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One-pot synthesis of tetrahydrobenzo[b]pyran and dihydropyrano[c]chromene derivatives in aqueous media by using trisodium citrate as a green catalyst

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ABSTRACT

Trisodium citrate, a natural non-toxic compound, is used as a catalyst for an efficient, rapid, one-pot synthesis of tetrahydrobenzo[b]pyrans and dihydropyrano[c]chromenes in moderate to excellent yields and under eco-friendly conditions. The catalyst is environmental benign, easy handling, non-toxic, stable in air, inexpensive and could be reused at least five cycles without losing its activities.

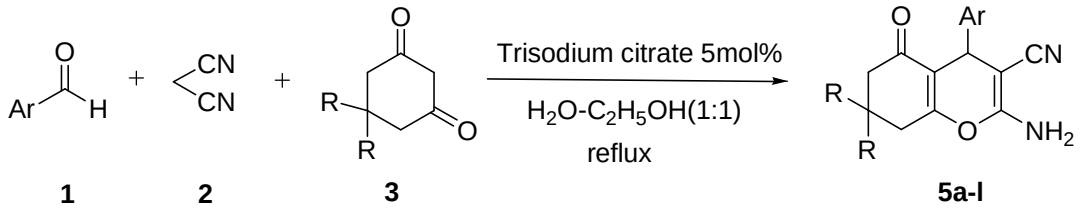
Key words: Tetrahydrobenzo[b]pyran, Dihydropyrano[c]chromene, Trisodium citrate, Green and eco-friendly conditions.

INTRODUCTION

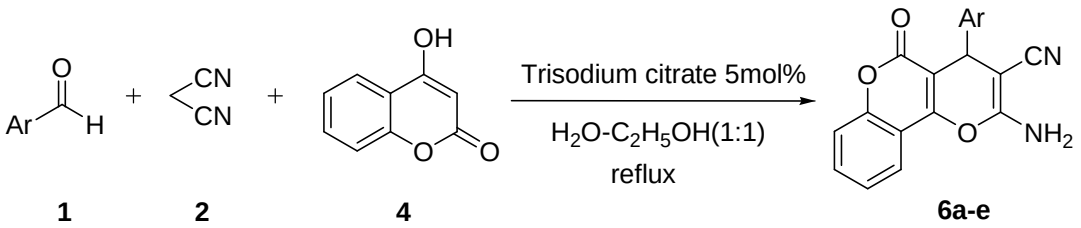
Tetrahydrobenzo[b]pyrans and dihydropyrano[c]chromenes have recently attracted much attention as an important class of heterocycles to their useful biological and pharmacological properties [1, 2]. These compounds are widely used as anticoagulant, spasmolytic, anticancer, diuretic and antianaphylactin agents in the field of drugs and pharmaceuticals [3-5]. Consequently, numerous technologies have been reported for the promoting synthesis of tetrahydrobenzo[b]pyran or dihydropyrano[c]chromene derivatives, including the use of microwave [6], ultrasonic irradiation [7]. A literature survey revealed the recent reports on several modified procedures using a variety of reagents, for example, hexadecyldimethylbenzyl ammonium bromide (HDMBAB) [8], TBAB [9, 10], fluoride ion [11], ionic liquids [12-14], $RE(PFO)_3$ [15], Na_2SeO_4 [16], high surface area MgO [17], solid acid [18] and $(NH_4)_2HPO_4$ [19, 20], as catalyst to synthesis of these heterocyclic compounds. However, some of the reported methods require prolonged reaction time, reagents in stoichiometric amount, use of expensive catalyst, low yields of products, toxic solvents.

The increasing attention during the last decades for environmental protection has led both

modern academic and industrial groups to develop chemical processes with maximum yield and minimum cost whilst using non-toxic reagents, solvents and catalysts or solvent-free. One of the tools used to combine economic aspects with the environmental ones is the multicomponent reaction (MCR) strategy. As part of our program aimed at developing new selective and synthetic useful methodologies based on the use of inexpensive and convenient available compound as catalysis of fine chemicals preparation, we have studied using the MCR strategy for the synthesis of tetrahydrobenzo[b]pyrans (Scheme-1) and dihydropyrano[c]chromenes (Scheme-2) using inexpensive and convenient available trisodium citrate as catalyst. To the best of our knowledge, this is the first report of using trisodium citrate as a green catalyst to catalyze one-pot multicomponent reactions.



Scheme-1: Preparation of Tetrahydrobenzo[b]pyrans



Scheme-2: Preparation of dihydropyrano[c]chromenes

MATERIALS AND METHODS

Melting points were measured on an Electrothemal X6 microscopy digital melting point apparatus. IR spectra were recorded on a Bruker Equinox-55 spectrometer using KBr pellets. ^{1}H NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on a Bruker AVANCE 300 (300MHz) instrument with TMS at δ=0.00 ppm as an internal standard. Benzaldehyde was purified by distillation. All other chemicals were of commercial grade without further purification.

General procedure for the synthesis of tetrahydrobenzo[b]pyran and dihydro -pyrano[c]chromene derivatives

In a typical reaction for the preparation of Tetrahydrobenzo[b]pyrans, an equimolar (1.0 mmol) mixture of an aromatic aldehyde, malononitrile, dimedone and trisodium citrate (5.0 mol%) were dissolved in 5.0 mL aqueous ethanol (50%) and vigorously stirred at reflux for the specific time indicated in Table 2. The progress of the reaction was monitored by TLC. After completion, water (15.0 ml) was added and just filtered to yield corresponding crude product. The crude product was further purified by recrystallization with methanol to afford pure product **5**. The catalyst was directly reused next turn after evaporation of solvent.

For the typical preparation of dihydripyrano[c]chromenes, the reaction of aldehyde (1 .0 mmol), malononitrile (1.0 mmol), 4-hydroxycoumarin (1.0 mmol), and trisodium citrate (5.0 mol%) was carried out as described above for specific times given in Table 3 and the desired product **6** was purified by recrystallization with ethanol. The corresponding products were identified by IR, ^{1}H NMR, and physical data (Mp) which are in agreement with those reported in the literatures.[15−25] The spectral data of selected compounds are given below:

2-amino-3-cyano-4-(4'-chlorobenzyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (5a):

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.93 (s, 3H), 1.02 (s, 3H), 2.10 (d, J = 16.1 Hz, 1H), 2.21 (d, J = 16.1 Hz, 1H), 2.50 (s, 2H), 4.19 (s, 1H), 7.05 (s, 2H), 7.18 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H) ppm; IR (KBr, cm^{-1}): 3381, 3184, 2959, 2188, 1674, 1635, 1604, 1365, 1216.

2-amino-3-cyano-4-(4'-nitrobenzyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (5e):

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.94 (s, 3H), 1.02 (s, 3H), 2.07 (d, J = 16.07 Hz, 1H), 2.21 (d, J = 16.03 Hz, 1H), 2.52 (s, 2H), 4.35 (s, 1H), 7.17 (s, 2H), 7.44 (d, J = 8.35 Hz, 2H), 8.14 (d, J = 8.35 Hz, 2H) ppm; IR (KBr, cm^{-1}): 3407, 3317, 3176, 2183, 1671, 1630, 1594, 1521, 1350, 1216, 1031.

2-amino-3-cyano-4-phenyl-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (5g):

^{1}H NMR (300 MHz, $CDCl_{3,}$): δ = 1.04 (s, 3H), 1.12 (s, 3H), 2.22 (d, J = 16.3 Hz, 1H), 2.23 (d, J = 16.3 Hz, 1H), 2.46 (s, 2H), 4.41 (s, 1H), 4.57 (s, 2H), 7.18-7.32 (m, 5H), ppm; IR (KBr, cm^{-1}): 3397, 3325, 3213, 2961, 2200, 1680, 1661, 1604, 1371, 1214, 1139, 1036.

2-amino-3-cyano-4-(4'-methoxybenzyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (5i):

^{1}H NMR (300 MHz, $CDCl_{3,}$): δ = 1.03 (s, 3H), 1.11 (s, 3H), 2.21 (d, J = 16.0 Hz, 1H), 2.22 (d, J = 16.0 Hz, 1H), 2.43 (s, 2H), 3.77 (s, 3H), 4.36 (s, 3H), 4.55 (s, 2H), 6.84 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H) ppm; IR (KBr, cm^{-1}): 3377, 3322, 3187, 2964, 2198, 1684, 1655, 1606, 1509, 1370, 1248, 1212, 1034.

2-Amino-4-(4-nitrophenyl)-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (6a):

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.68(s, 1H), 7.22-7.59 (m, 5H), 7.62 (s,2H), 7.71-7.77 (m, 1H), 7.90-7.93 (m, 1H), 8.18 (d, J = 8.7 Hz, 2H) ppm; IR (KBr, cm^{-1}): 3481, 3429, 3369, 3334, 2195, 1718, 1672, 1606, 1504, 1372, 1347, 1055.

2-Amino-4-phenyl-3-cyano-4H,5H-pyrano[3,2-c]chromene-5-one (6c):

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.45(s, 1H), 7.21-7.35(m, 5H), 7.42(s,2H), 7.44-7.52 (m, 2H), 7.74-7.68 (m, 1H), 7.89 (d, J = 1.5 Hz, 1H), 7.92 (d, J = 1.5 Hz, 1H) ppm; IR (KBr, cm^{-1}): 3378, 3285, 3180, 2199, 1710, 1675, 1638, 1607, 1491, 1382, 1059.

RESULTS AND DISCUSSION

Initially, the model reaction of 4-chlorobenzaldehyde, dimedone and malononitrile was explored in the presence of a variety of solvents (Table-1, entries 1-5). As shown in table 1, when using aprotic polar solvents such as dichloromethane or acetonitrile, the reaction was not completed even after 12 hours with the moderate yield. However, the protic solvents such as water and ethanol afford better yields. The mixture solvent of water and ethanol is the most suitable solvent for this transformation in terms of product yield and reaction rate. In order to optimize the conditions, the influence of the amount of trisodium citrate and the temperature were also examined (Table-1, entries 6-10), it was found that the optimal conditions to promote the reaction are using 5.0 mol% catalyst in aqueous ethanol solvent (H_2O-C_2H_5OH, 1:1, v/v) at reflux (Table 1, Entry 5).

Table-1: Optimization of the reaction conditions[a]

Entry	Solvents	T(°C)	Time(min)	Yield(%)[b]
1	H_2O	80	30	80
2	C_2H_5OH	reflux	90	90
3	CH_2Cl_2	reflux	720	65
4	CH_3CN	reflux	720	52
5	H_2O: C_2H_5OH =1:1	reflux	5	93
6	H_2O: C_2H_5OH =1:1	r.t	150	90
7	H_2O: C_2H_5OH =1:1	45	60	89
8	H_2O: C_2H_5OH =1:1	60	20	90
9[c]	H_2O: C_2H_5OH =1:1	reflux	8	87
10[d]	H_2O: C_2H_5OH =1:1	reflux	5	92

[a]*Reaction conditions: 4-chlorobenzaldehyde (1.0 mmol), malononitrile (1.0 mmol), dimedone (1.0 mmol), trisodium citrate (0.05 mmol), solvent (5.0 mL).*

[b]*Isolated yield.*

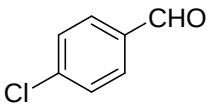
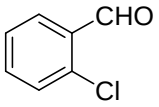
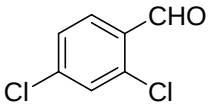
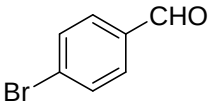
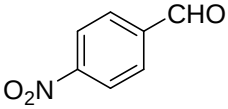
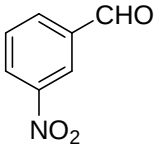
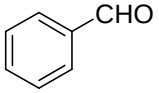
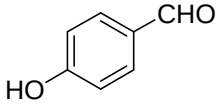
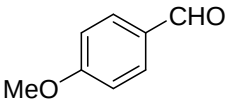
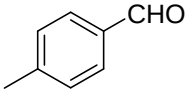
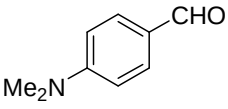
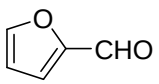
[c]*2.0 mol% of catalyst was used.*

[d]*10.0 mol% of catalyst.was used.*

Under the optimized reaction conditions, a range of substituted tetrahydrobenzo[b]pyrans (**5a-l**) were synthesized. The results were listed in Table-2. As can be seen from Table-2, in all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields under the optimized reaction conditions. It is worthy note that aromatic aldehyde with hydroxyl disfavored the reaction, which gives a comparative lower yield and cost longer reaction time (Table-2, entry 8). Other aromatic aldehydes bearing both electron-withdrawing and electron-donating substituents at *ortho*-, *meta*- or *para*-positions on the aromatic ring reacted with dimedone and malononitrile smoothly to afford the desired compounds in excellent yields (Table-2, entries 1-7, 9-11). Moreover, the heterocyclic aryl aldehyde also could be successfully converted to the corresponding compounds (Table-2, entry 12).

Table-2: The multi-component reaction of aromatic aldehydes, malononitrile and dimedone catalyzed by

trisodium citrate. [a]

Entry	Aldehyde	Product	Time(min) /Yield(%)[b]	mp°C (Lit mp)
1		**5a**	5/93	211-213 (213-215) [19]
2		**5b**	20/89	205-207 (200-202) [21]
3		**5c**	25/96	113-115 (116-118) [17]
4		**5d**	10/93	196-198 (201-203) [15]
5		**5e**	35/88	184-186 (181-184) [19]
6		**5f**	35/90	205-208 (204-205) [15]
7		**5g**	10/82	227-229 (226-228) [17]
8		**5h**	120/82	202-204 (204-205) [19]
9		**5i**	30/82	191-193 (194-196) [17]
10		**5j**	20/84	204-205 (208-210) [21]
11		**5k**	20/80	212-214 (212-213) [16]
12		**5l**	6/90	205-207 (205-206) [22]

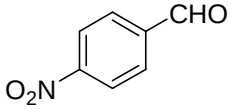
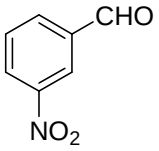
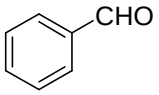
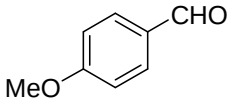
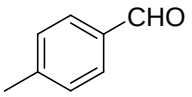
[a]*Reaction conditions: aromatic aldehyde (1.0 mmol.), malononitrile (1.0 mmol), dimedone (1 mmol), trisodium citrate (5.0 mol%), H_2O- C_2H_5OH (1:1, 5 mL), at reflux*

[b]*Isolated yield*

To extend the scope of the trisodium citrate catalyzed multi-component reaction, we

successfully synthesized 3, 4-dihydropyrano[c]chromene derivatives (**6a-e**) when using 4-hydroxycoumarin instead of dimedone in these MCRs under the mentioned optimal conditions. As shown in Table-3, when aromatic aldehydes bearing electron-withdrawing substituents (such as nitro group) (Table-3, entries 1-2) were employed, higher yields were obtained than those of electron-donating groups (such as methoxyl, and methyl) on aromatic ring (Table-3, entries 4-5).

Table-3: The multi-component reaction of aromatic aldehydes, malononitrile and 4-hydroxycoumarin catalyzed by trisodium citrate [a]

Entry	Aldehyde	Product	Time(min) /Yield(%)[b]	mp°C (Lit mp)
1		6a	10/85	260-262 (258-260) [20]
2		6b	60/85	248-250 (253-255) [23]
3		6c	40/65	246-248 (245-247) [14]
4		6d	80/78	232-235 (231-233) [24]
5		6e	60/72	246-248 (252-254) [23]

[a]*Reaction conditions: aldehyde (1 mmol), malononitrile (1 mmol), 4-hydroxycoumarin (1 mmol), trisodium citrate (5 mol%), H_2O- C_2H_5OH (1:1, 5 mL), at reflux.*

[b]*Isolated yield*

Table-4: Studies on reusability of trisodium citrate in the preparation of 4a

Entry	Number of recycle	Yield (%)
1	1	93
2	2	92
3	3	89
4	4	93
5	5	91

Apart from the eco-friendly conditions and the excellent results, the simplicity of product isolation and the possibility to recovery and recycle of the trisodium citrate offer a significant advantage. In this work, we chose the reaction of 4-chlorobenzaldehyde, malononitrile and dimedone as a model reaction to further explore the reusabilities of trisodium citrate. After the separation of products by filter, the catalyst was directly reused next turn after

evaporation of filtrate. As shown in Table-4, the recovered catalyst could be successively recycled in subsequent runs without noticeable decrease of yields.

Some catalysts have been reported to catalyze the tetrahydrobenzo[b]pyrans synthesis in water or aqueous media under reflux conditions. We took synthesis of **4a** for a representative example to show the advantage of this work in comparison with previously reported procedures. As shown in Table-5, our catalyst gives a comparative yield and costs less time than others. Moreover trisodium citrate is more stable in air and non-toxic compared with other catalysts.

Table-5: Comparison results of Trisodium Citrate with other catalysts reported in the literature

Entry	Catalysts	Catalyst; conditions	Time	Yield(%)
1	Trisodium Citrate	5 mol%; H_2O-C_2H_5OH; at reflux	5min	91[a]
2	HDBMB	12 mol%; water; 80°C	6h	94 [8]
3	TBAB	10 mol%;ethanol; at reflux	30min	95 [9]
4	TBAF	10 mol%; water; at reflux	30min	94 [11]
5	[TEBSA] HSO_4	10 mol%; H_2O; 90°C	1h	91 [12]
6	Na_2SeO_4	0.1g; H_2O-C_2H_5OH; at reflux	3h	90 [16]

[a] *This work*

CONCLUSION

We have developed a novel efficient methodology for the synthesis of tetrahydrobenzo[b]pyran and dihydropyrano[c]chromene derivatives via one-pot multicomponent reactions. The catalyst trisodium citrate is green, efficient, reusable, safe and inexpensive. Moreover, the experimental procedure for this reaction is remarkably simple and without the use of hazarded and/or expensive organic solvents. All the features make this protocol to be an attractive addition to existing methodologies.

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