

Solvent free Synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole Derivatives

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ABSTRACT: Each of the reported methods has its own merit, with at least one of the limitations of low yields, long reaction time, effluent pollution, harsh reaction conditions, and tedious workup procedures. Our interest in organic reaction is to carry out exclusively simple routes for the synthesis of different organic compound. We have synthesized 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazoles *via* multicomponent reaction of aromatic aldehydes, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one using IBX a catalyst.

KEYWORDS: aldehydes, malononitrile, IBX, solvent free, environmentally benign.

I. INTRODUCTION

Dihydropyrano[2,3-*c*]pyrazoles are very desirable as a type of heterocycles due to their potential uses in pharmaceutical field. They display a varied range of biological activities like anti-inflammatory [1], anticancer [2, 3], inhibitors of human Chk1 kinase [4], antimicrobial [5] and also as biodegradable agrochemicals [6]. Moreover, they play a main role as essential synthetic intermediates [7]. They are generally prepared by one-pot three component condensations of malononitrile, aldehyde and 3-methyl-1-phenyl-2-pyrazolin-5-one using $\text{KF}/\text{Al}_2\text{O}_3$ in DMF at room temperature [8]. The utilisation of water as reaction medium for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles is demonstrated by using various phase transfer catalysts such as triethylbenzylammonium chloride (TEBA) [9] and hexadecyltrimethylammonium bromide (HTMAB) [10]. Similarly, the use of the neutral organo-catalyst DL-proline using the grinding technique [11] and a surfactant such as *p*-dodecylbenzenesulfonic acid [12] (DBSA) has recently been demonstrated. Solvent-free reaction conditions along with microwave irradiation technique using piperidine as the base have also been introduced for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles [13]. A clean and simple synthesis of 6-amino-4-aryl-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles was accomplished in good to excellent yields *via* the one-pot three component condensation of 3-methyl-1-phenyl-2-pyrazolin-5-one, an aromatic aldehyde, and malononitrile catalysed by sulfamic acid in ethanol [14]. In recent years, the catalytic activity of Cesium fluoride has emerged as a useful acid imparting high regio- and chemoselectivity in various chemical transformations [15-18].

Hypervalent iodine (V) reagents specially *o*-iodoxybenzoic acid (IBX) are leading choice as oxidizing agents. The popularity of hypervalent iodine (V) reagents has increased due to their chemoselectivity and metal free nature, attracting organic chemist to use these reagents in total synthesis of many complex molecules including natural products. Development of new transformations by using hypervalent iodine reagents is an active research area in the last two decades. These include C-C, C-N bond formation, oxidative cyclization and oxidative rearrangement, lactone formation and activation of C-H bonds and many others [19].

Iodobenzoic acid (IBX) is the important member of Hypervalent Iodine Family due to its acidic, and oxidising properties. Importance of IBX can be easily understood by seeing recently published paper in hypervalent iodine

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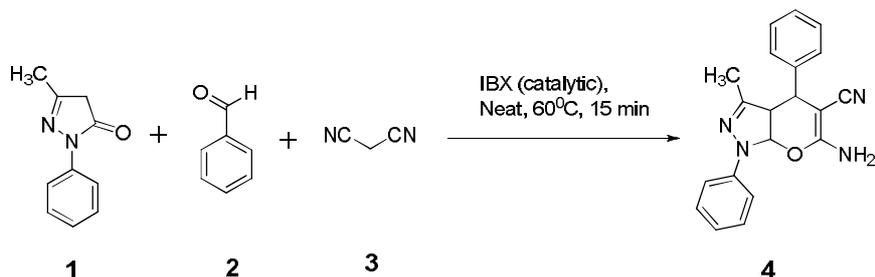
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chemistry. IBX exist as two tautomers and one of which is the carboxylic acid. The acidity of IBX can be determined in water (pKa 2.4) and DMSO (pKa 6.65) [20] is known to affect organic reactions, for instance acid catalysed reactions. Renowned scientist working on searching and developing the new properties of IBX and making the processes much better and highly efficient. IBX can also be available as silica gel or polymer supported. Among all these important properties of IBX, recently it can be seen that IBX can be used as catalyst. Use of IBX is really beneficial according to hazardness and cost of the processes.

In the course of our investigation to develop new method for the synthesis of multifunctional benzopyran derivatives using IBX as a catalyst. Herein we report a one pot three component and highly efficient method for synthesis of 6-amino-5-cyano-3-methyl-1,4-diphenyl-1,4-dihydropyran[2,3-c]pyrazole catalyzed by IBX without solvent. This is an efficient synthesis carried out without solvent and followed by green chemistry protocols as well.

II. RESULT AND DISCUSSION

In our initial experiment, Benzaldehyde (**2**) was reacted with malononitrile (**3**) and 3-methyl-1-phenyl-2-pyrazolin-5-one (**1**) in presence of IBX (*o*-iodoxybenzoic acid) as a catalyst at 60°C gave 6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyran[2,3-c]pyrazole-5-carbonitrile (**4**). This reaction was carried out without solvent at 60°C and time duration required was 15 min. The reaction scheme is as follows.



Scheme 1

The catalyst plays a crucial role in the success of the reaction in terms rate of the reaction and yield. We have also optimized the quantity of catalyst for the reaction of benzaldehyde, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one heated at 60°C at room temperature. As the amount of IBX was increased from 10 mol% to 40 mol% there was dramatically continuous improvement in the reaction rate and yield of the product. Increasing the amount catalyst from 40-60 mol% did not show any significant improvement in the reaction rate and yield of the product. Finally, 40 mol% of the catalyst showed the better optimistic condition to forward the reaction.

Table 1: Optimization of Catalyst^a

Entry	IBX (mol%)	Time	Yield (%) ^b
1	10	5 hr	60
2	20	1 hr	72
3	30	25 mins	85
4	40	15 mins	92
5	50	15 mins	90
6	60	15 mins	92

^a Reaction condition: Benzaldehyde (1 mmol), malononitrile (1 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one (1 mmol) and IBX (40 mol %) at 60°C. ^b Yields were isolated.

Choosing an appropriate solvent is of crucial importance for the successful organic synthesis. For optimization, the reaction of benzaldehyde (1 mmol), malononitrile (1 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one (1 mmol) was

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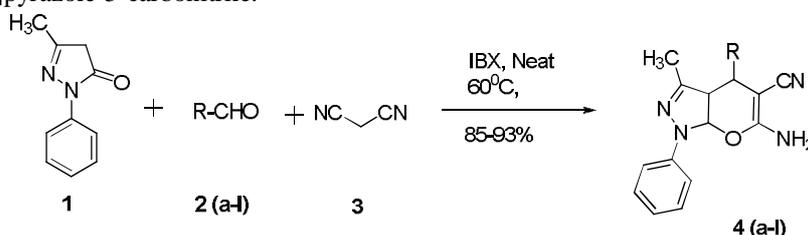
examined in various solvent with 40 mol% of IBX (Table 2) at 60 °C. The use of solvents retards the rate of reaction which ultimately resulted into decrease in the product yield with prolonged reaction time (Table 2, entry 2-7). After complete optimization neat reaction with IBX was found to be appropriate reaction media and catalyst for this reaction (Table 1, entry 1).

Table 2: Effect of solvent

Entry	Solvent	Time (Min)	Yield (%) ^a
1	IBX	15 min	92
2	EtOH	45 min	79
3	DMF	75 min	73
4	THF	65 min	68
5	Water	50 min	88
6	DCM	55 min	72
7	1,4-Dioxane	60 min	60

^aIsolated yield

Table 3: Reactivity of differently substituted aldehyde towards synthesis of 6-amino-3-methyl-1,4-diphenyl-1,4-dihydroprano[2,3-c]pyrazole-5-carbonitrile.



Scheme 2

Sr. No	Entry	R (2)	Yield (%) ^a	M.P. (°C)	
				Found	Reported ^{8,10,12f}
1	4a	-C ₆ H ₅	92	169-171	168-170
2	4b	4-OCH ₃ -C ₆ H ₄	90	171-172	170-172
3	4c	4-OH-C ₆ H ₄	85	210-212	211-212
4	4d	2-Cl-C ₆ H ₄	92	145-146	144-146
5	4e	3- Cl-C ₆ H ₄	90	158-159	158-159
6	4f	4- Cl-C ₆ H ₄	92	175-176	174-175
7	4g	2,4- Cl ₂ -C ₆ H ₄	93	184-186	182-184
8	4h	3-NO ₂ -C ₆ H ₄	92	191-192	188-190
9	4i	4- NO ₂ -C ₆ H ₄	93	195-197	194-196
10	4k	4-(CH ₃) ₂ N-C ₆ H ₄	No reaction		
11	4l	-CH ₃			

^aIsolated yield

In order to explore the scope of the methodology wide range of structurally diverse and functionalized aromatic aldehydes were examined, which underwent cyclocondensation with excellent yields.

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Reactions which having differently substituted aromatic aldehyde (**entry 4a-4i**) gave better yields of their products with increased reaction rate. By looking towards the substituted groups present on aldehydes and yield obtained it was noticed that reactivity of aldehydes does not show any major affect in the formation of product. Reaction with electron withdrawing (**entry 4c, 4d-4i**) and electron donating (**entry 4b**) substituents on aromatic ring gave appreciable yield of their corresponding product. Reaction of aliphatic aldehyde (**entry 4l**) fails to give the product and it may be due to very low reactivity of aliphatic aldehyde as compared to aromatic aldehyde.

IBX behaves as a acid, proton donor in the reaction progress for the formation of product **4**. IBX behaves as a acid, proton donor in the reaction progress for the formation of product **4**. In the first step aromatic aldehyde was condensed with malononitrile using catalytic amount of IBX to afford alpha-cynocinnamionitrile derivative by following Knoevenagel condensation reaction pathway. The active methylene group attacked on electrophilic C=C of alpha - cynocinnamionitrile. Carbonyl oxygen underwent keto-enol tautomerism and resulted hydroxy group attacked on nearer nitrile and further tautomerisation of imine to amine gave corresponding final product.

III. EXPERIMENTAL RESULTS

General procedure: A mixture of benzaldehyde (1 mmol), malononitrile (1 mmol) and 3-methyl-1-phenyl-2-pyrazolin-5-one (1 mmol) in presence of IBX (40 mol%) was stirred at room temperature for appropriate time. Course of the reaction was monitored by TLC. After completion of reaction, mixture was poured on ice cold water and obtained solid product was collected by filtration. Further purification was accomplished by recrystallization from ethanol to afford final product which was in full agreement with the spectral data.

Spectral analysis: 6-Amino-4-(2-chlorophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (4d)
IR: IR (KBr, cm^{-1})= 3062, 2228, 1201, 755. ^1H NMR (CDCl_3 , 200 MHz) δ (ppm) = 1.89 (s, 3H, CH_3), 4.66 (s, 1H, -CH), 4.69 (s, 2H, $-\text{NH}_2$), 7.27-7.68 (m, 9H, Ar-H) MASS : 363 [M+1].

IV. CONCLUSION

It can be concluded that, introduction of IBX (o-iodobenzoic acid) can be considered as an interesting new alternate route for synthesis of 1,4-dihydropyrano[2,3-c]pyrazol-5-yl. Merits of this method include solvent-free, highly inexpensive, ease of handling reaction condition. Increased rate and productivity of the product shows the future aspect of the present catalyst in synthetic field. Therefore with increasing "green" concern, the solvent-free conditions employed in the present method will make it environment friendly and useful for industrial applications.

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