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Catalytic C–C Bond Formation Promoted by Mg–Al–O–*t*-Bu Hydrotalcite

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Abstract—Mg–Al–O–*t*-Bu-hydrotalcite catalyst was found to be an efficient, environmentally attractive and selective solid base catalyst for 1,4 Michael addition. Mg–Al–O–*t*-Bu hydrotalcite is also effective for simple synthesis of α,β-unsaturated esters and nitriles by condensation of the corresponding activated carboxylic esters or nitriles with various aldehydes by Knoevenagel condensation. These reactions proceeded at room temperature at a greater rate in the presence of Mg–Al–O–*t*-Bu hydrotalcite than in the presence of any of the other catalysts examined. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

There has been increasing attention on the design and use of environmentally compatible solid acid/base catalysts targeted to minimise the emission of effluents in the chemical industry due to the increasing demands of environmental legislation. The challenge is to perform heterogeneous catalytic reactions for C–C bond formation in the laboratory, bulk and fine chemical industries. The versatile Michael and Knoevenagel reactions have numerous applications in the elegant synthesis of fine chemicals[1,2] and are classically catalysed by bases[3,4] or suitable combinations of amines and carboxylic or Lewis acids under homogeneous conditions. The employment of these bases/acids in the reactions encounters two main environmental problems affecting environment, i.e. the necessity to dispose huge amounts of organic waste due to formation of undesirable side products resulting from polymerisation, bis-addition and self condensation and total dissolved salts formed requiring the neutralisation of soluble bases with acids or acids with bases. There are few reports available under the category of heterogeneous catalysis for Michael additions and Knoevenagel condensations mediated particularly by aluminum oxide,[5] xonotlite/potassium *tert*-butoxide,[6,7] cation-exchanged zeolites,[8] alkali containing MCM-41,[9] $AlPO_4$–Al_2O_3 catalysts.[10] The incorporation of alkali metal cations[9,11] such as Cs^+ or Na^+ in zeolites and mesoporous molecular sieves by cationic exchange provides low basicity useful for a small range of organic reactions only. Na^+ clusters introduced in the zeolites by impregnation with sodium azide[12] afford strongly basic sites, which catalyse side chain alkylations also. In view of these limitations, the development of an efficient and selective solid acid-base catalyst for the construction of a C–C bond continues to be a challenging exploration in organic synthesis.

Hydrotalcites

Layered double hydroxides (LDHs) or hydrotalcite-like compounds (HTLCs)[13] are of current interest and have several applications in organic chemistry. The structure of hydrotalcite consists of brucite [Mg $(OH)_2$] type octahedral layers in which a part of the M(II) cations are isomorphously substituted by M(III) cations. The excess positive charge of the octahedral layers resulting from this substitution is compensated by interstitial layers built of anions such as carbonates, nitrates, chlorides, cyanides and crystal water. These materials are represented by the general formula $[\mathrm{M(II)}_{(1-x)}\ \mathrm{M(III)}_x.(\mathrm{OH})_2]^{x-}[(\mathrm{A}^{n-})_{x/n}\mathrm{Y}\cdot\mathrm{H_2O}]^{x-}$ where M(II) is a divalent cation such as Mg, Cu, Ni, Co, Mn, Zn; M(III) is a trivalent cation such as Al, Fe, Cr, Ga; A^{n-} is the interlayer anion such as OH^-, Cl^-, CO_3^{2-}, NO_3^-, SO_4^{2-} and the value of x is in the range of 0.1–0.33. As part of our research programme aimed at unravelling and developing the synthetic utility of solid bases in fine chemicals synthesis, we envisaged the use 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.[14] LDHs upon thermal decomposition at about 450°C provide a highly active homogeneous mixed oxide which is a potential basic catalyst for a variety of organic transformations such as aldol condensation,[15] olefin isomerisation,[16] epoxidations of activated olefins with hydrogen peroxide,[17] alkylations of

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Keywords: Mg–Al–O–*t*-Bu-HT hydrotalcite; solid base catalyst; Michael additions; Knoevenagel condensation.

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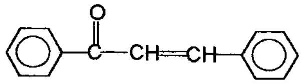
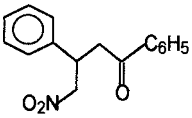
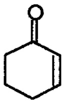
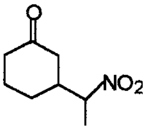
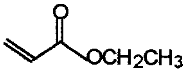
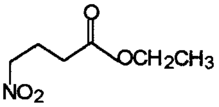
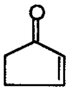
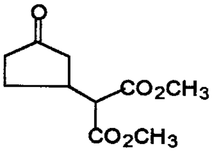
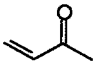
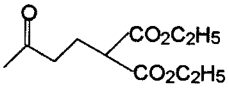
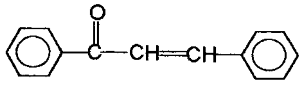
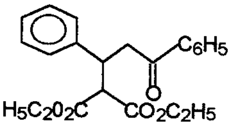
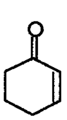
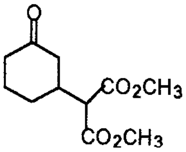
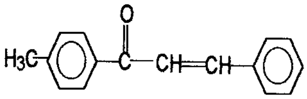
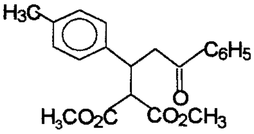
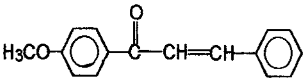
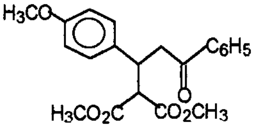
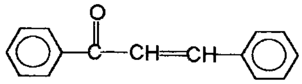
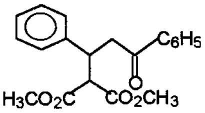
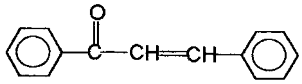
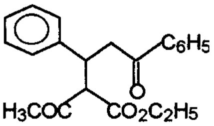
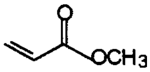
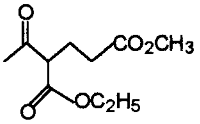
Table 1. Michael addition catalysed by Mg–Al–O–*t*-Bu hydrotalcite catalyst

Entry	Acceptor (**1**)	Donor (**2**)[a]	Time [h]	Product (**3**)	Isolated yield (%)	STY[b]
a		NM	0.16 20[c]		93 95[c]	30.00 6.38
b		NE	0.5 20[d] 2[e]		98 93[d] 100[e]	6.70 0.04 0.14
c		NM	0.75 2[f]		96 77[f]	4.12 0.11
d		DMM	0.83		94	4.82
e		DEM	0.5 3[g] 72[h] 48[i] 4[j]		98 78[g] 70[h] 90[i] 90[j]	9.01 0.06 0.55 0.05
f		DEM	2 48[h] 6[k]		95 75[h] 96[k]	3.49 21.85 0.11
g		DMM	1		90	4.10
h		DMM	1		96	6.79
i		DMM	1.3		95	5.27
j		DMM	1		92	6.25
k		EAA	0.16 8[c]		86 85[c]	33.02 17.00
l		EAA	0.33 3[g] 4[l] 4[j]		90 81[g] 88[l] 80[j]	11.71 0.58 0.09 0.04

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[a] DMM: Dimethyl malonate; NM: Nitromethane; NE: Nitroethane; DEM: Diethyl malonate; EAA: Ethyl acetoacetate.

[b] Space time yield (STY)=gram of product obtained per gram of catalyst per hour.

[c] Using $Ba(OH)_2$ as a catalyst Ref. 7b.

[d] Using Amberlyst A-27 as catalyst, 200 mg of catalyst per 1 mmol of substrate, Ref. 25.

[e] Using KF/Alumina (basic) as catalyst, 3 g of catalyst per 5 mmol of substrate, Ref. 24.

[f] Using KF/Alumina (basic) as catalyst, 5 g of catalyst per 9.2 mmol of substrate, Ref. 24.

[g] Using zeolite as catalyst, 1 g of catalyst per 1 mmol of substrate, Ref. 28.

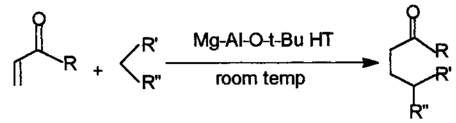
[h] Using potassium *tert*-butoxide on Xonotlite as catalyst, Ref. 7a.

[i] Using $Ni(acac)_2$ as catalyst, Ref. 27.

[j] using Al_2O_3 as catalyst, 1 g of catalyst per 1 mmol of substrate, Ref. 26b.

[k] Using rehydrated Mg–Al hydrotalcite as catalyst, 1 g of catalyst per 2 mmol of substrate, Ref. 21.

[l] Using Al_2O_3 as catalyst, 500 mg of catalyst per 1 mmol of substrate Ref. 26a.



acceptor(**1**) donor(**2**) (**3**)

Scheme 1.

diketones,[18] nucleophilic halide exchange and Claisen–Schmidt condensation,[19] etc. We have recently reported aldol, Knoevenagel condensations[20] and Michael additions[21] catalysed by rehydrated Mg–Al hydrotalcite catalyst.

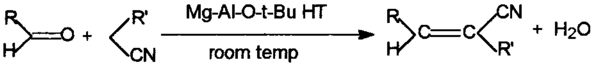
Later, we designed and developed Mg–Al–O–*t*-Bu hydrotalcite[22] for the first time. It was prepared by incorporating *tert*-butoxide anion into the interlayer of hydrotalcite to enhance the basicity of the hydrotalcite and we found it to be excellent for aldol condensation[22] and epoxidation of olefins.[23] Herein, we wish to report highly selective Michael and Knoevenagel reactions promoted by a Mg–Al–O–*t*-Bu hydrotalcite catalyst.

Results and Discussion

Michael addition

Results of Michael addition reactions are compiled in Table 1. The Mg–Al–O–*t*-Bu-hydrotalcite catalyst, **1**, was found to be an efficient and selective catalyst for 1,4 addition. Several structurally varying donors such as diethyl malonate, nitromethane, nitroethane, dimethyl malonate and ethyl acetoacetate underwent clean and remarkably fast Michael addition with a variety of acceptors including methyl vinyl ketone, methyl acrylate, ethyl acrylate, chalcones and substituted chalcones by this procedure (Scheme 1). The activity of catalyst **1** was compared with that of a variety of bases and other catalysts such as potassium *tert*-butoxide on xonotlite,[7a] barium hydroxide,[7b] alumina-supported potassium fluoride,[24] Amberlyst A-27,[25] aluminum oxide,[26] Ni(acac)$_2$[27] and NaY–Zeolite[28] (Table 1). The Michael reaction with earlier reported catalysts required longer reaction times and high catalyst loading and afforded low yields of the adducts. In the case of potassium *tert*-butoxide on xonotlite and alumina supported potassium fluoride, excess potassium *tert*-butoxide/fluoride was used for the preparation of the catalyst.

The Michael addition of nitroalkanes is a convenient method for the preparation of a number of useful synthetic intermediates, since the nitro group can be transformed into various functionalities. Several catalysts have been examined for this purpose but none has displayed optimum effectiveness. These reactions have various limitations. In particular, a large excess of nitroalkane is required. The catalyst **1** displayed increased activity by several-fold, in terms of space-time yield (STY) in the activation of nitroalkanes, over the other catalysts described in Table 1, say, for example, 4.7 times greater activity as Ba(OH)$_2$ in entry **a**, 223 times as active as Amberlyst A-27 and 48 times as active as KF-Al$_2$O$_3$ in entry **b**, 37 times as active as KF-Al$_2$O$_3$ in entry **3c**. It is significant to note that the interaction between α,β-unsaturated ketones and malonate derivatives catalysed by **1** provides a manifold increase in STY of Michael addition products. For instance, **1** shows an increased activity of 130 times over zeolite, 8 times over xonotlite, 18 times over Al$_2$O$_3$ in entry **e**, 31 times over rehydrated hydrotalcite in entry **f**. Similarly, in the reaction of α,β-unsaturated ketones with ethyl acetoacetate the catalyst **1** showed enhanced activity, say, 2 times over Ba(OH)$_2$ in entry **k**, 234 times over zeolite and 292 times over Al$_2$O$_3$ in entry **l**.



(**4**) (**5**) (**6**)

Scheme 2.

The Michael addition of cyclic enones (entries **b**, **d**, **g**, Table 1) with malonic esters and nitroalkanes was performed to demonstrate the versatility of the method with acceptors other than the usual Michael acceptors such as methyl vinyl ketone or acrylic esters. Excellent yields of adducts were obtained.

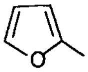
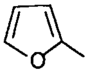
Knoevenagel condensation

Knoevenagel condensation involving various aromatic carbonyl compounds with (a) malononitrile and (b) ethyl cyanoacetate (Scheme 2) as the active methylene compound was carried out with Mg–Al–O–*t*-Bu hydrotalcite at room temperature (Table 2). The aromatic aldehydes readily condensed with malononitrile, while with ethyl cyanoacetate, the reaction is slightly slow. This may be attributed to the fact that abstraction of a proton from the active methylene group of ethyl cyanoacetate is difficult due to lower acidity.

As can be seen from Table 2, all reactions proceeded selectively to the dehydrated products without any side reaction. No self-condensation, Cannizaro products or hydrated products of Knoevenagel adducts were obtained. The reaction between benzaldehyde and ethyl cyanoacetate in the presence of Mg–Al–O–*t*-Bu hydrotalcite (entry **b**, Table 2) gave selectively the Knoevenagel adduct while the same reaction promoted by an alkali metal containing MCM-41[9] yielded a mixture of hydrated and dehydrated products. The rate of reaction is quite impressive and comparable with the recently reported Knoevenagel condensation under microwave irradiation[29] employing phosphorous pentoxide as dehydrating agent and chlorobenzene as an energy transfer medium for the removal of water.

The xonotlite-*tert*-butoxide[6] catalyst fails to initiate the condensation of furfuraldehyde with malononitrile (entry **i**, Table 2). However, the use of untreated xonotlite led to moderate yields of the adduct upon a longer reaction time. The Knoevenagel condensation for furfuraldehyde in the presence of AlPO$_4$–Al$_2$O$_3$ catalyst, required a large amount of catalyst and afforded poor yields of adducts.[10] Though this reaction was relatively facile with Al$_2$O$_3$, it required a large amount of catalyst.[5] In contrast to all of the above

Table 2. Knoevenagel condensation catalysed by Mg–Al–O-*t*-Bu hydrotalcite

Entry	R (**4**)	R′ (**5**)	Time (h)	Isolated Yields (**6**) (%)	M.P.[a]	STY[b]
a	C_6H_5	CN	0.16	99	82	33.72
			1[c]	43[c]		6.10
			24[d]	81[d]		0.48
			0.25[e]	80[e]		3.02
			0.05[f]	96[f]		9.09
b	C_6H_5	CO_2Et	0.33	98	52	22.20
			1[c]	82[c]		15.49
			1[e]	74[e]		0.46
			7[g]	81[g]		0.07
c	4-$OMeC_6H_4$	CN	0.33	96	98	21.19
			1[c]	77[c]		18.40
			24[d]	86[d]		0.66
			0.25[e]	79[e]		3.87
d	4-$OMeC_6H_4$	CO_2Et	0.33	98	86	27.44
			1[c]	86[c]		19.86
			1[e]	52[e]		0.40
e	4-Cl C_6H_4	CN	0.16	95	164	42.86
			1[c]	34[c]		6.39
			24[d]	65[d]		0.47
						4.06
f	4-Cl C_6H_4	CO_2Et	0.33	98	87	27.63
			1[c]	82[c]		19.27
			24[d]	85[d]		0.83
			1[e]	47[e]		0.73
g	3-$OMeC_6H_4$	CN	0.16	88	93	38.86
h	3,4,5$(OMe)_3C_6H_2$	CN	0.33	93	–	27.23
i		CN	0.08	96	63	65.89
			24[d]	84[d]		0.50
			0.25[e]	56[e]		2.135
j		CO_2Et	0.25	98	84	29.79
			24[d]	85[d]		0.67
			1[e]	89[e]		0.56
k	4-NO_2 C_6H_4	CN	0.16	96	82	45.84
			1[c]	40[c]		7.96
			24[d]	80[d]		0.66
			0.25[e]	82[e]		4.35
l	4-NO_2 C_6H_4	CO_2Et	0.33	95	170	26.44
			1[c]	83[c]		19.25
			24[d]	94[d]		0.91
			1[e]	85[e]		1.31
m	2-$OMeC_6H_4$	CN	0.16	96	78	42.39
n	2-$OMeC_6H_4$	CO_2Et	0.16	97	69	53.77
o	4-OHC_6H_4	CN	0.16	96	–	39.39
p	4-OHC_6H_4	CO_2Et	0.25	95	170	32.98

[a] Melting points reported are uncorrected.

[b] Space time yield (STY)=gram of product obtained per gram of catalyst per hour.

[c] Reaction with xonotlite-*tert*-butoxide as catalyst, Ref. 6.

[d] Reaction with untreated xonotlite as catalyst, Ref. 6.

[e] Reaction with $AlPO_4–Al_2O_3$ as catalyst, 1.5–3 g for 10 mmol, Ref. 10.

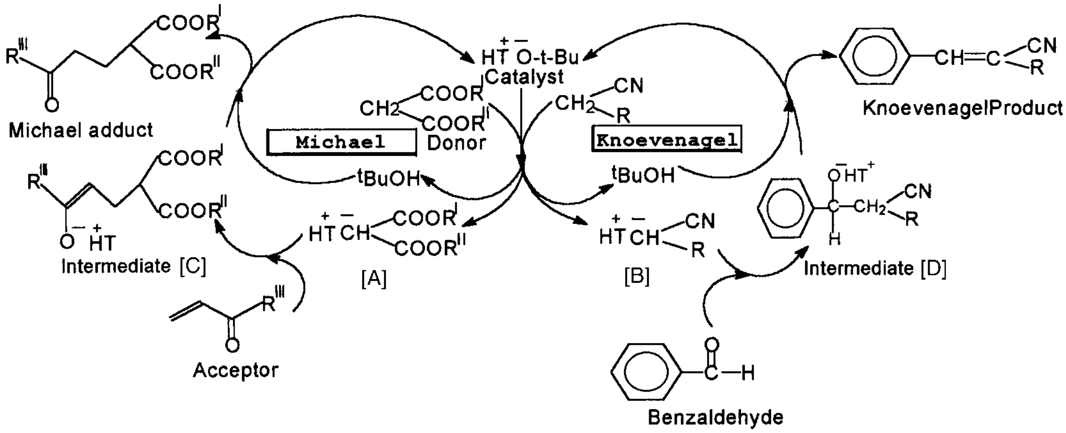
[f] Reaction with Al_2O_3 as catalyst, 3 g for 10 mmol, Ref. 5.

[g] Alkali metal containing MCM-41 as catalyst, Ref. 9.

mentioned methodologies, the Mg–Al–O–*t*-Bu-hydrotalcite is very effective for the said reaction, requiring very small amounts of the catalyst and proceeding at a much faster rate, viz. 5 min.

The superactivity of the catalyst, **1**, in comparison with catalysts previously described for both Michael and Knoevenagel reactions is well established as is evident from Tables 1 and 2. The activation of methylenes via abstraction of a proton to generate an anion is a prerequisite for the initiation of the reaction both in Michael and Knoevenagel reactions. The much greater activity of **1** over potassium *tert*-butoxide impregnated on the basic clay, xonotlite, assumes importance, as both the catalysts have the same species, viz. *tert*-butoxide but with a much higher loading on xonotlite. The superactivity of catalyst **1** is ascribed to the presence of the mobile interstitial anion, –O*t*Bu paired with Mg and Al main frame hydrotalcite which more effectively abstracts a proton from activated methylene groups to promote the higher rate of reaction.

The absence of any reaction, when Mg–Al hydrotalcite was employed as such in Knoevenagel and Michael reactions with any of the substrates described in Tables 1 and 2 is noteworthy. The recently reported rehydrated hydrotalcite[21] shows several disadvantages in the Michael additions such as high catalyst loading, longer reaction times and limited scope of utility (activating only the methylene group flanked by at least one electron-withdrawing nitrile group), when compared with the present catalyst **1**. The base strength



Scheme 3.

derived from Brönsted hydroxyl anions intercalated in rehydrated hydrotalcite of the rehydrated catalyst is not adequate to abstract a proton from the active methylene group of compounds such as dimethyl malonate, diethyl malonate and ethyl acetoacetate and consequently, there is no reaction with these substrates. In contrast, in the case of Mg–Al–O–*t*-Bu-hydrotalcite, the *tert*-butoxide anions are strongly basic to deprotonate even weakly activated methylenes to facilitate Michael reactions.

The plausible mechanism of the Michael[4c] or Knoevenagel reactions mediated by catalyst **1** is probably identical to that of the reactions promoted by homogeneous bases. In Michael reaction, the abstraction of a proton from the donor generates a carbanion [**A**], which can be stabilized by the cationic charge of hydrotalcite, as suggested in Scheme 3. It could be proposed that this carbanion further adds to the α,β-unsaturated ketone to form an intermediate enolate [**C**], which would take a proton from *in situ* formed *tert*-butanol to afford the final product and regenrated hydrotalcite alkoxide. Similarly, in the case of Knoevenagel condensation, the carbanion [**B**] formed by the abstraction of a proton from active methylene compound gets stabilized by the cationic charge of hydrotalcite. This stabilized carbanion attacks the electrophilic carbonyl carbon to form an intermediate [**D**] which in turn, abstracts a proton from in situ formed *tert*-butanol. Dehydration then takes place to form the Knoevenagel product.

An attempt was made to check the reusability of the catalyst in the following manner. The substrates, catalyst and solvent (Table 1, entry 1) were taken, and the reaction was performed as usual for a specified time. Then the stirring was stopped and the reaction mixture withdrawn by a glass syringe through a septum. Fresh substrates and solvent were added to the residual catalyst and the reaction performed under identical conditions. The activity and selectivity of the catalyst was found to be the same.

Conclusion

In summary, a new solid base catalyst Mg–Al–O–*t*-Bu-hydrotalcite has been developed by incorporating *tert*-butoxide into the brucite layer of hydrotalcite to achieve a higher order of basicity to enable the formation of C–C bonds by Knoevenagel condensations as well as Michael reactions with a high degree of selectivity at faster rates than any of the earlier catalysts. This new solid base catalyst is a practical alternative for application for both Knoevenagel and Michael reactions in view of the following advantages: (a) high catalytic activity under very mild liquid phase conditions (b) easy separation of the catalyst by simple filtration (c) waste minimization without any side reactions such as self condensation, bis-addition, dimerization or rearrangements (d) use of non-toxic and inexpensive catalysts (e) involvement of environmentally benign processes and (f) reusability of catalyst.

Experimental

Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use. All the reactions were conducted under an atmosphere of nitrogen. Melting points reported here are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz using $CDCl_3$ as internal reference. Mass spectra were obtained at an ionization potential of 70 eV [scanned on VG 70-70H (micro mass)]; only selected ions are reported here. Infrared spectra were recorded either as neat liquids or KBr pellets. Thin layer chromatography was performed on silica gel $60F_{254}$ plates procured from E. Merck. Elemental analysis was performed using a C, H, N analyser. Starting materials purchased from Aldrich or Fluka were used as such.

Preparation of catalyst

(a) Preparation of Mg–Al–NO_3 hydrotalcite: Mg–Al–NO_3 hydrotalcite catalyst was prepared in nitrogen atmosphere to avoid carbonation in air. Magnesium nitrate hexahydrate (30.8 g, 0.12 mol) and aluminum nitrate nonahydrate (15.0 g, 0.04 mol) were dissolved in 100 mL deionised and decarbonated water. The pH of the solution was adjusted to 10 by the addition of NaOH (2 M). The slurry was stirred for 2 h at room temperature, filtered and then dried under vacuum at 80°C. The reaction and filtration processes were executed under nitrogen atmosphere.

(b) Preparation of Mg–Al–O–t-Bu hydrotalcite: Mg–Al–

O–*t*-Bu hydrotalcite was prepared from Mg–Al–NO_3 hydrotalcite. A 0.1 M solution of potassium *tert*-butoxide was prepared by dissolving 1.12 g of potassium *tert*-butoxide in 100 mL of freshly dried THF. 1.214 g of Mg–Al–NO_3 hydrotalcite was added and the solution was stirred for 24 h in nitrogen atmosphere. It was then filtered under nitrogen. A white solid, Mg–Al–O–*t*-Bu hydrotalcite (1.382 g) was obtained. *t*-Butoxide was exchanged onto nitrate-saturated (MgAl) LDH to an extent of 12% (0.99mmol/ g *t*-butoxide) as indicated by chemical analysis.

General procedure for Michael reactions

In a typical procedure, the acceptor (2 mmol) and Mg–Al–O–*t*-Bu hydrotalcite (0.1 g) were stirred in 10 ml of methanol for 5 min. Then the donor (2 mmol) was added and the stirring continued till the completion of the reaction (as monitored by thin layer chromatography (TLC)). The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (Acme Synthetic Chemicals, 60–120 mesh silica gel using ethyl acetate/hexane).

General procedure for Knoevenagel condensation

In a typical procedure, aldehyde (2 mmol) and Mg–Al–O–*t*-Bu hydrotalcite (0.05 g) were stirred in 10 ml of dimethyl formamide for 5 min. To it, active methylene compound (2 mmol) was added and stirring continued till the completion of the reaction (as monitored by TLC). The catalyst was removed by filtration and the product was extracted with ethyl acetate. The ethyl acetate solution was then dried on anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/hexane, 95/5, v/v).

The products were fully characterised by their mp, ^1H NMR, Mass and IR spectroscopy and elemental analysis. These data for the Michael and Knoevenagel reactions are presented below in order of the products in Tables 1 and 2, respectively.

Michael reaction

4-Nitro-1,3-diphenyl-1-butanone (3a).[7b] white solid, mp 101°C; IR (neat) 1690, 1580, 1380 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.45 (d, 2H, $COCH_2$, J=6.8 Hz) 4.12–4.28 (m, 1H, PhCH), 4.61–4.88 (m, 2H, CH_2NO_2), 7.12–7.64 (m, 9H, aromatic), 7.95 (d, 2H, aromatic, J=6.3 Hz); MS (EI) *m/z* (M^+−NO) 222 (7), 117 (6), 105 (100), 77 (42), 51 (12).

3-(1-Nitroethyl)cyclohexanone (3b).[25] brown coloured liquid, IR (neat) 1720, 1560 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.39 (q, 1H, $CHNO_2$, J=5.4 Hz), 1.82–2.52 (m, 9H, $(CH_2)_5$); 1.45–1.62 (m, 3H, CH_3); MS (EI) *m/z* (MS (EI) *m/z* (M^+−NO) 125 (40), 124 (57), 97 (48), 81 (48), 69 (63), 55 (100), 39 (98).

Ethyl 4-nitrobutanoate (3c).[24] brown coloured liquid; IR (neat) 1730, 1560, 1320 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.48 (t, 2H, CH_2NO_2, J=5.4 Hz), 4.21 (q, 2H, OCH_2, J=4.5 Hz), 1.30(t, 3H, CH_3, J=4.5 Hz), 2.02–2.55 (m, 4H, CH_2, CH_2), MS (EI) *m/z* (M^+−NO) 141 (10), 123 (7), 55 (48), 41 (68).

3-[Bis(methoxycarbonyl)methyl]cyclopentanone (3d). Brown coloured liquide; IR (neat) 1710, 1160 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.27 (d, 1H, COCH, J=8.1 Hz), 2.62–2.82 (m, 1H, cyclic CH), 3.72 (s, 6H, OCH_3), 1.48–2.44 (m, 6H, $(CH_2)_2$); MS (EI) *m/z* (M^+−OCH_3) 183 (7), 132 (42), 83 (33), 69 (45), 55 (90), 39 (100). Anal. calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.54. Found: C, 56.54, H, 6.96.

4-[Bis(ethoxycarbonyl)methyl]2-butanone (3e).[27] brown coloured liquid; IR (neat) 1740, 1360 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.16 (q, 4H, OCH_2, J=8.1 Hz), 3.32 (t, 1H, COCH, J=7.7 Hz), 2.52 (t, 2H, $COCH_2$, J=7.2 Hz), 2.04–2.18 (s, m, 5H, $COCH_3$, CH_2CH_2), 1.25 (t, 6H, CH_3, J=8.1 Hz); MS (EI) *m/z* (M^+ peak) 230 (13), 184 (9), 173 (18), 55 (65), 43 (100).

Diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate (3f).[7a] White solid, mp 65°C; IR (neat) 1720, 1680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (t, 3H, CH_3, J=5.4 Hz); 1.28 (t, 3H, CH_3, J=5.4 Hz); 3.32–3.62 (m, 2H, $COCH_2$); 3.78 (d, 1H, COCH, J=8.6 Hz); 3.88–3.98 (m, 1H, PhCH); 4.10–4.25 (m, 4H, CH_2); 7.10–7.52 (m, 8H, aromatic), 7.85 (d, 2H, aromatic, J=5.9 Hz); MS (EI) *m/z* (M^+ peak) 368 (1), 249 (13), 209 (16), 105 (100), 77 (86), 51 (22).

3-[Bis(methoxycarbonyl)methyl]cyclohexanone (3g). Brown coloured liquid; IR (neat) 1740, 1780, 1140 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.78 (s, 6H, OCH_3), 3.30–3.42 (m, 1H, CH), 1.45–2.58 (m, 9H, $(CH_2)_5$); MS (EI) *m/z* (M^+ peak) 228 (1), 197 (7), 132 (33), 97 (96), 69 (69), 59 (72), 41 (100). Anal. calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.01. Found: C, 57.64; H, 6.70.

Dimethyl 2-[1-(4-methylphenyl)-3-oxo-3-phenylpropyl]-malonate (3h). White solid, mp 146°C; IR (neat) 1740, 1760, 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3), 3.35–3.55 (m, 2H, $COCH_2$), 3.78 (2s, 6H, OCH_3), 3.86 (d, 1H, COCH, J=9.5 Hz), 4.05–4.22 (m, 1H, PhCH), 7.32–7.75 (m, 7H, aromatic), 7.90 (d, 2H, aromatic, J=7.1 Hz); MS (EI) *m/z* (M^+ peak) 354 (3), 223 (50), 105 (100), 77 (60). Anal. calcd for $C_{21}H_{22}O_5$: C, 71.15; H, 6.26 Found: C, 70.66; H, 6.11.

Dimethyl 2-[1-(4-methoxylphenyl)-3-oxo-3-phenylpropyl]-malonate (3i): White solid, mp 141°C; IR (neat) 1720, 1680, 1510 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.35–3.50 (m, 2H, $COCH_2$), 3.74 (s, 9H, OCH_3), 3.84 (d, 1H, COCH, J=5.2 Hz), 4.05–4.18 (m, 1H, PhCH), 7.32–7.75 (m, 7H, aromatic), 7.90 (d, 2H, aromatic, J=4.5 Hz). MS (EI) *m/z* (M^+1 peak) 371 (6), 239 (21), 105 (100), 77 (31). Anal. calcd for $C_{21}H_{22}O_6$: C, 68.08; H, 5.99. Found: C, 68.10; H, 5.88.

Dimethyl-2-(3-oxo-1,3-diphenylpropyl)malonate (3j).[7b] White solid, mp 145°C; IR (neat) 1660, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.42–3.50 (m, 2H, $COCH_2$), 3.72–3.80 (m, 6H, OCH_3), 3.86 (d, 1H, COCH, J=9.5 Hz), 4.05–4.20 (m, 1H, PhCH), 7.32–7.75 (m, 8H, aromatic), 8.03 (d, 2H, J=6.8 Hz); MS (EI) *m*/*z* (M$^+$ peak) 340 (3), 249 (13), 209 (48), 105 (100),77 (33).

Ethyl 2-acetyl-5-oxo-3,5-diphenyl pentanoate (3k).[7b] White solid, mp 120°C; IR (neat) 1720, 1680 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.28 (t, 3H, CH$_3$, J=6.3 Hz), 2.32 (s, 3H, COCH$_3$), 3.28–3.46 (m, 2H, COCH$_2$), 3.86–4.05 (m, 2H, CH,CH); 4.12–4.25 (m, 2H, CH$_2$); 7.12–7.55 (m, 8H, aromatic), 7.82–7.95 (m, 2H, aromatic); MS (EI) *m*/*z* (M$^+$ peak) 320 (3), 247 (33), 144 (62), 105 (96), 77 (100), 51 (45), 43 (54).

1-Acetyl-5-methyl 2-acetyl pentanedioate (3l).[28] Pale yellow coloured liquid; IR (neat) 1760, 1700 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.32 (t, 3H, CH$_3$, J=6.6 Hz) 2.08–2.42 (m, 7H, CH$_2$CH$_2$, COCH$_3$), 3.52 (t, 1H, COCH, J=4.0 Hz), 3.70 (s, 3H, OCH$_3$), 4.12 (q, 2H, CH$_2$, J=6.6 Hz); MS (EI) *m*/*z* (M$^+$−OCH$_3$) 174 (9), 100 (60), 85 (18), 43 (100).

Knoevenagel condensation

Benzylidenemalonitrile (6a).[10] Pale yellow solid, mp 82°C; IR (KBr pellets) 2280, 1560, 1090 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.90 (d, 2H, aromatic, J=5.7 Hz), 7.76 (s, 1H, alkenic), 7.48–7.68 (m, 3H, aromatic); MS (EI) *m*/*z* (M$^+$ peak) 154 (100), 127 (53), 103 (48), 76 (10).

Ethyl 2-cyanocinnamate (6b).[10] Pale yellow solid, mp 52°C; IR (KBr pellets) 2240, 1610, 1200 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.45 (t, 3H, CH$_3$, J=7.1 Hz), 4.42 (q, 2H, CH$_2$, J=7.1 Hz), 7.48–7.64 (m, 3H, aromatic), 8.02 (m, 2H, aromatic), 7.98–8.08 (s, 1H, alkenic); MS (EI) *m*/*z* (M$^+$ peak) 201 (100), 172 (56), 156 (90), 128 (81), 77 (67), 51 (53), 43 (45).

***p*-Methoxybenzylidenemalonitrile (6c).**[6] Pale yellow solid, mp 98°C; IR (KBr pellets) 2280, 1560, 1210 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.62 (s, 1H, alkenic), 3.90 (s, 3H, OCH$_3$), 7.92 (d, 2H, aromatic, J=9.0 Hz), 7.01 (d, 2H, aromatic, J=9.0 Hz), MS (EI) *m*/*z* (M$^+$ peak) 184 (100), 141 (19), 114 (36), 88 (12), 57 (22), 43 (34).

2-Propionic acid, 2-cyano-3-(4-methoxyphenyl) ethyl ester (6d).[6] Pale yellow solid, mp 86°C; IR (KBr pellets) 2180, 1710, 1560 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.4 (t, 3H, CH$_3$, J=8.5 Hz), 4.38 (q, 2H, CH$_2$, J=8.5 Hz), 3.90 (s, 3H, OCH$_3$), 8.13 (s, 1H, alkenic), 8.02 (d, 2H, aromatic, J=9.5 Hz), 6.98 (d, 2H, aromatic, J=9.5 Hz); MS (EI) *m*/*z* (M$^+$ peak) 231 (100), 186 (24), 158 (7).

***p*-Chlorobenzylidenemalonitrile (6e).**[6] Pale yellow solid, mp 164°C; IR (KBr pellets) 2205, 1560, 1110 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.75 (s, 1H, alkenic), 7.56 (d, 2H, aromatic, J=9.0 Hz), 7.88 (d, 2H, aromatic, J=9.0 Hz); MS (EI) *m*/*z* (M$^+$ peak) 188 (100), 153 (51), 126 (16), 87 (7), 51 (30), 50 (36).

2-Propionic acid, 2-cyano-3-(4-chlorophenyl) ethyl ester (6f).[10] Pale yellow solid, mp 87°C; IR (KBr pellets) 2240, 1760, 1580, 1160 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.46 (t, 3H, CH$_3$, J=6.9 Hz), 4.39 (q, 2H, CH$_2$, J=8.8 Hz), 8.18 (s, 1H, alkenic), 7.95 (d, 2H, aromatic, J=9.3 Hz), 7.42 (d, 2H, aromatic, J=9.3 Hz); MS (EI) *m*/*z* (M$^+$ peak) 235 (100), 207 (56), 190 (80), 162 (50), 127 (48), 76 (50), 51 (27).

***m*-Methoxybenzylidenemalonitrile (6g).** Pale yellow solid, mp 93°C; IR (KBr pellets) 2240, 1610, 1190 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 3.90 (s, 3H, OCH$_3$), 7.74 (s, 1H, alkenic), 7.12–7.20 (m, 1H, aromatic), 7.38–7.48 (m, 3H, aromatic); MS (EI) *m*/*z* (M$^+$ peak) 184 (90), 141 (33), 114 (100), 88 (39), 64 (50); Anal. calcd for C$_{11}$H$_8$N$_2$O: C, 71.73, H, 4.34; N, 15.21. Found: C, 71.82; H, 4.31; N, 15.01.

***m*,*m*′,*p*-Trimethoxybenzylidenemalonitrile (6h).** Viscous liquid; IR (KBr pellets) 2260, 1580, 1120 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 3.98 (s, 3H, OCH$_3$), 3.90 (s, 6H, OCH$_3$), 7.62 (s, 1H, alkenic), 7.18 (s, 2H, aromatic); MS (EI) *m*/*z* (M$^+$ peak) 244 (3), 229 (7), 201 (13), 115 (30), 77 (100); Anal. calcd for C$_{13}$H$_{12}$N$_2$O$_3$: **C,** 63.93; H, 4.93; N, 11.47. Found: C, 63.02; H, 4.91; N, 10.82.

Furfurylidenemalonitrile (6i).[10] Pale yellow solid, mp 63°C; IR (KBr pellets) 2226, 1607, 1020 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.82 (s, 1H, aromatic), 7.45 (d, 1H, aromatic, J=5.2 Hz), 7.54 (s, 1H, alkenic), 6.70–6.78 (m, 1H, aromatic); MS (EI) *m*/*z* (M$^+$ peak) 144 (46), 115 (19), 88 (46), 51 (66), 38 (100).

Ethyl 3-furfurylidene-2-cyanopropionate (6j).[10] Pale yellow solid, mp 84°C; IR (KBr pellets) 2221, 1717, 1620, 1210 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.45 (t, 3H, CH$_3$, J=5.7 Hz), 4.38 (q, 2H, CH$_2$, J=5.7 Hz), 8.04 (s, 1H, alkenic), 7.45 (d, 1H, aromatic, J=5.4 Hz), 6.64–6.72 (m, 1H, aromatic), 7.76 (d, 1H, aromatic, J=5.4 Hz); MS (EI) *m*/*z* (M$^+$ peak) 191 (100), 163 (22), 146 (50), 119 (7), 63 (37).

***p*-Nitrobenzylidenemalonitrile (6k).**[6] Pale yellow solid, mp 82°C; IR (KBr pellets) 2180, 1560, 1180 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.62 (s, 1H, alkenic), 8.18 (d, 2H, aromatic, J=9.2 Hz), 8.38 (d, 2H, aromatic, J=9.2 Hz); MS (EI) *m*/*z* (M$^+$ peak) 199 (100), 153 (78), 126 (84), 141 (56), 114 (31).

2-Propionic acid, 2-cyano-3-(4 nitrophenyl) ethyl ester (6l).[6] Pale yellow solid, mp 170°C; IR (KBr pellets) 2260, 1740, 1580, 1120 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.46 (t, 3H, CH$_3$, J=7.1 Hz), 4.45 (q, 2H, CH$_2$, J=7.1 Hz), 8.14 (d, 2H, aromatic, J=9.5 Hz), 8.25 (s, 2H, alkenic), 8.35 (d, 2H, aromatic, J=9.5 Hz); MS (EI) *m*/*z* (M$^+$ peak) 246 (27), 218 (18), 202 (21), 127 (30), 57 (100).

***o*-Methoxybenzylidenemalonitrile (6m).** Pale yellow solid, mp 78°C; IR (KBr pellets) 2210, 1580, 1160 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 3.94 (s, 3H, OCH$_3$), 8.28 (s, 1H, alkenic), 8.20 (d, 1H, aromatic, J=9.5 Hz), 7.10 (t, 1H, aromatic, J=9.0 Hz), 7.58 (t, 1H, aromatic, J=7.1 Hz)), 6.98 (d, 1H, aromatic, J=8.5 Hz); MS (EI) *m*/*z* (M$^+$ peak) 184 (24), 141 (15), 114 (69), 88 (69), 39 (100); Anal. calcd for C$_{11}$H$_8$N$_2$O: C, 71.73; H, 4.34; N, 15.21. Found: C, 71.80; H, 4.24; N, 14.75.

2-Propionic acid, 2-cyano-3-(2-methoxyphenyl) ethyl ester (6n). Pale yellow solid, mp 69°C; IR (KBr pellets) 2364, 1707, 1598, 1258 cm^{-1}; ^{1}H NMR (200 MHz,

$CDCl_3$) δ 1.45 (t, 3H, CH_3, J=7.6 Hz), 4.40 (q, 2H, CH_2, J=7.6 Hz), 3.95 (s, 3H, OCH_3), 8.32 (d, 1H, aromatic, J= 8.7 Hz), 8.78 (s, 1H, alkenic), 7.10 (t, 1H, aromatic, J= 8.2 Hz), 7.48–7.56 (m, 1H, aromatic), 6.98 (d, 1H, aromatic, J=10.2 Hz); MS (EI) *m/z* (M^+ peak) 231 (100), 186 (33), 172 (69), 89 (19), 77 (30); Anal. calcd for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.62; N, 6.06. Found: C, 67.36; H, 5.52; N, 5.88.

***p*-Hydroxybenzylidenemalonitrile (6o).** Viscous liquid; IR (KBr pellets) 2280, 1580, 1220 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (s, 1H, alkenic), 6.92 (d, 2H, aromatic, J=8.0 Hz), 7.89 (d, 2H, aromatic, J=8.0 Hz); MS (EI) *m/z* (M^+ peak) 170 (100), 142 (7), 119 (22), 115 (9), 39 (7); Anal. calcd for $C_{10}H_8N_2O$: C, 70.58; H, 3.52; N, 16.47. Found: C, 70.70; H, 3.63; N, 15.48.

2-Propionic acid, 2-cyano-3-(4-hydroxyphenyl) ethyl ester (6p). Pale yellow solid, mp 170°C; IR (KBr pellets) 2230, 1720, 1620, 1220 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (t, 3H, CH_3, J=9.1 Hz), 4.38 (q, 2H, CH_2, J=9.1 Hz), 8.12 (s, 1H, alkenic), 7.94 (d, 2H, aromatic, J=5.7 Hz), 6.96 (d, 2H, aromatic, J=5.7 Hz); MS (EI) *m/z* (M^+ peak) 217 (92), 189 (43), 172 (100), 144 (33), 89 (45); Anal. calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 6.45; N, 5.06. Found: C, 66.16; H, 6.43; N, 5.11.

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