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Knoevenagel Condensation of Aldehydes with Meldrum's Acid in Presence of Phenyl boronic acid as a catalyst

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ABSTRACT

The Knoevenagel condensation of Meldrum's acid with aromatic aldehydes proceeded efficiently at room temperature in the presence of catalytic amounts of Phenyl boronic acid. This approach offers many advantages such as good product yields, short reaction yield, easy isolation of products.

Keywords: Active methylene compounds, Knoevenagel condensation, Meldrum's acid, Phenyl boronic acid, Room temperature.

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INTRODUCTION

Meldrum's acid (1) was first discovered in 1908[1]and its structure was determined as 2,2-dimethyl-1,3-dioxan-4,6-dione by Davidson and Bernhard[2]. Meldrum's acid is an active methylene compound with a rigid cyclic structure that exhibits unusually high acidity (pKa 4.83) [3] and can act as a methylene synthon as a result of hydrolysis, loss of an acetone molecule, and exhaustive decarboxylation[4]. The Knoevenagel condensation (see Figure 1) of Meldrum's acid with aromatic aldehydes (2) produces arylidene derivatives (3), which are 1,1-diactivated alkenes and have received considerable attention as versatile substrates in various types of reactions[5]. Arylidene derivatives may act as acceptors in the 1,4-addition of organometallic reagents[6] and as dienophiles in Diels–Alder and hetero-Diels–Alder reactions, [7] and they can assist in the synthesis of heterocyclic molecules[8] such as coumarines, [9] pyridines, [10] benzothiophenes, benzofuranes, and indoles. [11]

The Knoevenagel condensation of Meldrum's acid (1) with aromatic aldehydes (2) has been carried out using a variety of conditions such as microwave irradiation[12a,b] ultrasound irradiation, [12c] grinding, [13] and thermal heating. [14] Also, a wide range of catalysts such as surfactants, [15] pyridine, [2, 16a] piperidine glacial acetic acid in benzene, [16b,c] modified silica gel, [16d] K_3PO_4 in ethanol, [16e] heterogeneous basic catalysts such as $Zr(O_3POK)$, [16f] and anhydrous $ZnCl_2$ under solvent-free conditions[16g] were utilized to promote the condensation.

The uncatalyzed reaction has been reported at room temperature in highly polar solvents such as dimethyl-sulfoxide (DMSO) and dimethyl formamide (DMF), but these solvents are known to be highly toxic, teratogenic, and suspected carcinogens[17]. Further, this condensation can be complicated by a competing Michael addition of the Meldrum's acid with the resulting arylidene to form a bis-adduct (4).

There are several reports in the literature about the formation of the bis-adduct in the competitive Michael addition, but there is some uncertainty about the structure of substituted aldehydes or the precise reaction conditions that lead to the formation of these bis-adducts[17].

There is growing interest in the development of green chemical processes that are environmentally benign and do not lead to any hazardous by-products or solvent waste.

Therefore, we decided to examine the Knoevenagel condensation of Meldrum's acid with aromatic aldehydes in the presence of Pheyl boronic acid as a catalyst.

MATERIALS AND METHOD

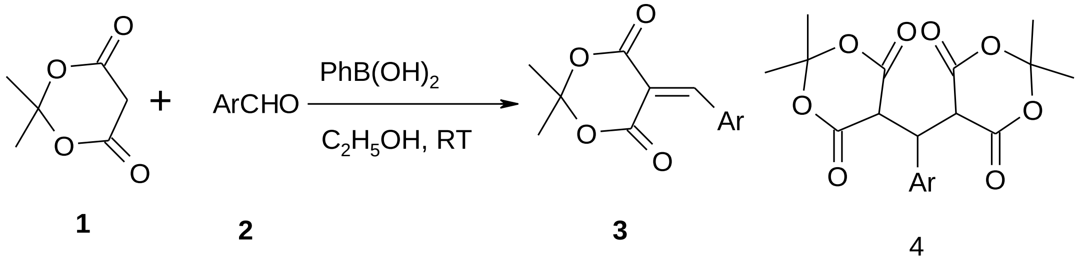
All commercial reagents are used as received without purification, and all solvents were reagent grade. The reaction mixture was stirred magnetically in a round flask and was monitored by TLC using 0.25 mm E-Merck silica gel plates, which were visualized in Iodine Chamber. Melting points were taken in open capillaries. The IR spectra were recorded on a perkin-Elmer 257 spectrometer using KBR discs. ^{1}H NMR in d$_6$on 300 MHz using TMS as an internal standard.

EXPERIMENTAL

General procedure for synthesis of arylidene Meldrum's acid

A mixture of aromatic aldehyde (2mmol), Meldrum's acid (2mmol), $PhB(OH)_2$ (10 mol%) and Ethanol(10ml) were stirred for 15-20 min at RT. The reaction progress was monitored by TLC. After the completion of the reaction, hot ethanol was added to the mixture and the catalyst was filtered off. After drying it was purified by recrystallization from hot ethanol, pure products were obtained. Spectral data of some products are given below.

Scheme 1



RESULTS AND DISCUSSION

The optimum condition was established by considering a reaction between benzaldehyde, and Medrum's acid as model reaction. It was performed in the presence of anhydrous Phenyl borornic acid as a catalyst with ethanol as a solvent**. (Scheme 1)**

The reaction between Meldrum's acid and 4-Nitro benzaldehyde in Phenyl boronic acid and solvent Ethanol was studied as a model reaction to select the most efficient solvent. A proper solvent for the reaction was selected by investigating the effect of different solvents on reaction time and yield of product for model reaction. We observed that the reaction time was long and yield of the corresponding product was low when the reaction was performed in solvents of low polarity (Table 1, Entries 1 and 2). Even in CH_3CN the reaction time and yield were not satisfactory (Table 1, Entry 3). The reaction gave maximum yield of product in short time period when it was performed in polar solvent such as C_2H_5OH (Table1, Entry-4)

Table 1: Investigation of solvent effect for the synthesis of Arylidene Meldrum's acid

Entry	Catalyst	Solvent	Time (min)	Yield[a] (%)
1	anhydrous $PhB(OH)_2$	$CHCl_3$	65	78
2	anhydrous $PhB(OH)_2$	CH_2Cl_2	50	72
3	anhydrous $PhB(OH)_2$	CH_3CN	55	83
4	anhydrous $PhB(OH)_2$	C_2H_5OH	45	92

[a]Isolated Yields

On the basis of results as shown in Table 1. C_2H_5OH was selected as the most appropriated solvent for ***Scheme1.***

To explore the versatility of the reaction, we selected a variety of substituted benzaldehydes and hetero-aromatic aldehydes and conducted condensation reactions with Meldrum's acid in Ethanol in the presence of catalytic amounts of phenyl boronic acid. The results are shown in Table 2. We did not find any difference in reactivity among substituted benzaldehydes based on isolated yields, because both activating and deactivating groups seem to work well in this set of conditions.

Table 2: **Synthesis of different arylidene Meldrum's acid derivatives using Phenyl boronic acid.**

Entry	Ar	Product	Yield (%)	M.P
1	$4\text{-}ClC_6H_4$	3a	92	154-156
2	$2\text{-}ClC_6H_4$	3b	85	134-135
3	$4\text{-}HOC_6H_4$	3c	94	194-196
4	$4\text{-}MeC_6H_4$	3d	97	113-115
5	$4\text{-}MeOC_6H_4$	3e	96	124-125
6	$2\text{-}MeOC_6H_4$	3f	98	101-103
7	$2,4\text{-}(MeO)_2ClC_6H_3$	3g	97	124-126
8	$4\text{-}Me_2NC_6H_4$	3h	96	174-176
9	$4\text{-}NO_2C_6H_4$	3i	92	215-217
10	$2\text{-}NO_2C_6H_4$	3j	85	118-119

The only issue we encountered during our investigation was with benzaldehyde in all our attempts, the bis-adduct (4) was isolated as the sole product. However, we did not find any bis-adduct when the substituted benzaldehydes were used in the reaction.

Spectral analysis of selected arylidene Meldrum's acid derivatives

5-(4-Dimethylaminobenzylidene)-1,1-dimethyl4,6-dioxo-1,3-dioxane(3h). Mp 162^0C, lit. 162–164;

IR(KBr): n¼1700, 1613, 1542, 1506, 1372, 1290, 1162 cm

^{1}H NMR($CDCl_3$/DMSO-d_6),$-8.31 (s, 1H), 8.22 (cd, 2H),6.71 (cd, 2H), 3.11 (s, 6H), 1.72 (s, 6H);

^{13}C NMR (CDCl$_3$/DMSO-d$_6$) $-165.2, 161.4, 158.0, 154.5, 138.9(2C), 120.2, 111.3 (2C), 105.1, 103.4, 40.0 (2C), 27.3 (2C).

5-(4-Hydroxybenzylidene)-1,1-dimethyl-4,6-dioxo1,3-dioxane(3c). Mp 193^{0}C, lit.192–194^{0}C; IR (KBr):n¼3273, 1748, 1697, 1586, 1574, 1450, 1394, 1278 cm

^{1}H NMR(CDCl$_3$/DMSO-d$_6$),$-10.62 (broad signal,1NH), 8.26 (s, 1H), 8.12 (cd, 2H), 6.90 (cd, 2H), 1.76 (s,6H)

^{13}C NMR (CDCl$_3$/DMSO-d$_6$) $-162.7, 162.2, 158.9, 156.2, 136.6(2C), 108.0, 102.2, 25.8(2C).

CONCLUSION

The Knoevenagel condensation between aromatic aldehydes with Meldrum's acid can be effectively performed at room temperature with Ethanol in the presence of catalytic amount of Phenyl boronic acid to provide a simple and efficient method for the synthesis of arylidene Meldrum's acid. This method has many advantages compared to the methods reported in the literature.

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