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SYNTHESIS OF TETRAHYDROBENZO[*b*]PYRAN DERIVATIVES USING SODIUM TRIFLUOROMETHANE SULPHONATE AS AN EFFICIENT CATALYST

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ABSTRACT

An efficient and convenient approach to the synthesis of 2-amino-3-cyano-4-aryl-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran derivatives using sodium trifluoromethanesulphonate as a catalyst is described. This method provides several advantages such as neutral conditions, high yields and simple work procedure.

Key words: Dimedone, Tetrahydrobenzo[***b***]pyran, Sodium trifluoromethanesulphonate.

INTRODUCTION

Recently, the development of environmentally benign clean procedures have become an important goal in organic synthesis. Water plays an essential role in life processes and also as a medium for organic reaction[1,2]. The use of water as aeration medium exhibits remarkable benefits because of its high polarity and immiscibility with organic compounds. Tetrahydrobenzo[*b*]pyrans are an important class of heterocyclic scaffolds in the field of drugs and pharmaceuticals[3]. These compounds are widely used as anti-coagulant[4], diuretic[5], spasmolytic[6], anticancer[7] and anti-anaphylactic agents[8-18]. They are also used for the treatment of neurodegerative disease, AIDS associated dementia and Down's syndrome as well as for the treatment of Schizophrenia and Myoclonus[19].

In recent years, 4H-benzo[*b*]pyrans and their derivatives have attracted considerable attention due to their wide spectrum of biological activities[20]. Furthermore, these compounds have also been employed as pigments and photoactive menerials[21]. These also constitute the structural unit of a series of natural products[22].

The importance of these compounds has led many workers to synthesize them by

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using different catalysts. Each method has its own advantages and disadvantages. A few common heterogeneous catalysts that have so far been used in this reaction are sodium bromide under microwave[23,24], hexadecyltrimethylammonium bromide (HTMAB)[25], triethylbenzylammonium chloride (TEBA)[26], (*s*)-proline[27], perfluorooctanoate[15], *N*-methylimodazole[28], tetrabutyl ammonium bromide[29], silica based sulphonic acid (SiO_2-Pr-SO_3H)[30], potassium phosphate[31], tetramethylammonium hydroxide[32] and sodium hyphochlorite[33].

A perusal of the literature reveals that sodium triflate has been used as a catalyst in Mannich-type reactions of imines with silicon enolates[34] and in two- or three-component aza Diels–Alder reactions[35] of Danishefsky's diene with imines/amines or aldehydes. Sodium triflate is also a versatile reagent in the synthesis of numerous inorganic complexes and in polymer chemistry[35-40]. Prompted by these reports, we report herein a three-component one-pot synthesis of tetrahydrobenzo[*b*]pyrans and its derivatives using sodium triflate as a catalyst.

EXPERIMENTAL

All melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on Perkin-Elmer FTIR 2000 spectrometer (KBr pellet). ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ or DMSO using TMS as an internal standard. Chemical shifts are expressed in δ (ppm) values with respect to TMS.

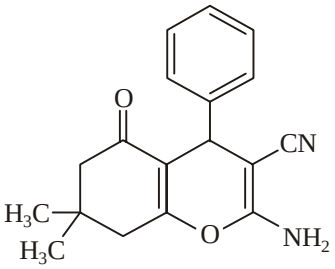
In a typical reaction, equimolar amount of aryl aldehyde X, malononitrile Y, and dimedone Z, were stirred at room temperature in the presence of sodium triflate (10 mol %) as catalyst in 10 mL of 50% aqueous ethanol for specific time as indicated in the Table 1. The progress of the reaction was monitored by TLC. Initially the reactants were soluble but as the reaction proceeds, a white precipitate starts appearing. After completion of the reaction, the precipitate was filtered off, washed with water and ethanol, and finally dried under vacuum. Crude products so obtained were purified by column chromatography on silica (60-100 mesh). All chemicals were purchased from Aldrich and used without purification.

Spectral analysis

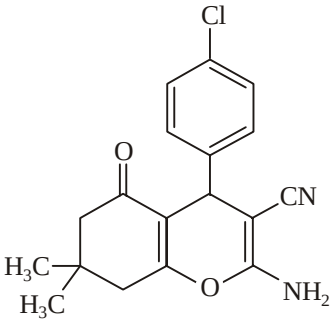
2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4H-benzopyran (a)

IR data (cm^{-1}): 3396 (NH_2), 3028 (C-H), 2198 (CN), 1682 (C=O), 1601 (C=C).

^{1}H NMR data in $CDCl_3$: 1.04 (s, 3H, C*H*$_3$), 1.11 (s, 3H, C*H*$_3$), 1.59 (s, 2H, C*H*$_2$), 2.45 (s, 2H, C*H*$_2$), 4.53 (2H, br s, NH_2), 4.40 (1H, s, C*H*), 7.21-7.28 (m, 5H, Ar*H*).



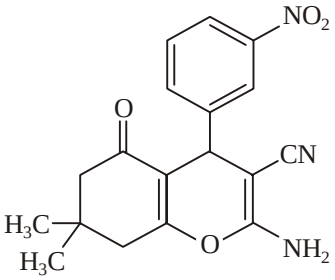
2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4′-chlorophenyl)-5-oxo-4H-benzopyran (b)



IR Spectral data (cm^{-1}): 3380.97 (NH_2), 2959.05 (C-H), 2188.75(CN), 1675.11(C=O), 1635(C=C), 1604.91(C=C).

^{1}H NMR Spectral data in DMSO (d-6): 0.94 (s, 3H, C*H*$_3$), 1.03 (s, 3H, C*H*$_3$), 2.08 (d, 1H, C*H*), 2.22 (d, 1H, C*H*)), 2.50 (s, 2H, C*H*$_2$), 3.33 (s, 1H, C*H*), 4.12 (2H, br s, N*H*$_2$), 7.06-7.38 [(d, 2H), (d, 2H), Ar-*H*]

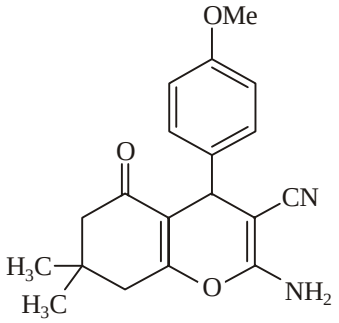
2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-4H-benzopyran (c)



IR Spectral data (cm^{-1}): 3380.98 (NH_2), 3184.26 (C-H), 2189.06 (CN), 1676.03 (C=O), 1635.52 (C=C), 1602.74 (C=C), 1490 (NO_2).

^{1}H NMR data in $CDCl_3$: 1.04 (s, 3H, C*H*$_3$), 1.13 (s, 3H, C*H*$_3$), 2.18 (d, 1H, C*H*), 2.24 (d, 1H, C*H*)), 2.44 (s, 2H, C*H*$_2$), 2.50 (s,1H, C*H*), 4.53(s, H, C*H*$_2$) 4.67 (2H, br, s, N*H*$_2$), 7.46-7.69 (m, 4H, Ar*H*)

2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4′-methoxylphenyl)-5-oxo-4H-benzopyran (d)

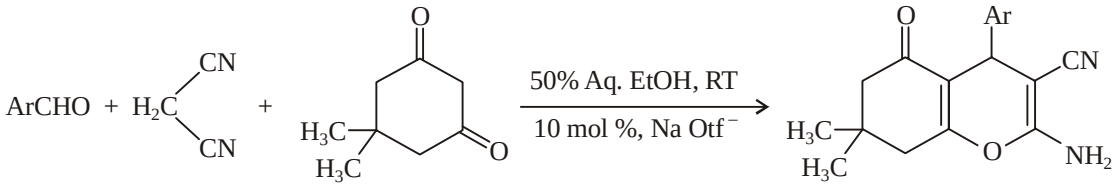


IR Spectral data (cm^{-1}): 3355.65 (NH_2), 2966.66 (C-H), 2193.78 (CN), 1683.35 (C=O), 1655 (C=C), 1605.86 (C=C).

^{1}H NMR data in $CDCl_3$: 1.03 (s, 3H, C*H*$_3$), 1.10 (s, 3H, C*H*$_3$), 1.55 (s, 2H, C*H*$_2$), 2.43 (s, 2H, C*H*$_2$), 3.77 (s, 3H, OC*H*$_3$), 4.36 (1H, s, C*H*) 4.47 (2H, br s, N*H*$_2$), 6.80-7.26 (5H, s, Ar*H*)

RESULTS AND DISCUSSION

A mixture of benzaldehyde (**X**,1 mmol), malononitrile (**Y**,1 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (**Z**, dimedone, 1 mmol) were stirred in the presence of sodium triflate (10 mol%) in aqueous ethanol (50%) at room temperature, to give desired products (**Scheme 1**).



(X) **(Y)** **(Z)** **[P (a-j)]**

Scheme 1

Synthesis of tetrahydrobenzo[*b*]pyran derivatives

It was observed that initially the reactants were soluble but as the reaction proceeds with time, an insoluble white solid begins to form. Although the reaction was attempted with 5 mol% of the catalyst, the desired product was isolated in low yields (about 20%) and the reaction was completed in 5 to 6 hrs. Therefore, all reactions were carried out with 10 mol% of the catalyst. The products were soluble either in chloroform or dimethylsulphoxide. It was found that addition of water facilitates the reaction and hence, 50% aqueous ethanol was found to be the solvent of choice. All reactions proceed smoothly to yield the desired product in excellent yields (Table 1). The purity of the compounds were checked by TLC using silica gel as an adsorbent, ethyl acetate (60%) and petroleum ether (40%) as mobile phase. All products were characterized by IR and ^{1}H NMR and Mass Spectral data analysis. The ^{1}H NMR spectra of 2-amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4′-methoxyphenyl)-5-oxo-4H-benzopyran (Table 1, entry **d**) in show below in Fig. 1.

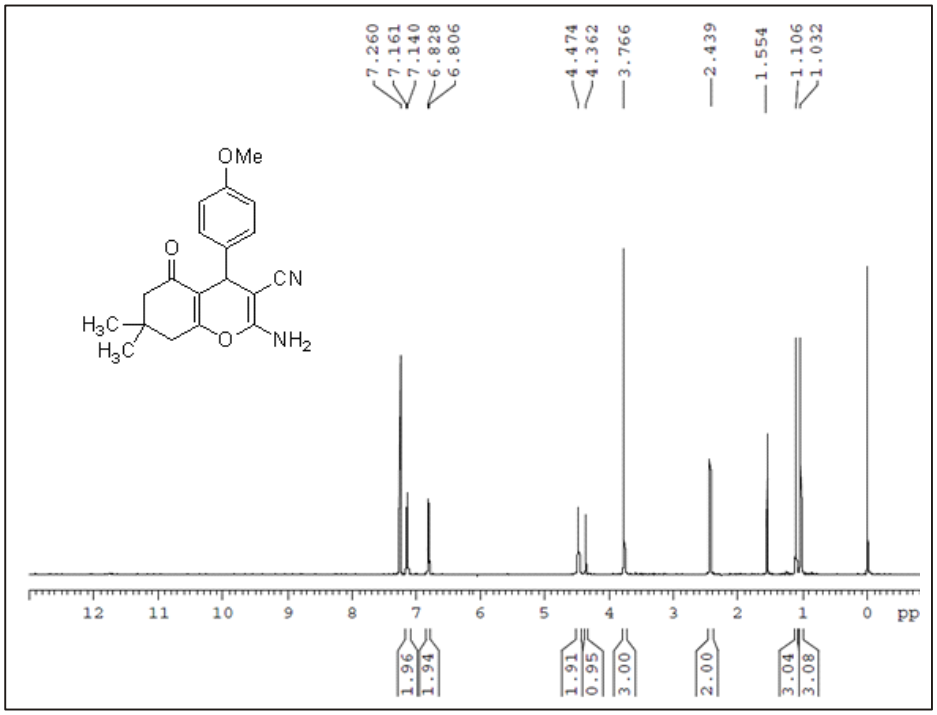


Fig. 1: ^{1}H NMR ($CDCl_3$, 300 MHz) of 2-amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4′-methoxyphenyl)-5-oxo-4H-benzopyran (d) at room temperature

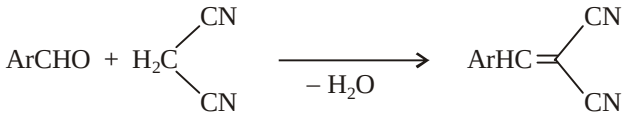
It was found that the aromatic aldehydes containing electron-donating groups (such as alkoxy or methyl, Table 1 entry **d**, **h** and **j**) took relatively longer reaction time, compared to aldehyde bearing electron -withdrawing group (Table1, entry **b**, **f**, **g**, and **c**).

Table 1: Synthesis of tetrahydrobenzo[*b*]pyrans catalyzed by sodium trifluoromethane-sulphonate

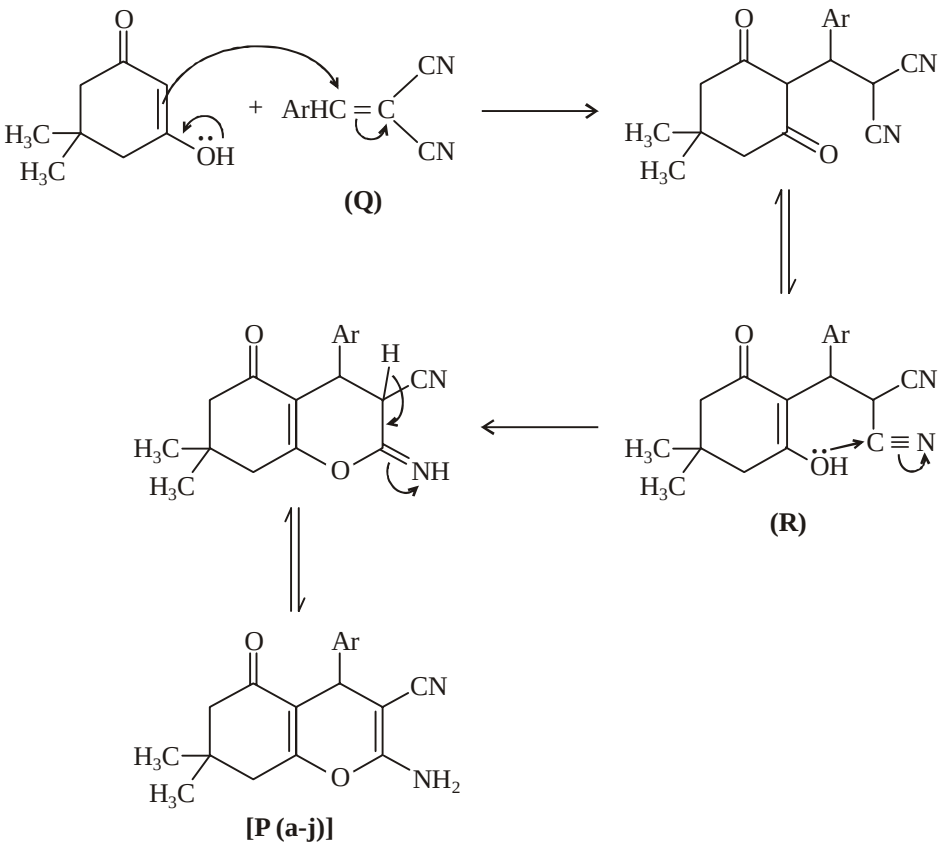
Product entry (P)	Ar	Time (min)	Yield* (%)	m.p. (°C)	
				Found	Reported
a	C_6H_5	40	95	225-228	226-228[27]
b	4-Cl- C_6H_4	35	89	209-211	209-211[26]
c	3-NO_2- C_6H_4	40	92	212-213	212-214[11]
d	4-OMe-C_6H_4	50	97	197-200	199-201[24]
e	4-OH- C_6H_4	35	89	201-202	204-205[15]
f	4-NO_2- C_6H_4	45	93	177-178	177-178[24]
g	4-Br- C_6H_4	30	95	208-209	208-209[15]
h	4-CH_3- C_6H_4	45	96	224-226	223-225[15]
i	3-OH- C_6H_4	35	91	230-232	231-233[15]
j	(4-OH, 3-OMe)-C_6H_4	50	92	227-228	228-230[33]

*Isolated yields

A tentative plausible mechanism for the reaction is drawn in **Scheme 2**. At first the reaction appears to proceed via initial formation of cyanoolefin as an intermediate, formed by the condensation of aryl aldehyde (X) with malononitrile (Y). This has been confirmed by a blank reaction where the (X) and (Y) were mixed without catalyst. Presumably, cyanoolefin intermediate (Q), in presence of sodium triflate, reacts with the active methylene moiety of (Z), giving intermediate (R) which subsequently cyclise to afford the desired product (P). The water molecule eliminated in the first step, plays a key role in the cyclization process.



(X) **(Y)** **(Q)**



Scheme 2

Proposed mechanism

In conclusion, we have shown that sodium triflate is an efficient catalyst for the synthesis of various tetrahydrobenzo[*b*]pyran derivatives under mild conditions.

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