Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(10):143-145
(http://derpharmachemica.com/archive.html)

An Efficient Synthesis of Dihydropyrano[3,2-*c*]chromene Derivatives via Green Approach

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ABSTRACT

A simple protocol for the efficient synthesis of dihydropyrano[3,2-c]chromene derivatives has been achieved by refluxing aromatic aldehydes, malononitrile, 4-hydroxycoumarin and 4-chlorophenylboronic acid. Particularly valuable features of this method include satisfactory yields of products and short reaction time.

Keywords: Dihydropyrano[3,2-*c*]chromene, 4-Chlorophenylboronic acid, Aromatic aldehydes, Synthesis.

INTRODUCTION

The development of environmentally benign, efficient, and economical methods for the synthesis of biologically interesting compounds remains a significant challenge in synthetic chemistry [1]. Green chemistry can be recognized as a pioneering approach, which widely reports intrinsic atom economy, energy savings, waste reduction, easy work-ups, and the avoidance of hazardous chemicals [2]. The 3,4-Dihydropyrano[3,2-c]chromenes derivatives are an important class of heterocyclic compounds having important pharmaceutical and biological activity. The 3,4-Dihydropyrano[3,2-*c*]chromenes and their derivatives are of considerable interest as they possess a wide range of biological properties, such as spasmolytic [3], diuretic [4], emetic [5], anti-HIV [6], anti-tumor [7], anti-Alzheimer [8], anti-bacterial [9] and anti-malarial activity [10].

Therefore, the development of new and efficient methodologies for the synthesis of 3,4-dihydropyrano[*c*]chromenes will be demanding in both synthetic organic and medicinal chemistry. However, in spite of their potential utility, some difficulties still exist in the synthesis, such as expensive or toxic reagent. Therefore, the development of new, simple and cheap methods for the synthesis of 3,4-dihydropyrano[*c*]chromene derivatives is of main importance. In continuation of our efforts to develop novel synthetic routes using catalysts in organic reactions, and due to our interest in the synthesis of heterocyclic compounds, herein, we wish to report an efficient synthesis of 3,4-dihydropyrano[*c*]chromenes derivatives by cyclo-condensation reaction of 4-hydroxycoumarin, aryl aldehydes and malononitrile using 4-chlorophenylboronic acid as a catalyst and water as a solvent.

MATERIALS AND METHODS

General

All solvents were used as commercial anhydrous grade without further purification. The column chromatography was carried out over silica gel (80-120 mesh). Melting points were determined in open capillary tube and are uncorrected. ^{1}H spectra were recorded on a Bruker 300 MHz spectrometer in DMSO-d6 solvent and TMS as an internal standard.

General procedure for synthesis of dihydropyrano[c]chromenes:
In a dry 50 mL round bottom flask was charged with substituted aromatic aldehydes (1 mmol), malononitrile (1 mmol), 4-hydroxycoumarin (1 mmol), 4-chlorophenylboronic acid (20 mol%) and water (25 ml) and the resulting mixture was stirred at 70 ^{0}C for 60-90 minutes. After completion of the reaction, as indicated by Thin-layer chromatography (TLC), the reaction mixture was filtered. The residual product was dried. The reaction products were identified by comparing their physical data. The crude products were re-crystallized from alcohol and weighed.

2-Amino-4-(4-nitrophenyl)-4,5-dihydro-5-oxopyrano[3,2-c]chromene-3-carbonitrile 4b: mp 249°C, ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) 4.48 (s, 1 H), 7.28 - 7.34 (m, 2 H), 7.68 - 7.71 (m, 2 H), 7.90 (dt, 1 H, *J1* = 8.1 Hz, *J2* = 1.19 Hz), 7.98 (dd, 1H, *J1* = 8.1 Hz, *J2* = 1.18 Hz), 8.32 (d, 2 H, *J* = 8.39 Hz). Elemental Analysis: C, 65.59; H, 3.06; Cl, 9.91; N, 7.89; O, 12.98.

2-Amino-4-(4-chlorophenyl)-4,5-dihydro-5-oxopyrano[3,2-c]chromene-3-carbonitrile 4c: mp 251°C, ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) 4.63 (s, 1 H), 7.11 (d, 2 H, *J* = 8.4 Hz), 7.58 (d, 2H, *J* = 8.4 Hz), 7.15-7.21 (m, 2 H), 7.52 (t, 1 H, *J* = 7.8 Hz), 7.91 (d, 1 H, *J* = 8.0 Hz). Elemental Analysis: C, 63.76; H, 2.97; N, 10.93; O, 22.34.

RESULTS AND DISCUSSION

In order to find the most appropriate reaction conditions and to evaluate the catalytic efficiency of 4-chlorophenylboronic acid, a model reaction study was conducted to determine the best conditions for the synthesis of 3,4-dihydropyrano[*c*]chromenes. The study of the effect solvent and temperature on the reaction was studied and summarized in the Table 1. The solvents $CHCl_3$, CH_3CN, ethanol and water were tested for condensation of 4-chlorobenzaldehyde, 4-hydroxycoumarin and malononitrile. The reaction was performed without any solvent reaction was not proceeded even at 70 ^{o}C temperature (Table 1, entry 1), then chloroform was used, the yield obtained was very low at same temperature (Table 1, entry 1). Then, more polar solvent Acetonitrile was employed at same temperature but there was no significant effect on yield (Table 1, entry 3), next, polar solvent which posses hydrogen bonding was selected which trigger the reaction but the yield obtained was poor (Table 1, entry 4). Finally, water was selected as the solvent at same temperature found to be the best among all, because the highest yield obtained (Table 1, entry 5). The reaction was found to proceed smoothly at 70 ^{o}C in the presence of 20 mol% 4-chlorophenylboronic acid catalyst in water.

Table 1: Synthesis of Dihydropyrano[3,2-c]chromene derivatives in different solvents

Sr. No.	Solvent	Temperature ^{o}C	Time (min)	Yield[a] %
1	Solvent free	70	150	None
2	$CHCl_3$	70	150	Trace
3	CH_3CN	70	180	Trace
4	Ethanol	70	80	20
5	Water	70	60	91

[a]*Isolated yield.*

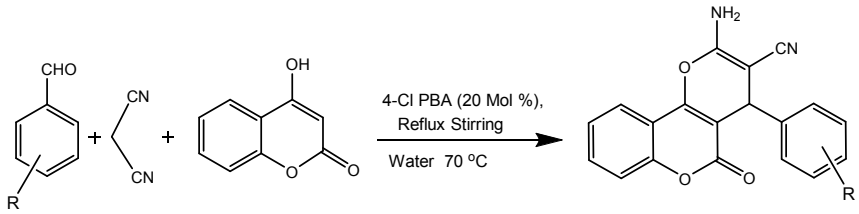
We also evaluated the catalyst required for the synthesis of compound 4b. Of the catalysts tested, including piperidine, morpholine, PTSA, catalyst free and 4-chlorophenylboronic acid, among a all 4-chlorophenylboronic acid was the most efficient in terms of reaction time and yield of product (Table 2, entries 1-5). Having established the reaction conditions for the multi-component reaction, the scope and limitations of the reaction with different substituted aromatic aldehydes, malononitrile and 4-hydroxycoumarin were investigated as summarized in Table 2.

Table 2 : O**ptimization of catalyst for synthesis of Dihydropyrano[3,2-c]chromenes**

Sr. No.	Catalyst	Temperature ^{o}C	Time(min)	Yield[a] %
1	Piperidine	70	200	85
2	Morpholine	70	190	60
3	PTSA	70	210	67
4	No Catalyst	70	300	45
5	4-Chlorophenylboronic acid	70	60	91

[a]*Isolated yield.*

Table 3: Synthesis of dihydropyrano[3,2-*c*]chromene derivatives by using 4-chlorophenylboronic acid as a catalyst in water solvent



1a-j 2 3 4a-j

Entry	R	Product	Reaction time (min)	Yield[a] %	M. P. (°C)
1	H	4a	60	94	248-250
2	4-NO_2	4b	70	89	250-252
3	4-Cl	4c	60	91	252-254
4	4-OCH_3	4d	65	90	237-239
5	3-OCH_3-4-OH	4e	60	95	235-237
6	3,4,5-OCH_3	4f	60	89	269-271
7	3,4-OCH_3	4g	70	89	281-283
8	3-Cl	4h	60	83	239-241
9	4-F	4i	65	85	260-262
10	4-OH	4j	60	90	265-267

[a]*Isolated yield.*

CONCLUSION

In conclusion, we have demonstrated a facile and efficient method for the one-pot three-component synthesis of dihydropyrano[3,2-*c*]chromene derivatives using 4-chlorophenylboronic acid as a catalyst at 70 ° C. Boronic acids are generally crystalline solids with high tolerance to air and moisture. This study offers a advantageous, excellent yield and cost-effective process for the synthesis of dihydropyrano[3,2-*c*]chromene derivatives.

Acknowledgment
We acknowledged, Dr. P. L. More, Principal and Dr. W. N. Jadhav, Head, Department of chemistry, Dnyanopasak College, Parbhani for providing necessary facilities.

REFERENCES

[1] Niknam. K, Borazjani N, Rashidian R, Jamili A. *Chin. J. Catal.* **2013**, 34**.**
[2] Kumar A. Gupta M K. Kumar M. *Green Chem.* **2012**, 14, 290.
[3] Ellis G. P, Weissberger A, Taylor, E C. *John Wiley: New York*, 2, **1997.**
[4] Hafes E. A. A, Elnagdi M. H, Elagamey A. G. A, EL-Taweel F. M. A. A. *Heterocycles* **1987**, 26, 903**.**
[5] Cannon J. G, Khonji R. R. *J. Med. Chem.* **1975**, 18, 110.
[6] Tanabe A, Nakashima H, Yoshida O, Yamamoto N, Tenmyo O, Oki T. *J. Antibiot.* **1988**, 41, 1708.
[7] Shijay G, Cheng H. T, Chi T, Ching-Fa Y. *Tedrahedron* **2008**, 64, 9143.
[8] Bayer T. A, Schafer S, Breyh H, Breyhan O, Wirths C, Treiber G. A. Clin *Neuropathol*. **2006**, 25, 163.
[9] Morgan L. R, Jursic B. S, Hooper C. L, Neumann D. M, Thangaraj K, Leblance B. *Bioorg. Med. Chem. Lett.* **2002**, 12, 3407.
[10] Bonsignore L, Loy G, Secci D, Calignano A. *Eur. J. Med. Chem*. **1993**, 28, 517.