

One Pot Synthesis of Dihydropyrano (2,3-c) pyrazoles Catalyzed by Bronsted Acid

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ABSTRACT:

An efficient and versatile multicomponent procedure for the synthesis dihydropyrano (2, 3-c) pyrazole derivatives promoted by Bronsted Acid as a catalyst is PTSA in protic solvent and These derivatives can be obtained series of dihydropyrano (2,3-c)pyrazoles from ethyl acetoacetate, hydrazine hydrochloride, malononitrile, and aromatic aldehydes in the presence of PTSA. This method was is used for environmentally friendly multicomponent cyclocondensation methods which have a series of intriguing advantages , including the use of a nontoxic solvent, inexpensive and readily available catalyst, simplicity in work-up, high yields (up to 91%). The compound can be confirmed by ¹HNMR, ¹³CNMR and LCMS. Besides, the study of the antimicrobial activity was against bacterial as well as fungal strains.

KEYWORDS:

Ethyl acetoacetate, hydrazine hydrochloride, malononitrile, aromatic aldehydes, Dihydropyrano (2, 3-c) pyrazoles, PTSA

1. INTRODUCTION

Approaches for synthetic methodologies to achieve functionalized and fused heterocyclic moieties are among the most difficult tasks for synthetic organic chemists working in the fields of medicinal and heterocyclic chemistry. Multicomponent (MCR) reactions can be used in a variety of ways to synthesize functionalized and fused heterocyclic moieties, and in recent years, there has been a lot of interest in this process. These methods have several advantages over traditional, step-by-step processes. They are crucial for the creation of multiple bonds in single-step MCRs, which are extremely valuable reactions that are frequently employed in the creation of bioactive heterocyclic compounds, where three or more starting materials combine to form an anticipated product .Additionally, MCRs save a significant amount of time and money by eliminating the need for intermediate separations or purifications, which is in line with the principles of green chemistry .Therefore, the creation of structural scaffolds or combinatorial libraries for heterocyclic chemistry and drug discovery has garnered a lot of interest in multi-component reactions (MCRs). Among the various classes of nitrogen-containing heterocyclic compounds, pyrano (2,3-c) pyrazoles are a noteworthy class that are essential as biologically active substances and offer an intriguing model for medicinal chemistry (1-5). Because of their important pharmacological and biological properties, structures containing the derivatives of Pyrano (2,3-c) pyrazoles have drawn the attention of synthetic organic chemists and biochemists.

The derivatives of the pyranopyrazoles are an efficient and attractive significant class of heterocyclic compounds are in either natural or synthetic molecules that have demonstrated a wide range of biological and pharmacological activities(6), Antimicrobial Activity [7], cytotoxic properties [8], antimalarial [9], p38 MAP Kinase[10], PPAR γ partial

agonists[11], This has been confirmed by numerous recent reports. Numerous methods have been reported for the preparation of different classes of dihydropyrano (2,3-c) pyrazole derivatives due to their wide range of biological significance as well as their industrial and synthetic applications. The majority of these methods have been carried out using a variety of catalysts. Despite their effectiveness, the reported methods' limited applicability stems from their use of toxic catalysts, lengthy reaction times, low product yields, and toxic organic solvents. In recent times, certain catalysts that are compatible with the environment, like Copperoxidenanoparticles (CuO NPs)[12], sodium benzoate[13], Cu²⁺ doped Ni-Zn Nano [14], Gluconic acid[15], heterogeneous catalyst[16], Nano-eggshell/Ti(IV)[17].

While each of these approaches has its own benefits, some of them frequently have one or more drawbacks, such as the use of costly reagents and catalysts, long reaction times, hard reaction conditions, high temperatures, laborious work-up procedures, and the production of large amounts of toxic wastes, which have a detrimental effect on the environment. These drawbacks also include low product yield, non-recyclable, hazardous organic solvents, and limited opportunities for practical applications. For the synthesis of this class of heterocyclic compounds, there is still a strong need for more environmentally friendly protocols as well as general, practical, efficient, high-yielding, and economical techniques that make use of innovative and effective catalysts.

In continue of our efforts into the development of the synthetic approaches promoted Bronsted acid catalysts. We report an efficient and versatile multicomponent procedure for the right pathway for the synthesis of dihydropyrano [2,3-c]pyrazoles via multi-component reactions of substituted aromatic aldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate used by PTSA. In addition to the evaluation of microbial activity of newly synthesized compounds were examined

2. Materials and Methods:

All chemicals, reagents and solvents were procured from Sigma Aldrich were used without purification. The titled derivatives can be measured by NMR spectra were recorded on 400 MHz for ¹H NMR and 100 MHz for ¹³C NMR using TMS as an internal reference for both of the cases. Here chemical shifts were reported in parts per million (ppm) and melting points were monitored by open glass capillary method and were uncorrected.

2.1. General procedure for the synthesis of Pyrano [2, 3-c] pyrazoles (5a-5h):

A mixture of ethyl acetoacetate (1.0 mol), malononitrile (1.0 mol), substituted aromatic aldehyde (1.0 mol), and hydrazine hydrochloride (1.0 mol) is taken 50mL RBF and P-toluene sulphonic acid (10 mg) was stirred in ethanol as a solvent under reflux conditions. After completion of the reaction, the mixture was cooled down to room temperature and poured in the crushed ice. The organic layer was dried over anhydrous Na₂SO₄ and the solvent was evaporated. The pure product was obtained through recrystallization in ethanol and water.

All the products reported here are known compounds and the spectroscopic data

2.1.1.5-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-6-carbonitrile(5a):

M.P- 175-177°C, Yellow solid, Yield- 86% ; ¹H NMR (400 MHz, CDCl₃) δppm: 1.212 (s, 3H, Me), 4.314 (s, 1H, 4H), 6.257 (s, 2H), 7.087-7.527 (m, 5H), 10.789 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δppm: 12.54, 33.64, 55.87, 115.36, 119.74, 127.51, 128.91, 133.55, 138.07, 156.14, 164.07. Molecular formulae: C₁₄H₁₂N₄O; Molecular weight (m/z):253.74 (M+H).

2.1.2.6-Amino-4-(4-hydroxyphenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5 carbonitrile (5b)

M.P-180-182°C, Yellow solid, Yield- 90% ; ¹H NMR (400 MHz, CDCl₃) δppm: 1.321 (s, 3H, CH₃), 4.258 (s, 1H, 4H), 6.269 (s, 2H, NH₂), 6.987 (s, 1H), 7.413 (d, 2H, J = 8.5 Hz, Ar), 7.646 (d, 2H, J = 10.8 Hz, Ar), 10.847 (s, 1H, -NH). ¹³C NMR (100 MHz, CDCl₃) δppm: 12.02, 36.27, 55.21, 102.34, 123.54, 128.45, 128.91, 129.05, 130.45, 138.71, 145.24, 156.18, 161.25; Molecular formulae: C₁₄H₁₂N₄O₂; Molecular weight (m/z): 269.45 (M+H).

2.1.3.6-Amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile (5c)

M.P-178-180°C. Yellow solid, Yield- 90% ; ¹H NMR (400 MHz, CDCl₃) δppm : 1.259 (s, 3H, Me), 3.712 (s, 3H, -OMe), 4.320 (s, 1H, 4H), 6.232 (s, 2H, NH₂), 7.320 (d, 2H, J = 7.8 Hz, Ar-H), 7.616 (d, 2H, J = 12.8 Hz, Ar), 10.791 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃) δppm: 12.27, 28.51, 56.82, 100.30, 110.24, 113.55, 123.34, 128.74, 129.05, 134.56, 137.21, 164.25. Molecular formulae: C₁₅H₁₄N₄O₂; Molecular weight (m/z): 283.58 (M+H).

2.1.4.6-Amino-4-(3,4-dimethoxyphenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile , (5d)

M.P-180-182°C; White solid; Yield- 91%; ¹H NMR (400 MHz, CDCl₃) δppm: 1.324 (s, 3H, Me), 3.674 (s, 3H, OMe), 3.757 (s, 3H), 4.410 (s, 1H, 4H), 6.159 (s, 2H,), 7.291-7.4124 (m, 2H, Ar-H), 7.614-7.830 (s, 1H, Ar-H), 10.954 (s, 1H,). ¹³C NMR (100 MHz, CDCl₃) δppm: 11.67, 30.51, 56.80, 60.28, 99.10, 102.32, 104.44, 121.83, 124.50, 126.54, 134.50, 145.14, 153.25, 156.36, 164.20. Molecular formulae: C₁₆H₁₄N₄O₃; Molecular weight (m/z): 313.68 (M+H).

2.1.5.6-Amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile, (5e)

M.P- 190-192°C. Yellow solid, Yield- 88% ; ¹H NMR (400 MHz, CDCl₃) δppm: 1.258 (s, 3H, Me), 4.239 (s, 1H, 4H), 6.149 (s, 2H), 7.236 (d, 2H, J = 8.8 Hz), 7.385 (d, 2H, J = 9.2 Hz), 10.912 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃) δppm: 11.50, 55.52, 98.86, 122.64, 128.57, 128.96, 129.12, 129.67, 130.28, 131.95, 136.87, 144.72, 156.19, 162.82. Molecular formulae: C₁₄H₁₁ClN₄O; Molecular weight (m/z): 288.89 (M+H).

2.1.6.6-Amino-4-(4-bromophenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile, (5f)

M.P. 171-173°C. Red solid, Yield- 89% ; ¹H NMR (400 MHz, CDCl₃) δppm : 1.597 (s, 3H, Me), 4.478 (s, 1H, 4H), 6.129 (s, 2H, NH₂), 7.468 (d, 2H, J = 6.4 Hz, Aromatic -H), 7.512 (d, 2H, J = 8.0 Hz, Ar-H), 10.914 (s, 1H, -NH). ¹³C NMR (100 MHz, CDCl₃) δppm: 12.47, 29.02, 42.55, 99.57, 115.80, 119.01, 122.87, 128.08, 130.22, 137.47, 141.23, 159.57. Molecular formulae: C₁₄H₁₁BrN₄O; Molecular weight (m/z): 332.25 (M+2).

2.1.7.5-amino-4-(4-cyanophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-6-carbo nitrile(5g)

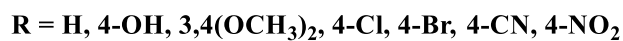
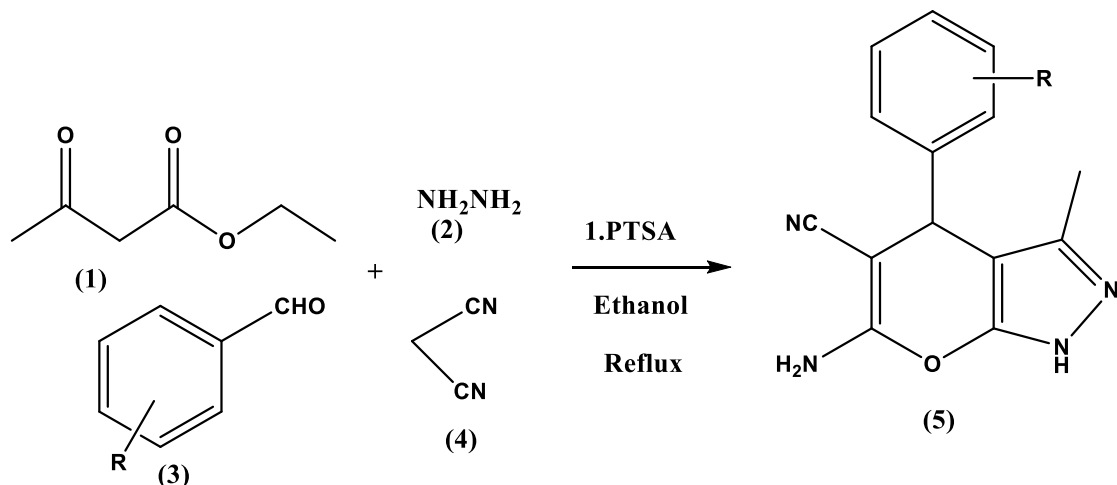
M.P, 202–204°C. Yellow solid; Yield- 85% ; ¹H NMR (400 MHz, CDCl₃) δppm : 11.258 (s, 1H acidic), 7.478 (d, J = 8.5 Hz, 2H), 7.240 (d, J = 6.4 Hz, 2H), 6.870 (s, 2H, NH₂), 4.411 (s, 1H, CH), 2.150 (s, 3H, -CH₃) ; ¹³C NMR (100 MHz, CDCl₃): 171.25, 166.87, 159.07, 143.88, 137.69, 122.54, 117.88, 114.98, 111.05, 110.45, 56.41, 15.60, 13.40. Molecular formulae: C₁₅H₁₁N₅O; Molecular weight (m/z): 278.21 (M+H).

2.1.8.6-Amino-4-(4-nitrophenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile(5h)

M.P-201-203°C. Yellow solid, Yield- 87% ; ¹H NMR (400 MHz, CDCl₃) δppm: 1.257 (s, 3H, Me), 4.312 (s, 1H, 4H), 6.417 (s, 2H, -NH₂), 7.414 (d, 2H, J = 8.0 Hz, Ar-H), 8.147 (d, 2H, J = 8.5 Hz, Ar-H), 10.541 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃) δppm: 11.17, 34.54, 56.47, 99.12, 123.04, 124.45, 128.74, 136.87, 148.31, 153.54, 154.14, 163.30. Molecular formulae: C₁₄H₁₁N₅O₃; Molecular weight (m/z): 298.52 (M+H).

3. RESULTS AND DISCUSSION:

Initially, the dihydropyrano (2,3-c) pyrazole analogous can be synthesized and simple, effective, and economical method. We used PTSA, a cheap and environmentally friendly catalyst, in this process. Bronsted acid, such as PTSA, was used as a catalyst in a one-pot reaction of substituted aromatic aldehydes, malononitrile, ethyl acetoacetate, and hydrazine hydrate to scaffold the dihydropyrano (2,3-c) pyrazole compounds (5a–5h) in a excellent (92%) with a straightforward workup process (Scheme-1).



(Scheme-1)

These analogous reactions were optimized using different catalysts, different amounts of catalyst, and different solvents. While varying amounts of catalyst were used during the reaction below, the highest product of the derivatives was obtained in the presence of protic acid), methanesulphonic acid (MSA) catalyst compared to oxidative related catalysts such as silica supported sulphonic acid (SSA), methanesulphonic acid (MSA), toluene sulphonic acid (PTSA), camphorsulphonic acid (CSA), and trichlorosalicylic acid (TCSA) (Table I).

Table-I: The effect of catalyst for preparation of titled derivatives

Entry	Catalyst	Time (hrs.)	Yield (%)
1	SSA	3	45
2	MSA	3	58
3	PTSA	3	91
4	CSA	3	70
5	TCSA	3	61

DMF, isopropanol acetonitrile, ethanol, and methanol were among the different solvents used in the model reaction that was investigated. With an 89% product yield, it was determined to be the most effective medium for the reaction. As a result, it was utilized as the solvent for further reactions due to its higher yield, environmentally friendly nature, and ease of work-up. The solvent significant role play is ethanol.

Table-II: The effect of solvent for preparation of titled derivatives

Entry	Catalyst	Time (hrs.)	Yield (%)
1	DMF	3	50
2	IPA	3	67
3	CH ₃ CN	3	55
4	EtOH	3	91
5	MeOH	3	69

Table -III illustrates a notable improvement in the targeted compounds, with 5c's yield being developed to 89%. The quantity of the catalyst used in the synthesis, the impact on the product yield, and the rate of reaction. The variation of the loaded catalyst was found to improve the product, as indicated in table III. The results could not be improved by using the maximum amounts of the catalyst. The yield unexpectedly dropped to 35%, as indicated in Table III, even though the reaction time was reduced to 1 hour by using 4.0 mmol% PTSA.

Table-III: The effect of loaded for preparation of titled

Entry	Amount catalyst(mmol)	Time (hrs)	Yield (%)
1	1.0	3	20
2	2.0	3	35
3	5.0	3	89
4	5.0	3	89
5	2.5	3	71

Following the acquisition of these investigative results, we set out to increase the yield of the product from the earlier study. The only idea was to increase the efficiency of the current method in terms of reaction time and product yield by adding varying amounts of suitable catalyst and solvents. After considering this and learning about the recently investigated methanesulphonic acid reaction medium, it was decided to utilize this system for our reaction.

We were ecstatic to learn that the model reaction using this reaction medium was completed in just 90 minutes (1.5 hours) and that it was occurring at a temperature of 60 to 70°C, which permitted a good product yield. Further experiments were carried out with varying concentrations of water and methanesulphonic acid to ascertain the appropriate amounts for the reaction in order to obtain the optimal experimental conditions. Our study showed that adding 0.50 g of preheated fly ash to water for the reaction yields the highest product yield.

4. ANTIMICROBIAL ACTIVITY OF COMPOUNDS

The desired derivatives were examined for their in-vitro antibacterial and antifungal activities following micro broth dilution method. The invitro antibacterial activity was examined against gram-positive (*B. subtilis* and *S.aureus*) and gram-negative (*E.coli* and *P.aeruginosa*) microorganisms. The invitro antifungal activity was evaluated against *A.Niger* and *C.albicans* microorganisms. The standard drugs were used for this study were Streptomycin and Ketozole for antibacterial as well as antifungal screening. The standard strains used for screening of antibacterial and antifungal activities were commercially purchased from the Culture collection and geneank (MTCC), Chandigarh, India. Mueller Hinton Broth was used as a nutrient medium for bacteria and Sabouraud dextrose Broth for fungal growth. Inoculums size

for test strain was adjusted to 108 CFU/mL by comparing the turbidity. The results were recorded in the form of primary and secondary evaluation. The stock solution (2000 µg/mL) of the compounds under investigation and standard drugs were prepared by successive two fold dilution

Table - IV. Antimicrobial activity of compounds (5a-5h):

Entry Strains	Antibacterial MIC (µg/mL)				Antifungal MIC (µg/mL)	
	B. subtilis	S. aureus	P. aeruginosa	E. coli	A. Niger	C. Albicans
5a	04	06	06	07	04	06
5b	21	22	22	19	17	16
5c	21	19	18	14	15	15
5d	18	21	20	21	15	16
5e	20	19	17	21	14	15
5f	20	21	21	22	17	18
5g	10	11	11	15	11	10
5h	09	10	09	09	08	07
Streptomycin	27	27	27	27	-	-
Ketonoazole	-	-	-	-	25	25
DMSO						

In the preliminary examination 500, 250 and 100 µg/mL concentrations of the compounds were used. The compounds found to be active in this primary screening were further examination. In secondary screening, 200, 100, 50 and 25 µg/mL concentrations were used. The inoculated wells were incubated overnight at 37°C in a humid atmosphere. The highest dilution showing complete inhibition was considered as a minimum inhibition concentration (MIC). The MIC values revealed that the synthesized compounds showed moderate to good inhibition. The compounds “3e and 3f exhibited good excellent activities against bacterial strains. The MIC values of antifungal activity shown that compound 3c and 3b exhibited good activity against all fungal strain. Antimicrobial activity of compounds (3a-3h) is listed in Table-IV

5. CONCLUSIONS

We have exclusively focused , an easy and an efficient method for synthesis of Synthesis of Dihydropyrano (2, 3-c) pyrazoles promoted by Bronsted Acid via one-pot four component condensation of ethyl acetoacetate, hydrazine hydrochloride, malononitrile, and aryl aldehydes in ethanol medium with PTSA as an efficient catalyst. The mildness of the conversion, the experimental simplicity, compatibility with various functional groups, excellent product yields and the easy work-up procedure make this approach attractive for synthesizing a variety of such derivatives. . In additionally, an excellent effect of antimicrobial potent activity of desired compounds was evaluated.

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