

Efficient $\text{MgBr}_2 \cdot \text{OEt}_2$ - catalyzed Knoevenagel condensation

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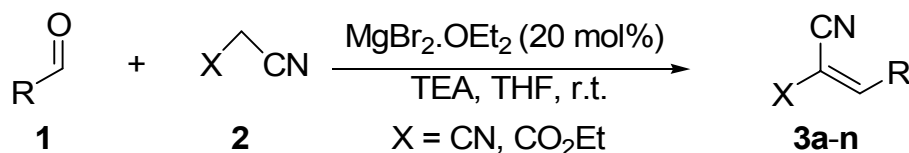
Abstract

An efficient room-temperature procedure was developed for Knoevenagel condensation of various aldehydes with malononitrile and ethyl cyanoacetate in the presence of triethylamine and catalytic amounts of magnesium bromide diethyl etherate.

Keywords: Magnesium bromide diethyl etherate, Knoevenagel condensation, catalytic reaction

Introduction

The synthesis of electrophilic olefins from active methylene and carbonyl compounds, known as the Knoevenagel condensation,¹ is one of the most well known reactions in organic chemistry owing to its applicability in the preparation of various synthetic targets.² Many modifications have been made to this process in recent years using Lewis acid catalysis,³ ionic liquids,⁴ microwave irradiation,⁵ quaternary ammonium salts,⁶ heterogeneous catalysts,⁷ and organo-base mediation.⁸ However, in many of these methods relatively harsh conditions are required, expensive reagents are involved, or a combination of several additives is employed. In recent years, magnesium bromide diethyl etherate ($\text{MgBr}_2 \cdot \text{OEt}_2$) has found many applications as a mild Lewis acid to effect various synthetic organic transformations.⁹ In this context, we have demonstrated the usefulness of $\text{MgBr}_2 \cdot \text{OEt}_2$ in Diels–Alder cycloadditions, Cannizzaro reactions, aldol condensation, α -aminonitrile syntheses, and alcohols protection.¹⁰ In continuation of these studies, we now introduce the application of $\text{MgBr}_2 \cdot \text{OEt}_2$ for efficient room-temperature Knoevenagel condensation of various aldehydes with active methylene compounds in the presence of triethylamine (TEA) (Scheme 1).

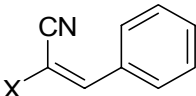
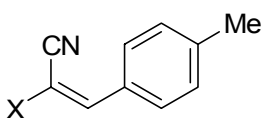
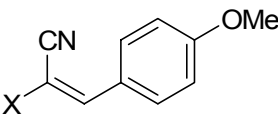
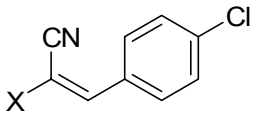
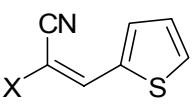
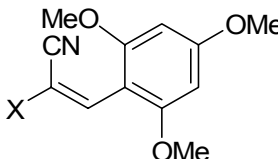
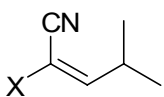


Scheme 1. $\text{MgBr}_2 \cdot \text{OEt}_2$ catalyzed Knoevenagel condensation of aldehydes.

Results and Discussion

We first examined the reaction between aromatic aldehydes and malononitrile in THF by using different quantities of $\text{MgBr}_2 \cdot \text{OEt}_2$ and equimolar amount of TEA. Optimum results were obtained when reactions were conducted in the presence of 20 mol% of $\text{MgBr}_2 \cdot \text{OEt}_2$ (Table 1).

Table 1. Knoevenagel condensation of **1** with **2** using $\text{MgBr}_2 \cdot \text{OEt}_2$ and TEA

Entry	R	Product	Yield % ^a ; X	M.p. °C (reported)
1	C_6H_5		98; CN (3a) 95; CO_2Et (3b)	80-81 (81-82) ^{6a} 52-54 (48-50) ^{6b}
2	4-Me C_6H_4		98; CN (3c) 96; CO_2Et (3d)	131-133 (134-135) ^{6a} 95-97 (94-95) ^{6b}
3	4-MeOC $_6\text{H}_4$		95; CN (3e) 95; CO_2Et (3f)	112-114 (113-114) ^{6a} 78-81 (79-81) ^{6b}
4	4-ClC $_6\text{H}_4$		97; CN (3g) 94; CO_2Et (3h)	162-164 (162-163) ^{6a} 88-90 (90) ^{6b}
5	2-thienyl		93; CN (3i) 93; CO_2Et (3j)	93-95 96-97
6	2,4,6-(MeO) $_3\text{C}_6\text{H}_2$		98; CN (3k) 96; CO_2Et (3l)	174-176 98-99
7	(Me) $_2\text{CH}$		83; CN (3m) 85; CO_2Et (3n)	oil ^{7e} oil ^{7e}

When a mixture of benzaldehyde and malononitrile was treated under the conditions cited, TLC showed complete disappearance of the starting aldehyde in less than 1h and the $^1\text{H-NMR}$ spectrum showed the presence of the compound **3a** as the sole product in the reaction mixture. Extraction of the reaction mixture gave 98% of the desired product (entry 1; X=CN). A control experiment confirmed the promoting effect of the catalyst. Thus, when the reaction mixture was stirred at room temperature for 24 h in the absence of $\text{MgBr}_2 \cdot \text{OEt}_2$ or TEA, the

formation of only small quantities of **3a** was detected and most of the starting materials were recovered. Under the same conditions other aldehydes reacted in a similar manner with malononitrile producing 93–98% yields of their respective products (entries 2–6; X=CN). The generality of the method was demonstrated by subjecting mixtures of the same aldehydes and ethyl cyanoacetate to similar reaction conditions. In each case, single geometric isomers were obtained in high yields within 1–2 hours as shown in Table 1 (entries 1–6; X=CO₂Et). Finally, the applicability of this procedure for Knoevenagel condensation of aliphatic aldehydes was examined. As a result, **3m** (**3n**) could be conveniently obtained when isobutyraldehyde was treated with malononitrile (ethyl cyanoacetate) under similar conditions (entry 7).

Conclusions

In conclusion, efficient condensation of malononitrile and ethyl cyanoacetate with various aldehydes was achieved in short time periods by using MgBr₂.OEt₂ as a catalyst under very mild conditions at room temperature. The use of an inexpensive medium, the rapid completion of reactions, and the high yields of products are all advantages of the present method.

Experimental Section

General Procedures. All reported yields are based on isolated compounds. Melting points were determined with a Buchi melting point apparatus and are corrected. TLC separations were carried out on silica gel plates with UV indicator from Aldrich; visualization was by UV fluorescence or by staining with iodine vapor. IR spectra were recorded on a FT-IR Bruker Vector 22 infrared spectrophotometer using KBr disks. NMR spectra were recorded on FT-NMR Bruker Ultra Shield™ (500 MHz) or Bruker AC 80 MHz as CDCl₃ solutions with TMS as internal reference. GC–MS were obtained on a Fisons 8000 Trio instrument at an ionization potential of 70 eV. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. Aldehydes were purified prior to use.

General procedure. To a mixture of 2.50 mmole of malononitrile (or ethyl cyanoacetate), 2.50 mmole TEA, and 0.50 mmole MgBr₂.OEt₂ in THF (5 mL), was added 2.50 mmole of the aldehyde, and the mixture was stirred at room temperature for 1–2 h (TLC; <10 min) until complete disappearance of the aldehyde. The mixture was diluted with 20 mL ether, and the organic phases was washed with H₂O and filtered through a short Na₂SO₄ column. The solvent was removed under reduced pressure and the product was recrystallized using hexane. The ¹H-NMR, ¹³C-NMR, IR, and mass spectra of the products were obtained. The structure and the geometry of the new products were determined by comparison of their spectroscopic properties with those available in the literature for known products.

2-(Thiophen-2-ylmethylene)malononitrile (3i). M.p: 93–95 °C; ¹H NMR (CDCl₃, δ, 500 MHz): 7.30–7.33 (m, 1H), 7.85–7.86 (m, 1H), 7.92–7.94 (m, 2H) ppm; ¹³C NMR (CDCl₃, δ, 125 MHz): 78.6, 113.4, 114.3, 129.5, 135.8, 137.4, 138.7, 151.6 ppm; IR (KBr disk) 2223, 1575, 736 cm⁻¹; MS: m/z = 160 (M⁺). (Found: C, 59.72; H, 2.55; N, 17.45. C₈H₄N₂S requires C, 59.98; H, 2.52; N 17.49%).

(E)-Ethyl 2-cyano-3-(thiophen-2-yl)acrylate (3j). M.p. 96–97 °C; ¹H NMR (CDCl₃, δ, 500 MHz): 1.43 (t, *J* = 7 Hz, 3H), 4.40 (q, *J* = 7 Hz, 2H), 7.27 (dd, *J* = 5, 4 Hz, 1H), 7.83 (d, *J* = 5 Hz, 1H), 7.87 (d, *J* = 4 Hz, 1H), 8.39 (s, 1H) ppm; ¹³C NMR (CDCl₃, δ, 125 MHz) 14.6, 62.9, 99.7, 116.1, 129.1, 135.6, 136.4, 137.7, 147.1, 163.0 ppm; IR (KBr disk): 2218, 1714, 1597 cm⁻¹; MS: m/z = 207 (M⁺). (Found: C, 57.82; H, 4.36; N, 6.68. C₁₀H₉NO₂S requires C, 57.95; H, 4.38; N, 6.76%).

(2,4,6-Trimethoxybenzylidene)malononitrile (3k). M.p. 174–176 °C; ¹H NMR (CDCl₃, δ, 500 MHz): 3.93 (s, 3H), 3.94 (s, 6H), 6.12 (s, 2H), 7.94 (s, 1H); ¹³C NMR (CDCl₃, δ, 125 MHz): 55.8, 56.2, 80.8, 90.8, 105.1, 114.3, 117.0, 150.8, 162.2, 167.6 ppm; IR (KBr disk) 2212, 1605, 821 cm⁻¹; MS: m/z = 244 (M⁺). (Found: C, 63.75; H, 4.95; N, 11.43. C₁₃H₁₂N₂O₃ requires C, 63.93; H, 4.95; N, 11.47%).

(E)-Ethyl 2-cyano-3-(2,4,6-trimethoxyphenyl)acrylate (3l). M.p. 98–99 °C; ¹H NMR (CDCl₃, δ, 500 MHz): 1.41 (t, *J* = 7 Hz, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 4.38 (q, *J* = 7 Hz, 2H), 6.14 (s, 2H), 8.46 (s, 1H); ¹³C NMR (CDCl₃, δ, 125 MHz) 14.7, 55.8, 56.0, 62.5, 90.8, 103.7, 105.0, 116.5, 147.8, 161.6, 164.4, 166.0 ppm; IR (KBr disk): ν = 2216, 1720, 1611 cm⁻¹; MS: m/z = 291 (M⁺). (Found: C, 61.64; H, 5.94; N, 4.51. C₁₅H₁₇NO₅ requires C, 61.85; H, 5.88; N, 4.81%).

Acknowledgements

We thank the Ministry of Science, Research and Technology of Iran for partial financial support of this work.

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