An efficient synthesis of benzochromeno-pyrazoles

Hossein Dianat, Alireza Nazif, Saeid Salimi

***Abstract*— A series of benzochromeno-pyrazole derivatives was synthesized by a catalyzed three-component reaction of aromatic aldehyde, 3-methyl-1H-pyrazol-5(4H)-one and α-or β-naphthol at reflux temperature. The novel efficient method has the advantages of simple work-up procedure, ease of operation, and excellent yield.**

***Index Terms*— Synthesis, pyrazole, catalyst.**

I. INTRODUCTION

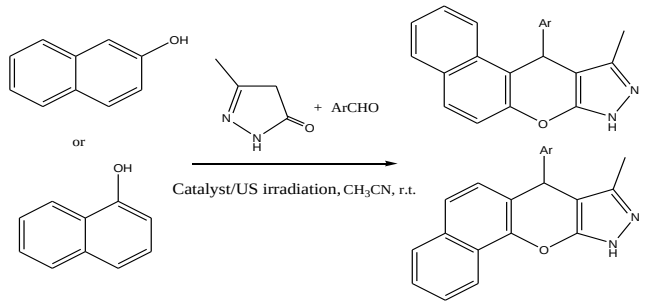
In the last two decades, multicomponent reactions (MCR) have drawn special attention due to the advent of high-throughput screening techniques that enabled rapid identification of potential new medicines among large collections of organic com- pounds. This required the development of new approaches to the synthesis of organic compounds. The methods that would provide rapid access to high-quality compound libraries came to be in high demand. The libraries were characterized by significant diversity with regard to both the core and the peripheral structure and were designed so as to contain a maximum number of so-called points of diversity. Multicomponent reactions ideally suited the new demand, and this, in turn, fueled more interest in the earlier developed reactions and in the invention of similar or even fundamentally new ones. In different reports, the potential benefits of MCR chemistry have been completely proved [1-6].

Chromene compounds occupy an important place in the realm of natural and synthetic organic chemistry. They are used as anticoagulants, additives in food and cosmetics, and in the preparation of insecticides, optical brighteners, and dispersed fluorescent and laser dyes [7-11].

Chromenopyrazoles are found in various naturally occurring compounds and a number of their derivatives both natural and synthetic are known to exhibit interesting biological properties [11]. Some procedure for synthesis of chromeno-pyrazole derivatives have been reported already. Kimura et al reported that the reaction of bezoic acid derivatives and 3-methyl-1-phenyl-5-pyrazolone results in synthesis of chromeno-pyrazole derivatives [12]. Abunada et al. studied synthesis of chromeno[3,4-*c*]pyrazole derivatives from hydrazonoyl bromides and substituted coumarins [13].

However, the development of a simple, efficient, and versatile approach for the preparation of chromenopyrazoles is still an active area of research for further improvements towards milder reaction conditions and higher product yields.

In the present study, an efficient, mild and catalyzed one-pot synthesis of benzochromeno-pyrazoles via three component condensation of aromatic aldehyde, 3-methyl-1H-pyrazol-5(4H)-one and *α*-or β-naphthol under reflux condition is reported (Scheme 1).



Scheme 1. One-pot synthesis of benzochromeno-pyrazoles

II. RESULTS AND DISCUSSION

Initially, to find out the appropriate reaction conditions, the reaction of *p*-nitrobenzaldehyde, 3-methyl-1H-pyrazol-5(4H)-one and β-naphthol with a variety of catalysts in acetonitrile at reflux temperature was chosen as a model. The catalytic efficiency of $Zn(OTf)_2$, HOTf, CH_3SO_3H, CF_3COOH and *p*-TSA which were available, was studied (Table 1, entry 1-7). In all cases 5 mol% of the catalyst was used. As shown in the Table 1, the best result was obtained when *p*-toluenesulfonic acid (*p*-TSA) was used as a catalyst (Table 1, entry 7).

The influence of solvent on the reaction was then studied for the model reaction in the presence of 5% *p*-TSA under reflux temperature to figure out the most appropriate medium. The best results were obtained in acetonitrile (Table 1). Therefore, acetonitrile was chosen as a solvent for further reactions.

Table 1.

1	$Zn(OTf)_2$	CH_3CN	72
2	HOTf	CH_3CN	74
3	CH_3SO_3H	CH_3CN	78
4	CF_3COOH	CH_3CN	80
5	*p*-TSA	CH_3CN	93
6	*p*-TSA	$ClCH_2CH_2Cl$	66
7	*p*-TSA	CH_2Cl_2	35
8	*p*-TSA	CH_3OH	76
9	*p*-TSA	THF	62
10	*p*-TSA	Toluene	10

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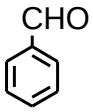
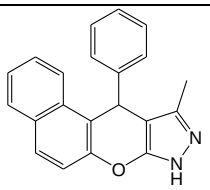
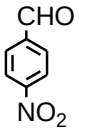
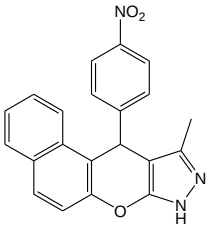
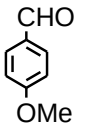
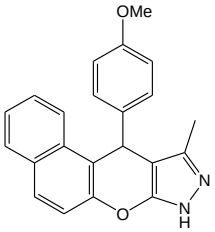
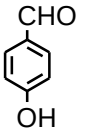
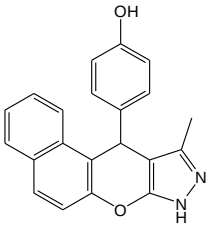
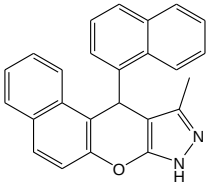
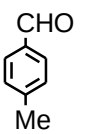
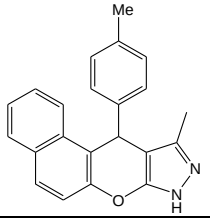
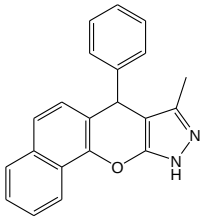
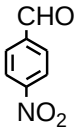
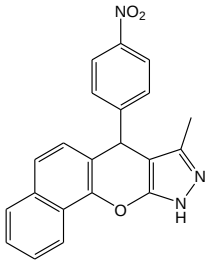
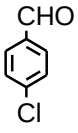
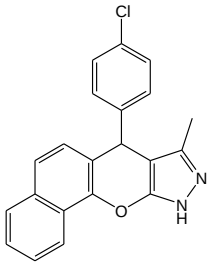
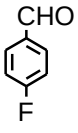
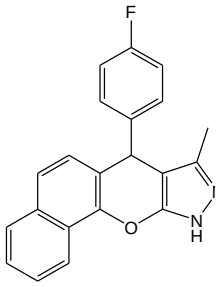
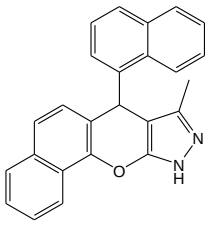
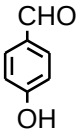
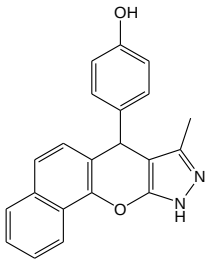
Hossein Dianat, Department of Chemistry, Sarvestan Branch, Islamic Azad University, Sarvestan, Iran
Alireza Nazif, Sarvestan Branch, Islamic Azad University, Sarvestan, Iran
Saeid Salimi, Sarvestan Branch, Islamic Azad University, Sarvestan, Iran

11	*p*-TSA	H_2O	42

a) Reaction of benzaldehyde, 3-methyl-1H-pyrazol-5(4H)-one, and β-naphthol in the presence of 5mol% catalyst under reflux condition **b**). Yields refer to isolated products

With the optimized reaction conditions in hand, a range of benzochromeno-pyrazoles was examined to explore the generality of this reaction, and the results are summarized in Table 2. Several aromatic aldehydes bearing different substituents were tried out in the reaction. It was found that variation of the substitution groups on the aromatic aldehydes doesn't have any significant influence on the chemical yield of the reaction. However, the reaction times were influenced by the substitution to some extent.

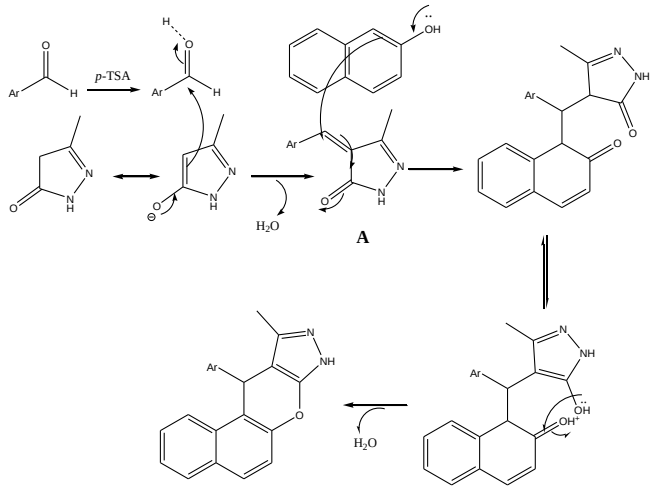
Table 2. Results of benzochromeno-pyrazole derivative synthesis using *P*-TSA/US irradiation

Entry	Naphthol	Aldehyde	Product	Time (min)	Yield (%)[a,b]
1	β-naphthol			50	93
2	β-naphthol			45	93
3	β-naphthol			55	90
4	β-naphthol			48	88
5	β-naphthol			45	90
6	β-naphthol			55	91
7	α-naphthol			40	90
8	α-naphthol			35	92
9	α-naphthol			50	88
10	α-naphthol			44	87
11	α-naphthol			47	90
12	α-naphthol			42	88

[a] Reaction condition: CH_3CN as solvent, aldehyde (1.1 mmol), 3-methyl-1H-pyrazol-5(4H)-one (1 mmol), α-or β-naphthol (1 mmol), under US irradiation at room temperature. [b] Isolated yield.

The probable mechanism for this transformation is depicted in Scheme 2. As shown the mechanism may involves the initial nucleophilic addition of 3-methyl-1H-pyrazol-5(4H)-one to the aldehyde, which may

be catalyzed by *P*-TSA, to give **A**, nucleophilic addition of *α*-naphthol/*β*-naphthol to the intermediate **A** and finally heterocyclization.



Scheme 2. The proposed mechanism to synthesis benzochromeno-pyrazoles

In conclusion, an efficient and convenient synthesis of benzochromeno-pyrazole derivatives accomplished via one-pot three-component condensations of aryl aldehydes, 3-methyl-1H-pyrazol-5(4H)-one and *α*-or β-naphthol under reflux temperature in the presence of catalytic amount of *P*-TSA has been described. Applicability of the method for the various compounds, high efficiency of the catalyst system, providing excellent yields of the products prove merit of this research.

III. EXPERIMENTAL

Flash column chromatography was performed using silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used, and compounds were visualized by irradiation with UV light or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Chemicals were either prepared in our laboratories or purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. Melting points were measured using a capillary tube method with a Bamstead Electrothermal 9200 apparatus. ^{1}H NMR spectra was recorded on a Bruker 100-MHz spectrometer in DMSO as the solvent and TMS as internal standard. Mass spectra were documented on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed on Thermo Finnigan EA1112 elemental analyser.

General procedure for preparation of benzochromeno-pyrazoles

A mixture of an aromatic aldehyde (1.1 mmol), 3-methyl-1H-pyrazol-5(4H)-one (1 mmol) and *α*-or β-naphthol (1 mmol), in the presence of *p*-TSA (5 mol%) in acetonitrile (10 mL) was stirred at reflux temperature (Table 2). The progress of the reaction was monitored by TLC. Upon completion of the reaction, the solvent was evaporated and the obtained product was recrystalized from ethanol to afford the pure products.

Characterizations of selected products are as follows:

*(Entry **2**):* m.p. 244 °C. IR (KBr) *(*ν_{max}, cm^{-1}*)*: 3315, 1575, 1514, 1423, 1265. ^{1}H NMR (DMSO-*d*6, 100 MHz): δ = 2.15 (s, 3H, Me), 6.17 (s, 1H, CH), 7.12–8.22 (m, 10H, ArH), 11.10 (s, 1H, NH). Mass m/z: 357 *(*M+*)*. Anal. Calcd for $C_{21}H_{15}N_3O_3$: C 70.58, H 4.23, N 11.76, Found: C 70.22, H 4.48, N 11.59.

*(Entry **3**):* mp. 210 °C. IR (KBr) *(*ν_{max}, cm^{-1}*)*: 3228, 1566, 1525, 1444. ^{1}H NMR(DMSO-*d*6, 100MHz): δ = 2.12 (s, 3H, Me), 3.65 (s, 3H, –OMe), 5.92 (s, 1H, CH), 7.06–8.02 (m, 10H, ArH), 11.30 (s, 1H, NH). Mass m/z: 342 (M+). Anal. Calcd for $C_{22}H_{18}N_2O_2$: C 77.17, H 5.30, N 8.18, Found: C 76.02, H 5.22, N 8.55.

*(Entry **5**):* mp. 275 °C. IR (KBr) (ν_{max}, cm^{-1}): 3424, 1555, 1512, 1404. ^{1}H NMR(DMSO-d6, 100MHz): δ = 2.10 (s, 3H, Me), 5.91 (s, 1H, CH), 7.10–8.30 (m, 13H, ArH), 11.10 (s, 1H, NH). Mass m/z: 362 (M+). Anal. Calcd for $C_{25}H_{18}N_2O$: C 82.85, H 5.01, N 7.73, Found: C 81.17, H 5.21, N 7.57.

*(Entry **8**):* mp. 275 °C. IR (KBr) (ν_{max}, cm^{-1}): 3331, 1572, 1516, 1407. ^{1}H NMR (DMSO-*d*6, 500MHz): δ = 2.13 *(*s, 3H, Me*)*, 5.94 (s, 1H, CH), 7.24–8.25 (m, 10H, ArH), 11.02 (s, 1H, NH). Mass m/z: 357 (M+). Anal. Calcd for $C_{21}H15N_3O_3$: C 70.58, H 4.23, N 11.76, Found: C 71.11, H 4.13, N 11.61.

*(Entry **9**):* mp. 233 °C. IR (KBr) (ν_{max}, cm^{-1}): ^{1}H NMR (DMSO-*d*6, 100MHz): δ = 2.07 (s, 3H, Me), 5.97 (s, 1H, CH), 7.20–7.92 (m, 10H, ArH), 10.45 (br, 1H, NH). Mass m/z: 346 (M+). Anal.Calcd for $C_{21}H_{15}ClN_2O$: C 72.73, H 4.36, N 8.08, Found: C 72.08, H 4.58, N, 7.86.

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