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Microwave-assisted an one–pot three component synthesis of 1,4-dihydropyrano [2,3-*c*] pyrazoles under solvent-free condition

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ABSTRACT

A three component coupling process for synthesis of 6-amino-4-aryl-5-cyano-3-methyl–1–phenyl-2-pyrazolin-5-one from 3-methyl-1-phenyl–2-pyrazolin-5-one, aromatic aldehydes, malononitrile sodium hydrogen sulfate ($NaHSO_4$) using as catalyst is described under microwave irradiation and solvent free condition. This method provides several advantages such as mild reaction condition, short reaction time, simple work up procedure and is environmentally friendly.

KEYWORDS

Multicomponent reaction;
Sodium hydrogen sulfate;
1,4 Dihydropyrano [2,3-*c*] pyrazoles;
Microwave irradiation.

INTRODUCTION

Pyrano [2,3-*c*] Pyrazole is a fused heterocycle comprised of Pyrazole and Pyran rings which are known as the sub-structural units of several biologically active compounds. Poly functionalized benzopyrans and their derivatives are a kind of very useful compounds[1,2]. They have been widely used as medicine intermediates due to their useful biological and pharmacological properties such as antibacterial, anti coagulant, anticancer, spasmolytic, hypnotic, diuretic, insecticide[3-6]. Some of the 2-amino-4*H*-Pyrans can be used as photoactive materials[7]. The 4*H*-Pyrans ring is also a structural unit of a number of natural products[8-10].

1,4-Dihydropyrano[2,3-c] pyrazoles are generally prepared by one pot three component condensations of malononitrile, aromatic aldehyde and 3-methyl-1-Phenyl-2-Pyrazolin-5-one using water as reaction medium demonstrated by using various phase transfer catalyst such as triethylbenzylammonium chloride (TEBA)[11], hexadecyl trimethyl ammonium bromide (HTMAB)[12], surfactant such as p-dodecylbenzensulfonic acid (DBSA)[13]. Similarly the use of the neutral organo–catalyst DL-proline using the grinding technique[14], piperidine[15], sulfamic acid[16], KF-montmorillonite[17].

In recent years, solvent-free reaction condition has been demonstrated to be an efficient technique for various organic reactions. It often lead to a remarkable decrease in reaction time, increased yields, easier workup, enhancement of regio and stereo selectivity of reaction matches with the green chemistry protocol[18]. Sodium hydrogen sulfate ($NaHSO_4$) is exploited as an efficient catalyst in organic synthesis[19]. However, there is not a single report on the use of sodium hydrogen sulfate as a catalyst for the synthesis of. 1,4-Dihydropyrano [2,3-*c*] pyrazoles. However, some of these previous methods have suffered from one or more drawbacks like use of expensive reagents. In order to eliminate high temperature requirement, long reaction time, low yield of product, the development of mild, efficient and versatile method is still strongly desirable. Herein we have

presented a novel, mild and efficient method for synthesis of 1, 4-dihydropyrano [2,3-*c*] pyrazoles using sodium hydrogen sulfate as mild catalyst and overcome all problems. In this methodology, the uses of hazardous organic solvents have been avoided during the synthesis. This method is quite satisfactory with respect to yield and the reaction time. Therefore the reactions carried out under solvent free condition are more beneficial as compared to conventional methods which involve the use of dangerous, flammable, carcinogenic solvents like alcohols, chloroform DMF etc.

EXPERI1MENTAL

Reagents and analysis

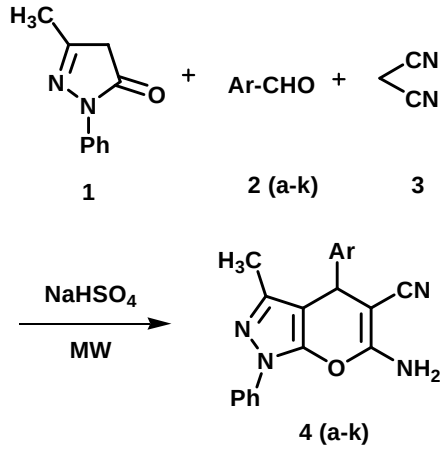
All the reagents and aromatic aldehydes were obtained from commercial suppliers used as such melting points were determined in open capillaries and are uncorrected. The completion of reactions was monitored by TLC. IR spectra were recorded on a matrix of KBr with Perkin-Elmer 1430 spectrometer.^{1}H-NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on Varian NMR spectrometer, Model Mercury Plus (400 MHz), Mass spectra [ES-MS] were recorded on a Water-Micro mass Quattro-II. For the microwave irradiation experiments described below, microwave oven equipped with a turntable was used (LG Smart Chef MS-255R operating at 2450 MHz having maximum output of 900 W).

General method for the synthesis of 1,4-dihydropyrano [2,3-*c*] pyrazoles (4a-4k)

A mixture of aromatic aldehyde (3 mmol), malononitrile (3 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one (3 mmol) and sodium hydrogen sulfate (10 mol%),) was taken in a beaker and the reaction mixture was irradiated in microwave oven at 180 W for 6–8 min. (as indicated by TLC). The reaction mixture was allowed to stand at room temperature to solidify. The crude product was collected, washed with Water and recrystallized from 95% ethanol to give pure 1,4-dihydropyrano [2,3-*c*] pyrazoles in good to excellent yields. All synthesized compounds were characterized by ^{1}HNMR and Mass. Also the melting points recorded and compared with the corresponding literature MP and found to be matching with those.

RESULT AND DISCUSSION

In our laboratory, continuing our interest in the synthesis of organic compounds by the multi-component reactions under microwave irradiation[20-23], Herein, we would like to report the synthesis of 1,4 dihydropyrano [2,3-*c*] pyrazoles under irradiated of microwave at.180W and solvent-free conditions (Scheme 1)



Scheme 1

In search for an efficient catalyst the reaction of benzaldehyde as a representative aldehyde, 3-methyl-1-phenyl-2-pyrazolin-5-one, malononitrile and 10 mol % of sodium hydrogen sulfate has been considered as a standard model reaction.

Initially, we examined the reaction without catalyst at different power for 15 min did not result in formation of the expected product Show in TABLE 1

TABLE 1: Comparative study of catalysts using various power of microwave 4a[a].

Entry	Power	Sodium hydrogen sulfate (mol %)	Time (min)[b]	Yield (%) [c]
1	100	Without	15	No reaction
2	150	Without	15	No reaction
3	300	Without	15	No reaction
4	450	Without	15	No reaction
5	650	Without	15	No reaction
6	850	Without	15	No reaction
7	100	10	15	75
8	150	5	10	80
9	150	10	6	90
10	150	15	6	90

[a]1 (3 mmol), 2.(3 mmol), 3 (3 mmol), sodium hydrogen sulfate under solvent free conditions. [b]Time in min. [c]Isolated yields based upon starting aldehyde.

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To determine the appropriate concentration of the catalyst sodium hydrogen sulfate, we investigate the model reaction at different concentrations of catalyst like 5, 10, and 15 mol %. The product formed in 80, 90 and 90 % yield respectively. This indicates that 10 mol% of sodium hydrogen sulfate is sufficient for the best result by considering the reaction time and yield of product.

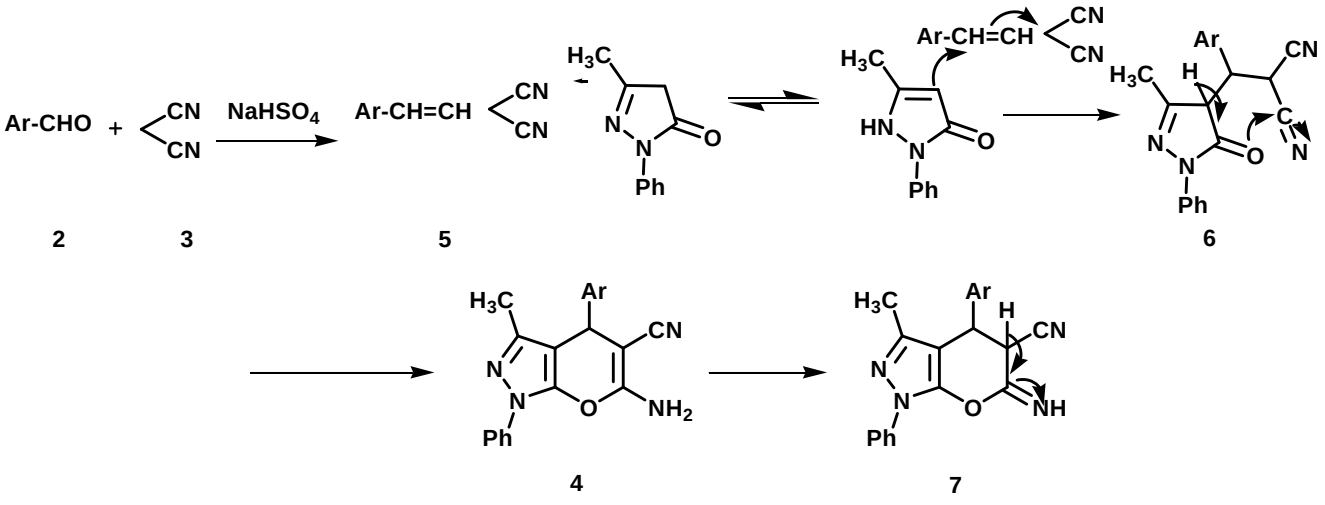
As we examined the reaction of 3-methyl-1-phenyl-2-pyrazolin-5-one aldehyde (3 mmol), malononitrile, (3 mmol) using sodium hydrogen sulfate (10 mol%) as catalyst under solvent free condition The reaction mixture was irradiated in microwave oven at 180W for appropriate time (6-8 min) The corresponding product was obtained in excellent yield. The experimental result is summarized in TABLE 2. Thus the methoxy substituted aromatic aldehydes (TABLE 2, Entry 4c and 4d) underwent a clean three component condensation to form the corresponding 1,4 dihydropyrano (2,3-*c*) pyrazoles in excellent yields. The other aromatic aldehydes [(TABLE 1, entries 4(e-j)] with electron releasing and withdrawing substituents produced 1,4-dihydropyranol (2,3-*c*) pyrazoles in good yields. However p-dimethylaminobenzaldehyde (TABLE 1, entry 4k) failed to produce any 1,4 dihydropyranol (2,3-c) pyrazole A similar failure was reported earlier[13].

TABLE 2: Microwave irradiation synthesis of compounds 4 (a–k) catalysed by $NaHSO_4$ [a]

Entry	Aldehyde	Time (min)[c]	Yield (%)[b]	M.P.(°C)	
				Found	Literature [13,16]
4a	C_6H_5	6	90	167-169	170-171
4b	4-MeC_6H_4	7	88	175-177	177-178
4c	4-$OMeC_6H_4$	6.3	86	170-172	171-172
4d	3-OMe, 4-$OMeC_6H_3$	8	86	189-191	191-193
4e	4-OHC_6H_4	6.5	84	208-209	210-212
4f	3-ClC_6H_4	5.5	89	156-158	158-160
4g	3-$NO_2C_6H_4$	5.2	90	187-189	190-191
4h	4-$NO_2C_6H_4$	6	91	194-195	195-196
4i	2-ClC_6H_4	5.5	87	143-145	145-146
4j	4-ClC_6H_4	5	88	174-175	175-176
4k	4-$NMe_2C_6H_4$		no reaction	-	-

[a]1 (3 mmol), 2 (3 mmol), 3 (3 mmol), sodium hydrogen sulfate (10 mol %) under solvent-free conditions. [b]Isolated yields based upon starting aldehyde. [c]Time in min.

A tentative reaction mechanism for the three components is shown in Scheme 2. One molecule of aromatic aldehyde **(2)** was firstly reacting with malononitrile **(3)** to form the dicyano-olefin **(5)** through Knoevenagel condensation. 3-methyl1-phenyl-2-pyrazolin-5-one **(1)** can then react with **(5)** give intermediate **(6)** throw Michael type addition. Intermediate **(6)** tautomerization and undergo cyclisation to the intermediate **(7)**. Then the intermediate **(7)** give finally the expected products **(4)**.



Scheme 2: Proposed mechanism and possible intermediates.

CONCLUSIONS

In conclusion, we have developed an environmentally friendly technique for the synthesis of 1, 4dihydropyranol (2,3-*c*) pyrazoles under solvent free condition. The advantage of the reported method is the use of cheap and easily available catalyst, easy work

up procedure and better yields.

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