



A SIMPLE, EXPEDITIOUS AND GREEN PROCESS FOR KNOEVENAGEL CONDENSATION OF PYRAZOLE ALDEHYDES

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Knoevenagel condensation of pyrazole aldehydes with malononitrile is selectively carried out using ammonium carbonate as a mild, cheap, efficient and selective catalyst, in aqueous media at ambient temperature under sonication. This method is green and providing an expeditious way for Knoevenagel condensation of pyrazole aldehyde.

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amino-functionalized mesoporous zirconia,¹³ CaMg(CO₃)₂,¹⁴ microporous carbon nitride,¹⁵ proline functionalized polyacrylonitrile fibre,¹⁶ sevelamer,¹⁷ basic ionic liquid supported on hydroxylapatite-encapsulated γ -Fe₂O₃ nanocrystallite,¹⁸ Ionic liquids,¹⁹⁻²² and very recently without catalyst.²³⁻²⁴ To eliminate or reduce some harsh reaction conditions, harmful and expensive reagents and solvents, we have developed a green method, for Knoevenagel condensation of substituted pyrazole aldehydes with malononitrile in an aqueous medium, using ammonium carbonate as cheap, environmentally friend catalyst. The striking features of reaction are shorter reaction time, ambient reaction temperature, cost effective, simple workup procedure, an aqueous medium (Scheme 1).

Introduction

Emil Knoevenagel (in 1890) developed a method for the synthesis of substituted alkenes, by the condensation of an aldehyde with active methylene compounds in the presence of base and water. Knoevenagel condensation is typical C-C bond forming reaction in organic synthesis. This reaction is useful to generate a variety of intermediates which are used in the synthesis of pharmaceutical precursors; because of this, Knoevenagel condensation has been extensively studied by researchers. Scientist and academicians are still inventing novel methods and catalysts for Knoevenagel condensation. Several methods have been developed by using the microwave,¹ or ultrasonication,² photochemical condensations with fruit extract as a catalyst,³ solvent free conditions.⁴ Recently Franca Bigi et al.,⁵ reviewed Knoevenagel reactions in an aqueous medium with and without a catalyst. According to Franca although reaction involves a dehydration step, the reaction can be carried out in water. Following this interpretation, we have carried out the Knoevenagel reaction of pyrazole aldehyde in water but resulted in lower yield due to less solubility of pyrazole aldehyde. Then we have carried out the reaction in the water-ethanol mixture and obtained a high yield of products; these results prompted us to investigate this reaction further.

In literature several methods have been reported for Knoevenagel condensation by using different solvents and homogeneous or heterogeneous catalyst such as, Ti(O-*i*-Pr)₄,⁶ I₂/K₂CO₃,⁷ Ti(O-*i*-Pr)₄/pyridine,⁸ calcined egg shells,⁹ hydroxyapatite supported CsCO₃,¹⁰ amino-functionalized mesoporous silica,¹¹ mesoporous Ni-Fe hydrotalcite,¹²

Experimental

All chemicals used were of the synthetic grade. The solvents were distilled before use. The progress of the reaction was monitored by TLC using ethyl acetate: n-hexane system. Melting points were recorded by using the open capillary method and are uncorrected. The Ultrasonicator used was made by Cyberlab Ultrasonic Stericleaner model number CB2080 with operation voltage 220 V AC and electric cycle 50/60 Hz. IR spectra were recorded on Shimadzu IR Affinity 1 instrument using KBr discs. H¹ NMR was recorded on BRUKER Avance II 400 NMR Spectrometer using DMSO d₆ as a solvent. The mass was recorded on WATERS, Q-TOF Micro mass (ESI-MS) using methanol as a solvent.

General procedure for the Knoevenagel condensation

In 50 mL round bottom flask pyrazole aldehyde (1 mmol), malononitrile (1 mmol), were taken in 10 ml water- ethanol (1:1) mixture and stirred for 3-5 minutes to mix the reaction mixture; after that ammonium carbonate (20 mol %) was added. The resulting reaction mixture was stirred for 3-20 minutes at reflux temperature, and the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was allowed to cool down to room temperature and then filtered off, washed with water and dried. Similarly, other derivatives were also prepared (Table-2). Similar results were obtained when the reactions were carried out using sonication method (Table 2).

Representative spectral data**2-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)malononitrile (3a)**

IR (KBr, cm^{-1}): 2942 (Ar-CH), 2225 (CN), 1642, 1533 (C=C); $^1\text{H NMR}$ (400 MHz, DMSO- d_6 , δ , ppm): 7.49-7.94 (m, 10H, Ar-H), 8.20 (s, 1H, Ar-H pyrazole), 9.21 (s, 1H, Vinyl CH); ESI-MS (m/z): 297(M+1); Molecular Formula: $\text{C}_{19}\text{H}_{12}\text{N}_4$.

2-((3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)malononitrile (3b)

IR (KBr, cm^{-1}): 2940 (Ar-CH), 2218 (CN), 1604, 1525 (C=C); $^1\text{H NMR}$ (400 MHz, DMSO- d_6 , δ , ppm): 7.49-7.95 (m, 9H, Ar-H), 8.26 (s, 1H, Ar-H pyrazole), 9.22 (s, 1H, Vinyl CH); ESI-MS (m/z): 378(M+1); Molecular Formula: $\text{C}_{19}\text{H}_{11}\text{BrN}_4$.

2-((3-(2,4-dichlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)malononitrile (3e)

IR (KBr, cm^{-1}): 3154 (Ar-CH), 2239 (CN), 1604, 1525 (C=C); $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ , ppm): 7.43-7.56 (m, 6H, Ar-H), 7.60 (s, 1H, Ar-H pyrazole), 7.78-7.80 (d, 2H, Ar-H), 9.05 (s, 1H, Vinyl CH); ESI-MS (m/z): 365(M+1); Molecular Formula: $\text{C}_{19}\text{H}_{10}\text{Cl}_2\text{N}_4$.

2-((3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)malononitrile (3f)

IR (KBr, cm^{-1}): 3141 (Ar-CH), 2233 (CN), 1587, 1512 (C=C); $^1\text{H NMR}$ (400 MHz, DMSO- d_6 , δ , ppm): 7.39-7.96 (m, 9H, Ar-H), 8.23 (s, 1H, Ar-H pyrazole), 9.21 (s, 1H, Vinyl CH); ESI-MS (m/z): 315(M+1); Molecular Formula: $\text{C}_{19}\text{H}_{11}\text{FN}_4$.

2-((3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)malononitrile (3g)

IR (KBr, cm^{-1}): 3411 (OH), 3134 (Ar-CH), 2233 (CN), 1579, 1518 (C=C); $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ , ppm): 6.93-6.95 (d, 2H, J = 8 Hz, Ar-H), 7.46-7.62 (m, 5H, Ar-H), 7.92-7.94 (d, 2H, J = 8 Hz, Ar-H), 8.16 (s, 1H, Ar-H pyrazole), 9.16 (s, 1H, Vinyl CH), 9.90 (s, 1H, Ar-OH); ESI-MS (m/z): 311(M-1); Molecular Formula: $\text{C}_{19}\text{H}_{12}\text{N}_4\text{O}$.

2-((1-phenyl-3-(pyridin-3-yl)-1H-pyrazol-4-yl)methylene)malononitrile (3h)

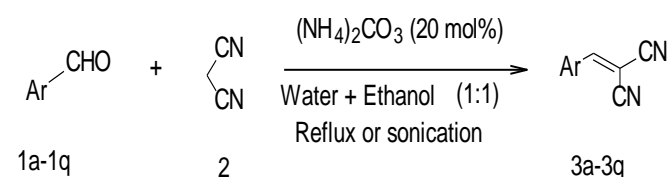
IR (KBr, cm^{-1}): 3133 (Ar-CH), 2230 (CN), 1594, 1521 (C=C); $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ , ppm): 7.47-7.58 (m, 4H, Ar-H), 7.73 (s, 1H, Ar-H pyrazole), 7.81-7.83 (d, 2H, Ar-H), 7.83-7.92 (d, 1H, Ar-H), 8.80-8.85 (m, 2H, Ar-H), 9.10 (s, 1H, Vinyl CH); ESI-MS (m/z): 298(M+1); Molecular Formula: $\text{C}_{18}\text{H}_{11}\text{N}_5$.

2-(4-(piperidin-1-yl)benzylidene)malononitrile (3q)

IR (KBr, cm^{-1}): 2957 (Ar-CH), 2233 (CN), 1604, 1521 (C=C); $^1\text{H NMR}$ (400 MHz, DMSO- d_6 , δ , ppm): 1.64 (q, 6H, CH_2), 3.51 (t, 4H, CH_2), 6.97 (d, 2H, Ar-H, J = 9 Hz), 7.82 (d, 2H, Ar-H, J = 9 Hz), 7.91 (s, 1H, Vinyl CH); ESI-MS (m/z): 238(M+1); Molecular Formula: $\text{C}_{15}\text{H}_{15}\text{N}_3$.

Result and Discussions

Owing to the importance of Knoevenagel condensation reaction to synthesise pharmaceutical intermediates, we have developed a green and efficient method, for the synthesis of heterocyclic, substituted alkenes, by reacting pyrazole aldehyde and malononitrile in the presence of ammonium carbonate (20 mol%) in water: ethanol (1:1) mixture at reflux temperature.



To optimize reaction conditions we have performed the reaction of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde with malononitrile and ammonium carbonate which was considered as a standard model reaction. In search of a suitable solvent, we have achieved reaction by using different solvent mixtures and results were summarized in (Table 1).

Table 1. The reaction of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde and malononitrile in the presence of 20 % and ammonium carbonate in 10 ml of the solvent system at reflux temperature.

Solvent (mL)	$(\text{NH}_4)_2\text{CO}_3$, mol %	Time min	Isolated yield, %
DMF	20	30	Nil
Acetonitrile	20	30	Traces
Dioxane	20	30	30
Methanol	20	30	40
Ethanol	20	30	45
DMF-water (1:1)	20	30	Traces
MeCN- H ₂ O (1:1)	20	30	Traces
Dioxane-Water (1:1)	20	30	25
Ethanol-water (1:1)	--	60	35
Ethanol-water (1:1)	10	60	60
Ethanol-water (1:1)	20	10	92

Water: ethanol (1:1) mixture is proved to be the best solvent system for this reaction. If the reaction was carried out either in water or ethanol; yield of product was decreased due to the higher solubility of either pyrazole aldehyde or ammonium carbonate. The amount of ammonium carbonate has a large influence on the reaction time and yield, the reaction in the absence or presence of 10 % ammonium carbonate only 30 or 60 % yield could be achieved, respectively, and unreacted aldehyde remained back even after 1 h reaction time.

Table 2. Reaction of 1H-pyrazole-4-carbaldehydes and malononitrile in the presence of 20 % and ammonium carbonate in EtOH: H₂O=1:1 (v/v) system under sonication

No.	R	Reflux temperature		Sonication		Melting points (°C)	
		Time, min	Yield, % ^a	Time, min	Yield, % ^a	Obtained	Reported
3a	1,3-diphenylpyrazol-1-H-4-yl	10	92	08	90	160–162	158-160 ^{1d}
3b	1-phenyl-3-(4-bromophenyl)-pyrazol-1H-4yl	10	91	12	92	193-195	--
3c	1-phenyl-3-(4-chlorophenyl)-pyrazol-1H-4yl	12	80	11	78	212-214	217-219 ^{1d}
3d	1-phenyl-3-(4-methoxyphenyl)-pyrazol-1H-4yl	15	90	10	85	176-177	176-177 ^{1d}
3e	1-phenyl-3-(2,4-dichlorophenyl)-pyrazol-1H-4yl	12	86	11	80	175-176	--
3f	1-phenyl-3-(4-fluorophenyl)-pyrazol-1H-4yl	15	80	09	73	217-218	--
3g	1-phenyl-3-(4-hydroxyphenyl)-pyrazol-1H-4yl	20	86	14	84	227-229	--
3h	1-phenyl-3-(3-pyridyl)pyrazol-1H-4yl	15	90	12	86	220-221	--
3i	phenyl	05	90	05	90	83-84	83-84 ^{4b}
3j	4-chlorophenyl	06	94	04	92	162-163	161 ^{4b}
3k	4-methoxyphenyl	06	95	04	96	114-115	113-114 ^{4b}
3l	4-hydroxyphenyl	07	90	05	92	188-189	190 ^{4b}
3m	4-fluorophenyl	05	92	06	90	121-122	122-124 ^{4b}
3n	4-bromophenyl	05	90	04	93	152-153	153-155 ^{4c}
3o	4-dimethylaminophenyl	04	95	02	92	180-181	179-180 ^{4c}
3p	4-nitrophenyl	03	92	03	91	159-161	161-162 ^{4c}
3q	4-(1-piperidinyl)phenyl	05	93	04	94	120-122	122-123 ³⁹

^aIsolated yield obtained after using 20 mol % ammonium carbonate in 10 ml of water-ethanol (1:1) solvent system.

We have also carried out the same reaction by using sonication to increase yield and reduce the period of reaction. But much difference was not found (Table 2).

Conclusion

The reported method described a simple and fast way for the condensation of pyrazole aldehydes with malononitriles, in 1:1 EtOH: an H₂O solvent mixture in the presence of 20 mol % (NH₄)₂CO₃ and under 10 min reflux or sonication.

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