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A Facile One Pot Synthesis Of Pyrano[2,3-C]Pyrazole Derivatives Using P-Toluene Sulfonic Acid In Aqueous Media

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ABSTRACT

A high yielding and fast method for the synthesis of 1,4-Dihydropyrano[2,3-c] pyrazole via one-pot, three component reaction of an aromatic aldehyde, malonitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one using p-toluene sulfonic acid as a catalyst is described

Keywords: *p-toluene sulfonic acid, 1,4-dihydropyrano[2,3-c]pyrazole, one-pot*

1. INTRODUCTION

4H-Pyran has been widely used as pharmaceutical intermediates because of their useful biological and pharmacological properties, such as antiallergic[1] and antitumor agents.[2] In addition, 2-amino-3-cyano-4H-pyrans possess photochemical activity[3] and polyfunctionalized 4H-pyrans are a common structural unit in a number of natural products.[4] The 4H-pyran ring can be transformed to pyridine systems which relate to pharmacologically important calcium antagonists of the DHP type. [5]

There are a lot of procedures described to prepare these compounds but most of them are toxic. The need to reduce the amount of toxic waste and by-products arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. One of the most promising approaches is using water as reaction media. Recently, a great attention has been focused on the use of water as green solvent in various organic transformations. Water is a desirable solvent for chemical reactions because it is safe, non-toxic, environmentally friendly, readily available, and cheap compared to organic solvents[6-8]. Since the pioneering studies on Diels–Alder reactions by Breslow[9,10], there has been increasing recognition that organic reactions can proceed well in aqueous media and offer advantages over those occurring in organic solvents such as rate enhancement and insolubility of the final products that facilitates their isolation. Herein, we would like to report a one-pot synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives by a three-component reaction of an aromatic aldehyde, malonitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one using p-toluene sulfonic acid as a catalyst in aqueous media (Scheme 1).

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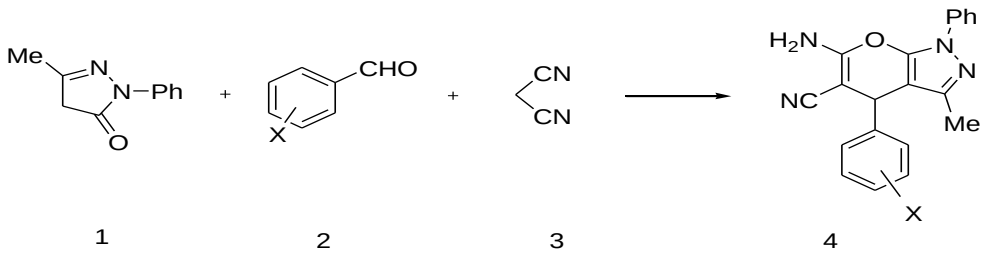


Scheme 1

2. EXPERIMANTAL

All products are known compounds and were characterized by mp, IR, ^{1}H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

2.1.Typical procedure for the synthesis of 1,4-dihydropyrano[2,3-c] pyrazole

A mixture of the aromatic aldehydes 1 (1 mmol), malononitrile 2 (1 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one 3 (1 mmol), and PTSA (0.05 g) in H_2O (5 mL) was refluxed for 45–55 min, then cooled to room temperature. The crystalline powder formed was collected by filtration, washed with water, and recrystallized from ethanol to give pure product (**4**).

4a: mp 172 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H (ppm): 1.93 (s, 3H, CH_3),4.68 (s, 1H,),4.75 (s, 2H, NH_2),7.16-7.32 (m, 10H, Ph); IR (KBr) (ν_{max}, cm^{-1}): 3472, 3320, 2195, 1660, 1590, 1264, 1125, 1027, 753.

4b: mp 177 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H (ppm): 1.78 (s,3H,CH_3), 2.28 (s, 3H,CH_3), 4.62 (s, 1H), 6.96 (s, 2H, NH_2), 7.02-7.78 (m, 9 H,Ph); IR (KBr) (ν_{max}, cm^{-1}): 3414, 3314, 2178, 1658, 1594, 1398, 1258, 1128, 1026, 754.

4c: mp 213 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H (ppm): 1.78 (s,3H,CH_3), 4.56 (s, 1H), 6.72-7.78 (m, 9 H, Ph), 7.12 (s, 3H, OH, NH_2); IR (KBr) (ν_{max}, cm^{-1}): 3416, 3320, 2178, 1658, 1594, 1398, 1258, 1128, 1026, 745.

4d: mp 191 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H (ppm): 1.94 (s, 3H, CH_3), 4.76 (s, 1H), 4.98 (s, 2H, NH_2), 8.12-8.95 (m, 9 H, Ph); IR (KBr) (ν_{max}, cm^{-1}): 3456, 3322, 2198, 1660, 1592, 1392, 1270, 1126, 1050, 758.

4e: mp 195 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H (ppm): 1.80 (s, 3H, CH_3), 4.96 (s, 1H), 6.98 (s, 2H, NH_2), 7.32-8.20 (m, 9 H, Ph); IR (KBr) (ν_{max}, cm^{-1}): 3430, 3340, 2192, 1665, 1596, 1354, 1124, 832, 754.

4f: mp 175 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H (ppm): 1.88 (s, 3H, CH_3), 4.74 (s, 1H), 6.32 (s, 2H, NH_2), 7.28-7.78 (m, 9 H, Ph); IR (KBr) (ν_{max}, cm^{-1}): 3468, 3325, 2200, 1662, 1596, 1390, 1262, 1122, 1016, 752.

4g: mp 173 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H (ppm): 1.78 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 4.88 (s, 1H), 6.96 (s, 2H, NH_2), 6.82-7.54 (m, 9 H, Ph); IR (KBr) (ν_{max}, cm^{-1}): 3395, 3322, 2192, 1660, 1595, 1394, 1250, 1128, 813.

3. RESULT AND DISCUSSION

p-Toluenesulfonic acid (PTSA) is commercially available and is a very cheap chemical with stability. Recently, it was shown that PTSA can be used as a substitute for conventional acidic catalytic materials. It has been used as an efficient acid catalyst for the synthesis of 4(3H)-quinazolinones, [11] for the regiospecific nitration of phenols[12] and for the carbonylation of formaldehyde.[13] As part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of fine chemicals,[14-16] then we decided to use this catalyst for the synthesis of 1,4-dihydropyrano[2,3-c]pyrazoles. In a typical procedure, benzaldehyde (1 mmol), malonitrile (1 mmol) with 3-methyl-1-phenyl-2-pyrazolin-5-one (1 mmol) in the presence of a catalytic amount of PTSA in water at reflux temperature afforded the desired 1,4-dihydropyrano[2,3-c]pyrazoles (**4a**) in 86% yield (Entry 1, Table 1). The reaction has been applied to a variety of aromatic aldehydes resulting in good yields. (As shown in Table 1) All aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as hydroxyl group, alkoxyl group) were employed and reacted well to give the corresponding product 4 in good to excellent yields under these reaction conditions. Thus, we conclude that no obvious effect of electron and nature of substituents on the aromatic ring were observed. We also found that the reaction did not proceed in the case in which aliphatic aldehyde was used. The reason we think this is the activity of aliphatic aldehydes is less than that of aromatic aldehyde.

Table1. Synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives catalyzed by PTSA.

Entry	X	Time (min)	Product	Mp (^{0}C)		Yield(%)[a]
				Observed	Reported	
1	H	55	4a	172	170-171[17]	86
2	4-Me	50	4b	177	177-178[17]	80
3	4-OH	45	4c	213	210-212[17]	90
4	3-NO_2	45	4d	191	190-191[17]	95
5	4-NO_2	45	4e	195	195-196[17]	95
6	4-Cl	50	4f	175	175-176[17]	95
7	4-OMe	45	4g	173	171-172 [17]	90

(a) Isolated yields

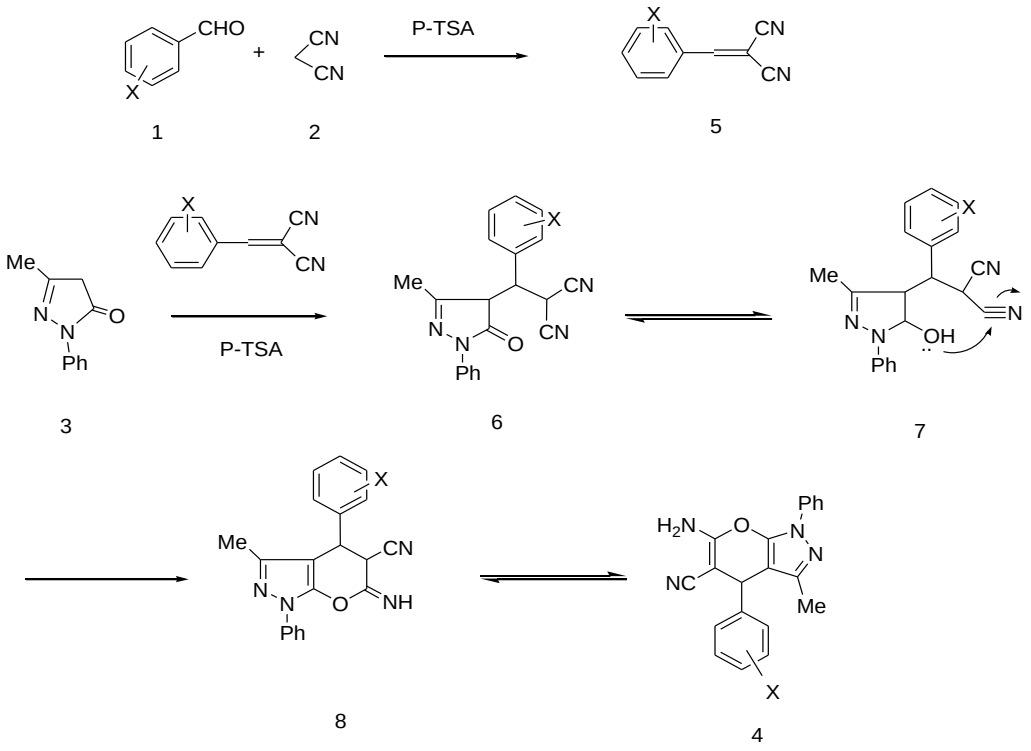
We performed the effect of various solvents on the synthesis of 4a. This reaction was carried out in various solvents such as water, chloroform, ethanol, CH_2Cl_2 and solvent-free. As shown in Table 2, the best results in terms of yield and time obtained in water.

Table 2. Synthesis of 3a with PTSA in the presence of different solvent.

Entry	Solvent	Temperature	Time(min)	Yield(%)[a]
1	water	reflux	55	86
2	ethanol	reflux	70	80
3	dichloromethane	reflux	120	65
4	chloroform	reflux	120	66
5	solvent-free	reflux	100	60

[a]Yield of isolated products.

We propose the possible following mechanism to account for the reaction. One molecule of aromatic aldehyde 1 was first condensed with matononitrile 2 to afford α-cyanocinnamonitrile derivative 5. The step (1 + 2→5) can be regarded as a fast knoevenagel addition. The active methylene of 3 by reaction with the electrophilic C=C double bond giving the intermediate 6. Then the intermediate 6 was cyclized by the nucleophilic attack of OH group on the cyano (CN) moiety and gave the intermediate 7. Finally the expected products 4 were afforded by isomerization (7→ 8 → 4). In this process, p-Toluene sulfonic acid could promote these reactions as a catalyst. (Scheme 2)



Scheme 2

In conclusion, we have described a highly efficient procedure for the preparation of pyrano[2,3-c] pyrazole derivatives by a three component condensation using PTSA as a catalyst. All the proposed reactions allowed the preparation of products in good yield without further purification. The reaction products were prepared in moderate to average yield, even with different substituted aldehydes. No harmful organic solvents are used. Moreover, the procedure offers several advantages including high yields, operational simplicity, cleaner reaction, minimal environmental impact, and low cost, which make it a useful and attractive process for the synthesis of these compounds.

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