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Efficient synthesis of Benzylidenethiazolidine-2, 4-dione derivatives using organo catalyst (DABCO) in aqueous media via simple Knoevenagel condensation reaction

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Abstract

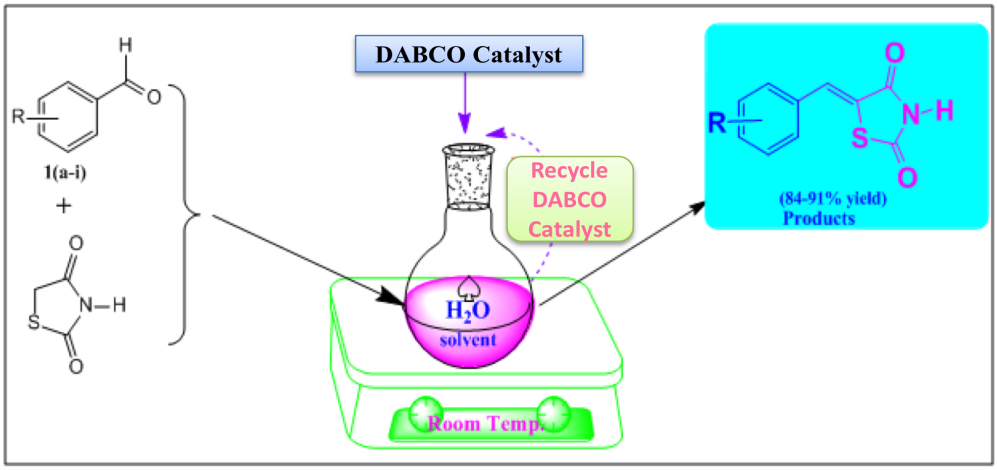
A simple, selective and environment-friendly procedure has been developed for simple Knoevenagel condensation reaction between aromatic aldehydes and active methylene compound (Thiazolidine-2,4-dione) using 1,4-diazabicyclo[2.2.2]octane (DABCO) as an efficient organocatalyst in the presence of aqueous ethanol solvent. The current methodology has the advantages of operational simplicity, mild reaction conditions and good to high yield of the products (84-91%). The synthetic method is simple as no special apparatus for work up are required and the compound formed is filtered and purified just by simple crystallization. The structure of different substituents containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as hydroxyl group, alkoxyl group) did not showed strongly obvious effects in terms of reaction time and yield of products. Products are characterized by IR, ^{1}HNMR, ^{13}CNMR, mass spectral analysis and are in a state of high purity.

1. Introduction

Knoevenagel reaction is a characteristic carbon and carbon bond formation reaction in organic chemistry [1, 2]. These reactions were first demonstrated by Emil Knoevenagel in 1894 between aldehydes/ketones and active methylene compounds. The synthesis of new heterocyclic compounds has been subject of great interest due to their wide applicability in the past few decades. The main objective of an organic and medicinal chemistry in present and future research is to design, synthesize and develop molecules possessing significant pharmacological outcome. Benzylidenethiazolidine-2,4-dione derivatives are biologically active heterocyclic compounds having five membered rings containing N and O as bioactive heteroatoms with multiple broad spectrum of biological activities including antimicrobial [3], antidiabetic [4], antiobesity [5], anti-inflammatory [6], antiproliferative [7] and antitumor activity. Recently, organocatalyst has increased extremely in the last few years as a result of both the novelty of the concept and more importantly, the efficiency and the selectivity of many organocatalyst reactions meet the standards of recognized organic reactions. One of these organo catalysts is the 1,4-diazabicyclo[2.2.2]octane (DABCO) which has received considerable attention as an inexpensive, eco-friendly, high reactive and non-toxic base catalyst for various organic synthesis, affording the products in excellent yields with high selectivity [9].

There are several methods reported in the literature for the synthesis of benzylidenethiazolidine-2, 4-dione derivatives. such as, sodium acetate in acetic acid under reflux conditions [10], sodium acetate in acetic acid under microwave irradiation [11], piperidine in ethanol under reflux conditions [12–14], piperidinium acetate in DMF under microwave irradiation [15], glycine and sodium carbonate in H2O under reflux conditions [16], grinding with ammonium acetate in the absence of solvents [17], $KAl(SO4)_2 \cdot 12H_2O$ in H_2O at 90°C [18], baker's yeast [19] and polyethylene glycol-300 at 100–120◦C [20]. Reported methods in the literature usually require forcing conditions, long reaction time, create wastes and involved organic solvents as well high energy to proceed. To the best of our knowledge, 1,4-diazabicyclo[2.2.2]octane (DABCO) has not been used as a catalyst for the synthesis of benzylidenethiazolidine-2, 4-dione derivatives and attracted our attention to investigate the application of DABCO as an efficient organocatalyst. The development of environmentally

benign and clean protocol has become the goal of synthetic methodology. Aqueous ethanol (ethanol:water) in place of organic solvents was used besides being non-hazardous, cheap, readily available and simple to handle. Therefore, we describe here a rapid, green, economically viable and easy protocol for the synthesis of benzylidenethiazolidine-2, 4-dione derivatives using DABCO as efficient organocatalyst via Knoevenagel condensation reaction in aqueous media (Scheme 1).



Scheme 1. Synthesis of substituted Benzylidenethiazolidine-2,4-dione derivatives.

2. Material and Methods

All chemicals were obtained from Merck and S.D. Fine Chem. Co. and used without further purification. Melting points were determined by open capillary method and were uncorrected. IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer using KBr pellet. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker instrument (^{1}H at 400 MHz and ^{13}C at 100 MHz) in DMSO-d_6 solvent and TMS as internal standard. Chemical shifts are reported in ppm. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. Reactions have been monitored by thin layer chromatography on 0.2-mm precoated plates of silica gel G60 F254 (Merck).

General procedure for the synthesis of Benzylidenethiazolidine-2, 4-dione derivatives

Substituted aromatic aldehydes **1** (1m mol) and active methylene compound (Thiazolidine-2,4-dione) 2 (1m mol) using 10 mole% organocatalyst 1,4-diazabicyclo[2.2.2]octane (DABCO) were taken in RB flask with 20 ml aqueous media(1 :1 ratio). The reaction mixture was stirred for 37-42 mins at room temperature and progress of reaction was monitored by TLC. The solid product was filtered, washed with cold water and recrystallized from ethanol to obtain pure Benzylidenethiazolidine-2, 4-dione derivatives with excellent yields (**84-91%**)

2.2. *Spectral data for synthesized* Benzylidenethiazolidine-2, 4-dione derivatives (**3a-i**)

2.2.1. (Z)-5-(4-methylbenzylidene) thiazolidine-2,4-dione **3a**

IR (KBr, *v* cm^{-1}): 3163 (NH), 1732, 1652 (C=O), 1461 (C=C), 795 (C-S-C str.). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.20 (s, 1H, NH), 7.20-7.39 (m, 4H, aromatic), 6.73 (s, 1H, CH), 2.91 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ =167.11 (C=O), 157.23 (C=O), 140.04 (C-CH3), 131.23 (C-5), 129.21 (C-6), 129.11 (C-4), 128.21 (C-1), 128.01 (C-3), 121.15 (C-8), 21.67(CH3) ppm; EI-MS (*m/z*): 218 [M^{+}]

2.2.2. (Z)-5-benzylidene)thiazolidine-2,4-dione **3b**

IR (KBr, *v* cm^{-1}): 3209 (NH), 1711, 1653 (C=O), 1429 (C=C), 791 (C-S-C str.). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.19 (s, 1H, NH), 7.31-7.39 (m, 5H, aromatic), 6.75 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ =166.13 (C=O), 158.65 (C=O), 132.11 (C-5), 130.09 (C-2), 129.37 (C-4), 128.85 (C-1), 128.23 (C-3), 127.31 (C-7), 120.15 (C-8) ppm; EI-MS (*m/z*): 204 [M^{+}]

2.2.3. (Z)-5-(4-methoxybenzylidene)thiazolidine-2,4-dione **3c**

IR (KBr, *v* cm^{-1}): 3126 (NH), 1789, 1637 (C=O), 1548 (C=C), 789 (C-S-C str.). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.21 (s, 1H, NH), 7.38-7.40 (m, 2H, aromatic), 7.22-7.25 (m, 2H, aromatic), 6.73 (s, 1H, CH), 4.67 (s, 2H, CH_2), 4.29 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ =167.21 (C=O), 161.63 (C-OCH3), 152.23 (C=O), 130.83 (C-6), 129.17 (C-4), 127.31 (C-7), 125.62 (C-5), 120.12 (C-8), 114.34 (C-1), 113.21 (C-3), 56.03 (CH3) ppm; EI-MS (*m/z*): 232 [M^{+}]

2.2.4. (Z)-5-(3,4-dimethoxybenzylidene)thiazolidine-2,4-dione **3d**

IR (KBr, *v* cm^{-1}): 3139 (NH), 1764, 1605 (C=O), 1467 (C=C), 788 (C-S-C str.). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.23 (s, 1H, NH), 7.08-7.32 (m, 3H, aromatic), 6.81(s, 1H, CH), 4.95 (s, 2H, CH_2), 4.78 (s, 2H, CH_2), 4.39 (s, 1H, OH), 4.34 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ =161.23 (C=O), 151.87 (C=O), 149.05 (C-OCH3), 138.11 (C-OCH3), 126.54 (C-5), 125.01 (C-7), 124.12 (C-6), 118.78 (C-8), 113.42 (C-1), 112.51 (C-4), 56.78 (CH3), 55.39 (CH3) ppm; EI-MS (*m/z*): 264 [M^+]

2.2.5. (Z)-5-(4-hydroxybenzylidene)thiazolidine-2,4-dione **3e**

IR (KBr, *v* cm^{-1}): 3121 (NH), 1749, 1636 (C=O), 1462 (C=C), 790 (C-S-C str.). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.20 (s, 1H, NH), 9.41 (s, 1H, OH), 7.31-7.32 (m, 2H, aromatic), 6.73-6.86 (m, 2H, aromatic), 6.67(s, 1H, CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ =159.12 (C=O), 147.76 (C-OH), 142.58 (C=O), 132.48 (C-5), 131.67 (C-4), 130.09 (C-6), 127.32 (C-7), 124.63 (C-5), 120.15 (C-8), 115.04 (C-1), 114.39 (C-3) ppm; EI-MS (*m/z*): 218 [M^+]

2.2.6. (Z)-5-(4-chlorobenzylidene)thiazolidine-2,4-dione **3f**

IR (KBr, *v* cm^{-1}): 3146 (NH), 1741, 1647 (C=O), 1457 (C=C), 794 (C-S-C str.). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.69 (s, 1H, NH), 7.37-7.43 (m, 4H, aromatic), 6.41 (m, 1H, CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ =161.17 (C=O), 149.45 (C=O), 135.58 (C-Cl), 132.48 (C-5), 130.33 (C-4), 129.13 (C-6), 129.34 (C-1), 128.11 (C-3), 127.21 (C-7), 120.12 (C-8) ppm; EI-MS (*m/z*): 239 [M^+]

2.2.7. (Z)-5-(4-nitrobenzylidene)thiazolidine-2,4-dione **3g**

IR (KBr, *v* cm^{-1}): 3129 (NH), 1723, 1631 (C=O), 1472 (C=C), 789 (C-S-C str.). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.73 (s, 1H, NH), 8.24-8.26 (m, 2H, aromatic), 7.02-7.19 (m, 2H, aromatic), 6.01(s, 1H, CH) ppm; EI-MS (*m/z*): 248 [M^+]

2.2.8. (Z)-5-(3-nitrobenzylidene)thiazolidine-2,4-dione **3h**

IR (KBr, *v* cm^{-1}): 3142 (NH), 1708, 1667 (C=O), 1466 (C=C), 793 (C-S-C str.). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.02 (s, 1H, NH), 8.59 (s, 1H, aromatic), 8.17 (s, 1H, aromatic), 8.24-8.26 (m, 2H, aromatic), 7.64-7.59 (m, 2H, aromatic), 6.94 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ =162.09 (C=O), 152.31 (C=O), 147.21 (C-NO2), 136.16 (C-6), 133.21 (C-5), 129.42 (C-1), 126.10 (C-2), 125.34 (C-7), 125.35 (C-4), 118.11 (C-8) ppm; EI-MS (*m/z*): 248 [M^+]

2.2.9. (Z)-5-(3-hyroxybenzylidene)thiazolidine-2,4-dione **3i**

IR (KBr, *v* cm^{-1}): 3137 (NH), 1721, 1634 (C=O), 1409 (C=C), 792 (C-S-C str.). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.23 (s, 1H, NH), 9.28 (s, 1H, OH), 6.84-7.25 (m, 4H, aromatic), 6.76 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ =167.13 (C=O), 159.24 (C=O), 156.31 (C-OH), 134.72 (C-5), 130.77 (C-1), 125.56 (C-7), 122.74 (C-6), 119.72 (C-2), 118.78 (C-8), 117.04 (C-4) ppm; EI-MS (*m/z*): 219 [M^+]

3. Results and discussion

We have reported the synthesis of benzylidenethiazolidine-2, 4-dione derivatives (3a-i) via simple Knoevenagel condensation reaction of substituted aromatic aldehydes 1 and active methylene compound (Thiazolidine-2,4-dione) 2 (1m mol each) using 10 mole% organocatalyst 1,4-diazabicyclo[2.2.2]octane (DABCO) in aqueous media (Table 1).

Table 1: Synthesis of Benzylidenethiazolidine-2,4-dione derivatives (**3a-i**).

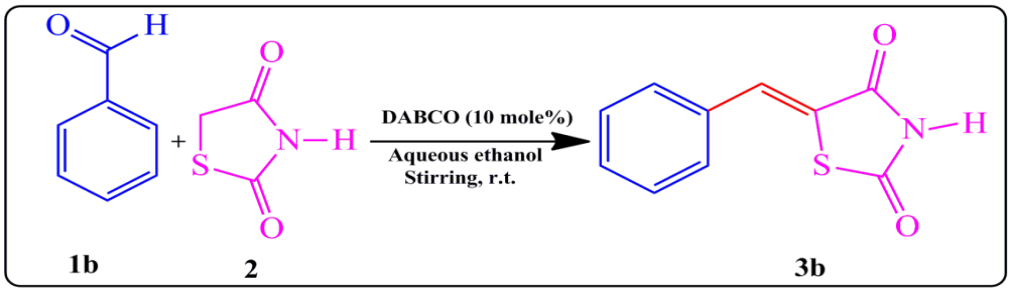
Entry	R	Product[a]	Yield (%)[b]	Time (min)	M.p.(˚C)
1	4-CH_3	**3a**	89	30	103-105
2	H	**3b**	91	27	87-89
3	4-OCH_3	**3c**	86	40	107
4	3, 4-OCH_3	**3d**	84	42	126-128
5	4-OH	**3e**	92	32	111-113
6	4-Cl	**3f**	88	41	109
7	4-NO_2	**3g**	87	35	123-125
8	3-NO_2	**3h**	86	37	131-133
9	3-OH	**3i**	87	35	118-120

[a]All products were identified by their physical and spectral data; [b]Isolated yields

Further, we have focused on systematic estimation of different solvents like aqueous ethanol, H_2O, DMF, DMSO and solvent less (Table 2, entry 1-5), for the synthesis of model product 3b using reaction mixture benzaldehyde, active methylene compound (Thiazolidine-2,4-dione) and 10 mole% organocatalyst 1,4-

diazabicyclo[2.2.2]octane (DABCO) were taken in RB flask using 20 ml aqueous ethanol solvent (1 :1 ratio) Table 2**.** The results indicated that the solvent has a significant effect on the product yield and completion of reaction time. We found that the best conversion was observed when the reaction was proceded in Ethanol:H_2O (Table 2, entry 1). The use of aqueous ethanol as solvent in the reaction medium exhibits a remarkable benefit such as, environmentally safe, devoid of any carcinogenic effects, comparatively cheaper to operate and simple work up. We further reported the reaction under solvent less conditions and found that it takes more time for reaction completion (47 minutes), further the yield of product is less amount 66% (Table 2, entry 5). In order to optimize the different amount of DABCO catalyst like 5 mole%, 10 mole%, 15 mole% for synthesis of model product 3b. We found that 10 mole% DABCO catalysts were proficient in furnishing the desired model product 3b in terms of reaction time and product yields (Table 3, entry 2). In the absence of catalyst, the reaction was complete after 48 minutes and yield of product only 61% (Table 3, entry 4).

Table 2: Optimization of different solvents for the synthesis of **3b** model product



Entry	Solvent	Time (min)	Yield (%)[a]
1	**EtOH:H_2O**	**27**	**91**
2	Water	35	71
3	DMF	32	67
4	DMSO	37	62
5	Solvent less	47	66

[a]Isolated yields.

Table 3: Optimization of DABCO (mol %) for synthesis of **3b** model product in aqueous ethanol[a].

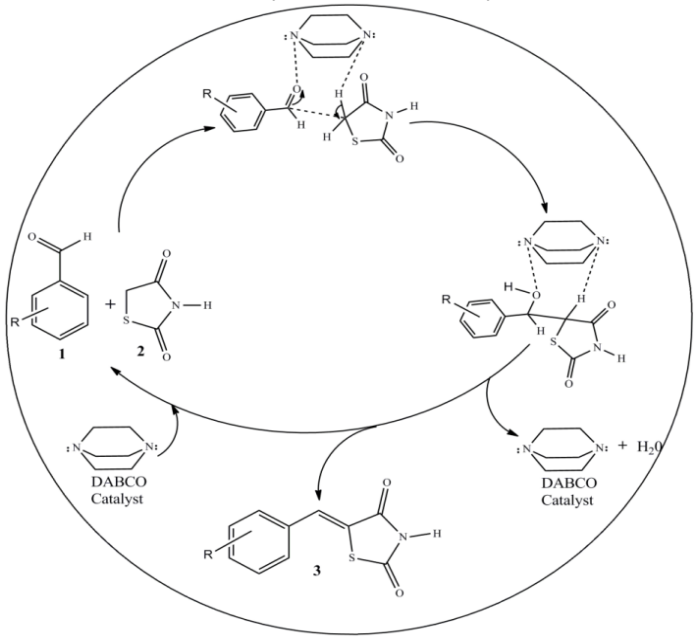
Entry	DABCO (mol%)	Time (min)	Yield (%)[b]
1	5	25	87
2	10	27	91
3	15	31	79
4	No catalyst	48	61

[a]Reaction condition: benzaldehyde (1 mmole) and Thiazolidine-2,4-dione **2** (1 mmol) using 20 ml aqueous ethanol solvent (1 :1 ratio). [b]Isolated yields.

The structural assignment of model product 3b was confirmed by IR, ^{1}HNMR, ^{13}CNMR and mass spectrometric analysis. The IR spectra exhibited sharp absorption bands at 3209, 1711- 1653, 1429, 791 cm^{-1}. Which are attributed to NH, C=O), C=C and (C-S-C str.). In the ^{1}H NMR spectrum of compound 3b**,** it showed the peaks at δ 11.19 (s, 1H, NH), 7.31-7.39 (m, 5H, aromatic protons) and 6.75 (s, 1H, CH) ppm; ^{13}C NMR spectrum of the compound **3b** showed 10 significant signals were recorded at δ 166.13 (C=O), 158.65 (C=O), 132.11 (C-5), 130.09 (C-2), 129.37 (C-4), 129.01(C-6), 128.85 (C-1), 128.23 (C-3), 127.31 (C-7), 120.15 (C-8) ppm; Molecular ion peak was observed in agreement with molecular weight of compound EI-MS (*m/z*): 204 [M^+]. Results indicated that a series of substituted aromatic aldehydes were successfully employed to prepare the corresponding product in excellent yields (83–94%) and there is no major effect on the yield of product by electron donating/withdrawing substituents.

1,4-diazabicyclo[2.2.2]octane (DABCO) is a nitrogen type catalyst which facilitates proton removal from active methylene compounds thereby increases reaction rate yields of desired products. Mechanistically, (DABCO) facilitate Knoevenagel condensation of substituted aromatic aldehydes with active methylene compound (Thiazolidine-2,4-dione) by loss of water molecule that leads to the formation of the targeted products. Plausible

mechanism for the synthesis of benzylidenethiazolidine-2, 4-dione derivatives is shown in Scheme 2



Scheme 2. Proposed mechanism for the synthesis of Benzylidenethiazolidine-2,4-dione derivatives

Conclusion

In conclusion, we have reported an efficient procedure for the synthesis of Benzylidenethiazolidine-2, 4-dione derivatives using aqueous ethanol as solvent and 1, 4-diazabicyclo[2.2.2]octane (DABCO) as organocatalyst. The synthetic method is simple as no special apparatus for work up are required and the compound formed is filtered and purified just by simple crystallization using 95% ethanol as solvent. The current methodology has the advantages of operational simplicity, mild reaction conditions and good to high yield of the products (**84-91%**).

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