YTTRIUM OXIDE: A HIGHLY EFFICIENT CATALYST FOR THE SYNTHESIS OF PYRANO[2,3-*d*]PYRIMIDINE DERIVATIVES IN AQUEOUS METHANOL MEDIA

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Synthesis of pyrano[2,3-*d*]pyrimidine derivatives has been achieved by one-pot three component condensation reactions of various aromatic aldehydes, malononitrile and barbituric acid in aqueous methanol using yttrium oxide (Y_2O_3) as a catalyst. The potential application of Y_2O_3 in various synthesis increasing rapidly due to its reaction simplicity, minimum reaction time, high yields, environment friendly procedure and low cost of chemicals. The reactants are completely soluble in 70 % aqueous methanol and afford high yield of products.

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Introduction

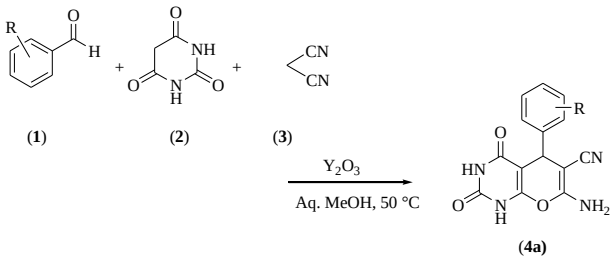
Development of novel synthetic methodologies to facilitate the preparation of the desired molecule is an intense area of research. In this regard, efforts have been made constantly to introduce new methodologies that are efficient and more compatible with the environment.

Multicomponent reactions (MCRs) have received considerable attention of synthetic organic chemist from the last century due to the synthesis of different biologically active important complex heterocyclic molecules in single step. MCRs have emerged as efficient, atom economic, time saving and powerful tools in modern synthetic chemistry, as they increases the efficiency of the reaction along with saving time, solvents and chemicals.[1-3] The MCRs are combined with heterogeneous catalysts which can be recycled to give a green touch to these reactions.[4] Research in MCRs is an encouraging and hot topic of organic chemistry, because of their advantages in preparation of heterocyclic small molecule libraries and in drug discovery procedures.[5]

The pyrano[2,3-*d*]pyrimidine show biological activities as potential antiviral and antileishmanial,[6] anti-HIV,[7] antitubercular and antimicrobial,[8] antimicrobial,[9] antiplatelet,[10] antifungal,[11] antiviral,[12] bronchiodilator and vasodilator,[13] antiallergic,[14] antihypertensive and hepatoprotective,[15] antimalarial,[16] *invitro* antibacterial and antifungal agent.[17]

Several catalysts have been used for the synthesis of various 7-amino-5-phenyl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*, 5*H*)-dione derivatives such as DABCO,[18] NaBr,[19] L-Proline,[20] Triethylamine,[21] DAHP,[22] $[KAl(SO_4)_2]$,[23] TBAF,[24] Piperidine,[25] $[bmim]BF_4$ [26] and K_2CO_3.[27] Many of the reported synthetic protocols are associated with the use of expensive reagents, extended reaction time, high reaction temperatures and tedious work-up procedures.

Herein we report the synthesis of pyrano[2,3-*d*]pyrimidine using recyclable and ecofriendly heterogenous catalyst yttrium oxide (Y_2O_3) by reacting aldehydes, malononitrile and barbituric acid in aqueous methanol (Scheme 1).



Scheme 1. Synthesis of pyrano[2,3-*d*]pyrimidine using Y_2O_3.

Experimental

All chemicals and reagents were purchased from commercial suppliers and used throughout without purification. Aromatic aldehydes, barbituric acid and malononitrile were purchased from Across organics. All solvents were purchased from Merck. Ethyl acetate, sodium sulphate and NaCl were purchased from Fisher Scientific.

The melting points of products are uncorrected. The ^1H NMR spectra was recorded on a Bruker Advance spectrometer operating at 400 MHz for ^1H at 295 K in $CDCl_3$. The chemical shifts were assigned in comparison with the residual proton and carbon resonance of the solvent DMSO (δ H=7.25 ppm) and TMS as the internal reference (δ=0 ppm). FTIR spectra were recorded on a Perkin-230 spectrometer in the range of 400-4000 cm^{-1} and peak positions are given as transmittance (%) against wave numbers (cm^{-1}).

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General procedure for synthesis of 7-amino-5-phenyl-1H-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-dione

In a round bottom flask, aromatic aldehyde (**1**) (1.00 mmol), barbituric acid (**2**), (1.00 mmol) and malononitrile (**3**) (1.00 mmol) and Y_2O_3 (10 mol %) in 70:30 MeOH:H_2O (2 mL) were taken and the reaction mixture was stirred at 50 °C. The progress of reaction was monitored by TLC using ethyl acetate-hexane (70:30) as a solvent system. The reaction mixture was quenched with crushed ice. The solid product was filtered, washed with ice cold water and recrystallized from ethanol to obtain pure pyrano[2,3-*d*] pyrimidine derivatives with excellent yields (90-96%).

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

IR (KBr): ν = 3441, 3352, 3189, 2982, 1726 cm^{-1}. ^1H NMR (400 MHz, DMSO-*d6*): δ = 10.87 (s, 1H, NH), 10.79 (s, 1H, NH), 6.98 (d, 2H, Ar-H), 6.82 (s, 2H, NH_2), 6.61 (d, 2H, Ar-H), 4.31 (s, 1H, CH) ppm.

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

IR (KBr): ν = 3203, 3103, 2853, 1755, 1675, 1574 cm^{-1}. ^1H NMR (400 MHz, DMSO-*d6*): δ = 11.44 (s, 1H, NH), 11.30 (s, 1H, NH), 8.00-8.26 (m, 4H, Ar-H), 7.5-7.6 (s, 2H, NH_2), 3.31 (s, 1H, CH) ppm.

Results and Discussion

We have carried out reaction of an aromatic aldehyde, barbituric acid and malononitrile in the presence of yttrium oxide (Y_2O_3) as a catalyst in aqueous methanol (Scheme l). We varied several reaction parameters in order to optimize the reaction conditions, including an amount of the catalyst yttrium oxide, reaction temperature and use of different solvents. The best reaction conditions are when aromatic aldehyde (1.0 mmol), barbituric acid (1.0 mmol), malanonitrile (1.0 mmol) and Y_2O_3 (10 %) were reacted in 2 mL of 70:30 MeOH:H_2O for 30 min at 50 °C. Under these conditions 90-96 % of the product was achieved. In the absence of the catalyst, however, the only traces of product were obtained. To evaluate the exact concentration of yttrium oxide required for the optimum reaction, we have investigated the model reaction for the synthesis of compound (**4a**) using different concentrations of yttrium oxide, keeping the other conditions constant (Table 1).

Table 1. Optimization of the amount of catalyst Y_2O_3.

S. No.	Y_2O_3, mol %	Solvent	Yield, %
1	No catalyst	MeOH; H_2O	Traces
2	2	MeOH; H_2O	30
3	4	MeOH; H_2O	50
4	6	MeOH; H_2O	60
5	8	MeOH; H_2O	80
6	10	MeOH; H_2O	90
7	12	MeOH; H_2O	90
8	14	MeOH; H_2O	90

The results revealed that, when the reaction was carried out in presence of yttrium oxide up to 6 mol % of catalyst, it gave lower yield of product even after prolonged duration. Whereas optimum yields of product, were obtained by using 10 mol % of catalyst in shorter time, this concentration was ideal to carry out reaction smoothly. Further increasing in concentration of catalyst does not affect the yield of reaction (Table 1, entry 6, 7, 8). In order to evaluate the effect of different solvents, reactions were carried out in various solvents as enlisted in Table 2. Ethanol and DMSO resulted in good yields of 80% and 78%, respectively, whereas, aqueous methanol furnished the product in excellent yield of 90 % (Table 2, entry 6), making it the most suitable solvent.

Table 2. Influence of solvent on synthesis of pyrano[2,3-*d*]pyrimidines derivatives.

S. No.	Solvent	Yield, %
1	Toluene	60
2	Acetonitrile	70
3	DMF	75
4	DCM	70
5	Ethanol	80
6	Methanol (70%)	90
7	DMSO	78

Furthermore to study the reusability of the catalyst yttrium oxide (Y_2O_3), we have carried out model reaction of synthesis of 7-amino-5-(4-bromophenyl)-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*, 5*H*)-dione by using 10 mol % of catalyst for up to 5 reruns. Recycling of the catalyst up to 3 runs show optimum results, after the 3rd run, it shows slightly decreased yield. The yields obtained by recycling of catalyst for the fresh run, 1st, 2nd, 3rd, 4th and 5th reruns are, 92 %, 87 %, 85 %, 82 %, 78 % and 71 %, respectively.

Table 3. Synthesized pyrano[2,3-*d*]pyrimidines derivatives.

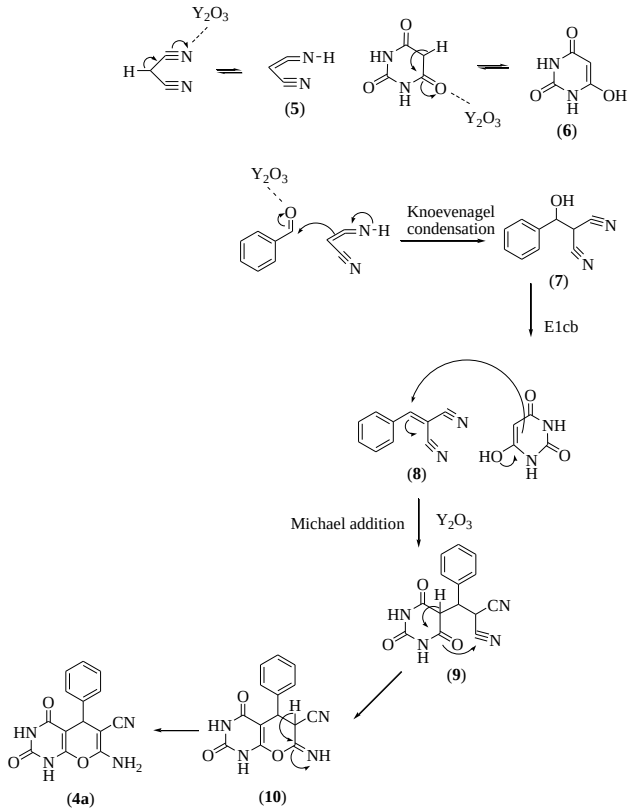
Compound	R	Time, min.	Yield, %	m.p., ^0C
4a	H	30	90	204-206
4b	4-Nitro	30	92	248-250
4c	4-Bromo	35	95	220-222
4d	4-Hydroxy	30	92	228-230
4e	2-Chloro	30	95	240-242
4f	2,4-Dimethoxy	35	90	235-237
4g	2- Nitro	40	91	257-258
4h	3- Nitro	30	90	273-275
4i	3,4-Dimethoxy	35	91	303-306
4j	4-Methoxy	40	92	290-293
4k	4-Methyl	32	95	206-208
4l	4-Chloro	30	88	242-244
4m	3-Methyl	35	91	198-200
4n	3-Bromo	30	93	220-222
4o	2-Methoxy	38	88	230-232

To study the effect of structure of the aldehyde on the yield of the product pyrano[2,3-*d*]pyrimidines derivatives were synthesized by treating different aldehydes. Notably, all the substrates were observed to be well tolerated under optimized reaction conditions furnishing the product in good to excellent yields. Formation of the desired product was

confirmed by comparing their melting point and IR and ^{1}H NMR spectra with those of the reported compounds**.** The yields and m.p. etc. of the various pyrano[2,3-*d*]pyrimidines derivatives are given in Table 3.

Reaction mechanism

In the presence of yttrium oxide, malononitrile, and barbituric acid undergo enolisation to give (**5**) and (**6**), respectively. Yttrium oxide acts as a lewis acid catalyst.[28] in Knoevenagel condensation of the aromatic aldehyde and (**6**) to give intermediate (**7**), which on E_1cb elimination gives intermediate (**8**). Michael addition reaction of (**6**) and (**8**) gives (**9**). The intermediate (**9**) on intramolecular cyclisation gives another intermediate (**10**), which on rearrangement gives the product pyrano[2,3-*d*]pyrimidine (**4a**).



Scheme 2. Plausible reaction mechanism for the synthesis pyrano[2,3-*d*]pyrimidines.

Conclusion

In present work, we have demonstrated the utility of the combination of yttrium oxide (Y_2O_3) and aqueous methanol for the synthesis of 7-amino-5-phenyl-1H-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-dione from aromatic aldehydes, barbituric acid and malononitrile at room temperature. The presence of Lewis acidic sites (Y^{3+}) in the catalyst and aqueous methanol are good combination for the synthesis. It is sufficient enough to catalyze the reaction at ambient temperature affording (i) use of minimum reaction temperature, (ii) reduced reaction times, (iii) non-toxic and economically use of heterogeneous catalyst, (iv) eco-friendly use of solvents, (v) high yield and (vi) easy separation are the significant advantages associated with the present protocol, which make it an attractive strategy for the synthesis 7-amino-5-phenyl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-dione from aromatic aldehydes. This present protocol highlights and explores not only the applications of aqueous methanol as an excelent solvent in organic synthesis but also the reusability of Y_2O_3 as a good heterogeneous catalyst for the synthesis of heterocyclic compounds.

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