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One-pot synthesis of tetrahyrobenzo[*b*]pyran and dihydropyrano[*c*]chromene derivatives using ammonium Alum in green media

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A variety of 4*H*-benzo[*b*]pyran and pyrano[*c*]chromene derivatives have been efficiently synthesized under green conditions. This inexpensive, non-toxic, eco-friendly protocol afforded the products in good to high yields.

Keywords: green chemistry, multi-component, benzopyran, pyranochromene, ammonium alum.

INTRODUCTION

The increasing attention during the past decade for environment protection has led to a new area called green chemistry. Elimination of dangerous toxic solvents and replacing it with water and environmentally friendly solvents is very important in green chemistry [1]. Development of chemical processes with the highest efficiency, lowest cost and use of non-toxic reagents and catalysts and also use of solvent-free mediums have been found of special interest [1]. In recent years, the use of water as a green solvent has been developed. Replacing of organic solvents with water has advantages such as availability, low cost and safety for the environment [2].

Multi-component reactions are powerful synthetic tools for the synthesis of compounds with biological activity [3]. Tetrahydrobenzo[b]pyran and dihydropyrano[c]chromene derivatives have been exhibited biological and pharmaceutical properties including anticancer and anticoagulation [4], diuretics [5], anti-Alzheimer's [6], anti leukemic [7], anti anaphylactic [8], anti-malarial [9], emetic [10]. Also these compounds have been used in pigments and cosmetics [5, 11].

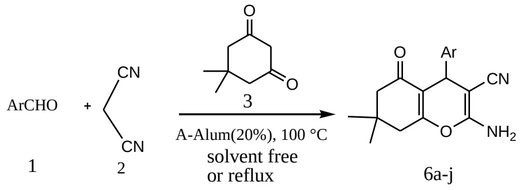
Several methods have been reported for the synthesis of tetrahydrobenzo[*b*]pyrans and dihydropyrano[*c*]chromenes. These compounds have been synthesized in the presence of various catalysts, such as di-ammonium hydrogen phosphate (DHAP) [12], TBAB [13], K_2CO_3 under microwave irradiation [14], S-proline [15], MgO [16], and sulfonic acid functionalized silica (SiO_2-$PrSO_3H$) [17]. Each of these reported methods has its own merits, with at least one of the limitation of drastic condition, long reaction times, low yields, and effluent pollution.

Ammonium alum (A-Alum) with mild acidity, involatility, inexpensivity and incorrosivity is insoluble in common organic solvents and partially soluble in water [18]. Hence it is good candidate for catalysis in green organic synthesis.

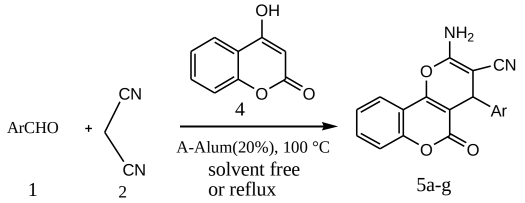
To the best of our knowledge, there are no reports on the use of A-Alum in organic reactions as a catalyst.

In continuation of our research devoted to the development of green organic chemistry and one-pot multi-component reactions for the synthesis of various heterocyclic compounds [19], herein we wish to report an efficient and green procedure for the preparation of tetrahyrobenzo[*b*]pyrans and dihydropyrano[*c*]chromenesvia a domino Knoevenagel-cyclocondensation reaction using $(NH_4)Al(SO_4)_2.12H_2O$ (A-Alum) as a catalyst in aqueous medium.

Scheme1



Scheme 2



EXPERIMENTAL

All of the products are known compounds and were identified by their physical and spectroscopic data with those reported in literature. Melting

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points were measured by using capillary tubes on an electro thermal digital apparatus and are uncorrected. The progress of reactions was monitored by TLC using *n*-hexane/ EtOAc (1:1 v/v) as eluent. IR spectra were recorded as KBr disc on a galaxy series FT-IR 5000 spectrometer. NMR spectra were recorded on 300 MHz brucker spectrometer in DMSO-d_6 with TMS as an internal standard. Microanalyses were performed by the Elemental Analyzer (Elemental, Vario EL III) at the Arak University.

General procedure for the synthesis of tetrahydrobenzo[b]pyran and dihydropyrano[c]chromene derivatives:

Method A: A mixture of an aldehyde (1 mmol), malononitrile (1 mmol), dimedone or 4-hydroxy coumarin (1 mmol) and A-Alum (20% mol) in 3 ml H_2O/EtOH (2:1) was refluxed with stirring for Adequate time. After the reaction completion (monitored by TLC), the reaction mixture was cooled to room temperature, filtered and washed with cool water. The crud product recystalized with hot ethanol.

Method B: A mixture of an aldehyde (1 mmol), malononitrile (1 mmol), dimedone or 4-hydroxy coumarin (1 mmol) and A-Alum (20% mol) was heated at 100°C under solvent free conditions. Completion of the reaction was followed by TLC, after the reaction was completed, the reaction mixture was cooled to room temperature and washed with cool water and then recrystallized with hot ethanol.

Selected data of products:

(6a): IR (KBr) (ν_{max}): 3393, 3317, 3185, 2958, 2196, 1687, 1652, 1367 cm^{-1}. ^1H NMR (DMSO–d_6): δ_H: 0.94 (3H, s, Me), 1.04 (3H, s, Me), 2.08 (1H, d, *J* = 16.0 Hz, H-6), 2.23 (1H, d, *J* = 16.0 Hz, H-6'), 2.50 (2H, m, CH_2), 4.11 (1H, s, H-4), 7.06 (2H, br s, NH_2), 7.19 (3H, m, H–Ar), 7.33 (2H, m, H–Ar) ppm. Anal. calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.97; H, 6.79; N, 9.42.

(6d): IR (KBr) (ν_{max}): 3533, 3364, 3153, 2966, 2193, 1685, 1658, 1367 cm^{-1}. ^1H NMR (DMSO–d_6): δ_H: 1.00 (3H, s, Me), 1.06 (3H, s, Me), 2.11 (1H, d, *J* = 16.0 Hz, H-6), 2.27 (1H, d, *J* = 16.0 Hz, H-6), 2.47–2.61 (2H, m, CH_2), 4.70 (1H, s, H-4), 7.15 (2H, br s, NH_2), 7.25 (1H, d, *J* = 8.4 Hz, H–Ar), 7.39 (1H, d, *J* = 8.4 Hz, H–Ar), 7.56 (1H, s, H–Ar) ppm. Anal. calcd for $C_{18}H_{16}Cl_2N_2O_2$: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.91; H, 4.63; N, 7.63.

(6g): IR (KBr) (ν_{max}): 3381, 3321, 3209, 2962, 2191, 1682, 1656, 1367 cm^{-1}. ^1H NMR (DMSO–d_6): δ_H: 0.97 (3H, s, Me), 1.06 (3H, s, Me), 2.10 (1H, d, *J* = 16.0 Hz, H-6), 2.27 (1H, d, *J* = 16.0 Hz, H-6'), 2.47–2.55 (2H, m, CH_2), 2.87 (6H, s, -N(Me)$_2$), 4.06 (1H, s, H-4), 6.66 (2H, d, *J* = 8.7 Hz, H–Ar), 6.95 (2H, br s, NH_2), 6.97 (2H, d, *J*=8.7 Hz, H–Ar) ppm. Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 71.49; H, 6.71; N, 12.33.

(6i): IR (KBr) (ν_{max}): 3387, 3323, 3213, 2968, 2191, 1683, 1656, 1520, 1346 cm^{-1}. ^1H NMR (DMSO–d_6): δ_H: 0.99 (3H, s, Me), 1.06 (3H, s, Me), 2.14 (1H, d, *J* = 16.0 Hz, H-6), 2.30 (1H, d, *J* = 16.0 Hz , H-6), 2.53–2.57 (2H, m, CH_2), 4.39 (1H, s, H-4), 7.24 (2H, br s, NH_2), 7.48 (2H, d, *J* = 8.4 Hz, H–Ar), 8.21 (2H, d, *J* = 8.4 Hz, H–Ar) ppm.

(5a): IR (KBr) (ν_{max}): 3378, 3285, 3180, 2199, 1710, 1675, 1638, 1607, 1491, 1382, 1059 cm^{-1}. ^1H NMR (DMSO–d_6): δ_H: 4.45 (1H, s, H-4), 7.21-7.35 (5H, m, H–Ar), 7.42 (2H, s, NH_2), 7.44-7.68 (2H, m, H–Ar), 7.89 (1H, d, *J* = 1.5 Hz, H–Ar), 7.92 (1H, d, *J* = 1.5 Hz, H–Ar) ppm.

(5b): ^1H NMR (300 MHz, DMSO-d_6): δ_H: 3.72 (3H, s, -OCH_3), 4.40 (1H, s, H-4), 6.87 (2H, d, *J* = 8.1 Hz, H–Ar), 7.18 (2H, d, *J* = 8.1 Hz, H–Ar), 7.37 (2H, br s, NH_2), 7.45 (1H, d, *J* = 8.3 Hz, H–Ar), 7.49 (1H, t, *J* = 7.8 Hz, H–Ar), 7.70 (1H, t, *J* = 7.7 Hz, H–Ar), 7.89 (1H, d, *J* = 7.7 Hz, H–Ar) ppm.

RESULTS AND DISCUSSIONS

For the primary study, the condensation reaction of benzaldehyde with malononitrile and dimedone in the presence of A-Alum was carried out in order to optimization of reaction conditions, such as the amount of catalyst, temperature and solvent of the reaction. As shown in Table 1 and 2, the best conditions for this reaction were 20%mol of A-Alum, reflux in Water/ethanol (2:1) as a green solvent or solvent-free at 100 °C.

Table 1. Optimization of catalyst amount and temperature.

Ent.	Ar	Prod.	Solvent	Time (min)	Yield (%)
1	C_6H_5	6a	EtOH/H_2O	110	85[a]
2	C_6H_5	6a	H_2O	180	65[a]
3	C_6H_5	6a	$CHCl_3$	120	10[a]
4	C_6H_5	6a	CH_3CN	120	35[a]
5	C_6H_5	6a	EtOH	120	70[a]

[a] Aqueous medium,

[b] Solvent-free medium.

To explore the generality of the reaction, we extended our study using different aromatic aldehydes containing both electron withdrawing and donating substitutes to prepare a series of 2-amino-7,7-dimethyl-5-oxo-4-(aryl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives

(Table 3). Also a series of 2-amino-4-(aryl)-5-oxo-4, 5-dihydropyrano [*3*,*2*-*c*]chromene-3-carbonitrile derivatives synthesized in good yields. Condensation of aldehydes, malononitrile and 4-hydroxycoumari under same conditions, afforded the above mentioned products (Table 4).

Table 2. Solvent selection for the reaction

Ent.	Ar	Prod.	Solvent	Time (min)	Yield (%)
1	C_6H_5	6a	$EtOH/H_2O$	110	85^a
2	C_6H_5	6a	H_2O	180	65^a
3	C_6H_5	6a	$CHCl_3$	120	10^a
4	C_6H_5	6a	CH_3CN	120	35^a
5	C_6H_5	6a	EtOH	120	70^a
6	C_6H_5	6a	Neat	75	90^b

[a] Reflux, 20% A-Alum.

[b] 100 °C, 20% A-Alum.

Table 3. Syntesis of tetrahydrobenzo[b]pyran.

Ent	Ar	Prod.	Metod A Time (min)	Yield (%)	Metod B Time (min)	Yield (%)
1	C_6H_5	6a	110	85	75	90
2	$4\text{-}Cl\text{-}C_6H_4$	6b	90	92	17	93
3	$4\text{-}CH_3O\text{-}C_6H_4$	6c	100	95	30	94
4	$2,4\text{-}Cl_2\text{-}C_6H_3$	6d	90	85	45	90
5	$3\text{-}OH\text{-}C_6H_4$	6e	90	80	30	91
6	$2,4\text{-}(CH_3O)_2\text{-}C_6H_3$	6f	90	91	25	96
7	$4\text{-}N(Me)_2\text{-}C_6H_4$	6g	110	89	20	87
8	$2\text{-}Cl\text{-}C_6H_4$	6h	120	83	45	85
9	$4\text{-}NO_2\text{-}C_6H_4$	6i	120	90	35	95
10	$2,4\text{-}Cl_2\text{-}C_6H_3$	6j	120	91	30	92

Method A: Reaction carried out in water/ethanol, reflux, 20% A-Alum.

Method B: Reaction carried out under solvent-free condition, 100 °C, 20% A-Alum.

Table 4. Synthesis of dihydropyrano[*c*]chromenes

Ent.	Ar	Prod.	Metod A Time (min)	Yield (%)	Metod B Time (min)	Yield (%)
1	C_6H_5	5a	140	83	80	90
2	$4\text{-}CH_3O\text{-}C_6H_4$	5b	123	64	115	93
3	$2,6\text{-}Cl_2\text{-}C_6H_3$	5c	60	52	45	90
4	$3\text{-}OH\text{-}C_6H_4$	5d	105	43	105	89
5	$2,4\text{-}(CH_3O)_2\text{-}C_6H_3$	5e	65	75	50	90
6	$4\text{-}N(Me)_2\text{-}C_6H_4$	5f	60	79	25	94
7	$2\text{-}Cl\text{-}C_6H_4$	5g	90	69	50	89

Method A: Reaction Reaction carried out in water/ethanol, reflux, 20% A-Alum.

Method B: Reaction carried out under solvent-free condition, 100 °C, 20% A-Alum.

CONCLUSION

We have been reported an efficient and simple method for synthesis of Tetrahydrobenzo[*b*]Pyrans and dihydropyrano[*c*]Chromenes. The use of inexpensive and environmentally friendly catalyst, elimination of toxic solvents, using water/ethanol as a green solvent, simple workup procedure, good yields and short reaction times are some advancement of this method.

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ЕДНОСТАДИЙНА СИНТЕЗА НА ТЕТРАХИДРОБЕНЗО[*b*]ПИРАНОВИ И ДИХИДРОПИРАНО [*c*]ХРОМЕНОВИ ПРОИЗВОДНИ С АМОНИЕВ АЛУМ В „ЗЕЛЕНА“ СРЕДА

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(Резюме)

Синтезирани са различни 4*H*-бензо[*b*]пиранови и пирано [*c*]хроменови производни при „зелени“ условия. Тези евтини, не-токсични, екологично съвместими се получават при добри до вискои добиви.