Guanidine Carbonate: Efficient Catalyst for Knoevenagel Condensation of Aryl Aldehydes with Meldrum's Acid

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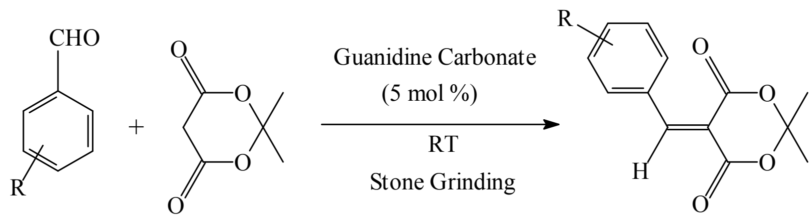
Abstract

Guanidine carbonate efficiently catalyzed the Knoevenagel condensation of aryl aldehydes and Meldrum's acid by stone grinding under solvent free condition. This method has been applied to a variety of substrates including electron donating substituents, electron withdrawing substituents, heterocyclic aldehydes and unsaturated aldehydes with excellent yields. The products obtained are extra pure so there was no need for the column chromatography techniques. The present methodology offers several advantages such as short reaction times, simple procedure and work-up steps, and purification of products by non-chromatographic methods, as well as inexpensive and non-toxic catalyst avoiding the use of organic solvent makes the process environmentally benign.

Keywords: Guanidine carbonate, Knoevenagel condensation, Meldrum's acid, Stone grinding.

1. Introduction:

The Knoevenagel condensation is a nucleophilic addition of an active methylene compound to carbonyl group of aldehydes and ketones to form a carbon-carbon double bond.[1-3] Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) is an active methylene containing compound having a rigid cyclic structure with high acidity.[4] The arylidine derivatives of Meldrum's acid are used as a intermediates in the synthesis of therapeutic drugs,[4] natural products,[5] cosmetics,[6] fine chemicals,[7-8] functional polymers,[9] agrochemicals,[10] materials for organic solar cells, and nonlinear optical application.[11-13] Recently, Knoevenagel condensation of Meldrum's acid with aryl aldehydes in the presence of amines, ammonium salts and Lewis acids in organic solvents was undertaken.[14-18] Also, various catalysts using a different of conditions have been employed for the Knoevenagel condensation of Meldrum's acid with aryl aldehydes such as pyrrolidinium acetate in benzene,[19] ethylammonium nitrate,[20] cellulose sulphuric acid,[21] K_3PO_4 in ethanol,[22] anhydrous $ZnCl_2$ under solvent-free conditions,[23]L-tyrosine under grindstone method,[24] Montmorrillonite clay K-10,[25] [Hmim]Tfa ionic liquid,[26] piperdine/glacial acetic acid in benzene,[27] cetyltrimethylammonium bromide (CTMAB) in water,[28] acidic alumina solid support under microwave irradiation,[29] visible light induced uncatalyzed in water-ethanol mixture,[30] and $TiCl_4$-THF complex in the presence of pyridine.[31] Uncatalyzed reactions were reported using DMF or DMSO as solvents, [32-33] These reported methods have their own merits and demerits such as, prolonged reaction time, use of hazardous catalysts, the use of high boiling solvent, use of acid or base catalyst, use of microwave or ultrasound irradiation, harsh reaction conditions, and tedious work-up procedures. Thus, there is need for the development of new environmentally friendly, cost effective procedure for the Knoevenagel condensation. Herein we report the application of guanidine carbonate in organic synthesis. Guanidine carbonate, alkaline, water soluble, safe, non-toxic, non-flammable, inexpensive and easily available applied for the Knoevenagel condensation of aryl aldehydes and Meldrum's acid. (Scheme 1)



1 2 3

Scheme 1: Guanidine carbonate catalyzed Knoevenagel condensation of Meldrums acid and aryl aldehydes

2. Experimental Work

2.1 Generals

All the melting points were determined by open capillary method. The purity of compounds was checked by Blaker-Flex silica gel 1B-F (1.55 cm) TLC plates, and the spots were detected by UV light absorption. ^{1}H NMR was taken on Brucker avance II-400 MHz spectrometer in DMSO using tetramethylsilane as an internal standard. The IR spectra were recorded using KBr disc on Shimadzu FTIR spectrophotometer. The chemicals used are of AR grade from Sd fine and Loba chemicals.

2.2 Typical procedure

The mixture of 4-Methoxybenzaldehyde (5 mmol), Meldrum's acid (5 mmol), Guanidine carbonate (5 mol %) was grinded in mortal using pastel at room temperature. After complete conversion (monitored by TLC) 10 ml water was added and a solid product was filtered and washed with water. The crude product obtained was recrystallized from ethanol. The MPs are took by open capillary method and matched with authentic samples. Some products are characterized by IR and ^{1}H NMR spectroscopy.

3. RESULTS AND DISCUSSION

Though, several approaches have been reported for Knoevenagel condensation. In the present investigation, we report the use of guanidine carbonate as a catalyst under solvent free condition at room temperature. Initially to optimize the reaction conditions for Knoevenagel condensation between Meldrum's acid (2) and 4-methoxybenzaldehyde (entry 4, 3d) was selected as the model reaction to determine the catalytic amount of guanidine carbonate, (Table 1) and to optimize the reaction conditions, (Table 2) Moderate to poor yields were obtained when reaction was carried out in organic solvents such as methanol, acetonitrile, tetrahydrofuran, ethanol, and dichloroethane (Table 3). Overall results are summarised. (Table 4) The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the solid product (3d) was isolated and characterized by melting point and compared with authentic sample. Table 4 reveals that the Knoevenagel condensation of Meldrum's acid with aromatic aldehydes consisting electron withdrawing groups (entry 2, 5, 6, 9, l2) and electron donating substituents groups (3, 4, 8, 11) in addition to these aldehydes we reports the heterocyclic (entry 7) and unsaturated aldehydes (entry 10) gave well to excellent yields in shorter reaction time when catalyzed by guanidine carbonate under solvent free condition. Hence guanidine carbonate is a more efficient catalyst for the Knoevenagel condensation under solvent free and at room temperature.

***Spectral data for some selected compounds*:**

5-(4-chlorobenzylidene)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione (3b): IR (KBr): 3110, 3005, 2870, 1720, 1695, 1570, 1480, 1385 cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d6): δ, 8.1 (s, 1H), 8.0 -7.0 (m, 4H), 1.6 (s, 6H)

5-(4-N,N-dimethylaminobenzylidene)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione (3c): IR (KBr) 3110, 3005, 2870, 2735, 1720, 1695, 1570, 1480, 1385 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6): δ 8.3 (1H, s), 6.5 - 8.2 (4H, m), 3.2 (6H, s), 1.7 (6H, s).

5-(4-Methoxybenzylidene)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione (3d): IR (KBr): 3110, 2930, 2800, 1740, 1660, 1570, 1440, 1370 cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d6): δ 8.1 (s,1H), 8.0 -7.0 (m, 4H), 1.5 (s, 6H).

5-(4-Hydroxybenzylidene)-2, 2-dimethyl-1, 3-dioxane-4, 6-dione (3k): IR (KBr): 3270, 2950, 2810, 1740, 1690, 1570, 1430, 1380 cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d6): δ 10.6 (br.s,1H), 8.1 (s,1H), 8.0 - 7.0 (m, 4H), 1.6 (s, 6H).

Table 1. Optimization of catalysts for Knoevenagel condensation of Meldrum's acid and aryl aldehydes.[a]

Entry	Catalyst	(mol %)	Time (min.)	Yields[a] (%)
1	-----------	1	60	No reaction
2	DBU	1	60	Trace
3	DABCO	1	60	Trace
4	Guanidine	1	60	Trace
5	Guanidine sulphate	1	60	Trace
6	Guanidine carbonate	1	60	58
7	Guanidine carbonate	5	48	89
8	Guanidine nitrate	1	60	45
9	Guanidine hydrochloride	1	60	52

[a]*p*-Methoxybenzaldehyde (5 mmol), Meldrum's acid (5 mmol), and guanidine carbonate (5 mol %) at room temperature.
[b]Isolated yields of pure products.

Table 2. Optimization of amount of catalyst for Knoevenagel condensation of Meldrum's acid and aryl aldehydes.[a]

Entry	Catalyst (mol %)	Time (min.)	Yield (%) [b]
1	00	60	No reaction
2	1	60	58
3	2	54	62
4	3	50	78
5	4	48	88

6	5	48	89
7	6	48	70
8	7	48	65

[a] Reaction conditions: (3d) 4-Methoxybenzaldehyde (5 mmol), Meldrum's acid (5 mmol), in presence of guanidine carbonate (5 mol%) at room temperature.
[b] Isolated yields.

Table 3: Optimization of solvent for Knoevenagel condensation of Meldrum's acid and aryl aldehydes.[a]

Entry	Solvent	Amount of catalyst (mol %)	Time (min)	Yield (%) [b]
1	No solvent	5	48	89
2	Methanol	5	90	68
3	Acetonitrile	5	130	82
4	Tetrahydrofuran	5	120	60
5	Ethanol	5	60	85
6	Dichloroethane	5	135	58

[a] Reaction conditions: (3d) 4-Methoxybenzaldehyde (5 mmol), Meldrum's acid in presence of guanidine carbonate (5 mol%) at room temperature.
[b] Isolated yields

Table 4. Guanidine carbonate catalyzed Knoevenagel condensation of Meldrum's acid and aryl aldehydes.

Entry	Aldehyde 1	Product 3	Time (Min.)	Yield[b] (%)	M.P. ^{0}C (Lit.)[4,25,26]
1	C_6H_5	3a	60	84	86-88 (85)
2	4-Cl C_6H_4	3b	90	85	158-160 (162)
3	4-Me_2N C_6H_4	3c	60	92	170-172 (173)
4	4-MeO C_6H_4	3d	48	89	121-123(124)
5	4-NO_2 C_6H_4	3e	120	86	214-216(217)
6	2-Cl C_6H_4	3f	80	82	134-136 (133)
7	2-Furyl	3g	140	90	98-100 (97)
8	3-OH C_6H_4	3h	80	73	210-212 (212)
9	2-NO_2 C_6H_4	3i	120	79	115-117 (119)
10	$C_6H_5CH=CH$	3j	180	86	106-108 (109)
11	4-OH C_6H_4	3k	60	84	200-201 (201)
12	3-NO_2 C_6H_4	3l	110	79	118-119 (119)

[a] Reaction conditions: (3d) 4-Methoxybenzaldehyde (5 mmol), Meldrum's acid (5 mmol), in presence of guanidine carbonate (5 mol%) at room temperature.
[b] Isolated yields

4. Conclusion

A simple workup procedure, mild reaction condition, selectivity, low toxicity, good to excellent yields make this methodology a valid alternative to other methods found in the literature for the

Knoevenagel condensation Meldrum's acid and aryl aldehydes.

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