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RESEARCH ARTICLE

Synthesis of Pyrazolo[4,3-*f*]pyrimido[4,5-*b*]quinoline-8, 10-dione Derivatives

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Abstract: Pyrazolo[4,3-*f*]pyrimido[4,5-*b*]quinoline-8,10-dione derivatives have been synthesized from one-pot condensation of 1-methyl barbituric acid, aromatic aldehydes and 5-aminoindazole utilizing bis[7-tert-butyl-2-anilinotropone] Ti complex in toluene under reflux condition.

Keywords: Pyrazolo[4,3-*f*]pyrimido[4,5-*b*]quinoline-8,10-dione, One-pot, Catalyst

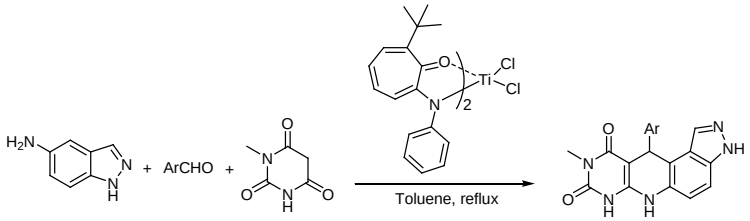
Introduction

Multi-component reactions (MCRs) occupy an outstanding position in organic and medicinal chemistry for their high degree of atom economy and applications in combinatorial chemistry[1]. Nevertheless, continued efforts are being made to explore new MCRs for developing popular organic reactions.

Pyrazole derivatives exhibit pharmacological activities such as hypotensive, antibacterial, anti-inflammatory and antitumor properties[1]. In particular, condensed pyrazoles are known for various biological activities, *e.g.* pyrazolo[3,4-*b*]quinolines as potential antiviral[1], antimalarial[2], lowering of serum cholesterol[3], pyrazolo[3,4-*c*]pyrazoles are useful for the treatment of esophageal and gastrointestinal mucosa injury[4], brain injury[5] and also as immunostimulatory[6], antianginal[7] and antitumor agents[8]. Pyrazolo[3,4-*f*] quinoline derivatives are a novel class of immunostimulant with potent *in vivo* effects in a murine infection model[9,10]. Pyrazolo[4,3-*f*] quinoline derivatives, one of the important kind of fused heterocyclic compounds, possess significant bioactivities such as antiviral and antibacterial activities, acting as potent remedies for treating atherosclerosis or restenosis, inflammatory disorders, demyelinating disorders and cancers[11,12].

The synthesis of the pyrazolo[4,3-*f*]quinoline derivatives have been conducted to either by multi-step reactions or by two-component condensations under heating conditions with relatively long reaction times and limited structural diversity of target molecules[13-16]. As a result, the development of a simple, straightforward and efficient methods for synthesis of pyrazolo[4,3-*f*]quinoline derivatives is strongly desirable. To the best of our knowledge, one-pot synthesis of pyrazolo[4,3-*f*]pyrimido[4,5-*b*]quinoline-8,10-dione derivatives, that may provide new classes of biological active for biomedical screening, using bis[7-tert-

butyl-2-anilinotropone] Ti complex has been never reported up to now. In the continuation of our general interest in the synthesis of heterocyclic compounds by the MCR reactions[17-19], Herein, we wish to report the details of this study (Scheme 1).



Scheme 1

Experimental

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 as KBr disk on a Shimadzu-IR 470 spectrophotometer and the results are report in cm^{-1}. ^1H NMR spectra was recorded on a Bruker 400-MHz spectrometer in DMSO-d_6 as the solvent, TMS was used as the internal standard and the results are reported in ppm. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel plates (60F-254). Elemental analyses were performed on Thermo Finnigan EA1112 elemental analyser. The procedure for synthesis of bis[7-tert-butyl-2-anilinotropone] Ti complex, the catalyst, has been reported elsewhere[20].

General procedure for synthesis of pyrazolo[4,3-f]pyrimido[4,5-b]quinoline-8,10-diones

In a round bottom flask purged by nitrogen gas already, a mixture of 1-methyl barbituric acid (1 mmol), aromatic aldehydes (1 mmol) and 5-aminoindazole (1 mmol), in the presence of bis[7-tert-butyl-2-anilinotropone] Ti 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 H_2O:EtOH (1:4) to obtain the pure desired product in high to excellent yield.

(4a): IR: (KBr, ν cm^{-1}): 3405, 3348, 3115, 1672, 1510, 1441, 1241, 1037, 965. ^1H NMR (100 MHz, DMSO-d^6): δ 12.10 (s, 1H, NH), 10.33 (s, 1H, NH), 9.35 (s, 1H, NH), 8.05 (s, 1H, ArH), 7.55–7.20 (m, 7H, ArH), 5.52 (s, 1H, CH), 3.20 (s, 3H, CH_3). Anal. Calcd. for $C_{19}H_{15}N_5O_2$: C, 66.08; H, 4.38; N, 20.28; Found: C 64.81, H 4.24, N 20.16.

(4b): IR: (KBr, ν cm^{-1}): 3335, 3188, 3088, 1668, 1522, 1352, 1217, 1094, 945, 809, 762. ^1H NMR (100 MHz, DMSO-d^6): δ 11.72 (s, 1H, NH), 10.12 (s, 1H, NH), 9.14 (s, 1H, NH), 8.11-7.95 (m, 3H, ArH), 7.85–7.75 (m, 2H, ArH), 7.52–7.40 (m, 2H, ArH), 5.75 (s, 1H, CH), 3.12 (s, 3H, CH_3). Anal. Calcd. for $C_{19}H_{14}N_6O_4$: C, 58.46; H, 3.61; N, 21.53; Found: C 56.77, H 3.51, N 21.37.

(4e): IR: (KBr, ν, cm^{-1}): 3355, 3194, 3012, 1685, 1554, 1445, 1212, 1078, 923. ^1H NMR (100 MHz, DMSO-d^6): δ 12.41 (s, 1H, NH), 9.83 (s, 1H, NH), 9.05 (s, 1H, NH), 7.95 (s, 1H, ArH), 7.55-7.35 (m, 4H, ArH), 7.24–7.14 (m, 3H, ArH), 6.85 (d, 2H, J = 7.7 Hz, ArH), 5.52 (s, 1H, CH), 3.71 (s, 3H, CH_3O), 3.08 (s, 3H, CH_3). Anal. Calcd. for $C_{20}H_{17}N_5O_3$: C, 63.99; H, 4.56; N, 18.66; Found: C 62.22, H 4.44, N 17.51.

(4f): IR: (KBr, ν cm^{-1}): 3327, 3220, 2995, 1670, 1578, 1464, 1281, 1232, 1139, 914. ^1H NMR (100 MHz, DMSO-d^6): δ 12.65 (s, 1H, NH), 11.15 (s, 1H, NH), 9.14 (s, 1H, NH), 8.12 (s, 1H, ArH), 7.40-7.15 (m, 4H, ArH), 6.73 (d, 2H, J = 7.5 Hz, ArH), 4.95 (s, 1H, CH), 3.10 (s, 3H, CH_3), 2.81 (s, 6H, CH_3). Anal. Calcd. for $C_{21}H_{20}N_6O_2$: C, 64.94; H, 5.19; N, 21.64; Found: C 62.18, H 5.04, N 20.97.

Results and Discussion

As a result of ligand-oriented catalyst design research in our laboratories, we have developed a new family of group 4 transition metal complexes bearing two aminotropone chelate ligands[20]. Choosing an appropriate solvent is of crucial importance for successful synthesis. To optimize the reaction solvent, the reaction of 4-nitrobenzaldehyde, 1-methyl barbituric acid and 5-aminoindazole was carried out in different organic solvents such as toluene, benzene, ethylacetate, 1,2-dichloroethane, acetonitrile 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 acetonitrile and DMF afforded poor results due to the coordinative interaction with the catalyst. Therefore, toluene was chosen as the best solvent for the subsequent reactions. The catalyst, bis[7-tert-butyl-2-anilinotropone] Ti complex, could efficiently catalyze the multicomponent reactions and as illustrated in Table 2, a various series of pyrazolo[4,3-*f*]pyrimido[4,5-*b*]quinoline-8,10-dione derivatives were synthesized in high to excellent yields.

Table 1. Influence of solvent on the reaction efficiency

Solvent	Toluene	Benzene	DMF	EtOAc	CH_3CN
Isolated Yield[a]	90	82	65	68	55

a) All the reactions were carried out at reflux condition for 6 h. Reaction conditions: 4-nitrobenzaldehyde (1.0 equiv), 1,3-indanedione (1.0 equiv) and 5-aminoindazole (1.0 equiv), catalyst (0.1 equiv)

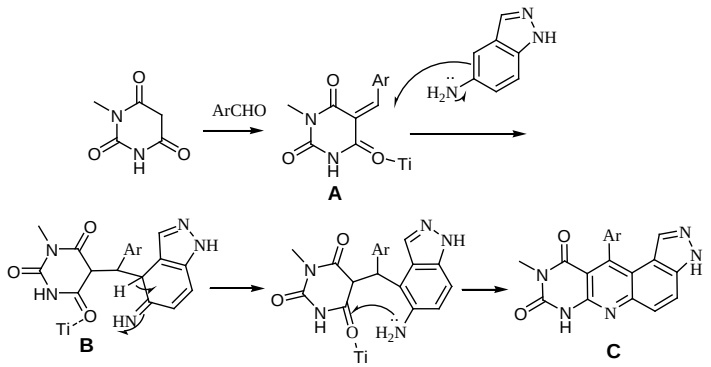
With the intention of providing more diversity to the pyrazolo[4,3-*f*]pyrimido[4,5-*b*] quinolinone structure, various aldehydes were examined and the reactions of aryl aldehydes, in combination with 1-methyl barbituric acid and 5-aminoindazole were tried out. The results revealed that this protocol 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 pyrazolo[4,3-*f*]pyrimido[4,5-*b*]quinoline-8,10-diones

Entry[a]	Ar	Product	Time, h	Yield(%)[a]
1	C_6H_5	**4a**	5	90
2	4-NO_2-C_6H_4	**4b**	4	90
3	2,4-$Cl_2C_6H_3$	**4c**	4.5	84
4	4-CH_3-C_6H_4	**4d**	5	90
5	4-CH_3O-C_6H_4	**4e**	6	92
6	4-$NMe_2C_6H_4$	**4f**	6	90
7	4-OH-3-$NO_2C_6H_3$	**4g**	5.5	85
8	3-NO_2-C_6H_4	**4h**	5	87

a) Isolated yields. References

Beside the high efficiency of the catalyst, due to the heterogeneous nature of the catalyst, the catalyst was simply filtered off which provides convenient work-up procedure. The possible mechanism may proceed via a sequence reaction of condensation, addition, cyclization, and dehydration (Scheme 2). First, the condensation between aromatic aldehyde and 1-methyl barbituric acid leads to intermediate A; Michael-type addition of 5-aminoindazole to A gives B, which upon intermolecular cyclization and dehydration furnishes the corresponding pyrazolo[4,3-*f*]pyrimido[4,5-*b*]quinolinone product.



Scheme 2

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