Tetrahedron Letters 51 (2010) 2924–2927

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot synthesis of 2-amino-5-nitro-4,6-diarylcyclohex-1-ene-1,3,3-tricarbonitriles by condensation of aldehyde, malononitrile, and nitromethane in the presence of Mg–Al HT under solvent-free condition

Siddheshwar W. Kshirsagar, Nitin R. Patil, Shriniwas D. Samant *

Department of Chemistry, Institute of Chemical Technology, N. M. Parekh Road, Matunga, Mumbai 400 019, India

ARTICLE INFO

Article history:
Received 4 February 2010
Revised 22 March 2010
Accepted 27 March 2010
Available online 31 March 2010

Keywords:
Michael addition
Mg–Al hydrotalcite
Cyclohexene
Multicomponent reaction

ABSTRACT

A multicomponent one-pot reaction of aromatic aldehyde, malononitrile, and nitromethane is carried out in the presence of HTs (different Mg/Al ratios) and other solid bases, where 2-amino-5-nitro-4,6-diphenylcyclohex-1-ene-1,3,3-tricarbonitriles are obtained. HT with Mg/Al = 5 is the best catalyst for the reaction. The reaction gives best results under solvent-free condition. The catalyst can be easily separated and is recyclable. Other parameters were optimized.

1. Introduction

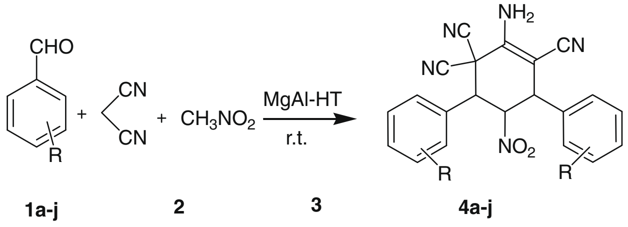
One-pot multicomponent reactions have emerged as an effective tool for atom economic and benign synthesis by virtue of their convergence, productivity, facile execution, and generation of highly diverse and complex products from easily available starting materials.[1] Such reactions can be planned by studying tandem nature of the constituent reactions. Knoevenagel–Michael reaction is one such tandem couple. Combining a Michael reaction with a reaction generating active alkene may lead to such a coupled reaction. The reactions of benzylidiene malononitrile with different nucleophiles have been extensively studied.[2] Among these, the reaction with nitromethane is particularly interesting. Texier-Boullet carried out the reaction of nitromethane with the condensation product of ethyl cyanoacetate and benzaldehydes under microwave irradiations (90 °C) and piperidine catalyst to obtain diethyl 2-amino-3-cyano-nitro-4,6-diarylcyclohex-1-ene-1,3-dicarboxylates.[3]

Subsequently, the reaction of nitromethane with benzylidene malononitrile was also studied and found to give 2-amino-5-nitro-4,6-diphenylcyclohex-1-ene-1,3,3-tricarbonitrile (**4a**).[4] The mechanisms of formation of different products in this reaction by changing the reaction parameters have been studied. It was noted that the course of the reaction strongly depended on the experimental conditions. The formation of functionalized cyclohexenes (**4**) in this reaction is interesting. Multicomponent reactions (MCRs) are synthetically rewarding due to their selectivity and convergence. On the basis of the above-mentioned observations, we decided to skip the step of preparation of benzylidene malononitrile and attempted an MCR of aryl aldehydes, malononitrile, and nitriomethane to obtain **4** (Scheme 1).

Mg–Al hydrotalcite (Mg–Al HT) is reported to be a tunable heterogeneous basic catalyst and has been used for different organic trasformations.[5] We have reported Mg–Al HT as an efficient catalyst in the synthesis of 2-aminochromene derivatives via a multicomponent strategy under microwave irradiations.[6] Earlier piperidine has been used for the above-mentioned Michael reaction. We decided to use Mg–Al HT with different Mg/Al ratio in this reaction.

2. Results and discussion

Mg–Al HTs with Mg–Al mole ratio 2, 3, and 5 were prepared by the reported procedure[7] and characterized by XRD, FT-IR, and DSC.



Where R = Cl, Br, NO_2, OH, OMe, Me, CN

Scheme 1.

---

* Corresponding author. Tel.: +91 22 4145616; fax: +91 022 24145614.
E-mail addresses: samantsd@yahoo.com, samantsd.ict@gmail.com (S.D. Samant).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.03.112

The catalysts were used as synthesized as well as calcined at 500 °C. The reaction of benzaldehyde (**1a**), malononitrile (**2**), and nitromethane (**3**) was selected as a model reaction for optimizing the reaction parameters such as aldehydes to nitromethane molar ratio, effects of solvents, catalysts study, catalysts amount, and reusability.[10] Texier-Boullet has reported that the molar ratio of benzylidene malononitrile to nitromethane is crucial and leads to the formation of different products.[4] Hence, the reaction was carried out using different molar ratios of benzaldehyde to nitromethane (Table 1). With aldehyde to nitromethane ratio 1:0.5, the reaction did not go to completion. The ratio 0.6 was found to give optimum yield of **4a**.

For all further reactions, 0.6 equiv of nitromethane was used. The reaction was attempted in different solvents and without solvent (Table 2). It was observed that the reaction under solvent-free condition gave better yield of the product. It is reported that the reaction of benzaldehyde (**1a**) and malononitrile (**2**) in water in the absence of a catalyst leads to the formation of benzylidene malononitrile.[8] However, the reaction of **1a**, **2**, and **3** in water in the absence of a catalyst failed.

The reaction was carried out using different HTs (Mg/Al = 2, 3, 5), calcined HTs (Mg/Al = 2, 3, 5), and classical bases at room temperature (Table 3). The HTs (Mg/Al = 2, 3, 5) were calcined at 500 °C to tune the basicity. The catalytic activity of the calcined HTs was found to be more than that of the corresponding uncalcined HTs. HT with Mg/Al = 5 is the best catalyst for this reaction. The nature, density, and strength of basic sites depend on Al content and Mg–Al HT (Mg/Al = 5) is known to be the strongest base among the all HT.[9] In the presence of classical catalysts such as NaOH, Na_2CO_3, MgO, piperidine, there was a decrease in the yield; and in the absence of a catalyst, the formation of benzylidine malononitrile was observed instead of **4a**.

For further reaction optimization, the calcined HT (Mg/Al = 5) was used. To optimize the catalyst quantity, the reaction was carried out with different quantities of the HT (Table 4) and 10% w/w of HT with respect to benzaldehyde was found to be optimal.

The hydrotalcite is a heterogeneous catalyst and could easily be separated from the reaction mixture by filtration. The recovered catalyst was used for successive runs to test its reusability. It was observed that there was a decrease in the yield of the product. Powder XRD of fresh calcined Mg–Al HT (Mg/Al = 5) and the used one shows that there is no change in structure and morphology of HT.

Under the optimized conditions, various substituted aromatic aldehydes (**1a**–**j**) were reacted to obtain the corresponding products (**4a**–**j**) (Table 5).

The low activity of 3-hydroxy-4-methoxy benzaldehyde is due to the fact that the phenolic group is acidic in nature and which may act as a poison to basic sites of hydrotalcites. The reaction was successful with the electron-donating as well as electron-withdrawing groups. The reaction was assumed to follow a path given in Scheme 2.

Table 2
Reaction of benzaldehyde, malononitrile, and nitromethane in the presence of Mg–Al HT (Mg/Al = 3) calcined at 500 °C at room temperature

Entry	Solvent	Yield of **4a** (%)
1	DMF	52
2	H_2O	61
3	MeOH	40
4	Neat	67

Reaction conditions: Benzaldehyde (5 mmol), malononitrile (5 mmol), nitromethane (3 mmol), HT (0.05 g), room temperature (29 °C), time = 5 h, solvent (2 ml).

Table 3
Reaction of benzaldehyde, malononitrile, and nitromethane in the presence of different catalysts at room temperature

Entry	Catalyst	Yield of **4a** (%)
1	Mg/Al: 2 HT	31
2	Mg/Al: 3 HT	40
3	Mg/Al: 5 HT	49
4	Mg/Al: 2 HT[a]	43
5	Mg/Al: 3 HT[a]	67
6	Mg/Al: 5 HT[a]	72
7	NaOH	42
8	Na_2CO_3	45
9	MgO	40
10	Piperidine	58
11	No ctalyst	00

Reaction conditions: Benzaldehyde (5 mmol), malononitrile (5 mmol), nitromethane (3 mmol), catalyst (0.05 g), room temperature (29 °C), time = 5 h, a-calcined at 500 °C.

Table 4
Reaction of benzaldehyde, malononitrile, and nitromethane in the presence of Mg–Al HT (Mg/Al = 5) calcined at 500 °C at room temperature

Entry	Catalyst amount (g)	Yield of 4a (%)
1	0.01	22
2	0.03	50
3	0.05	72
4	0.07	73
5	0.10	66

Reaction conditions: Benzaldehyde (5 mmol), malononitrile (5 mmol), nitromethane (3 mmol), room temperature (29 °C), time = 5 h, Note: The catalyst reusability checked up to the four cycles with no subsequent loss in activity.

In conclusion, Mg–Al HT (Mg/Al = 5) calcined at 500 °C is found to be a simple and efficient solid base catalyst for MCR of aryl aldehyde, malononitrile, and nitromethane to obtain **4** under solvent-free condition at ambient temperature. This is the first report on one-pot synthesis of functionalized cyclohexenes through a three-component reaction in the presence of a solid catalyst.

Table 1
Reaction of benzaldehyde, malononitrile, and nitromethane in the presence of Mg–Al HT calcined at 500 °C at room temperature

Entry	Benzaldehyde (mmol)	CH_3NO_2 (mmol; equiv)	Yield of **4a** (%)	
			Mg/Al = 3	Mg/Al = 5
1	5.0	2.5; 0.5	62	64
2	5.0	3.0; 0.6	67	72
3	5.0	5.0; 1.0	69	71
4	5.0	10; 2.0	50	59

Reaction conditions: Benzaldehyde (5 mmol), malononitrile (5 mmol), nitromethane, HT (0.05 g), room temperature (29 °C) time = 5 h.

Table 5

Reaction of aldehyde, malononitrile, and nitromethane in the presence of Mg–Al HT [(Mg/Al = 5) calcined at 500 °C] at room temperature

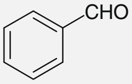
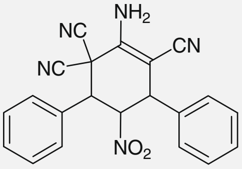
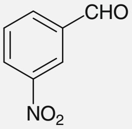
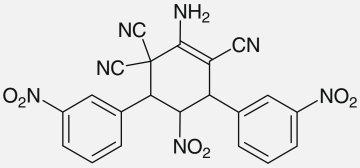
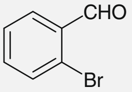
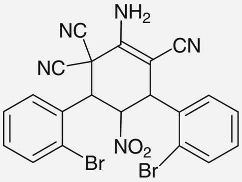
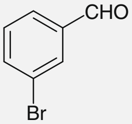
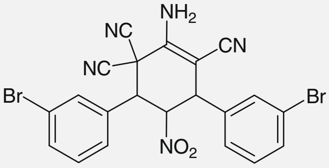
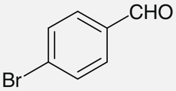
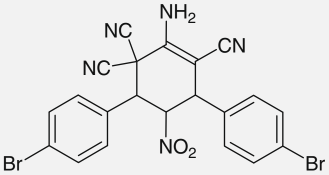
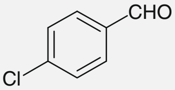
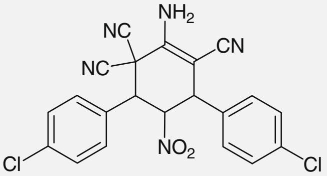
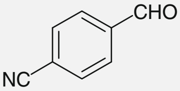
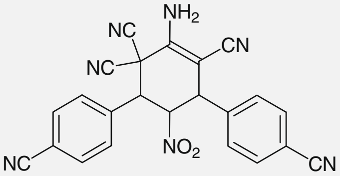
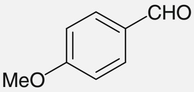
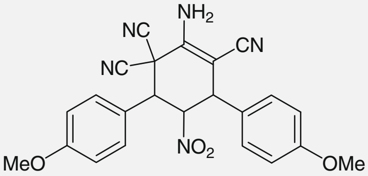
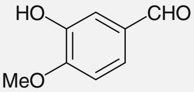
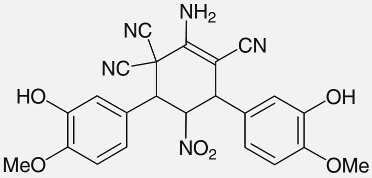
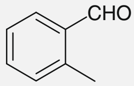
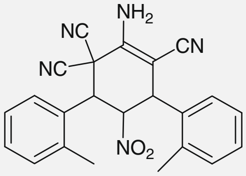
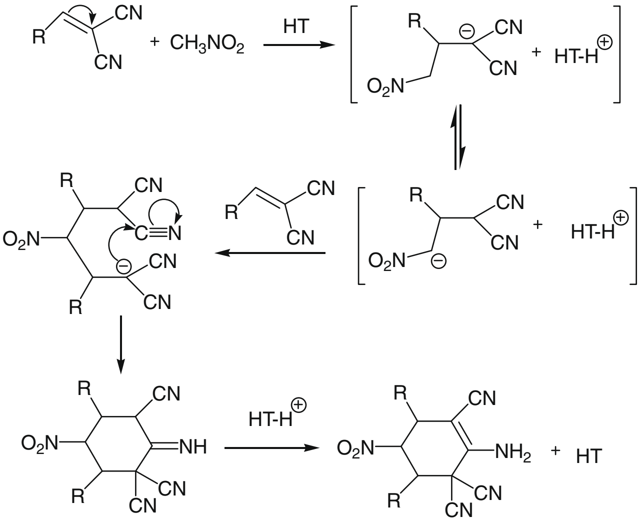
Entry	Aldehyde	Product	Time (h)	Yield of **4** (%)	Mp (°C)
a			5	72	207–210
b			5.5	66	188–190
c			4	87	128–131
d			4	48	235–236
e			4	90	225–227
f			4.5	84	240–242
g			5	81	230–234
h			7	72	243–244
i			10	30	225–226

Table 5 (*continued*)

Entry	Aldehyde	Product	Time (h)	Yield of **4** (%)	Mp (°C)
j			7.5	67	230–232

Reaction conditions: Aldehyde (5 mmol), malononitrile (5 mmol), nitromethane (3 mmol), HT (0.05 g), room temperature (29 °C). The entire compounds were characterized by NMR and FTIR.[11]



Scheme 2.

Acknowledgment

The authors thank the CSIR, New Delhi, for a Research Grant (No. 01(2056)/06/EMR-II). S.W.K. thanks the CSIR for providing Senior Research Fellowship.

References and notes

1. (a) Ugi, I.; Dombling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647; (b) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3221.
2. (a) Gerd, K.; Reza, N. J. M.; Jens, S. *Tetrahedron* **2003**, *59*, 3753; (b) Ibrahim, Nadia S. *Heterocycles* **1986**, *24*, 935; (c) Satoshi, K.; Koji, S.; Akio, S.; Hiroshi, M. *Synthesis* **1980**, 366; (d) Ming-Zhu, P.; Kimiaki, I. *Tetrahedron Lett.* **1997**, *38*, 5301; (e) Shujiang, T.; Bo, J.; Junyong, J.; Yan, Z.; Runhong, J.; Chunmei, L.; Dianxiang, Z.; Longji, C.; Qingqing, S. *Synlett* **2007**, 480; (e) Xavier, M.; Nuno, M.; Genevieve, B. *Synlett* **1997**, 845; (f) Zhuang-Ping, Z.; Wen-Zhen, Y.; Rui-Feng, Y. *Synlett* **2005**, 2425.
3. Michaud, D.; Ayoubi, S. A. E.; Dozias, M. J.; Toupet, L.; Texier-Boullet, F.; Hamelina, J. *Chem. Commun.* **1997**, 1613.
4. Michaud, D.; Hamelina, J.; Texier-Boullet, F.; Toupet, L. *Tetrahedron* **2002**, *58*, 5865.
5. (a) Shen, J.; Tu, M.; Hu, C. *J. Solid State Chem.* **1998**, *137*, 295; (b) Sels, F. B.; De Vos, D. E.; Jacobs, P. *Catal. Rev.* **2001**, *43*, 443.
6. Surpur, M. P.; Kshirsagar, S. W.; Samant, S. D. *Tetrahedron Lett.* **2009**, *50*, 719.
7. (a) Cavani, F.; Trifiro, F.; Voccari, A. *Catal. Today* **1991**, *11*, 173; (b) Reichle, W. T.; Kang, S. Y.; Everhordt, D. S. *J. Catal.* **1986**, *101*, 352.
8. Deb, M. L.; Bhuyan, P. J. *Tetrahedron Lett.* **2005**, *46*, 6453.
9. Di Cosimo, J. I.; Diez, V. K.; Xu, M.; Iglesia, E.; Apesteguia, C. R. *J. Catal.* **1998**, *178*, 499.
10. *Typical reaction procedure*: In a 50 ml round-bottomed flask, aldehyde (5 mmol), malononitrile (0.33 g, 5 mmol), and calcined HT (Mg/Al = 5) (0.05 g) were stirred at room temperature till the consumption of aldehyde (TLC). Nitromethane (0.18 g, 3 mmol) was added and the reaction mixture was stirred at room temperature (29 °C) to complete the reaction (TLC). To the flask, chloroform (20 ml) was added to dissolve the product and the catalyst was filtered and washed with chloroform (10 ml). The filtrate was concentrated (up to the 5–10 ml) under reduced pressure and the product was purified by column chromatography on silica gel (60–120 mesh). Eluent-pet ether/ethyl acetate: 100/90.
11. The spectral data of all unknown compounds are given here. *Compound* **4a**: FTIR (KBr) ν: 3434, 3340, 3219, 2203, 1648, 1561, 1363, 690 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H: 4.13 (d, 1H, J = 12 Hz), 4.31 (d, 1H, J = 10 Hz), 5.15 (s, 2H), 5.31 (dd, 1H, J_1 = 12 Hz, J_2 = 10 Hz), 7.21–7.47 (m, 10H) ppm. Anal. Calcd for $C_{21}H_{15}N_5O_2$; C, 68.28; H, 4.09; N, 18.96. Found: C, 67.86; H, 3.88; N, 18.75.
    Compound **4b**: FTIR (KBr) ν: 3400, 3356, 3229, 2208, 1648, 1562, 1533, 1354, cm^{-1}. ^{1}H NMR (DMSO, 400 MHz) δ_H: 4.60 (d, 1H, J = 10 Hz), 5.26 (d, 1H, J = 12 Hz), 6.55 (br s, 1H), 7.72–7.89 (m, 10H) ppm.
    Compound **4e**: FTIR (KBr) ν: 3453, 3313, 3212, 2225, 1653, 1562, 1362 cm^{-1}. ^{1}H NMR (DMSO, 400 MHz) δ_H: 4.34 (d, 1H, J = 10 Hz), 4.97 (d, 1H, J = 12 Hz), 5.83 (dd, 1H, J_1 = 12 Hz, J_2 = 10 Hz), 7.31–7.72 (m, 10H) ppm.
    Compound **4f**: FTIR (KBr) ν: 3458, 3317, 3218, 2223, 1653, 1563, 1364, 1094, 831 cm^{-1}. ^{1}H NMR (DMSO, 400 MHz) δ_H: 4.36 (d, 1H, J = 10 Hz), 4.99 (d, 1H, J = 12 Hz), 5.84 (dd, 1H, J_1 = 12 Hz, J_2 = 10 Hz), 7.38–7.62 (m, 10H) ppm.
    Compound **4g**: FTIR (KBr) ν: 3449, 3345, 3215, 2208, 1645, 1557, 1362 cm^{-1}. ^{1}H NMR (DMSO, 400 MHz) δ_H: 4.33 (d, 1H, J = 10 Hz), 4.95 (d, 1H, J = 12 Hz), 6.04 (br s, 1H), 7.31–7.69 (m, 10H) ppm.
    Compound **4h**: FTIR (KBr) ν: 3439, 3351, 3208, 2208, 1646, 1558, 1363, 1185, 825 cm^{-1}. ^{1}H NMR (DMSO, 400 MHz) δ_H: 3.75 (s, 3H), 4.28 (d, 1H, J = 10 Hz), 4.83 (d, 1H, J = 12 Hz), 5.53 (t, 1H, J_1 = 12 Hz, J_2 = 10 Hz), 6.95–7.48 (m, 10H) ppm.
    Compound **4i**: FTIR (KBr) ν: 3467, 3362, 3223, 2208, 1648, 1514, 1360, 1281 cm^{-1}. ^{1}H NMR (DMSO, 400 MHz) δ_H: 3.76 (s, 3H), 3.77 (s, 3H), 4.16 (d, 1H, J = 10 Hz), 4.70 (d, 1H, J = 12 Hz), 5.27 (dd, 1H, J_1 = 12 Hz, J_2 = 10 Hz), 6.60–6.98 (m, 8H), 9.23 (s, 1H), 9.33 (s, 1H) ppm.
    Compound **4j**: FTIR (KBr) ν: 3446, 3356, 3226, 2205, 1646, 1553, 1355, 1094, 747 cm^{-1}. ^{1}H NMR (DMSO, 400 MHz) δ_H: 2.20 (s, 3H), 4.92 (d, 1H, J = 10 Hz), 5.22 (d, 1H, J = 12 Hz), 5.71 (t, 1H, J_1 = 12 Hz, J_2 = 10 Hz), 7.15–7.76 (m, 10H) ppm.