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MULTI COMPONENT SYNTHESIS OF DIHYDROPYRANO (2, 3-C) PYRAZOLES CATALYZED BY BRONSTED ACID AND STUDIED ANTIMICROBIAL ACTIVITY

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ABSTRACT

A simple one-pot multicomponent method that uses Bronsted Acid as a catalyst for methanesulphonic acid for the first time to synthesize a series of dihydropyran (2, 3-c) pyrazole derivatives from ethyl acetoacetate, hydrazine hydrochloride, malononitrile and aryl aldehydes in the presence of methane sulphonic acid. These environmentally friendly multicomponent cyclocondensation methods 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 95%) and a green protocol. The compound can be evaluated by ^{1}HNMR, ^{13}CNMR and LCMS. In addition to the evaluated antimicrobial activity.

KEYWORDS

Ethyl acetoacetate, Hydrazine hydrochloride, Malononitrile, Aryl aldehydes, Dihydropyrano (2, 3-c) pyrazoles, Multi Component and Methanesulphonic acid.

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INTRODUCTON

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.

Pyranopyrazoles derivatives are a significant class of heterocyclic compounds with both natural and 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], PPARγ 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 Copperoxide nanoparticles (CuO NPs)[12], sodium benzoate[13], Cu^{2+} 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 the present work reported the one pot multicomponent synthesis of Dihydropyrano (2, 3-c) pyrazoles Catalyzed by Bronsted Acid methane sulfonic acid as a catalyst. This compounds were obtained by the reaction ethyl acetoacetate, hydrazine hydrochloride, malononitrile, and aryl aldehydes in the presence of methane sulphonic acid in ethanol as a solvent. The excellent yield was obtained during the synthesis.

MATERIAL AND METHODS

All chemicals were purchased from Sigma Aldrich were used without purification. NMR spectra were recorded on400 MHz for ^{1}H NMR and 100 MHz for ^{13}C 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. Physical and spectral data of the obtained products (5a-5h) were compared with reported literature data.

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

A mixture of ethyl acetoacetate (1.0mol), malononitrile (1.0mol), substituted aromatic aldehyde (1.0 mol), hydrazine hydrochloride (1.0mol) and methanesulphonic acid (15mg) was stirred in ethanol as a solvent under reflux conditions. After completion of the reaction, the mixture was cooled down to room temperature. The organic layer was dried over anhydrous Na_2SO_4 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

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

M.P- 154-156°C, Yellow compound, Yield-82%; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 1.285 (s, 3H, Me), 4.463 (s, 1H, 4H), 6.447 (s, 2H), 7.018-7.427 (m, 5H), 11.135 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 10.54, 34.64, 56.87, 114.36, 118.74, 126.51, 128.96, 134.55, 139.07, 155.14, 162.07. Molecular formulae: $C_{14}H_{12}N_4O$; Molecular weight (m/z): 253.54 (M+H).

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

M.P-189-191°C, Yellow compound, Yield-89%; 1H NMR (400 MHz, $CDCl_3$) δppm: 1.687 (s,3H, CH_3),4.388 (s, 1H, 4H), 6.451 (s, 2H, NH_2), 6.795 (s, 1H), 7.327 (d, 2H, J = 8.0 Hz, Ar),7.637 (d, 2H, J = 10.4Hz, Ar), 11.108 (s, 1H, -NH). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 11.025, 36.247, 54.214, 99.347, 122.54, 128.58, 128.97, 129.32, 130.07, 136.74, 145.22, 156.17, 161.08; Molecular formulae: $C_{14}H_{12}N_4O_2$; Molecular weight (m/z): 269.45 (M+H).

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

M.P-174-176°C. Yellow compound, Yield-88%; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 1.578 (s,3H, Me), 3.767 (s, 3H, -OMe), 4.354 (s, 1H, 4H), 6.202 (s,2H, NH_2), 7.321 (d, 2H, J = 7.6 Hz, Ar-H),7.657 (d, 2H, J = 12.4 Hz, Ar), 11.324 (s, 1H, NH-).^{13}C NMR (100 MHz, $CDCl_3$) δppm: 11.257, 28.54, 56.87, 100.35, 110.09, 113.65, 122.34, 128.22, 129.53, 134.04, 136.26, 164.10. Molecular formulae: $C_{15}H_{14}N_4O_2$; Molecular weight (m/z): 283.04 (M+H).

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

M.P-188-189°C; White solid; Yield-88%; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 1.895 (s, 3H, Me), 3.685 (s, 3H, OMe), 3.789 (s, 3H), 4.425 (s,1H, 4H), 6.357 (s, 2H,), 7.289-7.475 (m, 2H, Ar-H), 7.658-7.838 (s, 1H, Ar-H), 11.240 (s, 1H,). 13C NMR (100 MHz, $CDCl_3$) δppm: 10.66, 30.54, 56.82, 60.22, 99.13, 102.39, 104.40, 121.84, 124.59, 126.49, 134.51, 145.69, 153.20, 156.15, 163.19. Molecular formulae: $C_{16}H_{14}N_4O_3$; Molecular weight (m/z): 313.68 (M+H).

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

M.P-195-197°C. Yellow compound, Yield- 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 1.664 (s, 3H, Me), 4.447 (s, 1H, 4H), 6.458 (s, 2H), 7.234 (d, 2H, J = 8.0 Hz), 7.359 (d, 2H, J = 9.6 Hz), 11.627 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 11.52, 55.56, 98.84, 122.60, 128.58, 128.98, 129.05, 129.66, 130.38, 131.02, 136.84, 144.76, 156.14, 162.87. Molecular formulae: $C_{14}H_{11}ClN_4O$; Molecular weight (m/z): 288.36 (M+H).

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

M.P.178-180°C.White solid, Yield- 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 2.012 (s,3H, Me), 4.524 (s, 1H, 4H), 6.312 (s, 2H, NH_2), 7.466(d, 2H, J = 6.8 Hz, Aromatic -H), 7.574 (d, 2H, J =8.4 Hz, Ar-H), 10.957 (s, 1H, -NH). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 11.47, 28.02, 41.55, 98.57, 114.80, 118.01, 121.87, 129.08, 131.22, 138.47, 140.23, 158.57. Molecular formulae: $C_{14}H_{11}BrN_4O$; Molecular weight (m/z): 332.24 (M+2).

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

M.P, 204–206^{o}C.Yellow solid; Yield-83%; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 11.748(s, 1H acidic), 7.431 (d, J = 8.0 Hz, 2H), 7.245(d, J = 6.8 Hz, 2H), 6.871 (s, 2H, NH_2), 4.654 (s, 1H, CH), 2.151 (s, 3H, -CH3) ; ^{13}C NMR (100MHz, $CDCl_3$): 170.25, 165.87, 158.07, 142.88, 136.98, 123.54, 118.88, 115.98, 112.05, 110.58,56.44, 15.66, 13.47. Molecular formulae: $C_{15}H_{11}N_5O$; Molecular weight (m/z): 278.57 (M+H).

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

M.P-198-200°C.Yellow compound, Yield-85%; ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 1.684 (s, 3H, Me), 4.486 (s, 1H, 4H), 6.587 (s, 2H, -NH_2), 7.442 (d, 2H, J = 8.4 Hz, Ar-H), 8.284 (d, 2H, J = 8.0 Hz,

Ar-H), 11.574(s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 10.74, 34.82, 57.87, 99.54, 122.49, 124.84, 128.80, 135.41, 147.36, 152.02, 154.62, 162.35. Molecular formulae: $C_{14}H_{11}N_5O_3$; Molecular weight (m/z): 298.52 (M+H).

RESULTS AND DISCUSSION

Initially, the dihydropyrano (2, 3-c) pyrazole derivatives can now be synthesized using a new, simple, effective and economical method. We used methanesulphonic acid, a cheap and environmentally friendly catalyst, in this process. Bronsted acid, such as methanesulphonic acid, was used as a catalyst in a one-pot reaction of substituted aldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate to create the dihydropyrano (2, 3-c) pyrazole compounds (5a–5h) in a high-yield (89%) with a straightforward workup process (Scheme No.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), camphorsulphonicacid acid (CSA) and trichlorosalicylic acid (TCSA) (Table No.1).

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 No.3 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 No.3. 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 4.0mmol% CSA.

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^{o}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.

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 *in-vitro* antifungal activity was evaluated against A.Niger and C.albicans microorganisms. The standard drugs were used for this study were Streptomycin and Ketonozole 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 108CFU/mL by comparing the turbidity. The results were recorded in the form of primary and secondary evaluation. The stock solution (2000µg/mL) of the compounds under investigation and standard drugs were prepared by successive two fold dilution.

In the preliminary examination 500, 250 and 100µg/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 25µg/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 No.4.

Table No.1: The effect of catalyst for preparation of titled derivatives

Entry	Catalyst	Time (hrs.)	Yield (%)
1	SSA	3	45
2	MSA	3	89
3	PTSA	3	76
4	CSA	3	70
5	TCSA	3	67

Table No.2: The effect of solvent for preparation of titled derivatives

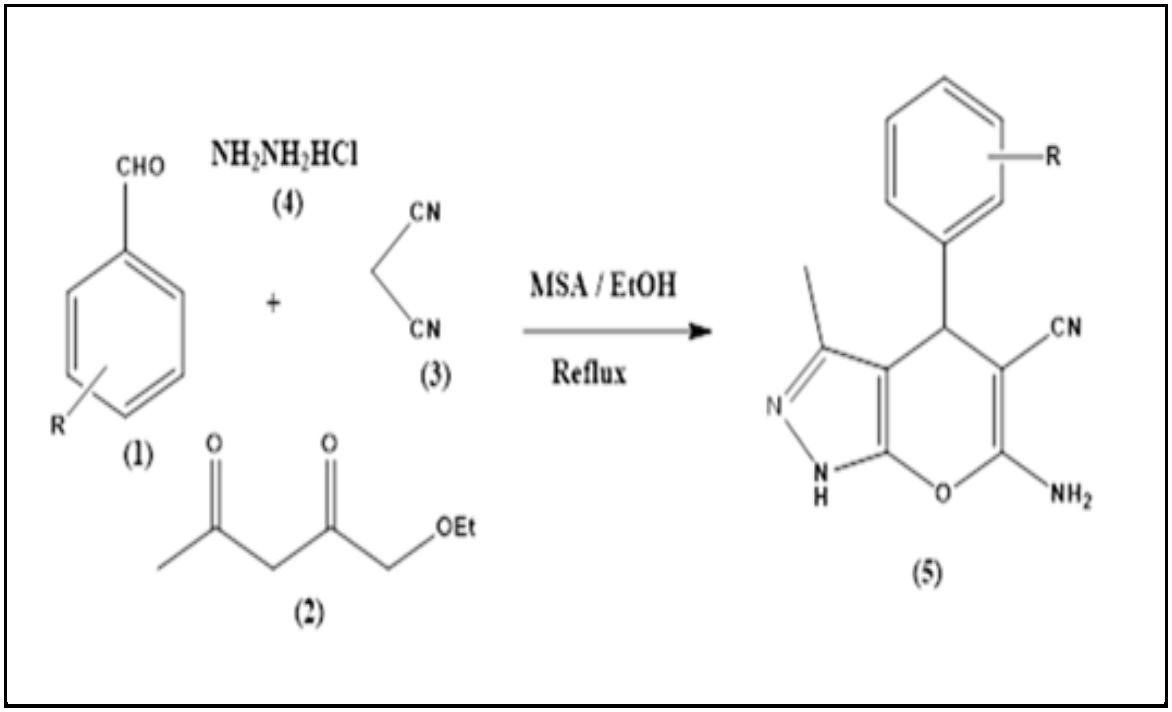
Entry	Catalyst	Time (hrs.)	Yield (%)
1	DMF	3	50
2	IPA	3	67
3	CH_3CN	3	55
4	EtOH	3	89
5	MeOH	3	69

Table No.3: 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	4.0	3	89
4	6.0	3	89
5	2.5	3	71

Table No.4: Antimicrobial activity of compounds (5a-5h)

Entry	Antibacterial MIC (µg/mL)				Antifungal MIC (µg/mL)	
Strains	***B. subtilis***	***S. aureus***	***P. aeruginosa***	***E. coli***	***A. Niger***	***C. Albicans***
5a	06	07	09	08	06	05
5b	22	23	21	18	18	17
5c	20	18	19	15	14	14
5d	19	20	21	22	16	15
5e	19	20	18	20	16	16
5f	20	21	21	22	17	18
5g	11	12	12	14	10	09
5h	10	11	08	08	09	09
Streptomycin	27	27	27	27	-	-
Ketonozole	-	-	-	-	25	25
DMSO						



Scheme No.1: R=H, 4-OH, 3, 4-$(OCH_3)_3$, 4-CI, 4-Br, 4-CN, 4-NO_2

CONCLUSION

We have focused a new, an easy and an efficient process for synthesis of Synthesis of Dihydropyrano (2, 3-c) pyrazoles Catalyzed by Bronsted Acid derivatives via one-pot four component condensation of ethyl acetoacetate, hydrazine hydrochloride, malononitrile and aryl aldehydes in ethanol medium with methane sulphonic acid 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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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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