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A new strategy for the synthesis of 2-amino-4H-pyran derivatives in aqueous media using DABCO-Cucl complex as a novel and efficient catalyst

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2-Amino-4H-pyran derivatives are reported to have a broad spectrum of biological and pharmacological activities. Some are endowed with anticoagulant, spasmolitic, diuretic, anticancer and antianaphylactin. On the other hand, some 2-amino-4H-pyrans also can be employed as cognitive enhancers, for the treatment of neurodegenerative disease, including Alzheimer's disease, amyotrophic. In this research, 2-amino-4H-pyran derivatives were synthesized with good yields *via* a one-pot multi–component reaction of aldehyde, malononitrile, and dimedone in the presence of DABCO-CuCl as a catalyst in water.

KEYWORDS

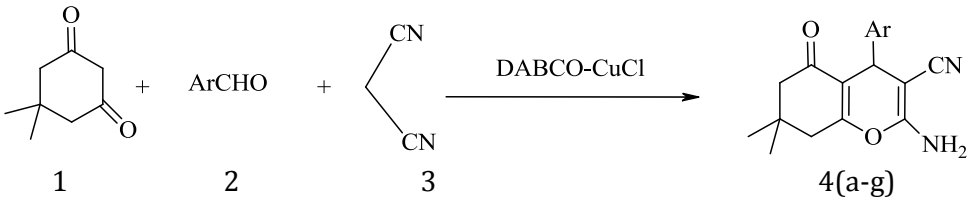
2-Amino-4H-Pyran; multi–component reaction; one-pot; DABCO-CuCl.

Introduction

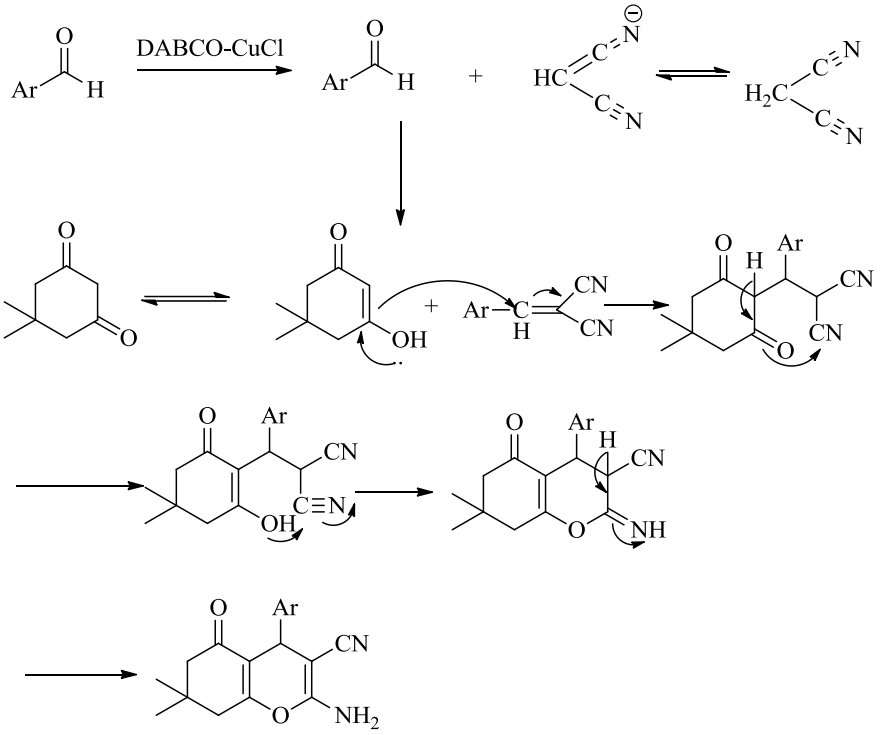
Tetrahydrobenzo [b] pyran derivatives are reported to have a broad spectrum of biological and pharmacological activities [1]. Some are endowed with anticoagulant, spasmolitic, diuretic, anticancer and antianaphylactin [2]. On the other hand, some 2-amino-4H-pyrans also can be employed as cognitive enhancers for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease as well as for the treatment of schizophrenia and myoclonus [3]. It has also been reported that some of benzopyran derivatives have photochemical activities [4]. Some natural compounds of plant origin contain heterocycles of pyran and benzopyran [5,6]. The red, purple, and blue pigments in flower petals are called anthocyanins, the various glycosides of benzoperlium cations. For example, dolphinidine chloride is a blue pigment, and Khellin is a natural compound used to treat short of breath and is the raw material of many fully synthetic pyranes that have interesting biological properties.

Due to the importance of pyrans, different methods have been proposed for their synthesis [7-12].

Developing highly expedient methods for the synthesis of heterocyclic compounds, in this report, we wished to introduce DABCO-CuCl complex as a mild and highly efficient medium for the preparation of 2-amino-4H-pyrans under refluxing conditions (Scheme 1). The proposed mechanism for the synthesis of 2-amino-4H-Pyran derivatives in the presence of DABCO- CuCl complex as follows (Scheme 2).



SCHEME 1 synthesis of 2-amino-4H-pyran



SCHEME 2 Mechanism of the synthesis of 2-amino-4H-pyran

Experimental Phase

General

All products were characterized by mp, IR, ^{1}HNMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}H and ^{13}CNMR spectra were recorded on a Bruker DRX Avance spectrometer at 500 and 125 MHZ, respectively, with $CDCl_3$ as a solvent. IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

Typical procedure for preparation of2-amino-4H-pyran derivatives

A mixture of an appropriate benzaldehyde (1mmol), malononitrile (1mmol), dimedone (1mmol) and DABCO-CuCl complex (0.05 g) in water were refluxed for appropriate time as indicated in Table 1. After completion of the reaction which was monitored by TLC, the mixture was filterated and cooled to room temperature; the precipitate was filtered and washed with ethanol. The crude products were purified by recrystallization from Ethanol.

4a. IR (KBr) (ν_{max}, cm^{-1}): 3390, 3290, 2935, 2200, 1685, 1600. ^1H NMR ($CDCl_3$, 500 MHz) δ_H (ppm): 0.98 (3 H, s), 1.05 (3 H, s,), 2.15-2.24 (1 H, dd), 2.45–2.55 (2 H, dd), 4.32 (1 H, s), 6.08 (2 H, s, NH_2), 7.15–7.30 (5 H, m, ArH).

4b. IR (KBr) (ν_{max}, cm^{-1}): 3410, 3310, 3005, 2200, 1695, 1605. ^1H NMR ($CDCl_3$, 500 MHz) δ_H (ppm): 0.95 (3 H, s), 1.04 (3 H, s), 2.10-2.27 (1 H, dd), 2.47–2.55 (1 H, dd), 4.20 (1 H, s), 7.08 (2 H, s, NH_2), 7.17-7.54 (4 H, m, ArH).

Results and discussion

In connection with the development of efficient protocols for the preparation of biological active heterocycles, herein, we selected DABCO-CuCl as a new catalyst to synthesis of pyridine dicarbonitriles. The reaction of various aldehydes, malononitrile, and dimedone in the presence of DABCO-CuCl as a catalyst in water afforded 2-amino-4H-pyran. It is noteworthy to mention that the effect of the nature of the substituents on the aromatic ring showed no apparent effect on this conversion (Table 1), because they were obtained in high yields in relatively short reaction times. The results are shown in Table1.

We performed the effect of various solvents on the synthesis of 4a. This reaction was carried out in various solvents and the best results in terms of yield and time obtained in water (Table 2).

To optimize the amount of catalyst, 1 mmol of malononitrile, 1 mmol of aldehyde, 1 mmol of dimedone, and various amounts (0.01, 0.02, 0.03, 0.05, and 0.08 g) of DABCO-CuCl complex as a catalyst were used. Table 3 represents the test results performed to optimize the amount of catalyst in the presence of different amounts of DABCO-CuCl complex. The results presented in the table show that the amount of 0.05 g of DABCO- CuCl complex had the best efficiency and use of an increased amount of catalyst did not make much difference.

After comparing the results for the synthesis of substituted 2-amino-4H-Pyran with other methods, it was revealed that the DABCO- CuCl complex catalyst performed the reaction faster and more efficiently (Table 4).

In the following part, the reusability of DABCO- CuCl complex was investigated. At the end of the reaction, the catalyst was recovered by a simple filtration, washed with hot methanol, dried and subjected to a second run of the reaction process. To assure that the catalysts were not dissolved in methanol, they were weighed after filtration and before use and reuse for the next reaction. In Table 5, the comparison of efficiency of DABCO-CuCl complex in synthesis of 4a after five times is reported. As shown in Table 5, the first reaction using recovered DABCO- CuCl complex afforded a similar yield to that obtained in the first run. In the second, third, fourth and fifth runs, the yields gradually decreased.

TABLE 1 Synthesis of substituted 2-amino-4H-Pyran catalyzed by DABCO-CuCl complex

Entry	X	Product	Yield(%)[a]	m.p.(°C)	
				Found	Reported[13]
1	H	4a	93	224-225	226-228
2	4-Cl	4b	96	206-208	207-209
3	4-NO_2	4c	97	178-179	177-178
4	3-NO_2	4d	98	210-212	208-211
5	4-CH_3	4e	93	213-215	214-216
6	4-OCH_3	4f	91	200-202	198-200
7	4-OH	4g	90	205-207	206-208
8	2-Cl	4h	95	209-211	208-210

Yields refer to isolated products.

TABLE 2 Synthesis of 4a in the presence of different solvents using DABCO-CuCl complex as a catalyst

Entry	Solvent	Yield(%)[a]
1	THF	68
2	C_2H_5OH	87
3	CH_3CN	85
4	$CHCl_3$	71
5	Solvent-free	90
6	water	93

Yields refer to isolated products

TABLE 3 Comparison of amount of catalysts for the synthesis of 4a

Entry	Solvent	Yield (%)[a]
1	0.02 g	80
2	0.03 g	89
3	0.05 g	93
4	0.08 g	93

Yields refer to isolated products

TABLE 4 Comparison of various catalysts for the synthesis of substituted 2-amino-4H-Pyran

Entry	Catalyst	Yield (%)	Time(min)	Ref
1	NaBr	60-95	15-20	[14]
2	(S)-Proline	78-98	30	[15]
3	HDMBAB	84-93	7-8(h)	[16]
4	Na2SeO4	80-98	3(h)	[17]
5	TMAH	79-93	2(h)	[16]
6	TBAF	73-98	30-300	[18]
7	MgO	90-96	22-33	[19]
8	DABCO- CuCl complex	90-98	10-20	Present study

Yields refer to isolated products

TABLE 5 Reuse of the nano DABCO-CuCl complex for synthesis of (4a)

Entry	Run	Yield(%)a
1	First	93
2	Second	91
3	Third	90
4	Fourth	88
5	Fifth	85

Isolated yields

Conclusion

In this study, we delved into the development of highly expedient methods for the synthesis of heterocyclic compounds and in continuation of our investigation on the use of water as solvent for chemical preparation, we reported here a facile and improved protocol for preparation of 2-amino-4H-pyrans, from benzaldehydes, malononitrile, dimedon and DABCO-CuCl complex as a catalyst in water at ambient conditions. The advantages of the present procedure include experimental simplicity, easy work-up procedure, use of an easy to handle, safe reagent and high yields of products.

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