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Montmorillonite K-10 catalysed one-pot three component condensation for the synthesis of tetrahydrobenzo[b]pyrans and pyrano[2,3-d]pyrimidines

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ABSTRACT

A clean and simple synthesis of tetrahydrobenzo[*b*]pyrans and pyrano[2,3-*d*]pyrimidinederivatives was accomplished in good to excellent yields *via* one-pot, three component condensation of cyclic 1,3-dicarbonyl compounds, aromatic aldehydes and malonitrile in ethanol solvent catalyzed by montmorillonite K-10.

KEYWORDS

Multi-component reactions;
Heterogeneous catalysis;
Montmorillonite K-10;
Tetrahydrobenzo[b]pyrans;
Pyrano[2,3-d]pyrimidines.

INTRODUCTION

Multi-component reactions (MCRs) are of increasing importance in organic and medicinal chemistry[1]. Selectivity, atom economy, time saving, environmental friendliness, cost effectiveness and reconciliation of molecular complexity with experimental simplicity are some of the significant advantages of MCR strategies over conventional linear type synthesis[2]. The development of MCRs for the generation of combinatorial libraries of heterocyclic compounds is in current demand from the viewpoint of drug discovery process[3].

4H-Benzo[b]pyrans represent a heterocyclic ring system of considerable interest because of several biological activities associated with this scaffold[4]. Some analogues have been found to act as anti-cancer, antianaphylactic, diuretic, spasmolytic and anti-coagulant agent[5]. Furthermore, the sub-structural unit of 4Hbenzo[b]pyrans is prevalently found in natural products and photo-active materials[6]. This valuable class of heterocycles is generally prepared by base (triethylamine or piperidine) catalyzed three component condensations of malonitrile, aldehyde and dimedone in organic solvents like DMF[7] or acetic acid[8]. The utilization of water as reaction medium for the synthesis of 4H-benzopyrans is reported using hexadecyl trimethyl ammonium bromide[9] and S-proline[10] as the catalysts. The solvent free reaction conditions like microwave irradiation[11] and solid state heating have also been introduced for the synthesis of 4H-pyrans[12]. Although most of these processes offer distinct advantages, they suffer from certain drawbacks such as long reaction time, unsatisfactory yields due to side product formation, need of special apparatus, use of toxic organic solvents and tedious work-up procedure. Therefore, the development of new, efficient methods for the preparation of 4Hbenzo[b]pyrans is desired.

The last two decades have witnessed an explosive growth in the application of heterogeneous catalysis brought about by inorganic solids such as montmorillonite K-10[13]. The commercially available montmorillonite K-10 is an inexpensive, non-toxic and recyclable inorganic solid material possessing both Bronsted and Lewis acidity. In continuation of our work on MCRs

TABLE 1: Formation of pyrano[2,3-d]pyrimidines in ethanol

Entry	Ar	Reaction time (h)	Yield (%)[a]	M. P. (^{0}C) found	M. P. (^{0}C) reported
6a	C_6H_5-	10	73	226-227	225[14]
6b	4-MeO-C_6H_4-	10	76	202-203	not available
6c	4-Cl-C_6H_4-	10	80	194-195	not available
6d	3-NO_2-C_6H_4-	10	79	213-214	not available

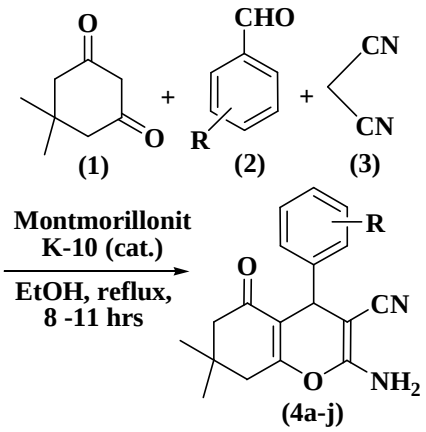
[a]Isolated yield after recrystalization

and clay catalysis[14], here in we wish to report another remarkable catalytic activity of montmorillonite K-10 for the one-pot three component condensation of malonitrile, aldehyde and dimedone to form variously substituted 4H-benzo[b]pyrans (SCHEME 1).

In an initial experiment a mixture of benzaldehyde (3 mmol), malonitrile (3 mmol) and dimedone (3 mmol) in ethanol (15mL) was refluxed in the presence of catalytic quantity of montmorillonite K-10 (20% wt.) for 10 hrs. After the completion of reaction, the insoluble montmorillonite K-10 was filtered from the reaction mixture. The resulting filtrate was poured into crushed ice and the crude product was recrystallized from ethanol to afford **(4a)** in 83% yield. The filtered catalyst, montmorillonite K-10 was washed with acetone several times and subjected to thermal activation at 120^{0}C. The reuse of recycled montmorillonite K-10 for second and third time resulted in the formation of **(4a)** with 69 % and 48 % yield respectively (TABLE 1, entry 5).

In order to study the influence of different acid catalysts on the reaction, other acids were also investigated for the formation of **(4a)**. In absence of any acid catalyst, the above reaction resulted in the formation of products such as 2-(4-methoxybenylidene)-5,5-dimethyl cyclohexane-1,3-dione (34% yield) and 2-(4-methoxy benzylidene)malonitrile (53 % yield), due to the Knoevenagel condensation reaction between anisaldehyde and dimedone or malonitrile respectively. However, when the reaction was subjected to the treatment of different acid catalysts such as PTSA, amberlyst-15, montmorillonite KSF, montmorillonite K-10 and zeolite-HY, the desired product was obtained in 17, 38, 64, 82 and 57 % yields, respectively. In each case, the reaction mixture was refluxed for 10 hrs and 20 % weight of the catalyst with respect to the total weight of all the reactants was considered. Thus, montmorillonite K-10 was found to be, above all, the excellent heterogeneous acid catalyst for the synthesis of **(4a)**.

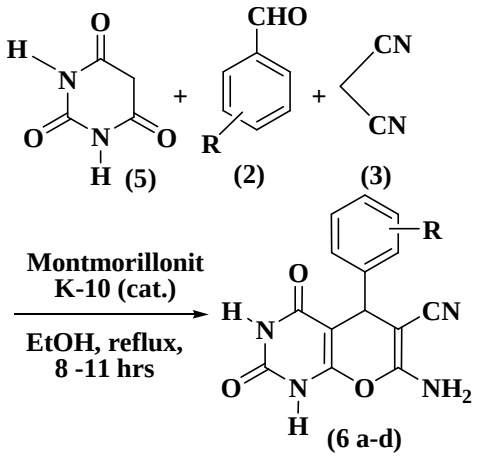
With this result in hand, other aromatic aldehydes



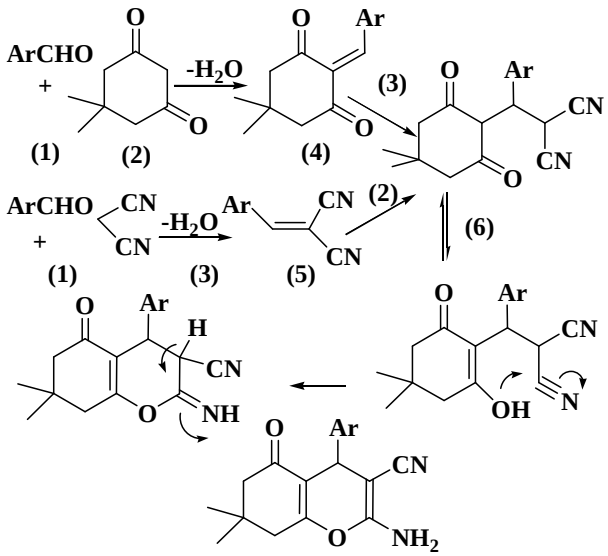
SCHEME 1

have been reacted with malonitrile and dimedone under similar experimental conditions and the results are listed in TABLE 2. It is important to note that the reaction is applicable only to malonitrile whereas ethylcynoacetate and cynoacetamide failed to react under similar experimental conditions. Benzaldehyde and other aromatic aldehydes containing electron-donating groups (such as methoxy, hydroxyl groups) or electron-withdrawing groups (such as nitro, halide) were employed and reacted well to give a corresponding 4Hbenzo[b]pyrans in good to excellent yields. In all the cases, the reactions proceeded smoothly with 20 % weight of montmorillonite K-10 with respect to the total weight of all the reactants. The structures of the products were confirmed from spectroscopic data and melting points and found to be comparable with those of literature data. The IR spectra exhibited sharp bands at 3335 cm^{-1} (NH_2) and 2187 cm^{-1} (CN). The NMR spectra showed the absence of methylene protons of the dimedone and the presence of characteristic peak at δ= 4.17- 4.54 ppm for H-4 of **4(a-j)**.

Having succeeded with dimedone, the reaction of barbituric acid (2 mmol), anisaldehyde (3 mmol) and malonitrile (3 mmol) in ethanol (15 mL) using montmorillonite K-10 (20 % wt.) was examined (SCHEME 2). After refluxing the above reaction mixture for 8 hours,



SCHEME 2



SCHEME 3: Mechanism of tetrahydrobenzo[b]pyran formation

the formation of corresponding pyrano[2,3-d] pyrimidines **(6b)** was realized in 73 % yield. The results are summarized in TABLE 2 for the reactions of other aldehydes.

Mechanistically, the formation of tetrahydro benzo[b]pyrans will proceed through Knoevenagel condensation followed by Michael addition. As earlier mentioned the formation of Knoevenagel condensation products such as **(4)** and **(5)** were observed in absence of the catalyst, montmorillonite K-10. This fact is supported by the literature evidence that Knoevenagel condensation of aromatic aldehyde with malonitrile and dimedone can take place even in absence of any catalyst[15]. The formation of tetrahydrobenzo[b]pyrans is, therefore,

TABLE 2: Montmorillonite K-10 catalysed synthesis of 4H-benzo[b]pyrans (4a-j) in ethanol under refluxing conditions

Product	Ar	Reaction time (h)	Yield[a] (%)	Mp (^oC) found	Mp (^oC) reported (lit)[8,9]
(4a)	C_6H_5	10	83	223-225	226-228
(4b)	4-$MeOC_6H_4$	11	82	200-202	198-200
(4c)	4-HOC_6H_4	13	76	212-213	214-215
(4d)	4-MeC_6H_4	12	81	214-216	214-216
(4e)	4-$NMe_2C_6H_4$	10	80	223-224	220-222
(4f)	4-MeO-3-	12	83	239-242	237-238
(4g)	OH-C_6H_3	10	87	207-209	207-209
(4h)	4-ClC_6H_4	13	78	222-224	224-226
(4i)	2-$NO_2C_6H_4$	13	84	208-210	210-212
(4j)	3-$NO_2C_6H_4$	12	80	131-133	130-132

[a]Isolated yields after recrystalization.

relied on the success of Michael addition reaction. Based upon this hypothesis, we carried out the independent reaction of isolated cyano-olefin with dimedone in absence of montmorillonite K-10. In this case, the reaction did not take place and the unreacted cyano-olefin and dimedone were quantitatively recovered. Thus, this experiment indicates that montmorillonite K-10 is essential for promoting Michael addition. The role of montmorillonite K-10 is to enhance the nucleophilic character of the reactive methylene carbon of dimedone or malonitrile to facilitate the Michael addition for the formation of key intermediate **(6)**. Finally **(6)** undergoes intramolecular cyclisation via the nucleophilic attack of −OH group on the cyano moiety to form tetrahy drobenzo[b]pyrans.

In summary, a highly efficient methodology for the synthesis of 4H-benzo[b]pyrans and pyrano[2,3-d]pyrimidines by three component condensations of aromatic aldehyde, malonitrile and cyclic 1,3-dicarbonyl compounds in the presence of catalytic quantity of montmorillonite K-10 is reported. High yields of the products, simple product isolation technique, recyclability of the catalyst and overall .green. reaction conditions are important features of this methodology.

EXPERIMENTAL

Mnotmorillonite K-10 was purchased from Lancaster Chemicals and used as received without any pretreatment or activation. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. 1H NMR spectra were obtained with

a Varian 400-MHz spectrometer with TMS as an internal standard. The IR spectra were recorded (KBr) on a Perkin-Elmer FT-IR spectrophotometer.

General procedure for the preparation of 4HBenzo[b]pyrans and pyrano[2,3-d]pyrimidines

A mixture of an aromatic aldehyde (3 mmol), malonitirle (3 mmol), appropriate cyclic 1,3-dicarbonyl compounds (3 mmol) and montmorillonite K-10 (20 mole %) in ethanol (20 ml) was refluxed for the time as mentioned in TABLE 1. The progress of the reaction was monitored by thin layer chromatography. After the completion of the reaction, the mixture was cooled to room temperature and montmorillonite K-10 was filtered off. The resulting filtrate was then poured into crushed ice and the crude product was purified by recrystallization using ethanol (95%). Data of the selected compounds are shown below.

Spectral data of selected products

2-Amino-5,6,7,8-tetrahydro-5-oxo-4-(4′-N, N-dimethylaminophenyl)-4H-benzo[b]-pyran-3-carbonitrile

Crystalline yellow solid, Mp 221-223^{0}C (Lit. Mp 220–222^{0}C) IR (KBr): 3387, 3312, 2961, 2853, 2189, 1687, 1604, 1456, 1253, 1038, 967, 843, 768cm^{-1}. 1HNMR ($CDCl_3$): δ = 0.91 (s, 3H), 1.00 (s, 3H), 2.19 (d, J = Hz, 2H), 2.39 (d, J = Hz, 2H), 3.08 (s, 2H, br.), 3.33 (s, 6H), 4.00 (s, 1H), 6.60 (d, J = Hz, 2H), 6.87 (d, J = Hz, 2H)

2-Amino-5,6,7,8-tetrahydro-5-oxo-4-(4′-chloro phenyl)-4H-benzo[b]-pyran-3-carbonitrile

Crystalline yellow solid, Mp 208 - 210^{0}C (Lit. Mp 207-209^{0}C) IR (KBr): 3379, 3193, 2953, 2173, 1604, 1596, 1398, 1227, 1032, 857, 738 cm^{-1}. 1HNMR ($CDCl_3$): δ = 0.95 (s, 3H), 1.01 (s, 3H), 2.25 (d, J = 7 Hz, 2H), 2.43 (d, J = 7 Hz, 2H), 3.33 (s, 2H, br.), 4.17(s, 1H), 7.16 (d, J = Hz, 2H), 7.31 (d, J = Hz, 2H)

2-Amino-5,6,7,8-tetrahydro-5-oxo-4-(4′-methoxy phenyl)-4H-benzo[b]-pyran-3-carbonitrile

Crystalline yellow solid, Mp 200-202^{0}C (Lit. Mp: 198-200^{0}C) IR (KBr): 3373, 3191, 2962, 1654, 1598, 1406, 1253, 1154, 1034, 969, 768 cm^{-1}. 1HNMR ($CDCl_3$): δ = 0.88 (s, 3H), 0.96 (s, 3H), 2.03 (d, J =7.2 Hz, 2H), 2.16 (d, J = 7.3 Hz, 2H), 3.48 (s, 2H, br.), 3.64 (s, 3H), 4.05 (s, 1H), 6.90 (m, 4H).

2-Amino-5,6,7,8-tetrahydro-5-oxo-4-(3′ - nitrophenyl)-4H-benzo[b]-pyran-3-carbonitrile

Crystalline yellow solid, Mp 211-213^{0}C (Lit. Mp 210-212^{0}C) IR (KBr): 3432, 3335, 3203, 2958, 2875, 2187, 1659, 1598, 1533, 1377, 1252, 1039, 908, 824, 733 cm^{-1}. 1HNMR ($CDCl_3$): δ = 0.94 (s, 3H), 1.03 (s, 3H), 2.12 (d, J = 7.1 Hz, 2H), 2.23 (d, J = Hz, 2H), 3.36 (s, 2H, br.), 4.40 (s, 1H), 7.64 (m, 2H), 8.02 (m, 2H).

7-Amino-2,3,4,5-tetrahydro-5-(4′-chlorophenyl)-2,4-dioxo-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile

Crystalline yellow solid, Mp 194-195^{0}C. IR (KBr): 3379, 3217, 3090, 2926, 2850, 2204, 1755, 1575, 1422, 1228, 1201, 1091, 839, 808, 792 cm^{-1}. 1HNMR ($CDCl_3$): δ = 4.26 (s, 1H), 7.16 (s, 2H, br), 7.24 (d, 2H, J = 8.47 Hz), 7.35 (d, 2H, J = 8.45 Hz), 11.08 (s,1H, br), 12.10 (s, 1H, br).

7-Amino-2,3,4,5-tetrahydro-5-(3′-nitrophenyl)-2,4-dioxo-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile

Crystalline yellow solid, Mp 213-214^{0}C IR (KBr): 3529, 3371, 3167, 3032, 2957, 2856, 2193, 1753, 1602, 1562, 1425, 1199, 829, 680 cm^{-1}. 1HNMR ($CDCl_3$): δ = 4.47 (s, 1H), 7.28 (s, 2H, br), 7.61 (t, 1H, J = 7.90 Hz), 7.75 (d, 1H, J = 7.82 Hz), 8.09 (m, 2H), 11.11 (s, 1H, br), 12.17 (s, 1H, br).

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