Catalysts **2015**, *5*, 1649-1656; doi:10.3390/catal5041649

OPEN ACCESS

catalysts

ISSN 2073-4344

www.mdpi.com/journal/catalysts

Article

PEG_{1000}-Based Dicationic Acidic Ionic Liquid Catalyzed One-Pot Synthesis of 4-Aryl-3-Methyl-1-Phenyl-1*H*-Benzo[*h*]pyrazolo [3,4-*b*]quinoline-5,10-Diones via Multicomponent Reactions

Yi-Ming Ren *, Shuo Jin, Hai-Jun Yan and Ze Zhang

Department of Biochemical Engineering, Anhui Polytechnic University, Wuhu, 241000, China; E-Mails: shuojin1991@sina.com (S.J.); hjyan1993@sina.com (H.J.Y.); zzhang1973@sohu.com (Z.Z.)

***** Author to whom correspondence should be addressed; E-Mail: yimingren@ahpu.edu.cn; Tel./Fax: +86-553-287-1254.

Academic Editor: Jason P. Hallett

Received: 1 September 2015 / Accepted: 21 September 2015 / Published: 25 September 2015

Abstract: A novel and green approach for efficient and rapid synthesis of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones has been accomplished by the one-pot condensation reaction of aromatic aldehydes, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and 2-hydroxynaphthalene-1,4-dione using PEG_{1000}-based dicationic acidic ionic liquid (PEG_{1000}-DAIL) as a catalyst was reported. Recycling studies have shown that the PEG_{1000}-DAIL can be readily recovered and reused several times without significant loss of activity. The key advantages are the short reaction time, high yields, simple workup, and recovered catalyst.

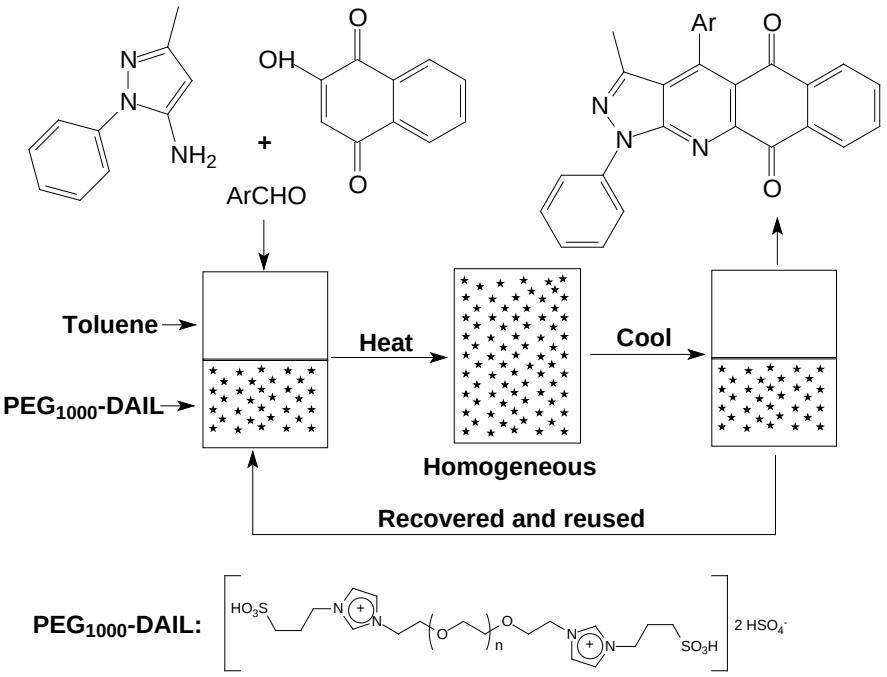
Keywords: pyrazolo[3,4-*b*]quinoline; ionic liquids; poly(ethylene glycol); thermoregulated; recyclable

1. Introduction

Green organic chemistry offers enhanced chemical technology procedures economics concomitant with a reduced environmental degradation. From this viewpoint, it is desirable to achieve multi-bond formation in one operation. Multicomponent reactions (MCRs) allow the creation of several bonds in a single operation and are attracting increasing attention as one of the most powerful emerging synthetic tools for the creation of molecular diversity and complexity [1].

In recent years, pyrazolo[3,4-*b*]quinoline derivatives have been studied as antiviral [2], antimicrobial [3] and oncogenic Ras inhibiting [4]. Due to the presence of versatile biological activities in pyrazolo[3,4-*b*]quinolines, several attempts have been made to provide a convenient synthetic route for this fused ring system. Among these reactions, the most straightforward synthesis of these compounds involves the three-component condensation of aromatic aldehydes, 5-amino-3-methyl-1-phenylpyrazole and dimedone under thermal [5] or microwave condition [6]. However, most of the reported methods require prolonged reaction time, reagents in stoichiometric amount, toxic solvents, and generate moderate yields of the product. Recently, Wu *et al*. [7–9] and Khurana *et al*. [10] reported a new route for preparation of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones by the one-pot condensation reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, 2-hydroxynaphthalene-1,4-dione and aromatic aldehydes under solvent-free conditions [7] or water as solvent [8,9].

Ionic liquids (ILs), as a new class of catalysts or solvents, have attracted growing research interest recently because of their unique properties like reusability, nonflammable, negligible vapor pressure, wide liquid range and high thermal stability [11–17]. Among the numerous ILs developed, poly(ethylene glycol) linked dicationic neutral ionic liquids (PEG-DILs) [18,19] and poly(ethylene glycol) linked dicationic acidic ionic liquids (PEG-DAILs) has been explored as a powerful catalyst for various organic transformations [20–27]. The PEG-D(A)ILs and toluene have the advantages of both homogeneous and heterogeneous phase at different temperatures (biphasic conditions at lower temperatures and monophasic at higher temperatures) with the ease of product as well as catalyst separation [18,23].



Scheme 1. PEG$_{1000}$-based dicationic acidic ionic liquid (PEG$_{1000}$-DAIL) catalyzed the synthesis of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones.

To the best of our knowledge, there is no report on the application of PEG$_{1000}$-DAIL as acid catalysts for the preparation of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones. This paper forms part of our ongoing interest in ILs [18–22] and MCRs [1,28–31]. We report herein a simple and

efficient procedure for the preparation of 4-aryl-3-methyl-1-phenyl-1*H*-benzo [*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones using PEG_{1000}-DAIL as an effective and reusable catalyst (Scheme 1).

2. Results and Discussion

Initially, the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, benzaldehyde and 2-hydroxynaphthalene-1,4-dione was explored in order to search for the optimal conditions. The results collected in Table 1 clearly suggest that PEG_{1000}-DAIL catalyzed efficient for the three-component reaction, and the yield rose to 89% (Table 1, entries 8 and 9) by increasing the temperature. Increasing the reaction temperature could remarkably enhance both reaction yield and rate, perhaps because ionic liquid and toluene could form a homogeneous phase at high temperature. The results showed that the appreciable temperature was reflux temperature, 110 °C (Table 1, entry 9).

Table 1. Optimizing the reaction conditions.

Entry	*T* (°C)	Time (h)	Yield (%) [a]
1	r.t.	6	8
2	40	6	21
3	50	6	30
4	60	6	43
5	70	6	51
6	80	6	65
7	90	6	81
8	100	5	89
9 [b]	110	3	89, 89, 87, 86, 86, 84

[a] Isolated yields; [b] The PEG_{1000}-DAIL was run for six consecutive cycles.

The condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, benzaldehyde and 2-hydroxynaphthalene-1,4-dione under the conditions described in Table 1 with PEG_{1000}-DAIL as catalysts was run for six consecutive cycles with satisfying results (Table 1, entry 9). The underlayer of PEG_{1000}-DAIL was reused without any treatment and the work-up procedure of recycling is accomplished by simple phase separation only.

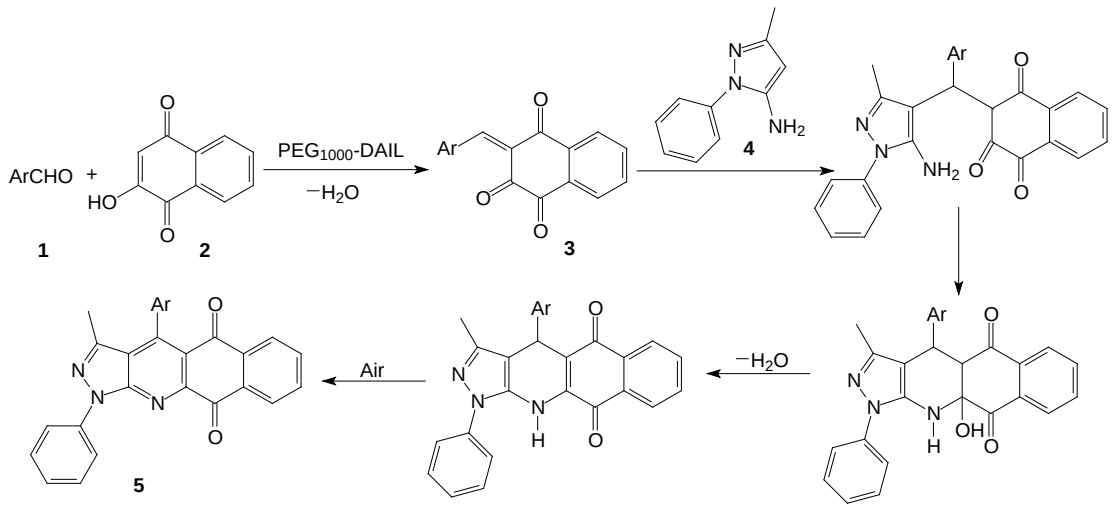
Under the optimized reaction conditions, we investigated the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, 2-hydroxynaphthalene-1,4-dione with various aromatic aldehydes (Table 2). Table 2 showed the aromatic aldehydes with electron-donating groups such as methoxy, methyl proceeded at faster rates than those with electron-withdrawing groups such as chloro, nitro. However, the whole reaction proceeded at reflux temperature within 6 h in excellent yields.

A plausible reaction pathway for this transformation is proposed in Scheme 2 [7]. The reaction occurs via initial formation of heterodiene **3** by the Knoevenagel condensation of aromatic aldehyde **1** to the 2-hydroxynaphthalene-1,4-dione **2** by loss of water molecules. Subsequent Michael-type addition of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **4** to the heterodienes **3** followed by cyclization, dehydration, and air oxidation afford the corresponding products **5**.

Table 2. PEG_{1000}-DAIL catalyzed the synthesis of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones.

Entry	Ar	Time (h)	Yield (%) [a]	mp (°C)	mp (°C) [Ref.]
1	C_6H_5	3	89	264–266	266–267 [8]
2	4-ClC_6H_4	3.5	91	243–245	243–245 [8]
3	2-ClC_6H_4	4	86	228–229	229–230 [8]
4	4-$CH_3C_6H_4$	2.5	88	276–277	276–277 [8]
5	4-$CH_3OC_6H_4$	3	89	275–276	274–275 [8]
6	4-$NO_2C_6H_4$	4	90	325–327	326–328 [8]
7	3-$NO_2C_6H_4$	5	85	288–289	288–289 [8]
8	4-FC_6H_4	5	91	282–284	282–283 [8]
9	3,4-$Cl_2C_6H_3$	6	87	268–270	269–270 [8]

[a] Isolated yields.



Scheme 2. Plausible reaction pathway for the synthesis of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones.

3. Experimental Section

3.1. General Procedure

The PEG_{1000}-DAIL was prepared by the procedure given in the literature [23]. All the other chemicals and reagents are obtained from commercial resource. Commercially available reagents were used without further purification. All products were known compounds and were identified by their Mp, NMR, IR and Anal. Calcd.Melting points were obtained with a Shimadzu DSC-50 thermal analyzer from Shimadzu Corporation, Kyoto, Japan. NMR spectra were recorded with a Bruker Advance instrument from Bruker Corporation, Karlsruhe, Germany. IR (KBr) spectra were recorded on NICOLET Impact410 spectrophotometer from Nicolet Corporation, Denver, USA. Elemental analyses were performed by a Vario-III elemental analyzer from Elementar Corporation, Hanau, Germany.

3.2. General Experimental Procedure for the Synthesis of 4-Aryl-3-Methyl-1-Phenyl-1H-Benzo[h]pyrazolo[3,4-b]quinoline-5,10-diones

To a solution of aromatic aldehyde (1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol) and 2-hydroxynaphthalene-1,4-dione (1 mmol) in toluene (1.5 mL) was added PEG_{1000}-DAIL (1 mL) at room temperature. Then the mixture was refluxed for the specified time and monitored by TLC. After the reaction, the mixture was cooled to room temperature, the upper toluene that contained the expected product was separated by decantation. The toluene was evaporated and the pure products were obtained by purification through recrystallized from ethanol. The underlayer of PEG_{1000}-DAIL was reused without any treatment.

4. Conclusions

In conclusion, we have successfully developed an easy and efficient method to prepare a variety of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones from the reaction of different aromatic aldehydes, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and 2-hydroxynaphthalene-1,4-dione in the presence of PEG_{1000}-DAIL. The advantages of our protocol include high yields, easy isolation of the compounds, short reaction times, the elimination of the metals, and good thermoregulated biphasic behavior of PEG_{1000}-DAIL. Moreover, the PEG_{1000}-DAIL could be readily recovered and reused for several consecutive cycles, thus making this methodology environmentally more acceptable.

Supplementary Materials

The supplementary information contains experimental procedure, ^{1}H NMR, ^{13}C NMR, Anal. Calcd. and IR spectra for all products in Table 2.

Acknowledgments

The project sponsored by the Natural Science Foundation of the Anhui Higher Education Institutions of China (No. KJ2015A033), the National Innovation Program for University Students (No. 201410363062), the Key Laboratory of Chemical and Functional Materials and Technology of the Anhui Polytechnic University (No. KLCFMT1501) and the Anhui Polytechnic University for Young Elite Talents (No. 2013RZR002ZD).

Author Contributions

Yi-Ming Ren contributes to the experimental design. Shuo Jin, Hai-Jun Yan and Yi-Ming Ren contribute to all the experimental data collection. Yi-Ming Ren wrote the first draft of the manuscript that was then extensively improved by Ze Zhang.

Conflicts of Interest

The authors declare no conflict of interest.

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