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An Efficient multicomponenet synthesis of Tetrahydrobenzo Pyrans

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ABSTRACT

The one-pot, three-component tandem Knoevenagel–cyclocondensation reaction of dimedone malononitrile and different aldehydes was catalyzed by sodium oxalte for the first time in this work. After being heated at a temperature 50°C in EtOH:wate (1:1), these compounds underwent cyclization, yielding the corresponding tetrahydrobenzo[b]pyrans that are useful to medicininal field. Because the developed method doesn't require specialist equipment like microwaves, or ultrasounds, etc the approach is adaptable and convenient. Green reaction conditions, the use of commercially available catalyst, easy workup, and comparatively shorter reaction periods are also noteworthy aspects of this high-yielding protocol.

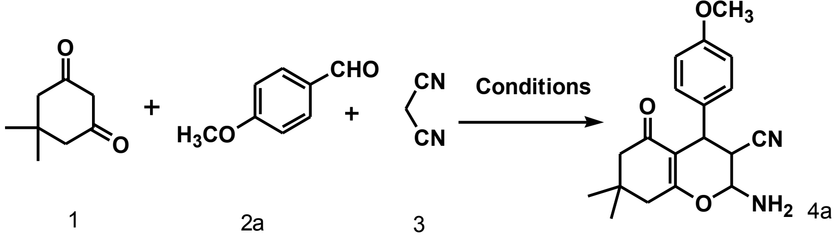
I. INTRODUCTION

The majority of naturally occurring substances having heterocyclic rings are very important in terms of their biological activity. Benzopyran is an example of a heterocyclic compound that has oxygen as a heteroatom and its annulated heterocyclics, such as chromenes, that exhibit important biological functions [1-3]. Among the qualities shown by the compounds containing benzopyran are, anticancer [4], diuretic [5], anti-inflammatory [6], anticoagulant [7], anti-HIV [8], anti viral [9], antitumoral [10], antimalarial [11], antihyperglycemic, and antidyslipidemic [12]. Some of the biological activities that are exhibited along with therapeutic activity towards anti-neurodegenerative disordersare Alzheimer's, Huntington's and Parkinson disease [13-15]. The multicomponent synthesis of tetrahydrobenzo[b]pyrans involve the reaction of dimedone , 4-OMe benzaldehyde, and malononitrile which was performed under a variety of conditions, which includes use of ultrasonic irradiation [16], microwaves [17] and different catalysts reagents such as DABCO [18], heteropolyacids [19], diammonium hydrogen phosphate [20], DMAP [21], acidic and basic ionic liquids [22], ZnO-β-Zeolite [23] and many more [24-27]. Even though these techniques have significant advantages, several of them nevertheless have drawbacks, including high temperatures, poor yields, the use of toxic solvents, lengthy reaction times, and high catalytic loading. Thus, the development of a practical, safe and more widespread method to get beyond these drawbacks continues to be a problem for organic chemists who need to prepare 2-amino-3-cyano-4H-pyrans. Therefore, here we report for the first time convenient sodium oxalate catalyzed multicomponent reaction of an aldehydes, malonitrile and dimedone for the synthesis of 2-amino-3-cyano-4H-pyrans in the presence of Water: EtOH. sodium oxalate was utilized as an efficient oraganocatalyst in this reaction. Additionally, since most organic solvents are hazardous or flammable and significantly raise the cost of overall synthesis, developing chemical reactions in aqueous or aqueous/organic media has garnered a lot of attention recently. Since water is an environmentally benign reaction medium, it must be used in place of costly and hazardous organic solvents. In this case, the aqueous ethanol medium was used as a low-cost, secure, and environmentally beneficial method.

II. RESULTS & DISCUSSION

The synthesis of tetrahydrobenzo[b]pyrans (4a-f), using sodium oxalte has never been reported before. In order to optimize the reaction conditions, dimedone (1), 4-OMe benzaldehyde (2a), and malononitrile (3) were initially selected as the model substrates. Reaction temperatures, the role of solvents, and impact of catalyst loading were investigated. (Table 1).

Table 1: Optimization of reaction conditions.

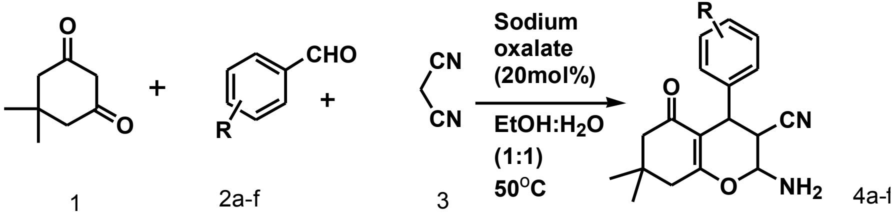


Sr. No	Solvent	Amount of Catalyst (mol%)	Temperature (°C)	Time (min)	Yield (%)
1	ACN	20	R.T	180	Trace
2	ACN	20	Reflux	180	Trace
3	DCM	20	Reflux	180	Trace
4	EtOH	20	R.T	180	30
5	EtOH	20	Reflux	120	45
6	Water	20	Reflux	120	20
7	EtOH:Water (1:1)	20	Reflux	60	89
8	EtOH:Water (1:1)	20	50 °C	60	90
9	EtOH:Water (1:1)	30	Reflux	60	89
10	EtOH:Water (1:1)	10	Reflux	60	70

The most efficient catalyst loading, according to the results, was 20 mol% sodium oxalte, which produced greater yields (91%) in shorter reaction time (60 min). The best solvent was found to be EtOH:Water (1:1) at a temperature 50 °C out of a variety of solvents that were used, including acetonitrile, dichloromethane, ethanol, and water. Consequently, the optimized reaction conditions were 20 mol% sodium oxalte in EtOH:Water (1:1) at a temperature 50 °C within 60 minutes (Table 1, entry 8).

After finding the proper reaction parameters, we studied the scope of this three component reaction by varying different aromatic aldehydes (Table 2, entry 1-6). The reactions proceeded efficiently under green reaction conditions. Interestingly, almost all the substrates gave the required tetrahydrobenzo[b]pyrans (4a-f) in good to excellent yields of 86-91% within the specified time (Table 2, entry 1-6).

Table 2: Synthesis of tetrahydrobenzo[b]pyrans (4a-f).



Entry	Product	R	Reaction Time (min)	Yield (%)[a]	Melting point (mp, °C)	
					Observed	Literature
1	4a	4-CH_3O	60	91	202-204	199-201[25]
2	4b	H	80	90	228-230	224-226[24]
3	4c	3-NO_2	80	86	212-214	204-206 [24]
4	4d	2-Cl	90	87	200-202	189-190 [26]
5	4e	4-Cl	60	88	213-215	215-217[25]
6	4f	4-CH_3	60	90	214-216	208-210 [27]

[a] Isolated Yields

IV. CONCLUSION

In conclusion, sodium oxalate found to be an effective catalyst for the one-pot synthesis of tetrahydrobenzo[b]pyrans (4a-f) in aqueous ethanol. This work offers a number of significant advantages over published protocols, including the use of metal-free catalyst, short reaction time, high yields, eco- friendly reaction conditions, and the lack of harmful organic solvents.

Experimental section

Material and methods

All of the chemicals and solvents used for present study were used of AR grade and used without further purification. The melting points were determined in open capillary tubes with no corrections. A Bruker Advance NEO 500MHZ spectrometer was used to record NMR spectra. Formation of the compounds was checked by thin-layer chromatography (TLC) on aluminum sheets with silica gel.

Typical Procedure for the synthesis of tetrahydrobenzo[b]pyrans (4a-f).

In a 25 mL round bottom flask (RBF) a mixture of an aromatic aldehyde 2 (1.0 mmol), malonitrile 3 (1.1mmol) and sodium oxalate (20 mol%) in 5 mL EtOH:H_2O (1:1) was stirred for 10 minutes at room temperature. After that dimedone **1** (1mmol) was added to the reaction mixture. The reaction mixture was stirred at 50 °C for the appropriate time (Table 2, entries 1-6). With the use of TLC, the reaction's progress was monitored. After completion of the reaction, the reaction mixture was cooled to room temperature. 5mL water was added and stirring was continued until a solid mass precipitated out that was filtered followed by washing with water to obtain crude product. The obtained product was washed with a mixture of hexane : Ethyl acetate (80:20) and dried to afford the final pure products.

Spectral Data:

III.

2-Amino-4-(4-methoxy-phenyl)-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-3-carbonitrile (4a):

M. p. 202-204°C; 1HNMR (DMSO, 500 MHz)/δ (ppm): 7.04-7.05 (d, 2H), 6.82 (s, 2H), 6.84-6.93 (d, 2H), 4.11 (s, 1H), 3.71 (s, 3H), 2.22 (d, 1H), 2.07 (d, 1H), 1.03 (s, 3H), 0.94 (s, 3H).; ^{13}C NMR (DMSO, 100 MHz)/ δ (ppm): 196.52, 162.00, 158.29, 157.80, 136.73, 128.09, 119.66, 113.55.

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