume of waste is significantly reduced.[2]

Commercial ISOLUTE® Si-carbonate [silica trimethylammonium carbonate; Si-TMS$(CO_3^{-2})_{0.5}$] is a bound equivalent of tetramethylammonium carbonate, which has traditionally been used as a quaternary anion-exchanger for quenching, neutralizing and desalting organic mixtures. Recently more versatile applications have been reported such as organic acid scavenging for fast purification of amide and biaryl libraries.[3]

Results and discussion

During our studies into the chemistry of nitroalkanes,[4] and particularly to the search for more eco-friendly conditions for their use as stabilized carbanions,[5] we were attracted by ISOLUTE® Si-carbonate as a potential supported base to generate the nitronate forms under solvent-free conditions.

Henry[6] and Michael[4c] reactions, involving nitroalkanes, are two of the most used procedures for the generation of new

carbon–carbon bonds and for the preparation of polyfunctionalized structures. As routine procedures, these reactions are performed in the presence of different bases in homogeneous solutions of organic solvents or, alternatively, under heterogeneous catalysis[4c,7] and, for these purposes, even with the help of sonication,[8] high pressure[9,10] or the need for complex catalysts prepared by using toxic solvents[11] have been proposed. In addition, these methodologies very often suffer from different drawbacks such as: (i) (Henry reaction) low yields, retroaldol reaction, formation of side products due to the aldol condensation and/or Cannizzaro reaction of aldehydes or olefin formation, and (ii) (Michael reaction) low yields, multi-addition reactions, the need of a large excess of nitroalkanes that, for valuable nitro derivatives and for the production of waste, is a serious problem from both an economical and ecological point of view.

Thus, considering that over the past few years, a significant amount of research has been directed towards the progress of new technologies for environmentally benign processes, the development of new general, efficient eco-friendly catalytic procedures for both Henry and Michael reactions is desirable.

In this context, we report herein that commercial ISOLUTE® Si-carbonate has been found, in our laboratory, to be a new efficient catalyst for both the Henry and Michael reactions under solvent free-conditions.

Firstly, we chose two model reactions for these transformations in order to find the best reaction conditions and, as reported in Table 1 and 2, we examined the nitroaldol reaction of 1-nitrobutane with dihydrocynnamaldehyde (formation of **3a**) and the conjugate addition of 1-nitrobutane to ethyl vinyl

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Table 1 Best catalyst/substrate ratio for the Henry reaction

Catalyst/substrate	Yield (%) of **3a**
0.05	10
0.1	87
0.15	80

Table 2 Best catalyst/substrate ratio for the Michael reaction

Catalyst/substrate	Yield (%) of **5a**
0.05	73
0.1	87
0.15	86
0.2	70

ketone (formation of **5a**). The reactions were carried out at room temperature for 7 h, with different amounts of catalyst, and in both cases the more convenient catalyst/substrate ratio seems to be = 0.1.

In order to verify the efficiency of the method for the nitroaldol reaction, we tested a number of different nitroalkanes and aldehydes (Table 3). All the reactions were carried out at room temperature, mixing a stoichiometric amount of **1** and **2**, with 10 mol% of the catalyst and in the absence of any solvent.

By this method, simple and functionalized primary and secondary nitroalkanes give good results with both aliphatic and aromatic aldehydes. Moreover, 1-bromo-1-nitroalkan-2-ols (entry 9 and 10), an important class of compounds very useful for practical applications in the manufacturing photographic materials,[12] ink-based materials,[13] or for their important properties such as biocide[14] and antimicrobial activity,[15] can be efficiently prepared by our procedure.[16] Although the present method results in a diastereomeric mixture of nitroalcohols, according with most of the reported approaches, this doesn't seem to be a problem since the main uses are the conversion into α-nitro ketones[17] or conjugated nitroalkenes,[18] in which at least one stereogenic centre is lost.

The generality of our catalytic system has been extended to the Michael reaction, investigating the reactivity of a series of nitroalkanes with an array of electron-poor alkenes (Table 4).

The reaction works well with primary and secondary nitroalkanes and with different electron-poor alkenes, even with poor electrophilic alkenes, such as α,β-unsaturated esters (entry 5 and 11), α,β-unsaturated nitriles (entry 6) or α,β-unsaturated sulfones (entry 10), and with hindered electrophilic alkenes, such as 2-cyclohexen-1-one (72%, entry 3) and 2-cyclopenten-1-one (91%, entry 4) that, usually, give moderate yields.[19] In addition, a further class, 1-bromo-1-nitroderivatives (entry 7), can be efficiently prepared under our conditions.

It is important to point out that the use of the same catalyst for both Henry and Michael reactions, *via* nitroalkanes, offers an important opportunity for a one-pot Henry–Michael solventless process. In fact, as reported in Scheme 1, mixing dihydrocynnamaldehyde with nitromethane (1 equiv.) and catalyst (0.15 equiv.) at room temperature, followed, after 3 h (the reaction was checked by TLC), by the addition of methyl vinyl ketone (1 equiv.) and leaving the mixture for further 15 h, allows the direct preparation of the keto nitroalkanol **6**, in equilibrium with its ketalic form **7**, in 62% overall yield (**6/7** ≈ 5:1).
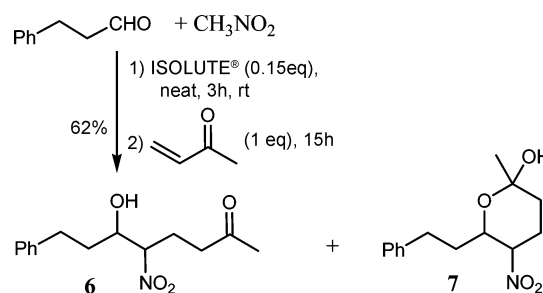
Scheme 1

Finally, we faced the problem of catalyst recycling: at the end of the model reaction (formation of **5a**) the catalyst was filtered, washed with EtOAc, dried under vacuum and reused. The catalyst could be utilized with comparable results at least for six further cycles (Table 5).

Conclusions

Following our procedures both nitroalkanols **3** (58–87%) and Michael adducts **5** (59–91%) can be efficiently

Table 3 Nitroalkanols **3** obtained by the Henry reaction

Entry	R	R[1]	R[2]	Reaction time/h	Yield (%)[a] of **3**
1	*n*-Pr	H	Ph(CH$_2$)$_2$	7	87 (**3a**)
2	*n*-Pr	H	Ph	16	78 (**3b**)
3	Ph(CH$_2$)$_2$	H	*n*-C$_5$H$_{11}$	5	82 (**3c**)
4	MeOCO(CH$_2$)$_4$	H	Ph	16	69 (**3d**)
5	MeOCO(CH$_2$)$_4$	H	*n*-C$_5$H$_{11}$	8	68 (**3e**)
6	Me	Me	Et	7	58 (**3f**)
7	Me	H	Ph	16	77 (**3g**)
8	*n*-Bu	H	*c*-C$_6$H$_{11}$	8	83 (**3h**)
9	Br	H	*n*-Bu	9	71 (**3i**)
10	Br	H	*m*-NO$_2$C$_6$H$_4$	16	63 (**3j**)

[a] Yield of pure isolated product

Table 4 Michael adducts **5** prepared

Entry	R	R^1	Electron-poor alkene **4**	Michael Adduct **5**	Reaction time/h	Yield (%)^a of **5**
1	n-Pr	H		**5a**	7	87
2	n-C$_5$H$_{11}$	H		**5b**	7	86
3	n-C$_4$H$_9$	H		**5c**	10	72
4	PhCH$_2$	H		**5d**	16	91
5	n-Pr	H		**5e**	30	62^b
6	PhCH$_2$	H	CN	**5f**	27	59^b
7	Br	H		**5g**	8	71
8	MeCO(CH$_2$)$_2$	H		**5h**	7	75
9	Me	Me		**5i**	16	85
10	n-C$_4$H$_9$	H	SO$_2$Ph	**5j**	20	61
11	Me	Me		**5k**	24	60

^{a} Yield of pure isolated product. ^{b} The reaction performed at 50 °C gave poor yield (45% for **5e** and 40% for **5f**, after 30 and 27 h, respectively), probably due to the partial desorption of the (low boiling) Michael acceptors.

Table 5 Yield of recycled catalyst in the model Michael reaction

	Yield (%) of **5a**
Initial reaction	87
1st recycle	80
2nd recycle	78
3th recycle	76
4th recycle	75
5th recycle	73
6th recycle	71
7th recycle	58
8th recycle	50

prepared under moderate reaction times, avoiding the need of any solvent and of expensive use of energy since all the reactions can be carried out at room temperature. Moreover, the very mild conditions needed (room temperature and 10% of the catalyst) favour the observed high chemoselectivity and prevent the typical side reactions of both Henry and Michael processes. Any work up can be avoided since the crude products can be charged, directly, onto a chromatographic column (see Experimental). In addition, the catalyst is easily commercially available and can be reused several times (at least six times, Table 5) with a modest decreasing of the yields. Moreover, under our conditions even a variety of 1-bromo-1-nitro derivatives can be easily obtained, and the one-pot Henry–Michael solvent-free process (Scheme 1) can be efficiently performed, giving rise to the one-flask formation of complex molecules with

evident synthetic advantages. Thus, our procedure represents an important improvement of the Henry and Michael reaction *via* nitroalkanes, especially from an economical and ecological point of view.

Experimental

Materials and methods

GLC analyses were performed with an SE-54 fused silica capillary column (25 m, 0.32 mm internal diameter), FID detector and nitrogen as carrier gas. GS-MS analyses were carried out by means of the EI technique (70 eV). All chemicals were purchased and used without further purifications; just some known nitroalkanes, such as 1-nitro-3-phenylpropane, 1-nitro-2-phenylethane, methyl 6-nitrohexanoate and 5-nitro-2-pentanone, were prepared by the standard procedures.[4,6a,7,19] ISOLUTE® Si-carbonate, capacity 0.17 mmol g^{-1}, was purchased by StepBio. Analytical data for **3a–j**, **5a–k** and **6** can be found in the ESI.†

Typical procedure for both nitroaldol and Michael reactions

To a stirred solution of nitroalkane (1 mmol) and the appropriate electrophile (1 mmol of **2** or **4**), 0.588 g (0.1 equiv) of ISOLUTE® Si-carbonate were added at room temperature, then the resulting mixture was mechanically stirred for the appropriate time (TLC and GC, Table 3 and Table 4). After that, the reaction can be treated differently bearing in mind two different goals: avoiding the work up (way a) or recycling the catalyst (way b).

Way a: The mixture was directly charged onto a chromatographic column (EtOAc–cyclohexane) for the immediate purification by flash chromatography, giving the pure product **3** or **5**.

Way b: The mixture was treated with EtOAc (20 mL) and the catalyst was recovered by filtration, then washed with further EtOAc, dried under vacuum and reused, while the organic layer was evaporated and the crude product purified by flash chromatography (EtOAc–cyclohexane), allowing the pure nitroalkanol **3** or **5**.

Acknowledgements

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