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

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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-Al2O3 supported ammonium dihydrogenphosphate [2], tungstate sulfuric acid [3], Fe3O4-TiO2@SO3H nanoparticles [4], nano-titania sulfuric acid (15-nm TSA) [5], nanostructured MgO [6], H3[NP,W9O31] [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).

It is used for activation of both CO2 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 CO2 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/hetarylmethanes [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°C [21].

Figure 1.
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-methylpyran [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 facit of it for the synthesis of heterocyclic compounds bearing pyrazole skeleton. To optimize the reaction conditions, we choose 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°C we got 85% of yield of the product. When 20mol% of triethanolamine was used then we got 92% of yield at 90°C 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$_2$| 10                     | reflux      | 60          | 41        |
| 3     | CH$_2$Cl$_2$| 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                     | 900°C       | 20          | 85        |
| 10    | Water   | 20                     | 900°C       | 15          | 92        |
| 11    | Water   | 20                     | reflux      | 15          | 93        |
| 12    | Water   | 30                     | 900°C       | 15          | 93        |

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 its 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 spectrophotometer. 1HNMR 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-methylpyran-[2,3-c]-pyrazole-5-carbonitrile**

To a stirred mixture of aromatic aldehyde (2mmol), malononitrile (2mmol) and triethanolamine (20mol %) in 10ml of water, 3-methyl-1H-pyrazol-5(4H)-one (2mmol) was added. The resulting mixture was stirred and heated at 90°C for appropriate
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 (%) |
|-------|----------|---------|-------------|-----------|
| 1     | 4-Methoxybenzaldehyde | 4a      | 15          | 92        |
| 2     | 4-Nitrobenzaldehyde    | 4b      | 12          | 87        |
| 3     | 4-Hydroxybenzaldehyde  | 4c      | 16          | 85        |
| 4     | 4-Bromobenzaldehyde    | 4d      | 17          | 92        |
| 5     | Benzaldehyde           | 4e      | 15          | 90        |
| 6     | 4-Fluorobenzaldehyde   | 4f      | 18          | 93        |
| 7     | 4-Chlorobenzaldehyde   | 4g      | 15          | 91        |
| 8     | 2-Chlorobenzaldehyde   | 4h      | 20          | 86        |
| 9     | Furfural               | 4i      | 20          | 81        |
| 10    | 4-(dimethylamino)benzaldehyde | 4j   | 17          | 82        |

Representative Spectral Data

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

White solid, δH NMR (400 MHz, DMSO-d6): 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: 3478, 3035, 2985, 2193, 1647, 1596, 1398, 1284, 870; ES-MS m/z: 296 (M + 1).

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

White solid, δH 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)

White solid, δH NMR (400 MHz, DMSO-d6): δ ppm 12.15 (s, 1H), 7.10–7.40 (m, 4H), 6.95 (s, bs, 2H), 4.63 (s, 1H), 1.81 (s, 3H); IR (KBr) cm⁻¹: 3478, 3035, 2985, 2193, 1647, 1596, 1398, 1284, 870; ES-MS m/z: 283 (M + 1)⁺.

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

Yellow solid, δH NMR (400 MHz, DMSO-d6): 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.

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