IJMPR 2024, 8(5), 60-64

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 6.669

MULTICOMPONENT ONE-POT SYNTHESIS OF 1,4-DIHYDROPYRANO [2,3-C] PYRAZOLE DERIVATIVES EMPLOYED CAMPHOR SULFONIC ACID AND BIOEVLUATION

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Article Received on: 04/03/2024
Article Revised on: 24/03/2024
Article Accepted on: 14/04/2024

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ABSTRACT

In the present work, a simple and an efficient protocol is developed for the synthesis of derivatives of dihydropyrano [2,3-c] pyrazole. These derivatives can be obtained by a one pot, multi component reactions of substituted aromatic aldehydes, ethylacetoacetate, hydrazine hydrate, malanonitrile in the presence of a catalytic amount of camphorsulfonicacid in ethanol medium. The structure of the derivatives evaluated by spectroscopic methods viz; ^{1}HNMR, ^{13}CNMR and LCMS and also structure of the compound was determined by elemental analysis. This method provides number of advantages such as high yield, shorter time of reaction, mild reaction condition, operational simplicity, easy work-up procedure with environment friendly nature. The purification of desired products has been developed by non-chromatographic methods. The antimicrobial activity was evaluated by these derivatives.

KEYWORDS: Multicomponent reaction, camphor sulfonic acid, substituted aromatic aldehydes, Ethyl acetoacetate, malononitrile, pyrano [2, 3-c] pyrazole and antimicrobial activity.

1. INTRODUCTION

The multi-component reactions (MCRs) have emerged as a great tool for synthetic transformations due to their operational simplicity, less hazardous and minimum side products with higher yields of desired products. They have advantages over multi step reactions in comparison with experimental procedures such as the yield of the desired products, time of the reactions, isolation of any intermediate compound, which saves time, energy and raw materials required for the reaction, making the protocol economically attractive and environmentally friendly.[1] In recent years, pyranopyrazoles have attracted great importance due to their biological and pharmaceutical activities.[2] In addition to their known bactericidal, fungicidal and herbicidal activities they exhibit analgesic, anti-inflammatory activity and also act as vasodilators, hypotensive and hypoglycemic agents.[3–5] Substituted pyranopyrazoles were firstly synthesized in 1973 by a reaction between 3-methyl-5-pyrazolone and tetracyanoethylene.[6] The 2-amino-4-substituted pyrano [2,3-c] pyrazole-3-carbonitriles were obtained in 1974 by the addition of malanonitrile to arylidene-3-methyl-2-pyrazolin-5-one.[7] Later on a number of synthetic methods were developed for the synthesis of pyrano pyrazoles, using arylidenemalanonitrile and 3-methyl-5-pyrazolone.[8] or 4-arylidine-3-methyl-5- pyrazolone and malanonitrile.[9] and also by the three component condensation of aromatic aldehydes, malanonitrile and3-methyl-5-pyrazolone.[10] Pyranopyrazoles are also synthesized by the condensation of two components.[11] Recently these compounds are synthesized by the condensation of four component reaction catalyzed by piperidine,[12] triethylamine,[13] L-proline or KF-alumina,[14] trichloroacetic acid,[15] iodine,[16] c-alumina,[17] ionic liquid,[18] amberlyst A21,[19] nanosized magnesium oxide,[20] Fe_3O_4 nanoparticles,[21] per-6-ABCD,[22] silicotungstic acid,[23] and isonicotinic acid.[24] Some of the reported methods suffer from one or more limitations such as prolonged reaction time, use of organic solvents, and harsh reaction conditions. Thus, the development of new environmentally friendly and more effective procedure for the synthesis of pyranopyrazoles and carrying out organic reactions in water is of significant interest. Water, due to its features such as ecological friendly, safe, non-toxic, non-flammable, clean, green, inexpensive as well as readily available has been recommended to be used as a solvent in organic syntheses.[25]

METHODS AND MATERIALS

Experimental

Melting points of the desired derivatives were determined using capillary melting apparatus, MELT-TEMP and were uncorrected. 1H NMR and 13C NMR nuclear magnetic resonance spectra were taken on Bruker ARX 400 NMR instrument with tetramethylsilanes as an internal standard. Chemical shifts are reported in parts per million (δ), and signals

were expressed as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiple). Coupling constant are in hertz (HZ). Mass spectra of these derivatives were recorded on Varian Saturn 2000 GC/MS. Each of the reaction was monitored and judged complete by removing aliquots at intervals and analysed by thin layer chromatography (TLC).

General procedures 6-Amino-4-phenyl-3-methyl-2,4-dihydropyrano[2,3-c]- pyrazole-5-carbonitrile

The substituted aromatic aldehyde (1 mmol), malanonitrile (1 mmol), ethylacetoactete (1 mmol), hydrazine hydrate (1 mmol), and camphorsulphonicacid acid (5 mol %) were added successively in 25 ml of ethanol and refluxed for the appropriate time. The progress of the reaction was monitored by TLC (ethyl acetate: n-hexane = 4:6). After completion of reaction, the reaction mixture was diluted with cold water. The solid crude products, which separated out, were filtered, washed with water and dried. The crude product was purified by recrystallization with ethanol to afford pure product.

Selected spectroscopic data

2.3.1. 6-Amino-4-phenyl-3-methyl-2,4-dihydropyrano [2,3-c]- pyrazole-5-carbonitrile (5a)

White solid, Yeild-84%;M.p 221–223^{0}C,1H NMR (400 MHz, $CDCl_3$)δppm: 1.170 (s, 3H, CH_3), 4.341 (s, 1H, C-4), 6.241 (s, 2H, NH_2), 7.017-7.257 (m, 3H, Ar-H), 7.258 (d, 2H, J = 7.6 Hz, Ar-H), 11.487 (s, 1H, NH) ppm; 13C NMR (100MHz,$CDCl_3$) δppm: 10.54, 35.84, 57.14, 78.09, 78.25, 80.58, 98.04, 121.33, 127.15, 127.88, 128.14, 134.74, 145.30, 155.85, 161.87; Molecular formula: $C_{14}H_{12}N_4O$;LCMS (m/z); 253.24 (M+H). Analysis of elements: Calculated; C- 66.65, H- 4.79, N- 22.21, and Obtained: C- 66.56, H- 4.77, N- 22.31.

2.3.4.6-Amino-4-(3,4,5-trimethoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5b)

White solid, Yeild-94%;M.P: 236–2380C; 1H NMR (400 MHz, CDCl3) δppm : 1.546 (s, 3H, CH3), 3.684(s, 3H, OCH3), 3.754 (s, 6H, 2OCH3), 4.585(s, 1H, C-4), 6.451(s, 2H, NH2), 6.884-6.987 (s, 2H, Ar-H), 11.258 (s, 1H, NH); 13C NMR (100 MHz ,CDCl3) δppm: 10.95, 36.88, 56.26, 60.25, 77.85, 79.58, 97.57, 105.85, 121.44, 134.85, 136.65, 140.09, 153.85, 155.17, 161.64; Molecular formula: C17H18N4O4;LCMS(m/z):343.56 (M+H); Analysis of elements: Calculated; C- 69.64 ,H- 5.30, N- 16.37, Obtained : C- 69.56 , H- 5.29 ,N- 16.42.

2.3.2.6-Amino-4-(3-nitrophenyl)-3-methyl-2,4-dihydropyrano-[2,3-c]pyrazole-5-carbo nitrile (5c)

White solid, Yeild-85%;M.p 235–237^{0}C, 1H NMR (400 MHz, CDCl3) δppm : 1.114 (s, 3H, CH_3), 4.210 (s, 1H, C-4), 6.118 (s, 2H, NH_2), 7.224 (d, 2H, J = 7.6 Hz, Ar-H), 7.347 (d, 2H, J = 8.0 Hz, Ar-H), 11.627 (s, 1H, NH) ppm; ^{13}CNMR(100 MHz ,$CDCl_3$) δppm: 11.12, 36.17, 56.07, 98.34, 120.22, 128.58, 129.08, 130.98, 136.74, 145.18, 155.99, 162.18; Molecular formulae: $C_{14}H_{11}N_5O_3$; LCMS(m/z): 299.74(M+H): Analysis of elements: Calculated; C- 56.57 H-3.73, N-23.56, Obtained: C-56.51, H-3.71 N-23.63.

2.3.3.6-Amino-4-(4-nitrophenyl)-3-methyl-2,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitrile (5d)

White solid, Yeild-85%;M.p: 242–244^0 C;1H NMR (400 MHz, CDCl3) δppm: 1.587 (s, 3H, CH_3), 4.318 (s, 1H, C-4), 6.507 (s, 2H, NH_2), 7.414 (d, 2H, J = 6.8 Hz, Ar-H), 8.147 (d, 2H, J = 8.0 Hz, Ar-H), 11.587(s,1H, NH) ppm; 13C NMR (100 MHz ,CDCl3) δppm: 9.97, 36.08, 54.88, 96.66, 120.87, 124.57, 128.84, 135.89, 146.13, 152.57, 155.78, 162.57; Molecular formulae: $C_{14}H_{11}N_5O_3$ MS (ESI+): m/z 299.08 $(M+H)^+$; Analysis of elements: Calculated; C- 56.57 ,H-3.73, N-23.56, Obtained : C-56.51 , H-3.71 ,N-23.63.

2.3.5.6-Amino-4-(2-thiophene)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5e)

White solid, Yeild-88%; M.P : 210–212^{0}C;^{1}H NMR (400 MHz, CDCl3) δppm: 1.587 (s, 3H, CH_3), 4.587 (s, 1H, C-4), 6.489(s, 2H, NH_2), 6.958 (d, 1H, J = 8.0 Hz, Ar-H), 7.224 (d, 1H, J = 9.2 Hz, Ar-H), 7.358 (d, 1H, J = 6.8 Hz, Ar-H), 11.518 (s, 1H, NH): ^{13}C NMR (100 MHz, CDCl3) δppm: 10.987, 32.54, 58.08, 98.66, 121.85, 124.05, 125.19, 126.85, 135.96, 150.74, 154.33, 161.74 ; Molecular formula: $C_{12}H_{10}N_4OS$; LCMS(m/z): 259.74 (M+H); Analysis of elements: Calculated; C-55.80,H-3.90, N-21.69, Obtained : C-55.72, H- 3.88, N- 21.76.

3. BIOLOGICAL EVALUATION

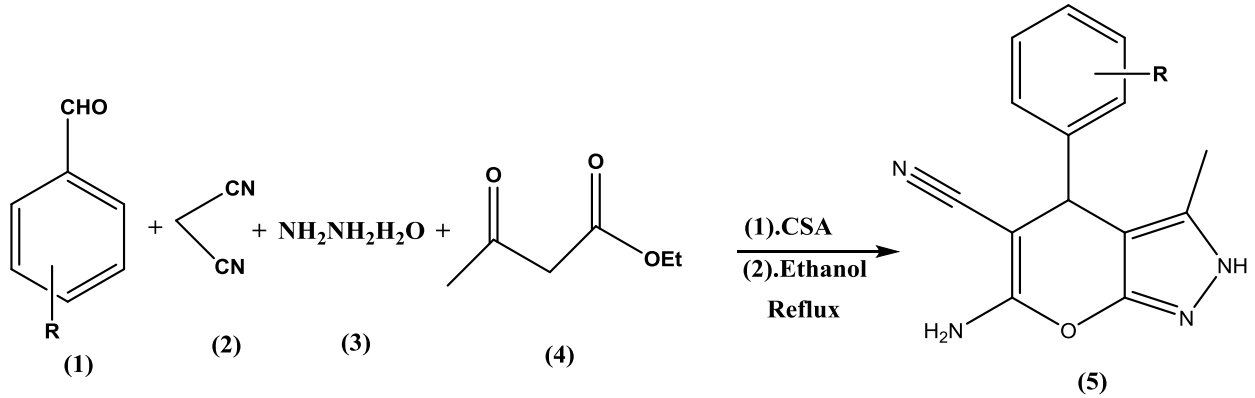
3.1. ANTIBACTERIAL ACTIVITY

Preliminary investigation of in vitro anti-microbial activity of desired analogous (7a-h) were evaluated by cup plate drugs biological method, different pathogenic strains Viz. S.aureus, B. substills (Gram-+ve), S. typhi and E.coli (Gram-ve) were employed using standard drug streptomycin for antibacterial growth respectively. Nutrient Agar Medium (NAM) is used to test for the antibacterial activity of titled compounds. The mixture of beef extract (5 g), peptone (8.5g), NaCl (5 g), agar-agar (22 g) 1000 ml distilled water is called NAM and pH was maintained to 7.0. NMA was sterilized in an auto clave at 120°C, 15 lbs pressure for 35 min. NAM was poured into petro dish as in a laminar air flow after sterilization and allowed to solidify. After, the solidification of NMA was in osculated with 100 µl of derived bacteria. The compounds was diluted in Dimethylsulphoxide (DMSO) with concentration of 100 ppm, 250 pm and 500ppm Whatsman No.1 filter paper disks were placed in the solution and kept for 1 min. After drying the disks were placed as NAM inoculated with bacteria and NAM plates were incubated at 37°C. Zones of inhibition were measured after 36 hrs compared with streptomycin. Each test was carried out three times and taken average value.

4. RESULTS AND DISCUSSION

Initially, aromatic aldehyde was selected as a probe aldehyde to optimize the amount of catalysts. The formation of the 5b initially, substituted benzaldehyde was selected as a probe aldehyde to optimize the amount

of catalysts. The formation of the 5b did not proceed in the absence of the camphorsulphonicacid even after refluxing the reaction mixture for 60 min. in ethanol. The amount of catalyst was optimized during the reactions and it is observed that 5 mol% catalysts were sufficient to forward the reactions in the push direction (Table-1). The major amounts of the catalyst did not develop the results to a greater extent. The results are summarized in Table-1. The aromatic aldehyde and other aromatic aldehydes having electron withdrawing groups and electron donating groups employed and reacted well to give corresponding pyranopyrazole derivatives. It has been observed that the time required to complete the reactions is slightly higher in the case of electron donating substituents. The present protocol was found well applicable for heterolysis moieties in respect of yield and reaction time but failed to give corresponding pyranopyrazoles derivatives.



(1) **(2)** **(3)** **(4)** **(5)**

(5a-5e)

R = H, 3,4,5(OCH_3)$_3$, 3-NO_2 ,4-NO_2, Thiophene

(Sheme-1)

The function of the catalyst in this investigation is the most important role synthesis of the titled derivatives. The rate of the complete reactants consumption, productivity development, short reaction time and utilization of solvents, chemicals as well as temperature optimization are dependent on catalyst. The scope of catalyst is very important performance during the mode reaction; it is very commercially availability, low cost price and easy workup.

Table 1: Comparison among the various catalyst synthesis of titled compound (5b).

Entry	Catalyst	Time (min)	Yield (%)
1	MSA	210	49
2	P-TSA	180	64
3	TCSA	120	55
4	CSA	60	94

The amount of catalyst is very most important role play in this reaction, 1mmole amount of the catalyst was utilized in starting, acquired traces amount of product and gradually increasing upto 10mmol amount of the catalyst during the reaction. Hence, maximum amount yield obtained (94). Further, amount of the catalyst increased up to entry "5" and get no improvement as shown Table-2

Table -2: Optimization of amount of catalyst 5 mol% camphorsulfonic acid for the synthesis of (5b).

Entry	Catalyst mole%	Time (min.)	Yield (%)
1	1	150	74
2	2	120	80
3	3	90	83
4	4	75	85
5	5	60	94
6	6	60	94

a All reactions were carried out in aqueous medium. b Isolated yields.

Following the above catalyst performed during the reaction process, we proceeded to the screening of solvent effects using a variety of solvents, including THF, CH_3CN, EtOAc, H_2O EtOH, MeOH, and Toluene. Our observations are identified that the good reaction conditions are those if without the use of solvents and also the completion of the reaction as well as for the yield of the desired product compared than those obtained in any of the solvents investigated (Table-3).

Table-3: Synthesis of 5b in the presence of 5 mol% camphorsulfonic acid different solvents.

Entry	Solvent	Time(min.)	Yield(%)
1	THF	150	58
2	Acetonitrile	120	50
3	Ethyl acetate	90	69
4	Water	75	45
5	Ethanol	60	90
6	MeOH	60	74

a Entry Solvents Time (min.) Yield (%)b

The aromatic aldehyde and other aromatic aldehydes having electron withdrawing groups and electron donating groups employed and reacted well to give corresponding pyranopyrazoles derivatives. It has been observed that the time required to complete the reactions is slightly higher in the case of electron donating substituents. The present protocol was found well applicable for heterolysis moieties in respect of yield and reaction time but failed to give corresponding pyranopyrazoles derivatives.

One-pot synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives of aromatic aldehyde and heteroaromatic aldehyde were used under optimized reaction conditions. This may be due to the sluggish product which was obtained from Knoevenagel condensation of aromatic aldehyde and heteroaromatic aldehyde with malanonitrile in the intermediate step. The structures of these compounds were deduced from their physical and spectroscopic data. All the products exhibited a singlet in 1 H NMR spectra at about d = 4.451–4.795 ppm for H-4 and also peaks at about d = 11.421–11.587 ppm for N–H group. The plausible mechanism for the synthesis of pyrano [2,3-c]- pyrazole derivatives in the presence of camphorsulfonic acid is represented in Scheme -1.

4.2. ANTIMICROBIAL ACTIVITY

All the desired compounds were evaluated by anti-bacterial activity as well as antifungal activity. The electron withdrawing group of compounds and electron releasing group compounds exhibited various potent activities against bacterial as well as fungal strains. Therefore, electron withdrawing group of compounds showed low biological potent activity compared with electron releasing groups. The electron donating group's exhibit "5b"" exhibited well to excellent activity. The compounds that containing electron donating group showed to moderate activity as shown in Table-4.

Table-4: Antimicrobial activity screening activity Titled compounds scaffold.

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substills	A. Niger	C. albicans
5a	05	07	06	04	04	05
5b	23	21	22	20	17	17
5c	12	10	12	14	11	10
5d	**13**	**15**	**16**	**13**	**10**	**10**
5e	**17**	**18**	**17**	**20**	**12**	**11**
streptomycin	27	27	25	25	NA	NA
Ketoconazole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

5. CONCLUSION

In conclusion, camphor sulfonic acid is an commercially available, inexpensive and an efficient catalyst for the synthesis of 1,4-dihydropyrano[2,3-c] pyrazole derivative employing multicomponent condensation strategy in ethanol promoted by camphor sulfonic acid . The present methodology furnishes the products very quickly with excellent yields, without any column chromatographic purification and is non-hazardous to environment.

6. ACKNOWLEDGMENTS

The Authors are grateful to management of PRISM PG&DG College for providing facility to project work.

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