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Potassium Phosphate Catalyzed a Rapid Three-Component Synthesis of Tetrahydrobenzo[*b*]pyran at Ambient Temperature

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Abstract An efficient, rapid, one-pot synthesis of tetrahydrobenzo[*b*]pyran is achieved via a three-component reaction of aldehydes, 1,3-diketone, malononitrile in 20% ethanol using anhydrous potassium phosphate as a catalyst at room temperature. The key advantages are the short reaction time, high yields, simple work-up, inexpensive catalyst and purification of products by non-chromatographic methods, i.e. by simple recrystallization from ethanol.

Keywords Three-component · Tetrahydrobenzo[*b*]pyran · Potassium phosphate · One-pot synthesis

1 Introduction

Tetrahydrobenzo[*b*]pyrans have recently attracted attention as an important class of heterocyclic scaffolds in the field of drugs and pharmaceuticals. These compounds are widely used as anti-coagulant, diuretic, spasmolytic, anticancer and anti-anaphylactin agents [1–5]. Also they can be used as cognitive enhancers for the treatment of neurodegenerative disease including alzheimer's disease, amyoprophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus [6]. Other than their biological importance, some 2-amino-4*H*-pyrans have been widely used as photoactive materials [7]. In addition, the tetrahydrobenzo[*b*]pyran nucleus is an important structural motif of a series of natural products [8, 9] and can be converted into pyridine systems which relate to pharmacologically important calcium antagonists of the dihydropyridine(DHP) [10, 11] type. The importance of these compounds has led the scientific community to synthesize them using the bicomponent condensation [12, 13] of dimedone with α-cyanocinnamonitriles or multicomponent condensation [14–19] of dimedone with aromatic aldehydes and malononitrile.

A detailed literature survey towards the multicomponent synthesis of tetrahydrobenzo[*b*]pyran revealed that most of the protocols employed for this reaction operate under high thermal activation [14–19], microwave activation [15, 20, 21] and ultrasonic irradiation [22, 23]. Recently, Fotouhi et al. [24] reported electrochemical synthesis of tetrahydrobenzo[*b*]pyran. There are a few protocols operable at room temperature using *N*-methylimidazole [25], (*S*)-proline [26] and (D,L)-proline [27]. Each of the above method has its own merit with at least one of the limitations of low yields, commercially unavailable catalysts, long reaction times, harsh reaction conditions and tedious work-up procedures. Hence, improved methods for multicomponent synthesis of tetrahydrobenzo[*b*]pyran using inexpensive and less toxic reagents coupled with simple reaction conditions and easier work-up procedures are required.

In our laboratory, we have studied alkylations of Meldrum's acid [28], nitroaldol condensation [29] and Michael addition of thiols to α,β-unsaturated ketones [30] using anhydrous K_3PO_4 as a base. Also, K_3PO_4 has been utilized for oxidative coupling of thiols to disulfides [31], dithiocarbamates [32], aza-Markovnikov addition of N-heterocycles to vinyl esters [33], while hydrated K_3PO_4 has frequently been used in transition metal catalyzed cross coupling reactions [34]. Thus we explored its efficacy in

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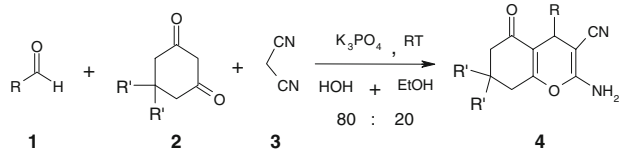
multicomponent synthesis of tetrahydrobenzo[*b*]pyrans (Scheme 1).

In continuation with our earlier experience with potassium phosphate in Michael additions [27], we envisaged that K_3PO_4 could be a suitable catalyst for the present transformation, as potassium is oxophilic, the central K^+ will make a strong co-ordinate bond with 'O' of 1,3-diketone to form its enolate ion (**6**). The counteranion PO_4^{3-} is sufficiently basic for the formation of cyanoolefin (**5**) and subsequent Michael addition of enolate of 1,3-diketone (**6**) on cyanoolefin (**5**), followed by cyclocondensation to form corresponding tetrahydrobenzo[*b*]pyran (**4**). To make the mechanism clear, we have carried out reaction of dimedone and aldehyde (1:1) in ethanol using K_3PO_4 at room temperature for an hour. However, we get reactants as it is instead of Knoevenagel adduct which illustrated reaction sequence. A plausible mechanism for the multicomponent synthesis of tetrahydrobenzo[*b*]pyran using K_3PO_4 in ethanol is proposed (Scheme 2).

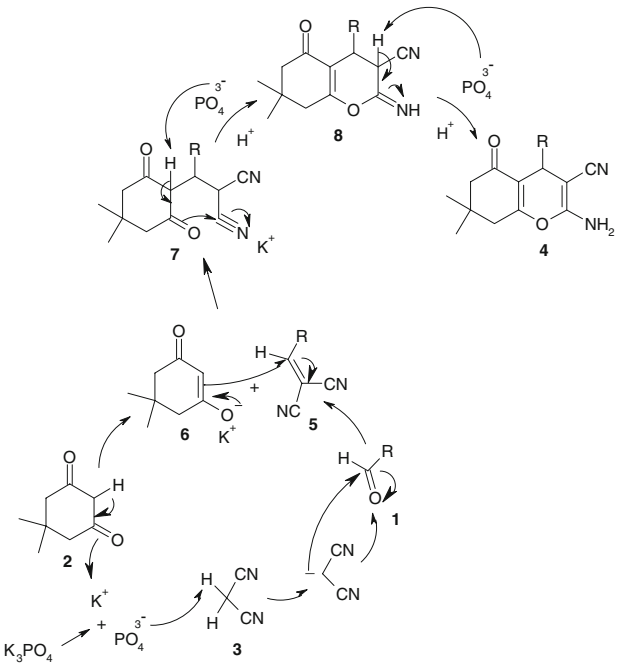
Initially, the reaction of anisaldehyde, dimedone, malononitrile and potassium phosphate was carried out in ethanol medium at room temperature. The corresponding 2-amino-3-cyano-7,7-dimethyl-5-oxo-4-(4′-methoxy phenyl)-5,6,7,8-tetrahydro-4H-benzo[*b*]pyran was obtained rapidly in excellent yield. Encouraged by this result, we then employed this reaction as a template to optimize the reaction conditions (Table 1).

A brief screening of solvents showed that water, chloroform, methanol, acetonitrile and ethanol were less effective than mixed solvent system $H_2O + C_2H_5OH$ (80:20, v/v). We also found that the reaction carried out with other potassium sources such as KH_2PO_4, K_2HPO_4, K_2CO_3 also gave inferior results. Upon examining the influence of the amount of anhydrous K_3PO_4 on the reaction, it was found that 15 mol% of anhydrous K_3PO_4 was sufficient to promote the reaction. In the presence of less than this amount, the yield dropped dramatically, even if longer reaction times were used (Table 1, entry 9). When the amount of anhydrous K_3PO_4 was increased over 15 mol% equivalent, neither the yield nor the reaction time was improved (Table 1, entry 10).

Using the optimized reaction conditions, a range of substituted tetrahydrobenzo[*b*]pyrans *4a–m* were synthesized (Table 2). This method was found to be equally effective for aromatic aldehydes bearing either electron-donating (Table 2, entries 4c–e, 4k) or electron-withdrawing substituents (entries 4g–j, l, m), cyclic aldehyde (entry 4b) as well as for heterocyclic aldehyde (entry 4f). Moreover, the variants of 1,3-diketones could be successfully used for the synthesis of tetrahydrobenzo[*b*]pyrans. The



Scheme 1 Three-component synthesis of tetrahydrobenzo[*b*]pyran



Scheme 2 A plausible Mechanism for formation of tetrahydrobenzo[*b*]pyran

Table 1 Optimization of reaction conditions for the synthesis of tetrahydrobenzo[*b*]pyran

Entry	Solvent[b]	Catalyst	Mol%	Time (min)	Yield (%)[a]
1	H_2O	K_3PO_4	15	120	74
2	$CHCl_3$	K_3PO_4	15	90	70
3	CH_3CN	K_3PO_4	15	90	65
4	CH_3OH	K_3PO_4	15	65	81
5	C_2H_5OH	K_3PO_4	15	60	87
6	$H_2O + C_2H_5OH$(90:10)	K_3PO_4	15	75	83
7	$H_2O + C_2H_5OH$(80:20)	K_3PO_4	15	50	94
8	$H_2O + C_2H_5OH$(70:30)	K_3PO_4	15	40	95
9	$H_2O + C_2H_5OH$(80:20)	K_3PO_4	10	80	81
10	$H_2O + C_2H_5OH$(80:20)	K_3PO_4	20	45	95
11	$H_2O + C_2H_5OH$(80:20)	K_2CO_3	15	75	77
12	$H_2O + C_2H_5OH$(80:20)	KH_2PO_4	15	90	70
13	$H_2O + C_2H_5OH$(80:20)	K_2HPO_4	15	80	81

[a] Reaction conditions: anisaldehyde (1 mmol), dimedone (1 mmol), malononitrile (1 mmol), H_2O + ethanol [80:20, 5 mL], room temp; yields refer to pure isolated products

[b] Entries in bracket indicate the ratio of H_2O to C_2H_5OH on volume basis

Table 2 Potassium phosphate catalyzed multicomponent synthesis of tetrahydrobenzo[*b*]pyrans at room temperature

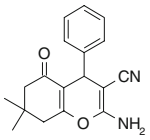
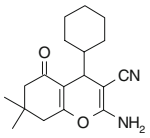
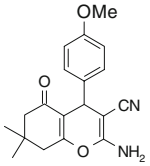
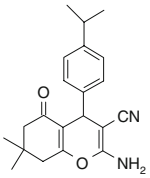
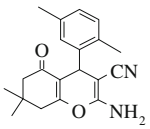
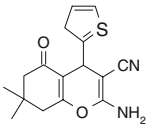
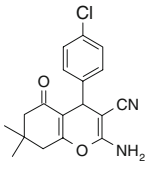
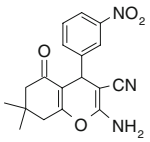
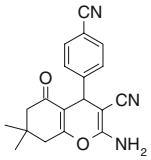
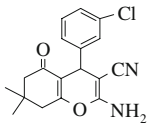
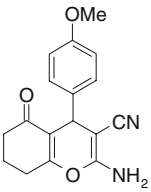
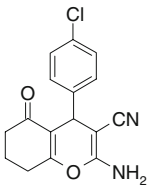
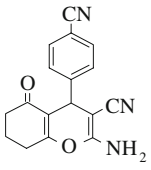
Entry	Product (4)	Time (min)	Yield (%)[a,b]	MP Obs. (L °C)
a		45	94	228–230 (228–230) [26]
b		30	91	209–210
c		50	94	200 (201) [24]
d		50	91	198–200
e		50	90	240–242
f		60	87	210–212 (209–211) [21]
g		60	93	211–212 (209–211) [26]
h		45	89	212–214 (212–214) [26]

Table 2 continued

Entry	Product (4)	Time (min)	Yield (%)[a,b]	MP Obs. (L °C)
i		60	91	224–226 (227–230) [19]
j		60	92	232–234 (236–237) [19]
k		60	91	193–195 (190–192) [17]
l		60	89	228–230 (225–227) [17]
m		60	87	234–236

[a] All products showed satisfactory spectroscopic data (IR, ^{1}H and ^{13}C NMR, MS)

[b] Yields refer to pure, isolated products

advantage of this method is its easy work-up, which includes pouring of the reaction mixture into ice water to precipitate a solid, which is filtered off to give sufficiently pure compounds. The products were isolated in better yields and in less reaction time than previously reported methods.

In summary, we disclose here an efficient method for multicomponent synthesis of tetrahydrobenzo[*b*]pyran at ambient temperature using anhydrous K_3PO_4 as an inexpensive catalyst. This procedure offers several advantages including mild condition, high yields, inexpensive catalyst,

wide scope of substrates and operational simplicity, simple work-up, and purification of products by non-chromatographic methods, i.e., by simple recrystallization from ethanol.

2 Experimental

2.1 General

IR spectra were recorded on a Perkin–Elmer FT-IR 783 spectrophotometer. NMR spectra were recorded on a BrukerAC-300 spectrometer in $CDCl_3$ using tetramethylsilane as internal standard. Melting points are uncorrected.

3 Typical Procedure

A mixture of aldehyde (1 mmol), malononitrile (1 mmol), 1,3-diketone (1 mmol) and K_3PO_4 (21 mg, 15 mol%) in 20% ethanol (5 mL) was stirred at r.t. for the time indicated in Table 2. The reaction mixture was poured into ice water and just filtered to yield corresponding tetrahydrobenzo[*b*]pyran. The residue was purified by recrystalization in ethanol to provide the desired product **4** (Table 2).

3.1 Spectral Data of Unknown Compounds

Entry 4b mp 209–210 °C; IR (KBr): 3414, 3327, 3249, 2923, 2193, 1675, 1654, 1594, 1380, 1251, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.11$ (s, 3H,CH_3), 1.16 (s, 3H, CH_3), 1.24–1.71 (m, 11H), 2.9 (s, 2H, $–CH_2$), 2.37 (s, 2H, $–CH_2$), 3.09 (d, $J = 2.7$ Hz, 1H, –CH), 4.53 (s, 2H, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.19, 26.31, 26.56, 27.41, 27.84, 29.27, 30.52, 32.05 34.74, 40.67, 43.79, 50.84, 58.91, 114.18, 120.23, 159.87, 163.12, 196.46; EIMS: m/z 300 (M^+).

Entry 4d mp 198–200 °C; IR(KBr): 3369, 3181, 2984, 2185, 1656, 1509, 1469, 1408, 1363, 1249, 778, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.05$ (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 2.22 (s, 2H, $–CH_2$), 2.45 (s, 2H, $–CH_2$), 2.83 (m, 1H, CH_3–CH–CH_3), 4.37 (s, 1H), 4.52 (s, 2H, NH_2), 7.12(s, 4H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.86, 27.75, 28.79, 29.64, 32.16, 33.63, 35.02, 40.66, 50.67, 63.59, 114.15, 118.81, 126.60, 127.29, 140.50, 147.42, 157.50, 161.46, 195.93; δ EIMS:m/z 336 (M^+).

Entry 4e mp 240–242 °C; IR(KBr): 3409, 3315, 3045, 2963, 2927, 2191, 1659, 1692, 1500, 1461, 1404, 1367, 814, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.06$ (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.21(s, 2H, $–CH_2$), 2.22 (s, 3H, $–CH_3$), 2.47 (s, 2H, $–CH_2$), 2.52 (s, 3H, $–CH_3$), 4.49 (s, 2H, NH_2), 4.63 (s, 1H, CH), 6.73 (s,1H), 6.87 (d, $J = 8$ Hz, 1H), 7.0 (d, $J = 8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.07, 21.13, 27.58, 28.95, 30.95, 32.29, 40.63, 50.60, 114.67, 127.75, 128.04, 130.41, 132.65, 135.56, 141.66, 157.13, 161.56,161.56, 195.95; EIMS: m/z 322 (M^+).

Entry 4m mp 234–236 °C; IR(KBr): 3423, 3334, 3190, 2918, 2228, 2199, 1679, 1653, 1602, 1498, 1456, 1416, 1332, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.05$ (m, 2H, $–CH_2–CH_2–CH_2$), 2.37(t, 2H, $–CH_2$), 2.61 (t, 2H, $CO–CH_2$), 4.47 (s, 1H), 4.66 (s, 2H, NH_2), 7.37(d, $J = 8$ Hz, 2H, Ar–H), 7.59(d, $J = 8$ Hz, 2H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.09, 27.04, 35.73, 36.61, 100, 110, 114.31, 118.41, 119.81, 128.82, 132.64, 148.61, 158, 163.89, 195.84; δ EIMS: m/z 290 (M^+).

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