Polyethylene glycol embedded tribromide as an efficient and reusable catalyst for the library synthesis of nitrogen containing heterocycles

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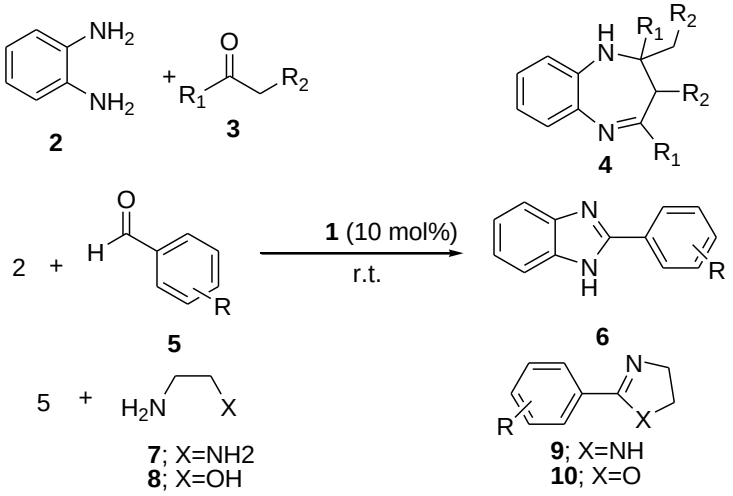
Abstract Potassium tribromide wrapped around polyethylene glycol ($\{K^+PEG_{400}\}Br_3^-$) was easily prepared by two step reaction of PEG_{400} with KBr followed by the addition of molecular bromine to give PEG embedded potassium tribromide as a dark viscous oil. The synthesized material was found to be an efficient, cost effective, environmentally benign and recyclable catalyst for the library synthesis of nitrogen containing heterocyclic compounds *via* multicomponent coupling reaction. The method offers a set of advantages such as facile synthesis, low cost, recycling ability and high product yields.

KEYWORDS: heterocycle, host-guest complex, polyethylene glycol, KBr, multi-component coupling.

Introduction

Synthesis of diverse range of heterocyclic compounds, particularly those possessing a number of biological as well as pharmacological applications is an important goal in the fields of organic synthesis and chemical biology. Multicomponent reactions (MCRs) serve as a rapid and efficient tool for the synthesis of such multi-functionalized ring systems by one pot operation [1-3]. These reactions offer a number of potential advantages over conventional multistep synthesis in terms of rapid synthesis, reduction of chemical waste, lower cost and simple isolation, purifications procedures. Heterocyclic compounds such as 1,5-benzodiazepines [4-6], benzimidazoles [7-9] imidazolines [10-12] and 2-oxazolines [13-16] constitute the largest diversity of organic molecules in medicinal chemistry because of their remarkable biological activities including anticonvulsant, anti- anxiety, and hypnotic agents. Some of the analogous of these heterocyclic compounds have been used widely for the synthesis of valuable fused rings compounds such as triazolo, oxazino or furano-benzodiazepines. Furthermore, they are used in photography and also as anti-inflammatory agents. More recently, the area of biological interest of 1,5-benzodiazepines

has been extended to antibiotics, and various diseases such as cancer, viral infection (HIV) and cardiovascular disorders [17-18]. Recently, one-pot syntheses of these heterocyclic compounds by condensation reactions employing several metal based and metal free catalytic systems have been reported [19-20]. However, in most of the cases, high loadings (up to 33 mol %) [21] of expensive catalysts and difficult recovery of the catalysts make the utility of these methods limited. The development of simple and environmentally benign synthetic methods for efficient preparation of these heterocyclic compounds and their libraries is therefore a significant challenge. Liquid polyethylene glycols (PEG's), have extensively been used as novel green solvents in synthetic organic chemistry. In addition, polyethylene glycols, also known as a "poor chemist's crown ethers" have been used as phase-transfer catalysts for catalytic reactions and have the tendency to form complexes with metal cations [22-23]. Based on the metal cation coordination ability of PEGs, recently we have developed a novel PEG wrapped potassium tribromide *via* a unique host–guest complex approach and utilized it for the synthesis of functionalized piperidines via multi-component coupling reaction [24]. In continuation to our on-going research, herein we report an efficient methodology for the synthesis of diverse range of heterocyclic compounds such as 5-benzodiazepine derivatives **4**, benzimidazoles **6**, imidazolines **9** and oxazolines **10** *via* the one-pot multi-component coupling which are essential components of various bio-active molecules (Scheme 1).



Scheme 1: Synthesis of heterocyclic compounds catalyzed by **1**

Experimental Section

Materials and Instrumentation. All the substrates, reagents, and solvents were commercially available and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz for $CDCl_3$ solutions. GC-MS (HP 5890, series II) analysis were carried out by using mass selective detecter (MSD) (30m × 0.30 mm); 50-250 ^{o}C, 8 ^{o}C/min, and GC (GC, Agilent 6820) analysis was carried out using a silicon OV-17 column (50 m x 0.26); 50-250 ^{o}C, 5 min isothermal, 8 ^{o}C/min, FID 250 ^{o}C. The bromine content of the catalyst **1** was determined according to the literature [28].

Synthesis of [{$K^{+}PEG_{400}$}Br_3^{-}] 1

To a 100 mL round bottomed flask, cooled in an ice bath and equipped with a dropping funnel and a condenser, were added, successively, 20 mL of MeOH and KBr (5 g) while maintaining the internal temperature between 10-15 ^{o}C. Molecular bromine, 10 mL, was then added by the dropping funnel (drop-wise). The solution was stirred for 10 minutes and the crude brown mixture became orange. Commercial PEG_{400} (20 g) was then added and the resulting mixture was stirred for 60 min 10 ^{o}C. The solvent was removed under reduced pressure and PEG embedded tribromide **1** was successively washed with Et_2O and dried under vacuum.

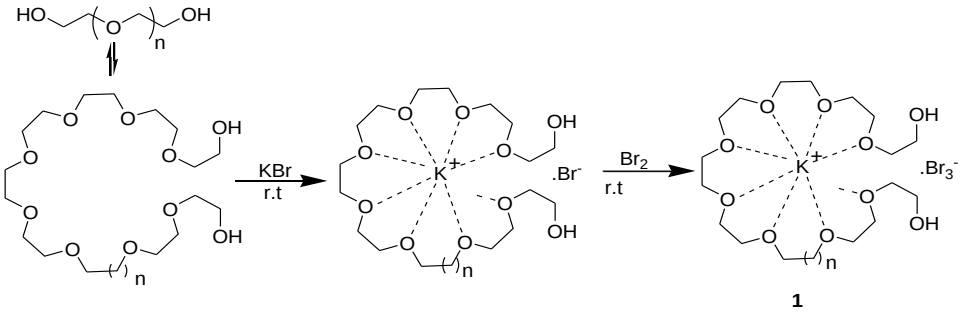
General experimental for the library synthesis of heterocyclic compounds

A mixture containing desired substrates as mentioned in Table 1 and catalyst **1** (10 mol%, 0.1 mmol) was stirred at room temperature under a nitrogen atmosphere. The reaction was monitored by TLC. At the end of the reaction, catalyst was easily recovered by extracting the reaction mixture with diethyl ether. The combined organic layer was washed with water, brine solution and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the residue so obtained was purified by column chromatography (SiO_2) by using EtOAc : hexane (1:4) as eluent to afford pure product.

Procedure for Regeneration and Reuse of 1 (Recycle 1). The filtrate originating from the above reaction containing [PEG.KBr] was treated with bromine and the resulting mixture was stirred to give [$PEG.KBr_3$] **1**. The regenerated catalyst **1** was successively used for the subsequent runs.

Result and discussion

In our investigations, we used PEG_{400}, which being liquid, can easily allow reactions to be run under solvent free conditions. The PEG_{400}-wrapped tribromide **1** was readily synthesized by treating PEG_{400} with KBr followed by its reaction with bromine (Scheme 2).



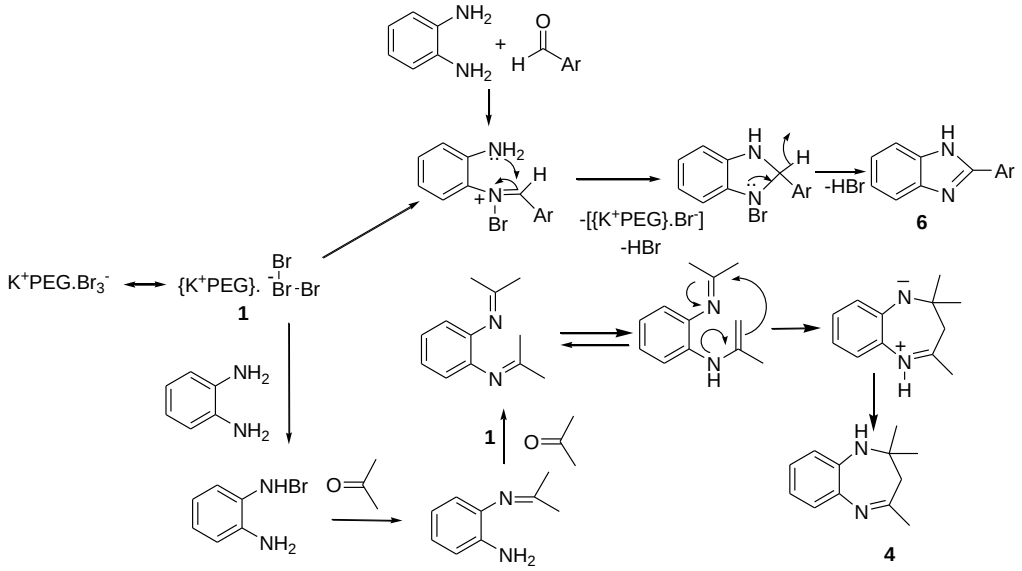
Scheme 2: Synthesis of tribromide **1**

We began this study by examining the condensation of *o*-phenylenediamine **2** with acetone in the presence of catalytic amount of **1** (10 mol %) under the solvent free conditions. The mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was isolated by extraction with diethyl ether followed by usual workup to afford 2,2,4-trimethyl-2,3-dihydro-1H-benzo-*b*-[1,4]diazepine **4a** in 98 % yield. The recovered PEG wrapped potassium bromide [K^+{PEG}Br] can readily be separated and converted to **1** for recycling experiments. In view of the success of the above reaction, we explored the scope of this reaction by varying the substrates under similar reaction conditions. The results of these experiments are summarized in Table 1. The reaction proceeded very cleanly under described experimental conditions and afforded excellent yield of the desired products. Further, cyclic ketones such as cyclohexanone and cyclopentanone reacted effectively to produce the corresponding fused ring benzodiazepines (Table 1, entry 3,4). In a controlled blank experiment between *o*-phenylenediamine and acetone, no reaction occurred in the absence of catalyst **1**. Similarly no reaction was taken place by using PEG_{400} alone under identical conditions. However, in the presence of KBr, the reaction between *o*-phenylenediamine and acetone afforded very poor yield of the desired product under otherwise similar reaction conditions. All the products were identified by comparing their physical and spectral data with the reported values.

To extend the scope of the reaction, we also studied the condensation of *o*-phenylenediamine **2** and aromatic aldehydes **5** under described experimental conditions. The results of these experiments are presented in Table 2. The progress of the reaction was monitored by TLC and products were analyzed by GC. In all cases, the reaction was found to proceed smoothly and provided high product yields without any evidence for the formation of any side product. The electronic effect of the substituents had marginal effect and therefore all the aromatic aldehydes bearing either electron-withdrawing or electron-donating functional groups were found to be suitable for the reaction (Table 2).

Furthermore we carried out the condensation of the aromatic aldehydes **5** with ethylene diamine **7** or ethanolamine **8** under identical reaction conditions. The reaction proceeded efficiently and provided the corresponding imidazolines **9a-9k** and 2-oxazolines **10a-10k** respectively in high to excellent yields. The results of these experiments are presented in Table 3.

The mechanism of the reaction is not clear at this stage, in analogy to the existing reports by using organic ammonium tribromides as catalyst [24], It is believed that the reagent **1** release Br^+ *in situ* which can act as oxidant [25-27] in the reaction medium and lead to the formation of benzimidazoles as shown in Scheme 3. The possible mechanism for the synthesis of 1,5-benzodiazepine could involve an intramolecular imine–enamine cyclization promoted by reagent **1**, as shown in Scheme 3.

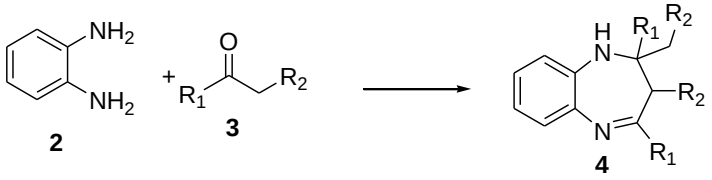


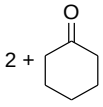
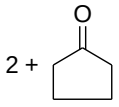
Scheme 3: Probable mechanism for the synthesis of 1,5-benzodiazepine **4**, benzimidazole **6**

Conclusion

In summary, we have developed a very simple, inexpensive and easily recyclable catalyst i.e. potassium tribromide wrapped around PEG_{400} for the one-pot synthesis of nitrogen containing heterocyclic library compounds such as 1,5-benzodiazepines, benzimidazoles, imidazoles and 2-oxazolines by using a catalytic amount of tribromide wrapped around PEG_{400}. The developed method has a number of advantages over the reported tribromides in terms of its easy synthesis, low cost, readily available precursors, higher stability, higher efficiency, versatility for the synthesis of a range of heterocyclic compounds and high product yields.

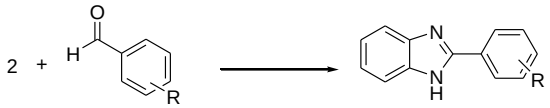
Table 1: One-pot synthesis of 5-benzodiazepines **4** catalyzed by PEG-wrapped KBr_3 **1**.[a]



Entry	Substrate	Product	Reaction Time (h)	Yield (%)[b]
1.	**2** + **3a** (R_1=CH_3, R_2=H)	**4a**	0.5 1.0	98 42 [c]
2.	2 + **3b** (R_1=Ph, R_2=H)	**4b**	0.5	96
3.	 **3c**	**4c**	0.5	93
4.	 **3d**	**4d**	0.5	93
5.	**2** + **3e** (R_1=CH_3, R_2=$CH(CH_3)_2$	**4e**	0.5	90
6.	**2** + **3f** (R_1=Et, R_2=Me)	**4f**	0.5	91
7.	**2** + **3g** (R_1=Et, R_2=H)	**4g**	0.5	90

[a]Reaction conditions: substrate **2** (1 mmol), **3** (2.5 mmol), catalyst 1 (10 mol%) at room temperature under nitrogen atmosphere; [b]Isolated yields; [c]using KBr as catalyst.

Table 2: One-pot synthesis of benzimidazoles **6** catalyzed by PEG-wrapped KBr_3 **1**[a]

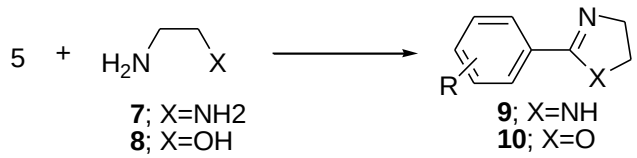


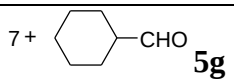
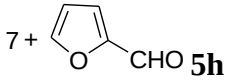
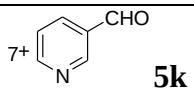
5 **6**

Entry	Substrate	Product	Reaction Time (h)	Yield (%)[b]
1	**2** + **5a** (R=H)	**6a**	4.0	90
2	**2** + **5b** (R=*p*-Me)	**6b**	4.5	89
3	**2** + **5c** (R=*p*-OMe	**6c**	4.0	90[f]
4	**2** + **5d** (R=*p*-NO2)	**6d**	4.0	90[f]
5	**2**+ **5e** (R=*p*-Cl)	**6e**	4.0	92
6	**2** + **5f** (R=*m*-NO_2)	**6f**	4.0	85

[a]Reaction conditions: substrate **2** (1 mmol), **5** (1 mmol), catalyst 1 (10 mol%) at room temperature under nitrogen atmosphere; [b]Isolated yields.

Table 3: One pot synthesis of imidazolines **9** and oxazolines **10** catalyzed by **1**[a]



Entry	Substrate	Product	Reaction Time (h)	Yield (%)[b]
1	**7** + **5a**	**9a**	1.0	95
2	**7** + **5b**	**9b**	1.0	94
3	**7** + **5c**	**9c**	1.0	94
4	5d + 7	**9d**	1.0	95
5	5e + 7	**9e**	1.0	95
6	 **5g**	**9g**	1.0	90
7	 **5h**	**9h**	1.0	93
8	**7** + **5i** (R=*o*-Cl)	**9i**	1.0	95
9	**7** + **5j** (R=*p*-N(Me_2)	**9j**	1.0	85
10	 **5k**	**9k**	1.0	80
11	**8** + **5a**	**10a**	1.0	95
12	**8** + **5b**	**10b**	1.0	94

13	**8** + **5c**	**10c**	1.0	94
14	**8** + **5d**	**10d**	1.0	95
15	**8** + **5e**	**10e**	1.0	95
16	**8** + **5g**	**10g**	1.0	90
17	**8** + **5h**	**10 h**	1.0	93
18	**8** + **5i**	**10i**	1.0	95
19	**8** + **5j**	**10j**	1.0	85
20	**8** + **5k**	**10 k**	1.0	80

[a]Reaction conditions: substrate **5** (1 mmol), **7** or **8** (1 mmol), catalyst 1 (10 mol%) at room temperature under nitrogen atmosphere; [b]Isolated yields.

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ABBREVIATIONS

PEG400, polyethylene glycol (MW400); TLC, thin layer chromatography.

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