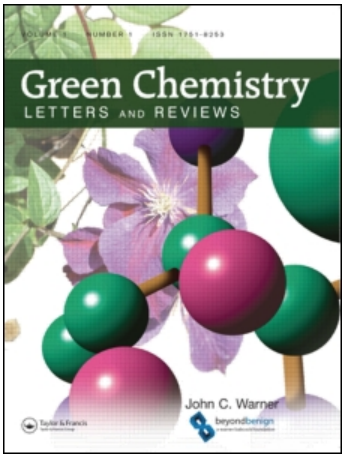

Green Chemistry Letters and Reviews
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t748292817

Knoevenagel reaction: alum-mediated efficient green condensation of active methylene compounds with arylaldehydes

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To cite this Article Suresh and Sandhu, Jagir S.(2009) 'Knoevenagel reaction: alum-mediated efficient green condensation of active methylene compounds with arylaldehydes', Green Chemistry Letters and Reviews, 2: 3, 189 — 192
To link to this Article: DOI: 10.1080/17518250903260925
URL: http://dx.doi.org/10.1080/17518250903260925

Green Chemistry Letters and Reviews
Vol. 2, No. 3, September 2009, 189–192

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RESEARCH LETTER

Knoevenagel reaction: alum-mediated efficient green condensation of active methylene compounds with arylaldehydes

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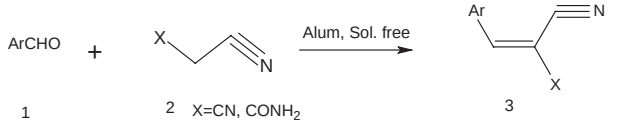
(Received 19 February 2009; final version received 14 August 2009)

A solvent-free stirred mixture of active methylene compounds, arylaldehyde and 10 mol% alum at 80°C afforded Knoevenagel products in excellent yields. The use of a green catalyst, the solvent-free conditions, and shorter reaction times are the main features of this efficient protocol.



Keywords: alum; active methylene compounds; Knoevenagel products

Introduction

The Knoevenagel reaction is a facile reaction used for the olefination of carbonyl compounds. Historically, it was reported in 1894 (*1*) that reacting formaldehyde, diethyl malonate, and diethyl amine as catalyst afforded the bis-product, which was actually a result of a Knoevenagel followed by a Michael reaction and not the true Knoevenagel product of present times. Subsequently, in a later attempt in 1896 (*2*) Knoevenagel could produce the desired product by reacting benzaldehyde, diethyl malonate with the catalyst piperidine at 0°C producing the product of conventional Knoevenagel reactions. These initial experiments made it clear that this reaction requires a subtle balance of reaction conditions, i.e. temperature, as well as catalyst to circumvent subsequent Michael addition onto highly electron-deficient alkenes produced in this reaction. Therefore, in subsequent years the reaction was fairly generalized. The interest in this reaction which was of academic nature shifted to several complex types of biologically significant products (*3*) via cascade reactions. Notable ones are derived from barbituric acid (*4,5*), Meldrm's acid (*6,7*), and the indole (*8,9*) scaffold. Because of the unique products obtained in this reaction in the present years, there has been considerable interest in the pursuit of facile and efficient catalysts. In this effort, a large number of catalyst have been developed such as $AlPO_4$–Al_2O_3, $ZnCl_2$, LiBr, CdI_2, K_3PO_4, $Fe_2(SO_3)_4$, $TiCl_3(SO_3CF_3)$, $FeCl_3$, $RuCl_3$, $InCl_3$, and Lanthanum triflates (*10–24*).

We and others have been exploring the use of alum in organic synthesis and its utility has already been demonstrated in Biginelli reactions (*25*), and Pechmann reactions (*26*). Alum has also been used for the synthesis of isoquinolonic acids (*27*), 2,3-dihydroquinazolin-4(1H)-ones (*28*), 1,3,4-oxadiazoles (*29–31*), and very recently used for the synthesis of 1,5-benzodiazepines (*32*).

Results and discussion

We report herein a very simple, green, and highly efficient method for the condensation of various aromatic and heteroaromatic aldehydes (*1*) with active methylene compounds (*2*) such as malononitrile and cyanoacetamide. The reactions were carried out at 80°C in the presence of 10 mol% of alum. It was exciting to observe that, except in few cases, all reactions proceed rapidly and were completed in just a few minutes, giving excellent yields of the Knoevenagel product **3** (Scheme 1).

Alum is an inexpensive, non-toxic, and commercially available compound that can be used in practice without any special precautions. At first, the reaction of 4-chlorobenzaldeyde with malonitrile was selected as a model reaction to examine the effects of the

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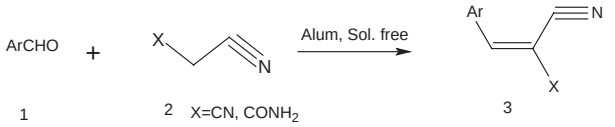
ISSN 1751-8253 print/ISSN 1751-7192 online

DOI: 10.1080/17518250903260925
http://www.informaworld.com



Scheme 1. Synthesis of Knoevenagel products.

catalyst ranging from 0 to 10% at room temperature. The best yield was obtained when the reaction was carried out in the presence of 10 mol% of alum under solvent-free condition at 80°C. No other by-product was formed during the course of the reaction. Electron-deficient aldehydes gave relatively higher yields than electron-rich counterparts (Table 1). In conclusion, we have demonstrated that the Knoevenagel condensation between aromatic and heteroaromatic aldehydes with active methylene compounds can be effectively performed solvent-free at 80°C temperature in the presence of a catalytic amount (10 mol%) of alum, which provides a simple route to the synthesis of tri-substituted alkenes. The present method has many obvious advantages compared to those reported in the literature, including simplicity of the methodology, ease of product isolation (only simple filtration), good yields, short reaction times, inexpensive catalyst, and environmental friendliness.

Experimental

Melting points were determined in open capillaries and are uncorrected. Reagent grade chemicals were purchased from commercial sources and used as received. IR spectra were recorded in KBr discs on a Perkin–Elmer 24OC analyzer. ^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) spectrometer using tetramethylsilane (TMS) as internal standard. The progress of the reaction was monitored by thin layer chromatography (TLC) run on silica gel G (Merck).

General procedure for the preparation of alkenes

To a stirred solution of malononitrile/cynoacetamide (2.2 mmol), alum (0.1 mmol) and benzaldehyde (2 mmol) were added. The progress of the reaction was monitored by TLC (eluent: petroleum ether–EtOAc, 3:1). The reaction was completed in 5–12 min time; the obtained product was washed with water and then filtered. Further purification for some samples was made by recrystallization from EtOH.

Physical and spectral data

Benzylidenemalononitrile **(3a):** mp 84–85°C (82.5–83.5°C); IR (KBr): 3016, 2217, 1590 cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.56 (s, 1H), 7.96 (d, $J=7.9$ Hz, 2H), 7.7–7.55 (m, 3H); ^{13}C NMR (DMSO-d6): δ 162, 134.8, 131.9, 131, 130, 114.4, 113.5, 82.

p-methoxybenzylidenemalononitrile **(3b):** mp 109–110°C (113°C); IR (KBr): 3126, 2229, 1583 cm^{-1}. ^{1}H NMR (DMS0-d6): δ 8.4 (s, lH), 8.0–7.15 (AA'BB' system, 4H), 9 (s, 3H); ^{13}C NMR (DMSO-d6): δ 164.3, 161, 134, 124.3, 115.8, 115.5, 114.2, 77, 56.

p-chlorobenzylidenemalononitrile **(3d)**: mp 161–162°C (161–162°C); IR (KBr): 3033, 2228, 1584 cm^{-1}; ^{1}H NMR (CDCl3): δ 8.55 (s, lH), 8.0–7.65

Table 1. Knoevenagel reaction catalyzed by alum under solvent-free conditions.

Product	Ar	R	Yield (%)[a]	Time (min.)	Melting point (°C)	
					Found	Reported (*10–19*)
3a	C_6H_5	CN	92	5	84–85	82.5–83.5
3b	p-$MeOC_6H_4$	CN	85	9	109–110	113
3c	p-OHC_6H_4	CN	87	11	190	188
3d	P-ClC_6H_4	CN	94	7	161	161–162
3e	p-BrC_6H_4	CN	92	8	159–160	162–164
3f	4-$Me_2NC_6H_4$	CN	90	6	179	183–184
3g	4-$NO_2C_6H_4$	CN	89	8	160	160.5
3h	C_6H_5	$CONH_2$	95	6	123	123.5
3i	p-$MeOC_6H_4$	$CONH_2$	88	10	215–216	215
3j	p-OHC_6H_4	$CONH_2$	86	12	255–256	258–259
3k	P-ClC_6H_4	$CONH_2$	92	7	207–208	208–209
3l	p-BrC_6H_4	$CONH_2$	90	8	222–224	220–221
3m	4-$Me_2NC_6H_4$	$CONH_2$	89	6	195–197	199–200
3n	3-NO_2-C6H4	$CONH_2$	90	8	156–159	161–163
3o	4-NO_2-C6H4	$CONH_2$	88	7	235–236	236–237

[a]In all cases, the yields are related to pure isolated compounds.

(AA'BB' system, 4H), ^{13}C NMR (CDCl3): δ 159.9, 139, 132, 130, 129.5, 113.8, 112, 82.

p-bromobenzylidenemalononitrile **(3e)**: mp 159–160°C (162–164°C); IR (KBr): 3106, 2228, 1584 cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.53 (s, IH), 7.85 (AA'BB' system, 4H); ^{13}C NMR (DMSO-d6): δ 160.8, 132.9, 132.3, 130.5, 128.5, 114.2, 113, 82.5.

p-N,N-(dimethylamino) benzylidenemalononitrile **(3f)**: mp 185–185.5°C (183–184°C); IR (KBr): 3117, 2208, 1568 cm^{-1}; ^{1}H NMR (CDC13): δ 7.85–6.65 (AA'BB' system, 4H), 7.45 (s, 1H), 3.15 (s, 6H); ^{13}C NMR (CDCl3): δ 159, 155, 134, 120, 117, 115.6, 112, 72, 41.

p-nitrobenzylidenemalononitrile **(3g)**: mp 157°C (160.5°C); IR (KBr): 3116, 2232, 1580 cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.7 (s, 1H), 8.45–8.1 (AA'BB' system, 4H); ^{13}C NMR (DMSO-d6): δ 159, 149.6, 136.6, 131.5, 124.3, 113.5, 112.5, 86.

Benzylidenecyanoacetamide **(3h)**: mp 123°C (123.5°C); IR (KBr) 3400, 3165, 2219, 1693, 1597 cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.2 (s, l), 7.95 (d, J = 8.1, 2H). 7.85 (br d, 2H), 7.56 (m, 3H); ^{13}C NMR (DMSO-d6): δ 163.1, 150.92, 132.65, 132.34, 130.34, 129.58, 116.79, 107.16.

p-hydroxybenzylidenecyanoacetamide **(3j)**: mp 255–256°C (258–259°C): IR (KBr): 3454, 3367, 3193, 2228, 1656, 1600 cm^{-1}; ^{1}H NMR (DMS0-d6): δ 10.52 (br s, lH), 8.07 (s, IH), 7.4 (AA'BB' system, 4H), 7.6–7.8 (br s, 2H); ^{13}C NMR (DMSO-d6): δ 163.8, 162, 151, 133.2, 123.2, 117.7, 116.8, 102.

p-chlorobenzylidenecyanoacetamide **(3k)**: mp 207–208°C (208–209°C); IR (KBr): 3455, 3155, 2212, 1703, 1601 cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.19 (s, lH), 7.96–7.8 (br s, 2H), 7.9 − 7.55 (AA'BB' system, 4H); ^{13}C NMR (DMSO-d6): δ 162.8, 149.5, 137.2, 132, 131.2, 129.7, 116.4, 107.8.

p-bromobenzylidenecyanoacetamide **(3l)**: mp 222–224°C (220–221°C); IR (KBr): 3440, 3153, 2215, 1699, 1601 cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.17 (s, IH), 7.96 (br s, 2H), 7.83 (AA'BB' system, 4H; ^{13}C NMR (DMSO-d6): δ 162.9, 149.8, 132.7, 132.2, 131.4, 126.3, 116.6, 107.8.

p-N,N-(dimethylamino) benzylidenecyanoacetamide **(3m)**: mp 195–197°C (199–200°C); IR (KBr): 3359, 3166, 2198, 1680, 1563 cm^{-1}; ^{1}H NMR (DMSO-d6): δ 7.98 (s, IH), 7.3 (AA'BB' system, 4H), 7.6–7.4 (br s, 2H), 3.02 (s, 6H); ^{13}C NMR (DMSO-d6): δ 163, 153, 151, 133, 119, 118.5, 112, 97.8, 40.

m-nitrobenzylidenecyanoacetamide **(3n)**: mp 162–163°C (161–163°C); IR (KBr): 3473–3331, 3200, 2216, 1703, 1597 cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.8 (t, J = 1.7 Hz, 1H), 8.42 (dd, J = 7.30, 0.9 Hz, 1H), 8.35 (s, lH), 8.3 (d, J = 7.3 Hz, 1H), 8.05–7.95 (2 br s, 2H), 7.9 (t, J = 7.3 Hz 1H); ^{13}C NMR (DMSO-d6): δ 162.5, 148.8, 148, 136.5, 133.5, 131.5, 126.5, 119.5, 116, 109.5.

p-nitrobenzylidenecyanoacetamide **(3o)**: mp 236–238°C (236–237°C); IR (KBr): 3439, 3197, 2225, 1692, 1601 cm^{-1}; ^{1}H NMR (DMSO-d6): δ 8.3 (AA'BB' system, 4H), 8.32 (s, IH), 8.1–7.9 (br d, 1H); ^{13}C NMR (DMSO-d6): δ 162.3, 149.1, 148.6, 138.4, 131.3, 124.5, 116.1, 111.

Conclusion

In conclusion, the present protocol employing catalytic amount of alum, is an efficient and mild one-pot strategy for the preparation of Knoevenagel products. The time required is drastically reduced compared to traditional methods, and products are obtained in excellent yields.

Acknowledgements

The authors wish to thank the Council of Scientific and Industrial Research (CSIR), New Delhi, India and Indian National Science Academy (INSA), New Delhi, India for financial support for this research project.

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