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Iranian Chemical Communication

Tetra-*n*-butyl ammonium hydroxide mediated one pot synthesis of Pyrano[2, 3-d]pyrimidinone derivatives

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Received: 7 April 2016, Accepted: 29 October 2016, Published: 29 October 2016

Abstract

Tetra-*n*-butyl ammonium hydroxide was used as a catalyst for one-pot, three component condensation reactions consisting of aromatic aldehyde, malononitrile and barbituric acid in ethanol: water solvent system at 60 ^{o}C. Current method has major advantages like mild reaction conditions with simple operation, high yields, by using a less toxic and lower costlier catalyst.

Keywords: Barbituric acid, malonitrile, aromatic aldehyde, tetra-n-butyl ammonium hydroxide.

Introduction

Globally accepted and experienced diverse biological activities, pyrano-pyrimidinones have addicted all the researchers across the globe towards synthesis of these aforesaid system or system like hetereocycles which are attached with another molecule possessing enhanced biological activity [1-3]. Thus these compounds attached with additional molecule possess unique biological activities like antibacterial, antihypertensive, atoprotective, antiallergic antitumor, cardiotonic, vasodilator, bronchiodilators, analgesics, herbicidal, antimalarial and antifungal properties [4-10].

Thus owing to their widespread pharmaceutical interests, importance of pyrano[2,3-d]pyrimidine which is a condensed Uracil derivatives has allured numerous researchers and scientists towards synthesizing these heterocyclic nucleus *via* different approaches including traditional thermal condition, ultrasonic, and microwave irradiation. In addition to these existing methods reported, different catalysts such as L-proline, N-methyl-morpholine, $H_{14}[NaP_5W_{30}O_{110}]$, triethylamine, (SBA-Pr-SO_3H), $[BMIm]BF_4$, $[KAl(SO_4)_2]$ under heating and diammonium hydrogen phosphate (DAHP) have been reported [11] for synthesizing these structurally diverse and biologically valued pyrano[2,3-d]pyrimidine derivatives which involves one pot multicomponent reaction of aromatic aldehyde, active methylene compounds *i.e.* malonitrile and barbituric acid. In addition to these existing methods, still there is great deal of scope to find newer straightforward and environmental friendly approaches for synthesizing these nucleuses with the use of basic catalysts like TBAOH. Thus

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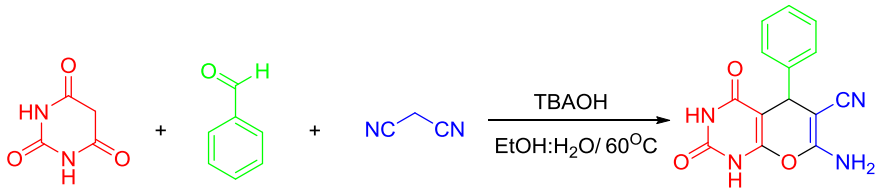
to shed light on the synthetic utility of Tetra-n-butyl ammonium hydroxide, which is not only a strong organic base but also acts as a phase transfer reagent and a surfactant. Tetra-n-butyl ammonium hydroxide has been used [12-13] during various organic transformations including Aldol, non-Sonogashira, Ullmann, elimination, Knoevenagel and addition type of reactions. In addition it has been used for hydrolysis of esters and amides, alkylation synthesis of nanoparticles and titanium silicate. Thus to explore newer synthetic applicability of tetra n-butyl ammonium hydroxide in organic synthetic methodologies, herein we wish to report a simple and efficient synthesis of highly functionalized pyrano[2,3-d]pyrimidine and their derivatives *via* three component condensations of aromatic aldehydes, malonitrile and barbituric acid in water: ethanol solvent at 60 ^{O}C (Scheme 1).



Scheme. 1

Results and discussion

In order to optimize the reaction conditions in terms of the amount of TBAOH (20% in water), time, solvent and temperature, a model reaction of benzaldehyde (1 mmol), malonitrile (1.0 mmol) and barbituric acid (1.0 mmol) were studied. The product was formed in very trace amount when the reaction was carried out not only in the absence of catalyst but also in absence of solvent. Thereafter, we have examined the effect of TBAOH in catalytic amount in aforesaid reaction condition then it is observed that in the absence of catalyst, the reaction takes longer time for completion and leads very little amount of yield of the product which may be due to the less solubility of reactants in the reaction medium causing them to react slowly.

Further addition of TBAOH in reaction systems having different solvent system was studied which showed that Ethanol: Water solvent system was best which not only accelerated the reaction but also given sufficient amount of the yield of the products. Further when the reaction was carried out at 60 ^{O}C, the reaction was completed within 20 minutes of time giving excellent amount of yield (Table 1). Thus, best results were obtained in the presence of 2 mL of TBAOH (Table 2) at 60 °C in Ethanol: Water solvent system under air. Further, a variety of different aromatic aldehyde (Table 3) was utilized under this transformation and all has given good to excellent amount of yields (79-88%) in the presence of 2 mL of aqueous solution of TBAOH.

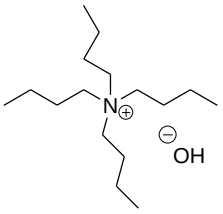
Table 1. Screening of Temperature in Solvent System

Entry	Solvent	Time(h:min)	condition	Yield
1	Ethanol:Water	02:00	RT	66%
2	Ethanol:Water	00:90	$40^{O}C$	82%
3	Ethanol:Water	00:20	$60^{O}C$	86%
4	Ethanol:Water	00:20	$100^{O}C$	84%

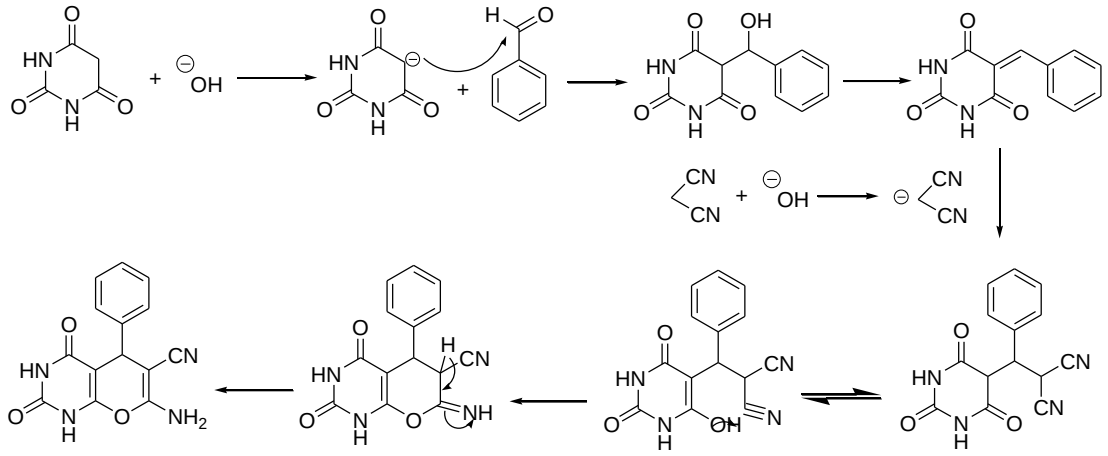
Table 2. Screening of Solvents

Entry	Solvent	Time	Yield
1	No Solvent	8 Hrs	Trace
2	No Catalyst	8 Hrs	Trace
3	Dichloromethane	8 Hrs	10 %
4	$CHCl_3$	8 Hrs	15 %
5	Water	2 Hrs	40 %
6	Ethanol	1.5 Hrs	60 %
7	Ethanol:Water	20 Min	86%

The mechanism of the reaction is below (Scheme 3).



Structure of Catalyst



Scheme 3.

Table 3. Synthesis of various pyrano [2, 3-*d*] pyrimidine derivatives

Entry	Compound	Ar	Time (Min)	Yield (%)	M.P. (°C)
1	**a**	Ph	20	86	204-206[a]
2	**b**	4-Me-Ph	20	88	162-164[a]
3	**c**	4-Me_2N-Ph	20	82	180-182[a]
4	**d**	4-NO_2-Ph	20	70	230-232[a]
5	**e**	3-NO_2-Ph	20	68	258-260[a]
6	**f**	2-Cl-Ph	20	71	207-209[a]
7	**g**	3-Cl-Ph	20	76	210-212[a]
8	**h**	4-Cl-Ph	20	86	230-232[a]
9	**i**	4-MeO-Ph	20	86	277-279[a]

[a]Melting points in line with reported values in literature [3,11].

Experimental

Chemicals were purchased from commercial suppliers and used without further purification. Yields refer to isolated products. Melting points were determined by an Electro thermal 9100 apparatus and are uncorrected. The IR spectra were obtained on a FT-IR Hartman-Bomen spectrophotometer as KBr disks, or neat. The ^{1}H NMR (400

MHz) spectra were recorded on a Bruker Avance NMR spectrometer in $CDCl_3$ solution. The progress of the reaction was monitored by TLC using silica-gel SILG/UV 254 plates. All products are known and were characterized by comparing their physical and spectral data with those of the authentic samples.

General procedure

A mixture of aldehyde (1 mmol), barbituric acid (1 mmol), and malonitrile (1 mmol), was taken in a round bottom flask, to which 2 ml of TBAOH (20% in water) was added at room temperature which was vigorously stirred at room temperature for 10 min. Further the reaction was subjected to heating in ethanol: water system at 60 °C for 20 minutes. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured on crushed ice. Further it was filtered off and washed with cold H_2O (3×10 mL). Finally the crude product was recrystallized from ethanol to give pure product in 86 % yield.

Analytical data of selected compounds

7-amino-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile (1a)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (s, 1H) 7.51-7.66 (m, 5H), 7.78 s, 2H), 7.89 (s, 1H), 7.92 (s, 1H); IR (KBr,cm^{-1}): *v* 3392, 3064, 2223, 1718, 1677, 1565, 676.

7-amino-2, 4-dioxo-5-(4-methylphenyl)-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile (2b)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.06 (s, 3H), 7.25 (s, 1H), 7.32 (d, 2H *J*HH = 8.0), 7.35 (d, 2H, *J*HH =8.0 Hz), 7.72 (s, 2H), 7.79 (s, 1H), 7.82 (s, 1H). IR (KBr, cm^{-1}): *v* 3446, 3034, 2220, 1746, 1655, 1585, 659.

7-amino-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile (1a)

M. P. 204-206, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (s, 1H) 7.51-7.66 (m, 5H), 7.78 (s, 2H), 7.89 (s, 1H), 7.92 (s, 1H). IR (KBr, cm^{-1}): *v* 3392, 3064, 2223, 1718, 1677, 1565, 676.

7-amino-2, 4-dioxo-5-(4-methylphenyl)-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile (2b)

M. P. 162-164, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.06 (s, 3H), 7.25 (s, 1H), 7.32 (d, 2H *J*HH = 8.0), 7.36 (d, 2H *J*HH =8.0), 7.72 (s, 2H), 7.80 (s, 1H), 7.82 (s, 1H); IR (KBr, cm^{-1}): *v* 3446, 3034, 2220, 1746, 1655, 1585, 659.

7-amino-2, 4-dioxo-5-(4-(dimethyamino) phenyl)-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile (3c)

M. P. 180-182, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 6H), 2.49 (s, 1H), 3.34 (d, 2H *J*HH = 8.0), 4.73 (d, 2H *J*HH = 8.0),6.80 (s, 2H), 6.86 (s, 1H), 6.96 (s, 1H); IR (KBr, cm^{-1}): *v* 3448, 2925, 2206, 1752, 1615, 1565, 599.

Conclusion

To sum up, in conclusion, we have explored nicely the unknown synthetic applicability of TBAOH as a commercially available, mild, straightforward, simple, environmental friendly organo-basic catalyst for the efficient synthesis of diverse Pyrano [2, 3-d] pyrimidinone derivatives in ethanol: water solvent system.

Acknowledgements

We are sincerely thankful to Dr. S. B. Munde, Principal, Shri Muktanand College, Gangapur, Dist-Aurangabad (MS), India, for his constant encouragement and providing us laboratory facilities during the work.

References

[1] M. Bararjanian, S Balalaie., B Movassagh., A. Amani, *J. Iranian Chem. Soc.*, **2009**, *6*, 436-440.
[2] S. Mashkouri, M. R. Naimi-Jamal, *Molecules*, **2009**, *14*, 474-475.
[3] A.A. Shestopalov, L.A. Rodinovskay, A.M. Shestopalov, V.P. Litvinov, *Russian Chem. Bull., Int. Ed*, **2004**, *53*, 2342-2348.
[4] E.M. Grivsky, S. Lee, C.W. Sigel, D.S. Duch, C.A. Nichol, *J. Med. Chem*, **1980**, *23*, 327-331.
[5] D. Heber, C. Heers, U. Ravens, Die Pharmazie, **1993**, *48*, 537-540.
[6] Y. Sakuma, M. Hasegawa, K. Kataoka, K. Hoshina, N. Kadota, *ChemAbstr.*, **1991**, *115*, 1646-1650.
[7] L.R. Bennett, C.J. Blankely, R.W. Fleming, R.D. Smith, D.K. Tessonam, *J. Med. Chem.*, **1981**, *24*, 382-386.
[8] J. Davoll, J. Clarke, F.E. Eislager, *J. Med. Chem*., **1972**, *15*, 837-840.
[9] E. Kretzschmer, *Pharmazie*, **1985**, *35*, 253-257.
[10] M.M. Ghorab, A.A. Hassan, *Phosphorus, Sulfur, Silicon & Related Elem*., **1998**, *141*, 251-256.
[11] C. Musstazza, M.R.D. Guidice, A. Borioni, F.J. Gatta, *Heterocycl. Chem.*, **2001**, *38*, 1119-1123.
[12] S.M. Enayatollah, *Hetero Letters*, **2015**, *1*, 37-40.
[13] J. Li, P. Huang, *Beilstein J Org Chem.*, **2011**, *7*, 426-432.
[14] K. Mosstafa, S. Mohammad, *Organic Chem Curr Res*, **2013**, *2*, 1000119-1000125.