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Novel approach for the synthesis of 13-(aryl)-3,6,12,13-tetrahydrochromeno[4,3-*b*]pyrazolo[4,3-*f*]quinolin-12-one compounds

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ABSTRACT

*A series of chromeno[4,3-*b*]pyrazolo[4,3-*f*]quinolinone derivatives has been synthesized via one-pot cyclocondensation of 3H-chromene-2,4-dione, aromatic aldehydes and 5-aminoindazole utilizing bis[2-(cyclohexylamino)troponone] Ti(IV) complex in toluene under reflux condition.*

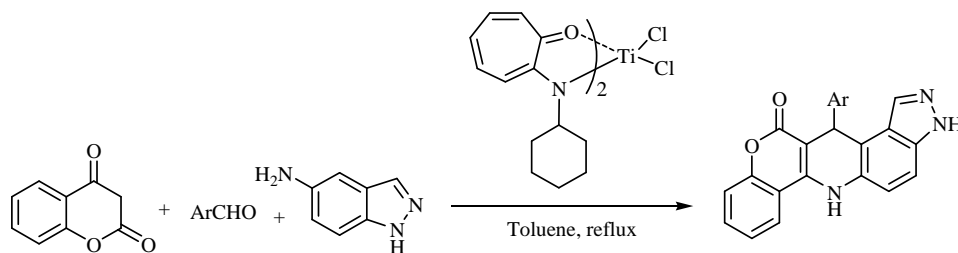
Keywords: Pyrazolo[4,3-*f*]pyrimido[4,5-*b*]quinolineone, One-pot, synthesis.

INTRODUCTION

The first multi-component reaction (MCR) was reported by Strecker in 1850 for the synthesis of amino acids [1]. In recent years, multi-component reactions (MCRs) have occupied an important part in modern synthetic organic chemistry due to their valued features such as convergence, productivity, facile execution, and generally high yield of products [2-4]. Recently, we have reported several MCRs on the synthesis of indenoquinolinones [5], pyranoindoles [6], phenanthroimidazoles [7].

Pyrazoles are known for various biological activities, e.g. pyrazolo[3,4-*b*]quinolines as potential antiviral [8], antimalarial [9], lowering of serum cholesterol [10], pyrazolo[3,4-*c*]pyrazoles are useful for the treatment of esophageal and gastrointestinal mucosa injury [11], brain injury [11,12] and also as immunostimulatory, antianginal [13] and antitumor agents [13]. Pyrazolo[3,4-*f*] quinoline derivatives are a novel class of immunostimulant with potent in vivo effects in a murine infection model [14,15].

The usage of organometallic compounds will provide a broad exploration for new methods and techniques in organic synthesis. Our interests lie in organometallics prompt us to make a utilization of such catalysts. In order to keep up with our recent research in this field [16,17], herein, one-pot Ti-catalyzed synthesis of 13-(aryl)-3,6,12,13-tetrahydrochromeno[4,3-*b*]pyrazolo[4,3-*f*]quinolin-12-one derivatives has been reported.



Scheme 1

EXPERIMENTAL SECTION

General

The procedure for synthesis of bis[2-(cyclohexylamino)troponone] Ti(IV) complex, the catalyst, has been reported elsewhere [18].

General procedure for synthesis of chromeno[4,3-b]pyrazolo[4,3-f]quinolinone derivatives

In a round bottom flask purged by nitrogen gas already, a mixture of 3*H*-chromene-2,4-dione (1 mmol), aromatic aldehydes (1 mmol) and 5-aminoindazole (1mmol), in the presence of bis[2-(cyclohexylamino)troponone] Ti(IV) complex (0.1 mmol) was stirred under reflux condition in dried toluene. The progress of the reactions were monitored by TLC (ethylacetate:*n*-hexane 1:5). Upon the completion of the reaction, the heterogeneous catalyst was separated from the mixture. After cooling to room temperature, the resulting precipitate was filtered off and washed with water. The solid was dried and crystallized from H₂O:EtOH (1:4) to obtain the pure desired product in high to excellent yield. The representative spectral data for the selected products are as follows:

4b: IR: (KBr, ν , cm^{-1}): 3375, 3218, 1670, 1561, 1475, 1387, 1277, 1159, 1044. ¹H NMR (100 MHz, DMSO-*d*₆): δ 12.60 (s, 1H, NH), 9.82 (s, 1H, NH), 8.28 (d, 1H, *J* = 7.4 Hz, ArH), 8.08-7.95 (m, 3H, ArH), 7.60-7.35 (m, 7H, ArH), 5.53 (s, 1H, CH). Anal. Calcd. for C₂₃H₁₄N₄O₄: C, 67.31; H, 3.44; N, 13.65%. Found: C, 66.28; H, 3.37; N, 13.54 %.

4e: IR: (KBr, ν , cm^{-1}): 3412, 3265, 1666, 1522, 1452, 1240, 1166, 1071. ¹H NMR (100 MHz, DMSO-*d*₆): δ 12.75 (s, 1H, NH), 10.15 (s, 1H, NH), 8.22 (d, 1H, *J* = 8.2 Hz, ArH), 8.00 (s, 1H, ArH), 7.65-7.45 (m, 4H, ArH), 7.40-7.27 (m, 3H, ArH), 6.82 (d, 2H, *J* = 8.4 Hz, ArH), 5.64 (s, 1H, CH), 3.62 (s, 3H, OMe). Anal. Calcd. for C₂₄H₁₇N₃O₃: C, 72.90; H, 4.33; N, 10.63; Found: C, 70.83; H, 4.22; N, 10.55 %.

4g: IR: (KBr, ν , cm^{-1}): 3357, 3282, 1668, 1562, 1473, 1414, 1263, 1121, 1065. ¹H NMR (100 MHz, DMSO-*d*₆): δ 12.88 (s, 1H, NH), 10.15 (s, 1H, NH), 8.37 (d, 1H, *J* = 7.6 Hz, ArH), 8.22 (s, 1H, ArH), 7.55-7.22 (m, 6H, ArH), 7.15-6.95 (m, 3H, ArH), 5.90 (s, 1H, CH). Anal. Calcd. for C₂₇H₁₇N₃O₂S: C, 72.47; H, 3.83; N, 9.39%; Found: C, 70.33; H, 3.71; N, 9.30 %.

4h: IR: (KBr, ν , cm^{-1}): 3345, 3188, 1662, 1645, 1524, 1447, 1255, 1155, 1036. ¹H NMR (100 MHz, DMSO-*d*₆): δ 12.75 (s, 1H, NH), 9.80 (s, 1H, NH), 8.18 (d, 1H, *J* = 6.8 Hz, ArH), 8.03 (s, 1H, ArH), 7.60-7.40 (m, 4H, ArH), 7.40-7.25 (m, 5H, ArH), 5.52 (s, 1H, CH). Anal. Calcd. for C₂₃H₁₄BrN₃O₂: C, 62.18; H, 3.18; N, 9.46%. Found: C, 60.16; H, 3.10; N, 9.36 %.

RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for successful synthesis. To optimize the reaction solvent, the reaction of 4-nitrobenzaldehyde, 3*H*-chromene-2,4-dione, and 5-aminoindazole was carried out in different organic solvents such as toluene, benzene, ethylacetate, 1,2-dichloroethane, and DMF at reflux condition. The results are summarized in Table 1. It was shown that the reactions in refluxing toluene afforded the best results. Polar solvents such as 1,2-dichloroethane and DMF afforded poor results. Therefore, toluene was chosen as the best solvent for the subsequent reactions. In addition, the catalyst, could efficiently catalyze the multicomponent reactions and as illustrated in Table 2, a various series of chromeno[4,3-*b*]pyrazolo[4,3-*f*]quinolin-12-one derivatives were synthesized in high to excellent yields.

Table 1. Influence of solvent on the reaction efficiency

Solvent	Toluene	Benzene	DMF	EtOAc	C ₂ H ₄ Cl ₂
Isolated Yield ^a	90	78	65	62	52

a) All the reactions were carried out at reflux condition for 6 h. Reaction conditions: 4-nitrobenzaldehyde (1.0 equiv), 3*H*-chromene-2,4-dione (1.0 equiv), and 5-aminoindazole (1.0 equiv), catalyst (0.1 equiv).

With the intention of providing more diversity to the chromeno[4,3-*b*]pyrazolo[4,3-*f*]quinolin-12-one structure, various aldehydes were examined and the reactions of aryl aldehydes, in combination with 3*H*-chromene-2,4-dione and 5-aminoindazole were tried out. The results revealed that this protocol could be applied to aromatic aldehydes with either electron-withdrawing as well as electron-donating groups (Table 2).

Table 2. Results on the synthesis of chromeno[4,3-*b*]pyrazolo[4,3-*f*]quinolinones

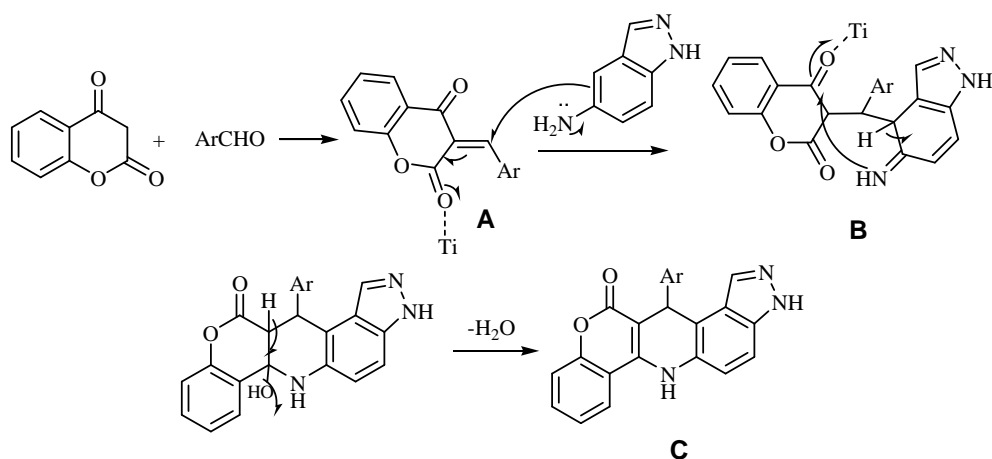
Entry ^{a,b}	Ar	Product	Yield(%) ^a
1	C ₆ H ₅	4a	90
2	4-NO ₂ -C ₆ H ₄	4b	92
3	3-NO ₂ -C ₆ H ₄	4c	90
4	4-CH ₃ -C ₆ H ₄	4d	88
5	4-CH ₃ O-C ₆ H ₄	4e	86
6	4-NMe ₂ -C ₆ H ₄	4f	84
7	2-Thienyl	4g	85
8	4-Br-C ₆ H ₄	4h	90

a) Isolated yields. b) Reaction conditions: 1.0 equiv. of 5-aminoindazole, 1.0 equiv. of aldehyde, 1.0 equiv. of 3*H*-chromene-2,4-dione, 10 mol% of Ti catalyst, 5 mL of CH₃CN as solvent and reflux condition for 6h.

The possible mechanism is likely involves a sequence reaction of condensation, addition, cyclization, and dehydration (Scheme 2). First, the condensation between aromatic aldehyde and 3*H*-chromene-2,4-dione leads to formation of intermediate **A**; Michael-type addition of 5-aminoindazole to **A** provides **B**, which upon intermolecular cyclization and dehydration furnishes the corresponding chromeno[4,3-*b*]pyrazolo[4,3-*f*]quinolinone product **C**.

CONCLUSION

In conclusion, the synthesis of a series of 13-(aryl)-3,6,12,13-tetrahydrochromeno[4,3-*b*]pyrazolo[4,3-*f*]quinolin-12-ones through an efficient one-pot multicomponent approach is described.



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