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One-pot and efficient synthesis of triazolo[1,2-a]indazole-triones catalyzed by poly(ethylene glycol) based magnetic dicationic ionic liquid

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ABSTRACT

An atom-efficient, eco-friendly, solvent-free, high yielding, multicomponent green strategy to synthesize triazolo[1,2-a]indazole-triones derivatives by the one-pot condensation of aldehyde, dimedone, and phenyl urazole is presented. A series of different substituted aromatic aldehydes including either electron-withdrawing or electron-donating groups used in this reaction participated well and gave the corresponding products in good to excellent yield. Poly (ethylene glycol) based magnetic room temperature dicationic ionic liquid, PEG-MRTDIL, was prepared by mixing PEG-DIL with anhydrous $FeBr_3$ under neat conditions. The catalyst was studied by UV and IR spectroscopy. This method provides several advantages such as environment benign, high yield, simple work up procedure and reusable catalyst.

Keywords: *One-pot, Urazole, Dimedone, Magnetic dicationic ionic liquid, Polyethylene glycol.*

1. Introduction

Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals and biologically active pharmaceutical vital for enhancing the quality of life [1]. Among a large variety of nitrogen-containing heterocyclic compounds containing an urazole (1, 2, 4-triazolidine-3, 5-diones) moiety are interesting because they constitute an important class of natural and non-natural products many of which exhibit useful biological activities and clinical applications. Urazole derivatives also exhibit anticonvulsant or fungicidal activity as well as catalytic activity in radical polymerization [2-5]. Novel methods for preparing heterocycles containing an urazole moiety have attracted much interest in recent years [6].

Solvents are chemical substances used in huge amounts for many different applications. In many cases, organic solvents are chemical substances derived from petrol, and have a negative impact on the health and the environment.

One of the key areas of Green Chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with environmentally benign solvents. The possibility of performing multicomponent reactions under solvent-free conditions, with a homogeneous catalyst could enhance their efficiency from economic and ecological points of view [7].

Poly ionic liquids, PILs, have stirred great interest in the fields of polymer chemistry and materials science, not only because of the combination of the unique properties of ILs with the macromolecular architecture, but also a matter of creating new properties and functions. The major advantages of using a PIL instead of an IL are the enhanced mechanical stability, improved process ability, durability, and spatial controllability over the IL species. [8-10].

A poly(ionic liquid) with $FeCl_4^-$ anions containing transition metal ions Fe^{3+} is also synthesized to test whether such kinds of anions can further increase the loss factor by Tang et. al, at 2008 [11].

In this field, PEG based dicationic ionic liquid has considerable advantages, including easy catalyst recovery and product isolation, and employment of a

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continuous flow method owing to the two-phase nature of the system, which make the technique attractive for industrial applications [12, 13].

In continuation of our work on the catalytic properties of magnetic ionic liquids [14], herein, we wish to report a simple, convenient and efficient method for the use of polymeric magnetic room temperature dicationic ionic liquid (PEG-MRTDIL) as catalyst for preparation of triazolo[1,2-a]indazole-trione derivateives under solvent free conditions.

2. Experimental

2.1. Material and methods

Melting points were measured on an Electro thermal 9100 apparatus and are uncorrected. ^{1}HNMR & ^{13}CNMR spectra were recorded on a Bruker Advanced DPX 400 MHz instrument spectrometer using TMS as the internal standard in $CDCl_3$. IR spectra were recorded on a BOMEM MB-Series 1988 FT-IR spectrometer. Phenyl urazole, dimidone and PEG-600 were purchased from Merck Company in high purity. Products were characterized by comparison of their physical and spectroscopic data with those of known samples. The purity of products and reaction monitoring was accomplished by TLC on silica gel Poly Gram SILG/UV 254 plates**.**

2.2. The synthesis of dichloro substituted PEG-600 (Cl-PEG-Cl)

PEG-600 (15 g, 0.025 mol) and pyridine (5 mL, 0.0625 mol) was dissolved in toluene (20 mL), stirred at 87 °C, thionyl chloride (5mL, 0.0625 mol) was added slowly, and the resultant reaction mixture was stirred for 15 h at 87 °C. Then the resulting solid was removed by filtration. After removal of the solvent under reduced pressure a viscous liquid residual was collected as dichloro substituted PEG-600 (13.75 g, 91.6 %).

2.2.1. Procedure for preparation of Poly (ethylene glycol) bis (methylimidazolium dichloride) (PEG-DIL)

1-Methylimidazole (2.2 mmol), and polyethylene glycol dichloride (1 mmol) were placed in a Pyrex glass tube, sealed and heated at 80 °C for 16 h, respectively. The excess of methyl imidazole was removed with ethyl acetate (3 × 2 mL). The product was washed with water (2 × 20 mL) and ether (2 × 10 mL), and dried under vacuum at 65 °C overnight to give colorless product in high yield (85 %).

2.2.2. Procedure for preparation of poly (ethylene glycol) based bis (methyl imidazolium) tribromochloroferrate (PEG-MRTDIL)

PEG-MRTDIL, was prepared by mixing PEG-DIL (1 mmol) with anhydrous $FeBr_3$ (2 mmol) at room temperature for 3h, a dark brown liquid was obtained. The obtained PEG-MDIL was extracted with small amount of ethyl acetate. The solvent was evaporated and the resulting clear brown liquid was dried in vacuum oven at 60 °C for 24 h. The PEG-MRTDIL was obtained in high yield (87 %).

2.3. Synthesis of Triazolo [1,2-a] indazole-trione derivatives: General Procedure

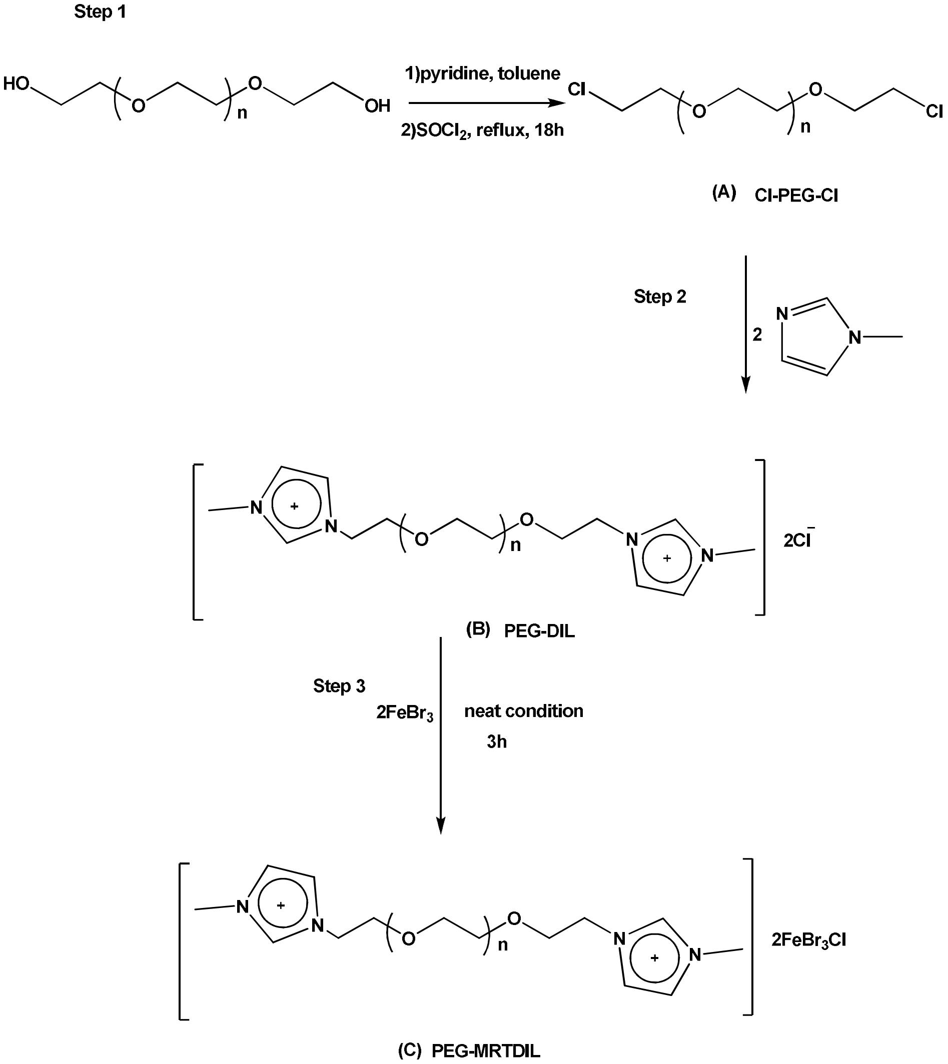
A mixture of dimedone (0.14 g, 1 mmol), phenyl urazole (0.16 g, 1 mmol), an aromatic aldehyde (1.2 mmol) and PEG-MRTDIL (0.1 g) was heated with stirring at 100 °C for an appropriate time (TLC). Completion of the reaction was indicated by TLC. After completion of the reaction, water (20 mL) was added to the mixture, and extracted product the insoluble crude product was dissolved in by ethyl acetate (3×10 mL). The organic phase was separated and evaporation of the solvent under reduced pressure. The solid product recrystallized from ethanol to afford the pure product 4a-k.

3. Results and Discussion

The magnetic polymeric ionic liquid (PEG-MRTDIL) was prepared following the straight-forward synthesis procedure shown in Scheme 1. The more straightforward method to access the ILPEG described herein consists of an alkylation reaction of an N-substituted imidazole with a functionalized PEG with a suitable leaving group (halogen) (Scheme 1, Route A). The functionalization of PEGs with halogens is classically achieved by using thionyl chloride under heating conditions in a suitable organic solvent (toluene) [15]. In the latest step, the anions of imidazolium based dicationic room temperature ionic liquid, Cl^-, were easily changed with $FeBr_3Cl^-$ anions by the simple mixing with $FeBr_3$ under neat conditions.

To characterize the PEG-MRTDIL, we used the FT-IR spectrum. The FT-IR spectrum of native PEG-MRTDIL sample is shown in Fig. 1. The results show that the band at about 3200–3500 cm^{-1} was attributed to the OH stretching vibrations. But, after functionalization, the bending vibration absorption peak of O–H at about 3200–3500 cm^{-1} disappeared. There are peaks at about1165 cm^{-1}, which were assigned to the characteristic absorption of $N–CH_2$ in functionalized PEG-MDIL. The absorption bands at 3152 and 3013 cm$^{−1}$ (imidazolium CH stretching modes), presented in the inset of Figure 1 demonstrate modification of the PEG. The absorption at 2911cm$^{−1}$ is usually assigned to CH_2 stretching of the polyether linkage chains. The absorption observed at 1571 cm$^{−1}$ is also characteristic of the imidazolium ring and is assigned to imidazolium ring stretching.

The UV spectrum is shown in Fig. 2. The UV–vis absorption spectra of PEG-MRTDIL in acetonitrile consist of two main bands at 310–425 nm and 240–300 nm (see Fig. 2a). The shorter wavelength band is



Scheme 1. Synthesis of PEG-MRTDIL.

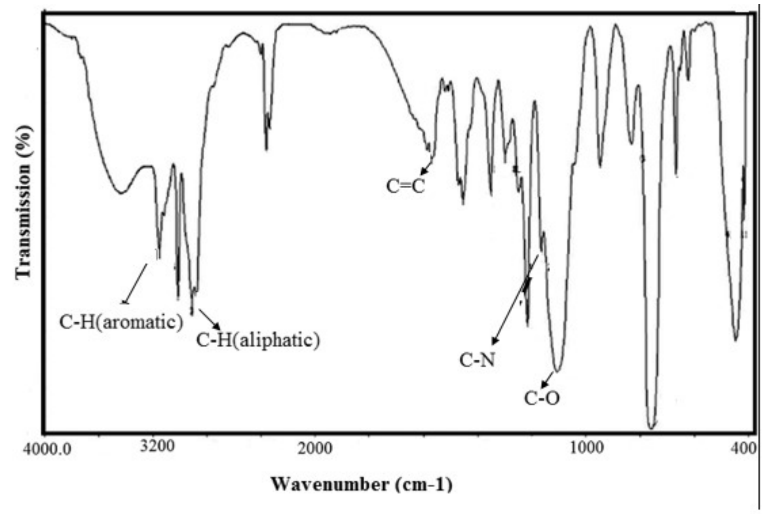


Fig. 1. FT-IR spectra of PEG-MRTDIL.

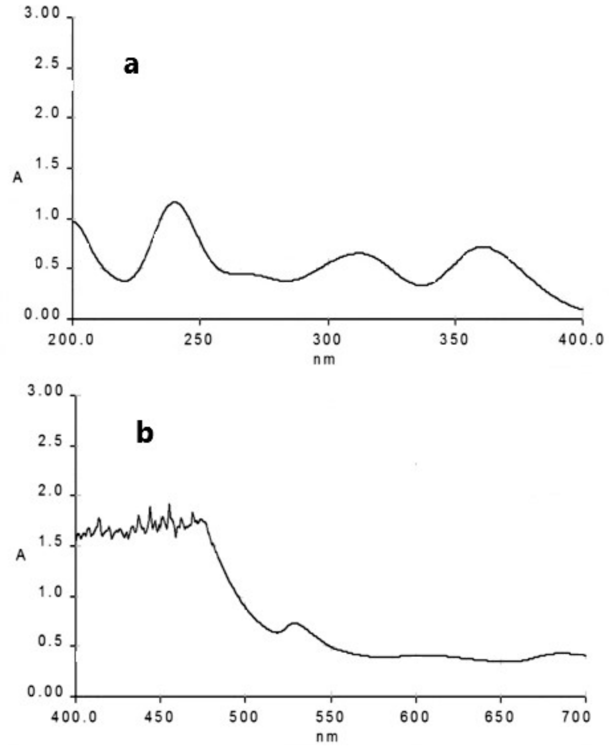


Fig. 2. (a) Visible spectrum of PEG-MRTDIL (200-400 nm), (b) UV spectra of PEG-MRTDIL, (400-700 nm).

attributed to the π → π* transition in the imidazole ring, and the longer wavelength band was found to be due to the n → π* transition. PEG-MRTDIL spectra exhibited absorption bands in the visible region at 534, 473 nm which are characteristic for the $FeBr_3Cl^-$ anion (Fig. 2b). The magnetic properties of the PEG-MRTDIL and $FeCl_3$ were measured by vibrating sample magnetometer**,** VSM, at the room temperature. The paramagnetic linear response of PEG-MRTDIL is similar to iron (III) chloride. From M *vs.* H curves, the magnetization value for PEG-MRTDIL at the same field was found to be 0.4 emu Oe g^{-1}, lower than of $FeCl_3$ (0.7 emu Oe g^{-1}) at 8 kOe. At the start of our investigations, the reaction of benzaldehyde, urazole and dimedone was selected as model system to demonstrate the catalytic effectiveness of PEG-MRTDIL. Next, to optimize the amount of catalyst and temperature, we also changed temperature and the amount of catalyst. We found that the best yields and time profiles were obtained with 0.1 gr of PEG-MRTDIL at 100 °C under solvent free conditions (Table 1).

Table 1. Optimization of the amount PEG-MRTDIL and temperature for the synthesis of H-triazolo [1,2-a]indazole-triones[a].

Temp. (°C)	PEG-MRTDIL (g)	Time (min)	Yield (%)
25	0.1	120	0
60	0.1	60	40
80	0.1	30	66
100	0.1	20	90
120	0.1	20	90
100	0	120	0
100	0.05	60	65
100	0.15	20	90
100	0.2	20	90

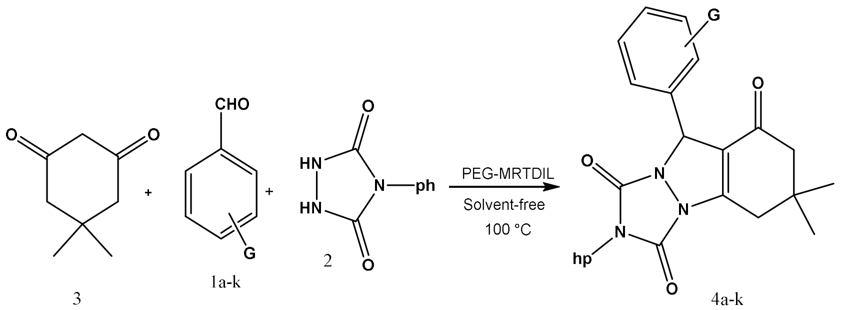
[a]Reaction conditions: benzaldehyde (1.2 mmol), dimedone (1 mmol), phenyl urazole. (1 mmol), X% g of PEG-MRTDIL, solvent free, different temperature.

A further increase in the amount of PEG-MRTDIL did not have any significant effect on the product yield (Table 1).

Under the optimized reaction conditions, a series of triazolo[1,2-a]indazoletrione derivatives 4a–k were synthesized (Scheme 2). The results are summarized in Table 2. As shown in Table 2, it was found that this method works with a wide variety of substrates. A series of different substituted aromatic aldehydes including either electron-withdrawing or electron-donating groups used in this reaction participated well and gave the corresponding products in good to excellent yield.

To compare the advantage of the use of PEG-MRTDIL over the reported catalysts, the model reaction of, dimedone, phenyl urazole and benzaldehyde was considered as a representative example (Table 3). The yield of product in the presence of PEG-MRTDIL is comparable with these catalysts. However, the reported procedures required longer reaction time (entry 3), strong acidic conditions (entries 1, 2, 4, 5), and low yield (entry 5). These results demonstrate that PEG-MRTDIL is an equally or more efficient catalyst for this three-component reaction.

The success of the above reactions prompted us to investigate the recyclability of catalyst. We carried out our study by using the reaction benzaldehyde, dimedone, and phenyl urazole under optimal conditions as a model study. When the reaction was completed as indicated by TLC, the reaction mixture was cooled to room temperature and the product was extracted by ethyl acetate. The product was washed with distilled water and the aqueous solution was evaporated under reduced pressure to get the catalyst, which was washed with diethyl ether, dried, and reused for the same reaction. The catalyst could be reused for fourth times without significant decrease in catalytic activity (Fig. 3).

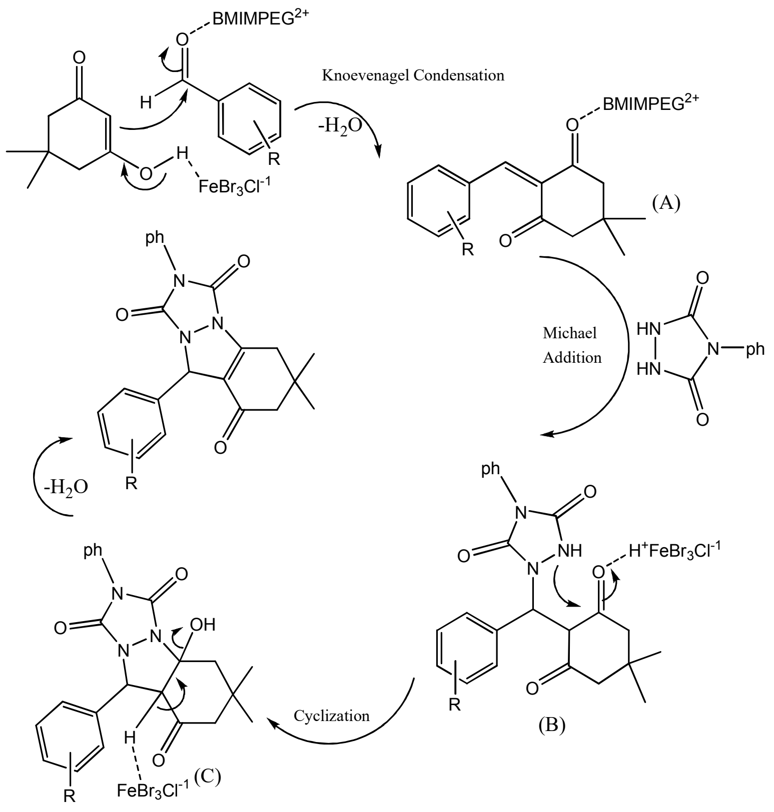


Scheme 2. Three-component reaction of dimidone, phenyl urazole, and aromatic aldehyde.

Table 2. Synthesis of triazolo[1,2-a]indazole-triones derivatives[a]

Entry	Product	R	Time (min)	Yield (%)	m.p. (°C) Found	m.p. (°C) Reported	Ref.
1	4a	H	20	90	186-188	188-190	[16]
2	4b	3-OCH_3	25	89	108-109	106-107	[17]
3	4c	4-CH_3	20	88	162-163	160-162	[16]
4	4d	2-Cl	35	87	171-173	173-175	[16]
5	4e	4-Cl	20	90	166-168	166-168	[16]
6	4f	3-NO_2	25	89	174-176	174-175	[6h]
7	4g	2,4-Cl_2	35	88	194-196	195-197	[17]
8	4h	4-Br	25	89	183-185	184-186	[6h]
9	4i	4-F	20	86	104-106	102-104	[16]
10	4j	4-NO_2	25	86	176-178	175-177	[16]
11	4k	4-CF_3	20	88	184-186	184-185	[17]

[a]Reaction conditions: Aldehyde (1.2 mmol); 5,5-dimethylcyclohexane-1,3-dione (1 mmol); phenyl urazole (1 mmol); PEG-MRTDIL (0.1 g), solvent free, 100 °C.



Scheme 3. A plausible reaction mechanism.

Table 3. Comparison of PEG-MRTDIL with reported catalysts in the reaction of dimedone, phenyl urazole, and benzaldehyde.

Entry	Reagent and conditions	Time (min)	Yield (%)	Ref.
1	PEG-SO_3H (10 mol %)/ solvent-free, 80°C	40	91	[6f]
2	Melamine trisulfonic acid (15 mol %)/ solvent-free, 80°C	30	94	[6i]
3	$H_4SiW_{12}O_4$ (3.5 mol %)/ solvent-free,100°C	70	88	[18]
4	Camphor-10-sulfonic acid (20 mol %)/ H_2O/ EtOH/ reflux	20	89	[19]
5	*p*-Toluenesulfonic acid (0.3 mmol)/ solvent-free, 80°C	15	78	[6h]
6	PEG-MRTDIL (01)/ solvent-free, 100°C	20	90	This Work

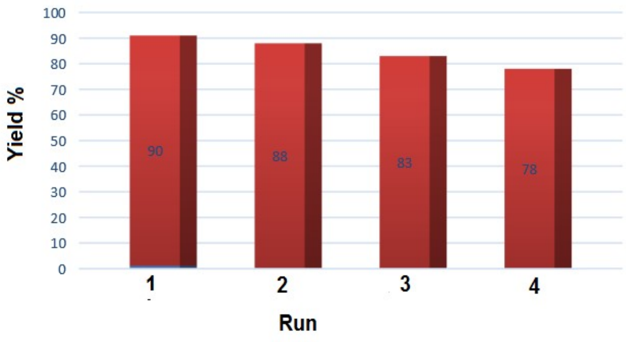


Fig. 3. Reusability of catalyst.

4. Conclusions

In conclusion, we have successfully developed simple procedure for the efficient synthesis of triazolo[1,2-a]indazole-triones using PEG-MRTDIL under mild reaction conditions. The mild reaction conditions, simple work-up in isolation of the products in good yields and high purity are features of this new procedure.

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