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Archives of Organic and Inorganic Chemical Sciences

DOI: 10.32474/AOICS.2018.03.000155

ISSN: 2637-4609

Research Article

An Efficient Protocol for the One Pot Synthesis of Pyranopyrazoles in Aqueous Medium using Triethanolamine as a Catalyst

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Received: 📅 May 25, 2018; **Published:** 📅 June 05, 2018

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Abstract

Triethanolamine is an efficient and green catalyst for the synthesis of 6-amino-1, 4-dihydro-4-substituted-3-methylpyrano-[2, 3-c] pyrazole-5-carbonitrile in aqueous medium reflux conditions. The procedure is easier, eco friendly, simple with easy workup affording good yield of the corresponding products.

Keywords: Multi component reaction; Water media; Pyranopyrazole; Catalyst; Triethanolamine

Introduction

The present scenario for organic synthesis indicates the crave for green and economical synthesis of organic compounds. One of it is multi component synthesis. Strecker's synthesis for amino acids was the first report on multi component reaction [1]. Last few decades show large development in it. The main aim of such reactions is to fasten the reaction rate by reducing number of steps involved and eventually increase the yield of reaction. In this context to achieve great efficiency catalysts are employed. Catalysts such as Nano α-Al_2O_3 supported ammonium dihydrogenphosphate [2], tungstate sulfuric acid [3], Fe_3-xTixO_4@SO_3H nanoparticles [4], nano-titania sulfuric acid (15-nm TSA) [5], nanostructured MgO [6], $H_{14}[NAP_5W_{30}O_{110}]$ [7] and Zno Nanoparticles [8] were used. Organic catalysts such as Triethylamine [9], DABCO [10], Tris-hydroxymethyl aminomethane [11] are also reported in various organic transformations. Triethanolamine contains basic tertiary amine and primary alcoholic part (Figure 1).

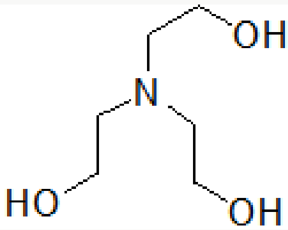


Figure 1.

It is used for activation of both CO_2 and epoxides to convert them in to cyclic carbonates [12]. It is also reported as a ligand for copper catalyzed hydroxylation of aryl halides in aqueous medium [13]. It is used as aqueous solvent for controllable preparation of ZnO nano flowers in sol gel technique [14]. Its aqueous solution is reported as electrolyte in CO_2 Photo electro-conversion catalyzed by Cu-Doped Graphene-Titania Catalyst [15]. Also it is found to increase the rate of oxidation of mesitylene catalyzed by cobalt bromide [16]. It is used as sacrificial electron donor in photocatalytic system [17]. Furthermore; it improved the catalytic performance of CuBr/PMDETA in the atom transfer radical polymerization [18]. It is also used as phase transfer catalyst for synthesis of 1-(arylsulfonyl) aryl/heterylmethanes [19]. It is used as medium for synthesis of 3-substituted coumarins using L-proline as a catalyst [20]. It is reported as catalyst in 10 mol% for synthesis of 2-amino-3-cyano-4H-pyran derivatives under ultrasound irradiation at 60^0C [21].

Citation: Jayant P S, Sandeep D P, Shrikant A D, Ashok M Z, Rajendra P P, et al. An Efficient Protocol for the One Pot Synthesis of Pyranopyrazoles in Aqueous Medium using Triethanolamine as a Catalyst. Arc Org Inorg Chem Sci 3(1)- 2018. AOICS.MS.ID.000155. DOI: 10.32474/AOICS.2018.03.000155.

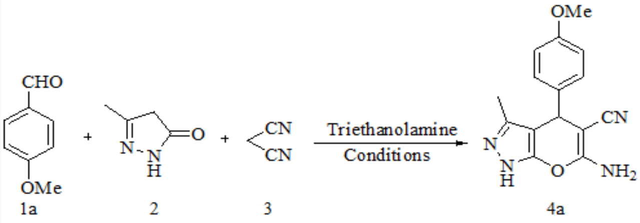
Synthesis of substituted pyrano-[2,3-d]-pyrimidines via one-pot three-component condensation of aromatic aldehydes, malononitrile and barbituric acid or 2-thiobarbituric acid using trace amounts of ionic liquid (choline chloride.$ZnCl_2$) and triethanolamine (0.1Mol%) at 75°C with stirring and under ultrasound irradiation [22] is also reported in literature. Herein we successfully attempted a fast and simple protocol for the synthesis of 6-amino-1,4-dihydro-4-substituted-3-methylpyrano [2,3-c]-pyrazole-5-carbonitrile by the one pot three component reaction of aromatic aldehyde, malononitrile and 3-methyl-1H-pyrazol-5(4H)-one using triethanolamine as a catalyst [23].

Result and Discussion

To explore the synthetic application of triethanolamine, in the present work we report the catalytic facet of it for the synthesis of heterocyclic compounds bearing pyrazole skeleton. To optimize the reaction conditions, we choosed anisaldehyde as the prototype. Initially, 10mol% of triethanolamine was taken for solvent free reaction at room temperature. But the reaction afforded a low yield of the product after 2 hour stirring. Then we used 10ml of water for room temperature stirring [24]. After 2 hours stirring it gave 62% of yield. The yield of reaction gets drastically changed on increasing temperature. At 90^0C we got 85% of yield of the product. When 20mol% of triethanolamine was used then we got 92% of yield at 90^0C in 10 ml water. Other solvents were also studied expecting better yield but other than ethanol and water we got poor yields (Table 1). Further increase of temperature and amount of triethanolamine did not improve yield significantly (Table 1). After optimizing the reaction conditions, differently substituted aldehydes with electron donating as well as electron withdrawing groups were reacted to examine the feasibility of this catalytic reaction (Scheme 1).

Table 1: Optimization of reaction conditions for the model reaction (Scheme)*

Entry	Solvent	Triethanolamine (mol%)	Temperature	Time (min.)	Yield (%)@
1	--	10	R.T.	60	60
2	$CHCl_3$	10	Reflux	60	41
3	CH_2Cl_2	10	Reflux	60	35
4	THF	10	Reflux	60	45
5	Acetonitrile	10	Reflux	60	55
6	Methanol	10	Reflux	60	64
7	Ethanol	10	Reflux	30	83
8	Water	10	R.T.	60	62
9	Water	10	900C	20	85
10	Water	20	900C	15	92
11	Water	20	Reflux	15	93
12	Water	30	900C	15	93



Scheme 1: Model reaction for the synthesis of pyranopyrazoles.

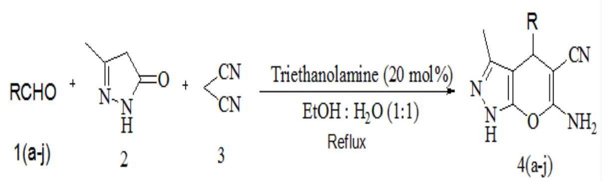
Almost all aldehydes bearing various substituents such as –Cl, F, $-NO_2$, -OMe etc afforded good yield of the corresponding products. All the synthesized compounds showed sharp peaks at 3410, 3356cm-1($-NH_2$) and 2190cm^{-1}(-CN) in IR spectra which supports for the formation of pyranopyrazole. The formed products being insoluble in water were easy to separate from the aqueous medium by simple filtration. The reason for catalytic activity of triethanolamine is it's solubility in aqueous medium and basic nature. Products are simply purified by re crystallization with ethanol. Thus the protocol described herein is efficient for the synthesis of pyrazopyrazoles which do not need purification by column chromatography.

Model reaction* for anisaldehyde (2mmol), malononitrile (2mmol) and 3-methyl-1H-pyrazol-5(4H)-one (2mmol) using the above cited conditions @Isolated yield.

Experimental

Melting points were recorded in open capillaries and were uncorrected. Progress of reaction was monitored by TLC (30% of ethyl acetate: n-hexane). IR spectra were taken by KBr disc on Shimadzu IR Affinity 1 spectrophometer. ^{1}HNMR spectra were recorded on a Varian 400MHz spectrophotometer in the specified solvents. Chemical shifts were expressed in δppm relative to TMS. Mass spectra were recorded on a Macro mass spectrometer (Waters) by electro spray method (ES).

General method for the synthesis of 6-amino-1, 4-dihydro-4-substituted-3-methylpyrano-[2,3-C]-pyrazole-5-carbonitrile



Scheme 2: General scheme for the one pot three component synthesis of pyranopyazoles using triethanolamine catalyst.

To a stirred mixture of aromatic aldehyde (2mmol), malononitrile (2mmol) and triethanolamine (20mol %) in 10ml of water, 3-methyl-1H-pyrazol-5(4*H*)-one (2mmol) was added. The resulting mixture was stirred and heated at 90^0C for appropriate

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reaction time (Table 2). After completion of reaction, the reaction mixture was cooled, filtered off the residue as the crude product which was further purified by re crystallization form ethanol (Scheme 2).

Table 2: Yield and reaction time of various pyranopyrazoles using triethanolamine.

Entry	Aldehyde	Product	Time (min.)	Yield (%)	Melting point (0C)	
					Obs.	Lit.(Ref.)
1	4-Methoxybenzaldehyde	4a	15	92	210-211	209-211 22
2	4-Nitrobenzaldehyde	4b	12	87	253-255	254-256 22
3	4-Hydroxybenzaldehyde	4c	16	85	222-224	221-223 22
4	4-Bromobenzaldehyde	4d	17	92	178-179	179-180 23
5	Benzaldehyde	4e	15	90	245-246	243-244 22
6	4-Flurobenzaldehyde	4f	18	93	171-172	171-172 22
7	4-Chlorobenzaldehyde	4g	15	91	230-232	230-232 22
8	2-Chlorobenzaldehyde	4h	20	86	245-246	244-245 22
9	Furfural	4i	20	81	241-242	240-242 22
10	4-(dimethylamino)benzaldehyde	4j	17	82	234-235	234-2358b

Representative Spectral Data

6-Amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methyl-pyrano[2,3-c]pyrazole-5-carbonitrile (4a)

White solid, [1]H NMR (400 MHz, DMSO-d$_6$): δ ppm 12.08 (s, 1H), 6.87-7.23 (m, 4H), 6.81 (bs, 2H), 4.45 (s, 1H), 3.78 (s, 3H), 1.81 (s, 3H); IR (KBr) cm-1: 3425, 3128, 2928, 2200, 1597, 1153, 1203; ES-MS m/z: 283.2 (M+1)+.

6-Amino-2,4-dihydro-3-methyl-4-phenylpyrano[2,3-c]pyrazole- 5-carbonitrile (4e)

White solid, M.P. 245-246 0C; 1H NMR (400 MHz, DMSO-d6) : δ ppm 12.10 (s, 1H), 7.10-7.40 (m, 5H), 6.85 (s, bs, 2H), 4.60 (s, 1H), 1.78 (s, 3H); IR (KBr) cm^{-1} : 3410, 3356, 3167, 2990, 1646, 1596, 1399, 1276, 870; ES-MS m/z: 253 (M + 1) $^+$.

6-Amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4g)

Off-white solid, M.P. 230-2320C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ ppm 12.15 (s, 1H), 7.10–7.40 (m, 4H), 6.95 (s, bs, 2H), 4.63 (s, 1H), 1.80 (s, 3H); IR (KBr) cm^{-1} : 3478, 3035, 2985, 2193, 1647, 1596, 1398, 1284, 870; ES-MS m/z: 287 (M + 1) $^+$.

6-Amino-4-(4-N, N-dimethylaminophenyl)-3-methyl-2, 4-dihydropyrano[2, 3-c]pyrazole-5-carbonitrile (4j)

Yellow solid, M.P. 234-235 0C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ ppm 12.10 (s, 1H), 6.70-7.15 (m, 4H); 6.55 (s, bs, 2H), 4.40 (s, 1H); 2.85 (s, 6H), 1.78 (s, 3H); IR (KBr) cm^{-1} : 3385, 3172, 2957, 2189, 1644, 1601, 1397, 1279, 868; ES-MS m/z: 296 (M + 1)$^+$.

Conclusion

In summary, we have developed an efficient protocol for the synthesis of pyranopyrazoles by a simple method using a catalytic amount of triethanol amine. Herein; not only the yield of reaction is improved but also the reaction time is reduced. The workup of the reaction is very simple which make it easier to isolate the product.

Acknowledgement

The authors are thankful to The Principal, Vinayakrao Patil Mahavidyalaya, Vaijapur for providing laboratory facilities and The Director, SAIF, Chandigarh for NMR and Mass analysis.

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DOI: 10.32474/AOICS.2018.03.000155