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RESEARCH ARTICLE

IODINE CATALYZED: ONE-POT SYNTHESIS OF 1, 4-DIHYDROPYRANO (2, 3-C) PYRAZOLE ANALOGOUS AND ANTIMICROBIAL ACTIVITY

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ABSTRACT

A simple and an efficient protocol wasfollowed for the synthesis of dihydropyrano(2,3-c) pyrazole analogous by a one pot and multicomponent reaction of ethyl acetoacetate, hydrazine hydrate, malononitrile and various substituted aldehydes in the presence of a catalytic amount of I_2 in ethanol solvent medium. The structures of all the newly synthesized derivatives have been interpreted on the basis of analytical and spectral dataviz IR, 1HNMR, 13CNMR and LCMS. The anti-microbial activity was screening exhibited that most of the obtained compounds were found to have significant anti-microbial activity activitiesThe advantages of this method serves as the various benefits such as major yield, low reaction time, mild reaction condition, operational simplicity, easy work-up method with environment friendly nature and purification of products by non-chromatographic methods has been enveloped.

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INTRODUCTION

Heterocyclic compounds with nitrogen hetero-atoms are all over the place and their uses in medicinal chemistry and agrochemicals are becoming more and more significant in various fields.The multi-component reactions (MCRs) have powerful and a great tool for synthetic transformations due to their operational simplicity, less hazardous and minimum side productswith higher yields of desired products. They have advantagesover multi step reactions in comparison with experimental procedures such as the yield of the desired products, time of thereactions, 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 been attracted a significant importance due to their biologicalpharmaceutical potentactivities (2)., antimicrobialactivity (3), anticanceractivity(4)anti-nflammatory (5), Anticorrosion (6), Antioxidant Activities(7), Antipsychotics (8), antitumor and antiangiogenic (9). antitumor and anti-malarial (10), Alzheimer's disease (11), HyperplasiaUrol (12)., antidiabetic drug (13) linagliptin antitubercular activity(14).Recently, four-component synthesis of Pyrano (2,3-c)pyrazoles have been done via the reaction of hydrazine hydrate, ethyl acetoacetate, malononitrile, and aromatic aldehydes using various catalysts such as: ionic liquids(15) , cesium fluoride(16), heteropolyacid(17), sodium bisulfite(18), samarium iodide(19), diradical Ni(II)-catalysts(20), Glycine-catalyzed(21), In continue of our efforts into the improvement of the synthetic approaches using iodine catalysts. We report an efficient pathway for the synthesis ofdihydropyrano (2,3-c)pyrazoles via multi-component reactions of substituted aldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate using I_2. In addition to the study of microbial activity of newly synthesized compounds were examined.

EXPERIMENTALMETHODS

Merck and Sigma Aldrich chemicals supply all of the synthetic grade and chemical reagents.

All newly analogous melting points were measured in an open capillary tube without correction. On a Broker (400MHz) spectrometer, the ^{1}HNMR spectra ($CDCl_3$) were acquired with TMS as the internal standard and the chemical shift indicated in δ ppm. Using an LCMS spectrometer, the molecular weight of the produced molecules was calculated. Iodine was utilized as a visualizing agent while thin layer chromatography was used to check the purity of all produced chemicals.

General Procedure: The Mixture Of Substituted Aromatic Aldehyde (1mol), Malononitrile (1mol), Ethyl Acetoacetate (1mol), Hydrazine Hydrate (1mol), And I_2 (2 Mol %) Were Added Successively In 20 Ml Of Ethanol And Refluxed For The Appropriate Time. The Progress Of The Reaction Was Examined 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

6-Amino-4-Phenyl-3-Methyl-2,4-Dihydropyrano(2,3-C)-Pyrazole-5-Carbonitrile (5a): White Solid, Yield-80% ; Mp-232–234 °C, IR (KBr) cm^{-1}: 3384, 3179,2179, 1650, 1594, 1405, 1048 Cm^{-1}; ^{1}HNMR(400 MHz,$CDCl_3$) δppm: 1.714 (S, 3H, CH3), 4.422 (S, 1H, C-4), 6.645 (S,2H, NH_2), 7.164 (M,3H,Ar-H), 7.232(d, 2H, J = 7.6 Hz, Ar-H), 11.774 (S, 1H, NH); ^{13}CNMR (100MHz,$CDCl_3$)δ ppm,: 0.95, 35.45, 57.07, 77.57, 74.90, 79.11, 99.54,120.84, 127.16, 127.89, 128.66, 136.35, 145.65, 154.66,164.81 Ppm; Molecular Formulae:$C_{14}H_{12}N_4O$; LCMS (M/Z): 253.13 (M+H)+

2.1.2.6- Amino-4- (4-Hydroxyhenyl)-3-Methyl-2,4-Dihydropyrano- (2,3-C)Pyrazole-5-Carbonitrile (5b) White Solid, Yield-90% , M.P 240–242 °C, IR (KBr) cm^{-1}: 3598,3412, 3225,2187, 1649, 1591, 1495, 1407, 1057, 824 Cm$^{-1;1}$H NMR(400 MHz,$CDCl_3$) δppm : 1.547 (S, 3H, CH_3), 4.471 (S, 1H,C-4), 6.587 (S, 2H, NH_2), 7.284 (d, 2H, J = 8.0Hz, Ar-H),7.381 (d, 2H, J = 12.4 Hz, Ar-H), 9.240(S,1H),11.668 (S, 1H, NH) Ppm; ^{13}CNMR (100MHz,$CDCl_3$)δ ppm:12.07, 36.25, 55.81, 102.84,122.87, 128.55, 128.92, 130.33, 136.06, 144.74, 155.12,162.07; Molecular Formulae:$C_{14}H_{12}N_4O_2$.LCMS (M/Z); 269.58 (M+H)+

Amino-4-(4-Methoxyhenyl)-3-Methyl-2,4-Dihydropyrano-(2,3-C)Pyrazole-5-Carbonitrile (5c): White Solid, Yield-88%; M.P 254–256°C, IR(KBr) cm^{-1}: 3401, 3231,2184, 1646, 1598, 1496, 1409, 1059, 824 Cm^{-1}; ^{1}HNMR (400 MHz,$CDCl_3$) δppm ; 1.247 (S, 3H, CH_3),3.744(S,3H,OCH_3), 4.404 (S, 1H,C-4), 6.781 (S,2H,NH_2),7.290 (d, 2H, J =6.8Hz, Ar-H),7.394 (d, 2H, J = 10.6 Hz, Ar-H),11.450 (S, 1H, NH) Ppm; ^{13}CNMR (100MHz,$CDCl_3$)δ ppm : 10.55, 34.58, 56.02, 100.84,121.78, 128.12, 128.77, 130.03, 134.88, 143.84, 156.12,161.97; Molecular Formulae:$C_{15}H_{14}N_4O_2$.LCMS (M/Z); 282.65 (M+).

2.1.4.6-Amino-4-(3,4,5-Trimethoxyphenyl)-3-Methyl-2,4-Dihydropyrano(2,3-C)Pyrazole-5-Carbonitrile(5d): White Solid, Yield-93%; Mp 239–241 °C;IR(KBr) cm^{-1}: 3420, 3218,2193, 1651, 1598, 1493, 1210, 1190 Cm1; ^{1} H (400 MHz,$CDCl_3$) δppm : 1.88 (S, 3H, CH_3), 3.66 (S, 3H,OCH_3), 3.73 (S, 6H, 2 · OCH_3), 4.57 (S, 1H, C-4), 6.46 (S,2H, NH_2), 6.84 (S, 2H, Ar-H), 12.08 (S, 1H, NH) Ppm; ^{13}CNMR (100MHz,$CDCl_3$)δ ppm : 12.21, 37.04, 56.94, 57.51,60.86, 76.74, 78.87, 79.19, 98.20, 104.47, 121.08, 136.67,138.84, 141.02, 153.94, 155.17, 165.90 ; $C_{17}H_{18}N_4O_4$, LC MS (M/Z): 343.07 (M+H) 2.1.5.6-Amino-4-(2-Nitrophenyl)-3-Methyl-2,4-Dihydropyrano-(2,3-C)Pyrazole-5-Carbonitrile (5e) White Solid, Yield-83%, Mp 248–250 °C, IR (KBr) cm^{-1}: 3411, 3229,2184, 1643, 1593, 1494, 1405, 1055, 824 Cm-1; ^{1}H NMR(400 MHz,$CDCl_3$) δppm : 1.847 (S, 3H, CH3), 4.624 (S, 1H,C-4), 6.881 (S, 2H, NH2), 7.254(d, 2H, J = 8.0 Hz, Ar-H),7.457 (d, 2H, J = 5.4 Hz, Ar-H), 12.014 (S, 1H, NH) ^{13}CNMR (100MHz,$CDCl_3$)δ ppm: 9.71, 35.54, 56.72, 97.16,120.65, 128.43, 129.33, 131.22, 135.67, 143.44, 154.68,160.88 Ppm; $C_{14}H_{11}N_5O_3$;LCMS(M/Z): 298.58 (M+H)+

Amino-4-(4-Nitrophenyl)-3-Methyl-2,4-Dihydropyrano-(2,3-C)Pyrazole-5-Carbonitrile (5f): White Solid, Yield-84% ; M.P-255–257°C; IR(KBr) cm^{-1}: 3532, 3228,2192, 1650, 1595, 1515, 1405, 1356, 857 Cm^{-1}; ^{1}HNMR(400 MHz,$CDCl_3$) δppm : 1.814 (S, 3H, CH_3), 4.587 (S, 1H,C-4), 6.817 (S, 2H, NH_2), 7.445(d,2H, J = 6.6 Hz, Ar-H),8.18 (d, 2H, J = 6.9 Hz, Ar-H), 12.14 (S, 1H, NH) Ppm; ^{13}CNMR (100MHz,$CDCl_3$)δ ppm: 9.70, 35.84, 55.85, 96.53,120.47, 123.87, 128.81, 135.85, 146.34, 152.07, 154.63,161.11; $C_{14}H_{11}N_5O_3$;LCMS(M/Z): 298.05 (M+H)+

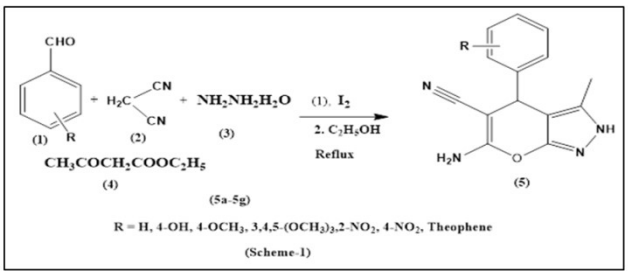
Amino-4-(2-Thiophene)-3-Methyl-2,4-Dihydropyrano(2,3-C)Pyrazole-5-Carbonitrile (5g) White Solid, Yield-87% ; Mp 212–214°C; IR(KBr) cm^{-1}: 415, 3212,2190, 1647, 1592, 1496, 1402, 1288; ^{1}H NMR(400 MHz,$CDCl_3$) δppm : 1.887 (S, 3H, CH_3), 4.578 (S, 1H,C-4), 6.571 (S, 2H, NH_2), 6.944(d, 1H, J = 5.2 Hz, Ar-H),7.1425(d, 1H, J = 8.0,14.2Hz, Ar-H), 7.378 (d, 1H, J = 7.6 Hz, Ar-H), 11.665 (S, 1H, NH) Ppm; ^{13}CNMR(100MHz,$CDCl_3$)δ ppm : 10.09, 30.74, 58.12, 98.74, 121.06, 123.11,125.19, 127.66, 138.75, 180.74, 155.26, 161.55 ;$C_{12}H_{10}N_4OS$ LCMS (M/Z): 259.17 (M+H)+ .

ANTIMICROBIAL SCREENING

Antimicrobial activity of synthesized compounds by disc diffusion test. Antimicrobial activities of the synthesized compounds were evaluated against Staphylococcus aureus (S. aureus), Escherichia coli, methicillin resistance Staphylococcus aureus (MRSA) Pseudomonas aeruginosa and Candida Albicans. Antibacterial activities of synthesized compounds detected by disc diffusion method and minimum inhibitory concentration (MIC) were used. Primary all of the bacterial isolates and candida Albicans cultured on Mueller Hinton agar (Merck, UK). These bacteria and candida Albicans were seeded in Mueller Hinton agar by the pour plate technique. Diameter paper discs with of each of the compounds (1.0% w/v) and methanol (as control) was applied to the agar plates and incubated at 37 °C or 48 h. The formation of an inhibition zone around the disc is an indication of antibacterial activity (3).

RESULTS AND DISCUSSION

Initially, in order to optimize the reaction parameters, we investigated the reaction of ethyl acetoacetate, hydrazine hydrate, malononitrile and various substituted aldehydes I_2 under different conditions.Whereas, the yield of theproduct reduced by decreasing the amount of the catalyst.



When the same reaction was performed in the absence of the catalyst, the corresponding product was obtained in only28% yield. The reaction condition of these derivatives was optimized at various catalyst, different amount of the catalyst and different solvent are used. The maximum yield of the compounds obtained in presence of zinc oxide (ZnO) catalyst than oxidative related catalyst such as titanium dioxide (TiO_2),copper oxide(CuO), Iodine whereas different amount of catalyst utilized during the reaction (Table-I).

Table I. The optimization of the catalyzed aryl aldehyde, ethyl acetoacetate, hydrazine hydrate, malononitrile I_2 (5c)

Entry	Catalyst	Time (hrs)	Yield (%)
1	ZnO	10	54
2	TiO_2	06	65
3	CuO	09	71
4	I_2	03	93

The different solvents were used during the reaction that were evaluated (DMF, Isopropanol acetonitrile, ethanol, methanol, cyclohexane) in the model reaction. It was found to be the best medium for the reaction, with 93% product yield and was therefore used as the solvent for subsequent reactions on the merits of higher yield, green nature and easy work-up. Table-II:

Table II. The Optimization of the solvent on aryl aldehyde, ethyl acetoacetate, hydrazine hydrate, malononitrile I_2 (5c)

Entry	Catalyst	Time (hrs)	Yield (%)
1	DMF	3	40
2	IPA	3	61
3	CH_3CN	3	55
4	EtOH	3	93
5	MeOH	3	65

The Optimization of the solvent on aryl aldehyde, ethyl acetoacetate, hydrazine hydrate, malononitrile I_2 (5c): A significant improvement was identified, the yield of 4c being increased to 93%. Use of only 1.5m mol% was sufficient to drive the reaction forwards within 3hrs. The maximum amounts of the catalyst did not improve the results. Although, use of 2.0mmol% Iodine permitted the reaction time to be enhanced to 1 h, the yield unexpectedly increased to 93%as shown Table-III.

Table III. The Optimization of the amounts of catalyst (I_2) in ethanol (5c)

Entry	Amount catalyst (mmol)	Time (hrs)	Yield (%)
1	0.5	3	Traces
2	1.0	3	35
3	1.5	3	51
4	2.0	3	93

The appreciable results, a series of substituted aldehydes were evaluated under optimized conditions and the results are shown in Table-1. It is indicated that the various substituted aromatic aldehydes bearing either electron donating or withdrawing substituents group in para propositions afford high yield of the adduct . Another important feature of this method is the applicable l of variety of functional groups under this reaction conditions. Here, we have found that the reaction of aromatic aldehydes having electron-withdrawing groups was rapid as compared to the reaction of aldehydes having electron donating groups. It clearly indicates that this method is better than the previously reported methods for the synthesis of 1, 4-Dihydropyrano (2,3-C) Pyrazole derivatives. The reusability of the catalyst again was investigated; the new results were showed that the catalyst activity slightly minimized for each run.

In continuation and progress of our research which was indicated the scope and limitations of the present investigation. There are the four component of the synthesis of dihydropyrano (2,3-c)pyrazole derivatives were utilized the hydrazine hydrate, ethyl acetoacetate, malononitrile with various kinds of aldehydes including electron-withdrawing groups and electron-releasing substituent's (Scheme 1). The corresponding 1,4-dihydropyrano (2,3-c)pyrazoles were afforded in considerable percentage of yields (85–98%) and short reaction times. However, aryl aldehydes containing and electron-releasing groups such as OH and OCH_3 reacted more slowly than aryl aldehydes with electron-withdrawing groups such as Cl ,CNand NO_2.

ANTIMICROBIAL ACTIVITY OF COMPOUNDS

The titled derivatives were evaluated for their in-vitro antibacterial and antifungal activities following micro broth dilution method. The invitro antibacterial activity was examined against gram-positive (Bacillus subtilis and Staphylococcus aureus) and gram-negative (Escherichia coli and P. aeruginosa) microorganisms. The invitro antifungal activity was evaluated against Aspergillus Niger and C.albicans microorganisms. The standard drugs used for this study were Streptomycin was used for antibacterial screening. Ketonozole was used for antifungal screening. The standard strains used for screening of antibacterial and antifungal activities were procured 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. 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. Antimicrobial activity of compounds (5a-5g) is listed in Table-IV

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

Entry	Antibacterial MIC (µg/mL)				Antifungal MIC (µg/mL)	
Strains	B. subtilis	S. aureus	P. aeruginosa	E. coli	A. Niger	C. Albicans
5a	07	05	07	09	05	08
5b	20	20	19	21	18	17
5c	19	20	18	16	16	16
5d	21	20	22	20	15	18
5e	14	12	12	10	05	07
5f	11	10	09	07	06	08
5g	13	15	16	16	17	17
Streptomycin	25	25	25	25	-	-
Ketonozole	-	-	-	-	22	22
DMSO						

CONCLUSION

In conclusion, $I_2$is a readily available, inexpensive, and efficient catalyst for the synthesis of 1, 4-dihydropyrano (2, 3-c) Pyrazole analogous were obtained. This methodology gives most an important and numerous attractive advantages such as minimized time of reaction, higher yield of the product, ease of product isolation, and complete variability of the catalyst, when compared with conventional method as well as with other catalysts which will have wide scope in organic synthesis. This simple procedure and solvent as ethanol conditions combined with easy recovery and reuse of this catalyst make this method economically and environmentally benign process. We believe that this procedure is convenient, economic and ecofriendly for the synthesis of 1, 4-dihydropyrano (2, 3-c) Pyrazole derivatives of biological and medicinal importance.

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