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Dibutylamine-catalyzed efficient one-pot synthesis of biologically potent pyrans

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ABSTRACT

An expedient, eco-friendly, and efficient procedure for the preparation of novel pyran derivatives have been developed through a solvent-free, one-pot reaction of various aldehydes, malononitrile, and either methylacetoacetate or ethyl benzoylacetate in the presence of dibutylamine (2.5 mol%) at room temperature. This procedure is advantageous because it is mild, environmentally friendly, gives high yields, and requires short reaction times. Furthermore, the product did not necessitate separation via extraction and column chromatography.

1. Introduction

Sustainable chemistry emphasizes the development of operationally simple and eco-friendly routes to the synthesis of biologically potent organic and medicinal compounds, which are the most significant objective compounds in synthetic chemistry. Conducting reactions in the absence of a solvent (i.e., neat conditions) is an important aspect of green chemistry;[1,2] furthermore, the completion of various transformations via a single process is highly compatible with the goals of green chemistry. A one-pot reaction in which three or more reactants combine to form a new compound without isolation of any intermediate is known as a multi-component reaction (MCR)[3] and is highly attractive because of their ability to generate two or more C–C, C–N, or C–O bonds in a single step.

Organocatalysis is presently one of the fastest growing fields of research in organic chemistry.[4] Even though chemical transformations that use organic catalysts, or organocatalysts, are currently standard and have been over the last century, the application of small natural molecules as organocatalysts in MCRs for diversity-oriented syntheses (DOSs) offers many advantages; e.g., they do not require moisture-sensitive Lewis acids, air-sensitive reagents, toxic metals, nor an inert atmosphere.

Synthetic heterocyclic compounds are most important in the fields of organic and medicinal chemistry because these compounds have a broad range of pharmacological applications. Pyrans are an important class of oxygen heterocycles that have various biological properties such as anti-leishmanial,[5] anti-HIV,[6] antioxidant,[7] anti-tumor,[8] and central nervous system (CNS) activities and effects;[9] they are also used for treatment of Alzheimer's disease[10] and schizophrenia.[11] Furthermore, some pyran derivatives have also been used for the preparation of laser dyes,[12]cosmetics and pigments,[13] agrochemicals,[14] nonlinear optical (NLO) properties,[15] photo chromic materials,[16] and photovoltaic application.[17,18] In addition, they also serve as intermediates for the synthesis of organic compounds, including lactones, imidoesters,[19] polyazanaphthalenes,[20] pyridin-2-ones,[21] pyrano[2]-pyrimidines,[22] and pyranopyridinederivatives.[23] The generation of pyrans are of significant interest given their wide range of applications. A variety of catalytic methods have been reported for the synthesis of pyrans; these include heterogeneous catalysis,[24–26] ionic liquids,[27] and base-promoted reactions under microwave irradiation[20] and thermal heating[28]. Chemical reactions under microwave irradiation at high temperatures in the presence of acids or metal catalysts are favourable for side reactions such as Knoevenagel condensation (KC) that form byproducts. Hence, the development of similar milder and environmentally sustainable procedures for the preparation of pyrans is needed.

Currently, reactions conducted under neat conditions were used for the synthesis of various chemicals. Furthermore, the cost effectiveness and reaction rates of various organic transformations are also being improved. The most significant goals of sustainable chemistry are to reduce the use of organic solvents, toxic reagents, and laborious work-up procedures associated with the synthesis of compounds. An extensive survey of the literature revealed that there are, to the best of our knowledge, no reports on the synthesis of pyrans promoted by a dibutylamineorganocatalyst. This is a continuation of our ongoing research interest in the growth of efficient, inexpensive, and new methodologies.[29–34] Herein, we report the eco-friendly one-pot synthesis of pyrans through a three-component condensation of aldehyde, malononitrile (MN), and methylacetoacetate (MAA) or ethyl benzoylacetate (EBA) in

the presence of a dibutylamineorganocatalyst under neat conditions at room temperature

2. Results and discussion

Generally, MCRs require elevated reaction temperatures, long reaction times, and high catalyst loading to promote the formation of the desired product. One-pot three-component reactions of aldehyde, MN, and MAA or EBA (1 mmol each) were first attempted using various types of catalysts at room temperature using the solvent-free method (Table 1). First, the experiments were performed in the absence of catalyst at room temperature for 14 h using the solvent-free method; however, no product formed (entry 1). Then, we tried acidic species such as $ZnCl_2$, $ZrOCl_2$, $ZrOCl_2{\cdot}SiO_2$, $BF_3{\cdot}OEt_2$, $BF_3{\cdot}SiO_2$, silica-supported $ClSO_3H$, and trifluoroacetic acid at room temperature for 6 h of reaction, which proved ineffective, whereas the same catalysts at 100 ℃ over 6 h of reaction resulted in relatively low product yields (entries 2–8). The addition of metal salts such as $Mg(ClO_4)_2$ and $Y(CF_3COO)_3{\cdot}nH_2O$ was also ineffective (entries 9 and 10). On the other hand, with heterogeneous catalysts like dimethylaminopyridine (DMAP) and diazabicycloundecene (DBU), a mixture of pyrans and KC products were observed in all cases based on thin-layer chromatography (TLC) analysis of the reaction mixture after 5 h. After stirring continuously for an additional hour, the mixture of products remained and very low yields of products were obtained (entries 11 and 12). We also attempted the reaction in the presence of base catalysts such as piperazine, pyrrolidine, morpholine, dimethylamine, and dibutylamine (DBA) (entries 13–17) with very similar pKa values, which were equally efficient at furnishing the desired product with good yields. Among these basic catalysts, dibutylamine furnished the product in the highest yield and shortest reaction time; the results are summarized in Table 1.

Table 1. Effect of various catalysts on the synthesis of compound **1** in the absence of solvent at room temperature.[a]

Entry	Catalyst	Catalyst amount (mol%)	Time (h)	Yield (%)[b]
1	Catalyst free	-	14	nr[c]
2	$ZnCl_2$	5	3	30
3	$ZrOCl_2$	5	6	25
4	$ZrOCl_2{\cdot}SiO_2$	5	6	32
5	$BF_3O(Et)_2$	5	6	42
6	$BF_3{\cdot}SiO_2$	5	6	48
7	$SiO_2{\cdot}SO_3H$	5	6	35
8	TFA	5	6	46
9	$Mg(ClO_4)_2$	5	6	nr[c]
10	$Y(CF_3COO)_3{\cdot}nH_2O$	5	6	nr[c]
11	DMAP	5	6	KC[d] (80)
12	DBU	5	6	KC[d] (85)
13	Piperazine	5	1	80
14	Pyrrolidine	5	1	82
15	Morpholine	5	1	84
16	Dimethylamine	5	1	90
17	Dibutylamine	1	0.5	80
18	Dibutylamine	1.5	0.5	85
19	Dibutylamine	2	0.5	94
20	Dibutylamine	2.5	0.3	98
21	Dibutylamine	3	0.3	98

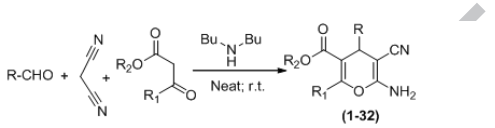
[a]Reaction conditions[35]: aldehyde (1 mmol), malononitrile (1 mmol), methylacetoacetate (1 mmol), DBA (2.5 mol%), neat, and r.t.

[b]Isolated yield measured gravimetrically.

[c]No reaction.

[d]Knoevenagel condensation.

The low toxicity, ease of handling, commercial availability, and economical aspects of DBA (low cost), as well as the ease of its removal (water washings) from reaction mixtures prompted us to choose it as a suitable organocatalyst for the synthesis of pyrans (Scheme 1).



Compound	1	2	3	4	5	6	7	8
R	Ph	2-CNPh	2-ClPh	2-BrPh	3-BrPh	4-BrPh	4-OMePh	3,5-OMePh
R_1	Me	Me	Me	Me	Me	Me	Me	Me
R_2	Me	Me	Me	Me	Me	Me	Me	Me
Yield (%)	96	94	97	98	97	98	98	96
Compound	**9**		**10**	**11**	**12**	**13**	**14**	**15** **16**
R	4-MePh		4-NO_2Ph	4-OHPh	3,4-OHPh	Ff	5-MeFf	iPr C_5H_{13}
R_1	Me		Me	Me	Me	Me	Me	Me Me
R_2	Me		Me	Me	Me	Me	Me	Me Me
Yield (%)	93		97	85	82	95	86	55 65
Compound	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
R	Ph	2-CNPh	2-ClPh	2-BrPh	3-BrPh	4-BrPh	4-OMePh	3,5-OMePh
R_1	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph
R_2	Et	Et	Et	Et	Et	Et	Et	Et
Yield (%)	95	94	96	98	95	98	97	96
Compound	**25**		**26**	**27**	**28**	**29**	**30**	**31** **32**
R	4-MePh		4-NO_2Ph	4-OHPh	3,4-OHPh	Ff	5-MeFf	iPr C_5H_{13}
R_1	Ph		Ph	Ph	Ph	Ph	Ph	Ph Ph
R_2	Et		Et	Et	Et	Et	Et	Et Et
Yield (%)	91		97	92	90	92	90	50 55

Scheme 1. Synthesis of a series of novel pyrans (**1-32**).

To determine the optimum catalyst loading of dibutylamine, model reactions were carried out using 1, 1.5, 2, 2.5, and 3 mol% dibutylamine under neat conditions at room temperature (rt), which afforded 80%, 85%, 96%, 98%, and 98% product yields, respectively. Increasing the amount of catalyst beyond 2.5% had no additional effect on the reaction progress. The results are summarized in Fig. 1.

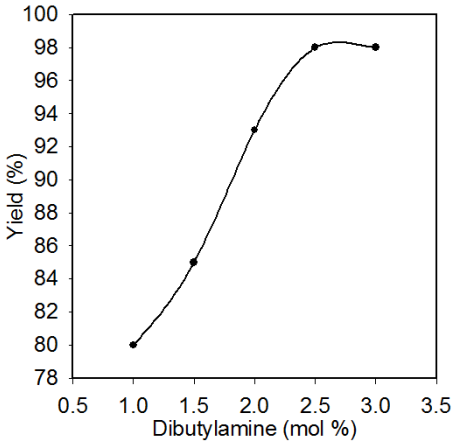


Figure 1. Effect of the amount of dibutylamine on the yield of **1**.Conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), methylacetoacetate (1 mmol), dibutylamine (2.5 mol%), neat, rt.

Consequently, we then explored the general applicability of the reaction conditions towards the synthesis of various substituted pyrans; the results are summarized in the experimental section. Firstly, reactions were performed between MAA, MN, and various aromatic aldehydes; aromatic aldehydes bearing electron-withdrawing as well as electron-donating groups on the aromatic ring were successfully utilized in the reaction, and the desired products were obtained in high yields within a short reaction time. The procedure was extended towards heteroaromatic and aliphatic aldehydes; in all cases, the respective pyrans were obtained with good yields within a short time. Additionally, we replaced MAA with EBA, which also generated the desired products in good yields. Among all the reactions the compounds **11**, **12**, **14** and **32** were are obtained not pure compounds because the compounds **11**, **12** substituted with hydroxy groups are less reactivity with MAA when compared to EBA. Furthermore the compound **14** is heterocyclic aldehyde is bearing methyl substitution at 5-position due to progress of the reaction is slow where as in the case of compound **32** is contains n-hexanaldehyde is aliphatic in nature and in general aliphatic aldehydes are less reactive than aromatic and heterocyclic aldehydes.

There are numerous advantages of dibutylamine in comparison with other catalysts used for the synthesis of pyrans. Recently, Khurana et al.[36] reported the use of task-specific ionic liquids (ILs) at 50–60 ^{o}C for the synthesis of pyrans. In 2011, Banerjee[37] established the synthesis of pyrans promoted by SiO_2 nanoparticles in ethanol at room temperature; however, this method required a long reaction time (2 h). Valizadehet al.[38] reported the synthesis of pyrans using ZnO/MgO-containing ZnO nanoparticles in the presence of ionic liquids at rt that required a tedious work-up procedure and resulted in a yield of 91%. Peng et al.[27]also reported the synthesis of pyrans in a 92% yield using amino-functionalized ILs with microwave irradiation as an additional energy source for product formation. Compared to the above-reported catalysts, the dibutylamine organocatalyst was superior for the synthesis of pyrans with high yields with no need for severe reaction conditions, additional energy (i.e., microwaves or, ultrasonication), and laborious work-up procedures; the full comparison is summarized in Table 2.

Table 2.Comparison of various catalysts used for the synthesis of 1.[a]

Entry	Catalyst (Mol%)	Solvent	Time (min)	Yield (%)	Ref.
1	[bmim]OH (25)	[bmim] OH	30	92	36
2	SiO_2 NPs (10mg)	EtOH	120	88	37
3	ZnO/MgO (10)	[bmim]BF_4	30	91	38
4	[2-aemim] [PF_6] (3 mL)	H_2O	1	93	27
5	Dibutylamine (2.5)	Neat	8	98	This work

[a]Reaction conditions: benzaldehyde = 1 mmol, malononitrile = 1 mmol, and methylacetoacetate = 1 mmol.

The syntheses of all the pyrans were confirmed using FTIR, ^{1}H, and ^{13}C NMRspectroscopy. In the ^{1}H NMR spectra, the –NH_2 proton signals appeared as a singlet in the region of 5.78–4.57 ppm. The Ar–CH proton signals also appeared as a singlet in the region of 5.27–4.28 ppm, confirming product formation; the remaining proton signals were observed in the expected regions. In the ^{13}C NMR spectra, the Ar–CH carbon signals were observed in the region of 44.1–36.8 ppm, confirming the formation of pyrans.[36] A detailed description of the spectral data for all compounds (**1–32**) is provided in the supporting information.

3. Conclusion

A straight-forward, efficient, and green procedure for the synthesis of pyrans using dibutylamine organocatalysts under solvent-free conditions was described. In this study, dibutylamine was used as a highly efficient organocatalyst for the multi-component synthesis of pyrans at room temperature. The availability of this non-toxic and low-cost catalyst as well as the resultant high yields, operational simplicity, and simple work-up make this an eco-friendly alternative to the presently accessible protocols.

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35. To a mixture of methyl acetoacetate or ethyl benzoylacetate (1 mmol) aldehyde (1 mmol), malononitrile (1 mmol) in 25mL reaction flask equipped with a magnetic stirring bar was added dibutylamine (2.5 mol%); the resulting reaction mixture was stirred at r.t. for the appropriate time (10–40 min). The progress of the reaction was monitored by TLC. After completion of the reaction, chilled water (10 mL) was added, and stirring was continued until a free–flowing solid was obtained. It was filtered and then washed successively with chilled water (40 mL) after that the products were dried at r.t. The identical experimental procedure is adapted for all the pyrans. All the new products were characterized by their melting points, IR, ^{1}H NMR, and ^{13}C NMR spectra. A detailed description of spectral data for all compounds **1**–**32** is given in supporting information.
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