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One-pot, Environmentally Benign Procedure for the Synthesis of tetrahydrotetrazolo[1,5-*a*]quinazolines Using [Bmim]Cl/$AlCl_3$ as a Task-specific Ionic Liquid

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Abstract

A practical and green approach for the one-pot multicomponent synthesis of fused tetrazolo[1,5-a]quinazoline derivatives has been described via the condensation of 5- aminotetrazole, dimedone, and various aldehydes using 1-butyl-3-methylimidazolium tetrachloroaluminate [bmim]Cl/$AlCl_3$, as a catalyst and task-specific ionic liquid medium. The catalyst was showed remarkable advantages in comparison with previous methods. Short synthetic route, operational simplicity, high-to-excellent yields, eco-friendliness and mild reaction conditions are the advantages of this method.

Keywords:*Ionic liquid, [Bmim]Cl/$AlCl_3$, Tetrahydrotetrazolo[1,5-a]quinazoline, 5-aminotetrazole.*

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Introduction

Multicomponent reactions (MCRs) combine at least three reactants in a single chemical event to generate a product containing most atoms of the starting materials [1-2]. Atom economy, mild conditions, efficiency, straightforward reaction design, high convergence and concomitant step economy of MCRs in combination with their general compatibility with green solvents would justify a central place in the toolbox of sustainable synthetic methodologies [3].

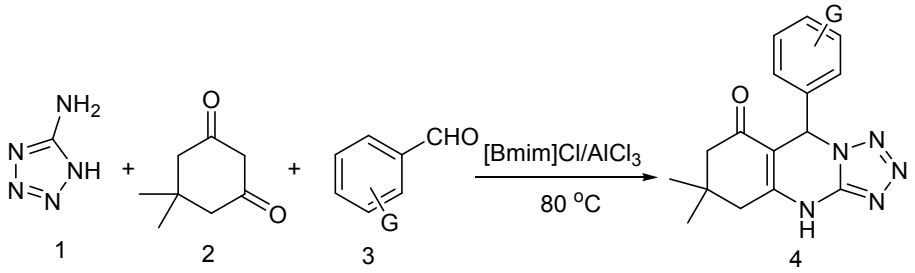
In recent years, ionic liquids have attracted the attention of organic chemists due to their eco-friendly nature, reusability and unusual physical properties [4-8]. Metal-ion containing ionic liquids has attracted extensive interest, as they can combine the advantages of both homogeneous and heterogeneous catalysis [9-10]. In this context, organoaluminate molten salts are the most investigated class of so-called ionic liquids, as their acidity can be modulated by changing the amount of $AlCl_3$ [11-12].

Tetrazoloquinazolinones or tetrazolopyrimidines are an important class of nitrogen-bridgehead fused heterocyclic compounds, which have attracted a considerable attention for their therapeutic activity [13-14].These compounds have also been tested for their potential pharmacological and biological activities in the treatment of obesity, atherosclerosis, diabetes, coronary heart disease, thyroid cancer, depression, glaucoma, hypercholesterolemia, hyperlipidemia, hypertension, hypothyroidism, cardiac arrhythmias, and congestive heart failure [13-22]. Hence, the synthesis of tetrazole derivatives is currently of great interest both in organic synthesis and medicinal chemistry.

In the last years, numerous methods have been developed for the synthesis of tetrazoloquinazolinones by using a broad variety of catalysts and conditions [23-28]. Although many of these procedures have valuable advantages, some have specific disadvantages. For example multistep synthesis, toxic metallic reagents, unsatisfactory yields, high cost of catalysts and solvents, long reaction times, multi-step synthesis of catalyst, the use of toxic catalyst and tedious separation procedures production of side products that would limit the use of these protocols in accordance with the principles of ‘‘Green Chemistry”. A new method has been reported by Kumar et al. which require heating at reflux condition in CH_3CN and the reaction time ranges from 3h to 5h [27]. However, this report is encountered with drawbacks related to use of moisture sensitive catalyst, its reuse, use of organic solvent and long reaction hours. Therefore, it is important to replace corrosive and hazardous catalysts with task-specific ionic liquids which are active under mild conditions for synthesis of tetrahydrotetrazolo[1,5-*a*]quinazoline derivatives.

In continuation of our previous studies on developing improved methodologies for synthesis of tetrahydrotetrazolo[1,5-*a*]quinazolines [28-29], herein we describe the synthesis of these compounds via a one-pot, three-component condensation of aldehydes, 5-aminotetrazole, and

dimedone at 80 °C under solvent-free conditions using [bmim]Cl/$AlCl_3$ ionic liquid (Scheme 1). To the best of our knowledge, this is the first report of the application of this ionic liquid [bmim]Cl/$AlCl_3$ in the synthesis of tetrahydrotetrazolo[1,5-*a*]quinazoline derivatives.



Scheme 1. Synthesis of tetrahydrotetrazolo[1,5-*a*]quinazolines.

Experimental

Materials and Instruments

All of the reagents were purchased from Merck, Fluka and Aldrich companies and used without further purification. Melting points were determined by a Gallenkamp melting point and are not corrected. Thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel 60 F_{254} was used to monitor the progress of reactions. Fourier transform infrared (FT-IR) spectra were obtained as KBr pellets on a Perkin–Elmer spectrophotometer. Nuclear magnetic resonance (^{1}HNMR and ^{13}CNMR) was recorded in DMSO solvent on Bruker Avance 400-MHz spectrometers at 400 and 100 MHz, respectively.

Synthesis of ionic liquid

The synthesis of organoaluminate task-specific ionic liquid has been carried out from a similar method in the literature [30]. [Bmim]Cl/$AlCl_3$ was prepared by slowly adding the weighed waterless $AlCl_3$ to 1-butyl-3-methylimidazolium chloride. The reaction mixture was left stirring overnight at room temperature in order to obtain a perfect homogenization of task-specific [bmim]Cl/$AlCl_3$. The whole reaction system was kept under dry nitrogen atmosphere to avoid hydrolysis of $AlCl_3$. Organoaluminate task-specific ionic liquid can be stored in dry inert atmosphere [30].

General procedure for the preparation of product

A dried test tube, equipped with a magnetic stir bar, was charged with a mixture of dimedone (0.28 g, 2 mmol), 5-aminotetrazole monohydrate (0.210 g, 2 mmol), aldehyde (2 mmol), and 1-butyl-3-methylimidazolium tetrachloroaluminate [Bmim]Cl/$AlCl_3$ ionic liquid (1 mmol, 50 mol%). The mixture was heated at 80 °C until the reaction was complete (monitored by TLC and visually, the

reaction mixture was solidified). After cooling, the reaction mixture was washed with water (10 mL) and the residue recrystallized from ethanol to afford the pure products. All compounds were known and characterized by NMR, IR and melting found to be identical with the ones described in literature [23-28].

Results and discussion

Literature surveys revealed that various catalysts such as $Hg(OAc)_2$, I_2, *p*-TSA, Fe_3O_4@SiO_2@Propyl–ANDSA and $AlCl_3$ have been employed in this reaction as demonstrated in Table 1 (Entries 1-5). We investigated the catalytic activity of the prepared [Bmim]Cl/$AlCl_3$ in this reaction, a model experiment was carried out using 2 equiv of each of 5-aminotetrazole monohydrate, benzaldehyde, and dimedone, and stirring at 80 °C in the absence of the catalyst. The progress of the reaction was monitored by TLC. The reaction did not proceed to completion even after 3h and no product was isolated (Table 1, Entry 10). In order to improve the yield and optimize the reaction conditions, the same reaction was carried out in the presence of [Bmim]Cl/$AlCl_3$ as a catalyst under similar conditions. Surprisingly, a significant improvement was observed and the yield of the product was enhanced to 95% after stirring the reaction mixture for 35 min (Table 1, Entry 6).

Table 1. Comparison of the efficiency of [Bmim]Cl/$AlCl_3$ with some other reports for the MCR of 4-chloro benzaldehyde, 5- aminotetrazole, and dimedone.

Entry	Catayst or reagent	Solvent	Temp	Time (min)	Yield (%)[a]	[Ref]
1	NaN_3/$Hg(OAc)_2$	HOAc	100 °C	360	68	[26]
2	I_2	*i*-PrOH	reflux	10	92	[25]
3	*p*-TSA	Solvent-free	80 °C	6	88	[28]
4	Fe_3O_4@SiO_2@propyl–ANDSA	H_2O/EtOH	100 °C	5	94	[23]
5	$AlCl_3$	CH_3CN	reflux	180	95	[27]
6	[Bmim]Cl/$AlCl_3$	-	80 °C	35	95	[b]
7	[Bmim]Cl/$AlCl_3$	-	25 °C	180	50	[b]
8	[Bmim]Cl	-	80 °C	30	10	[b]
9	$AlCl_3$	-	80 °C	30	60	[b]
10	-	-	80 °C	180	0	[b]

[a] *Yields refer to isolated pure products*
[b] *Referred to the present work.*

To illustrate the importance of [Bmim]Cl/$AlCl_3$ for the reaction, two blank experiments were conducted in the presence of [Bmim]Cl and $AlCl_3$ under optimized reaction conditions at 80°C. The yields in these cases were 10 and 60% after 30min, respectively (Table 1, Entries 8 and 9). As a

result, the [Bmim]Cl/$AlCl_3$ was a key component of the reaction. We also investigated the effect of temperature on the pilot reaction in the presence of 50mol% of [Bmim]Cl/$AlCl_3$ catalyst. It was found that the efficiency and yield of the reaction at 80°C were higher than those obtained at other temperatures. The yield of the reaction at room temperature was 50% after 3h. (Table 1, Entry 7). We also performed the model reaction using different quantities of catalysts. The best amount of catalyst was 50mol% [Bmim]Cl/$AlCl_3$.

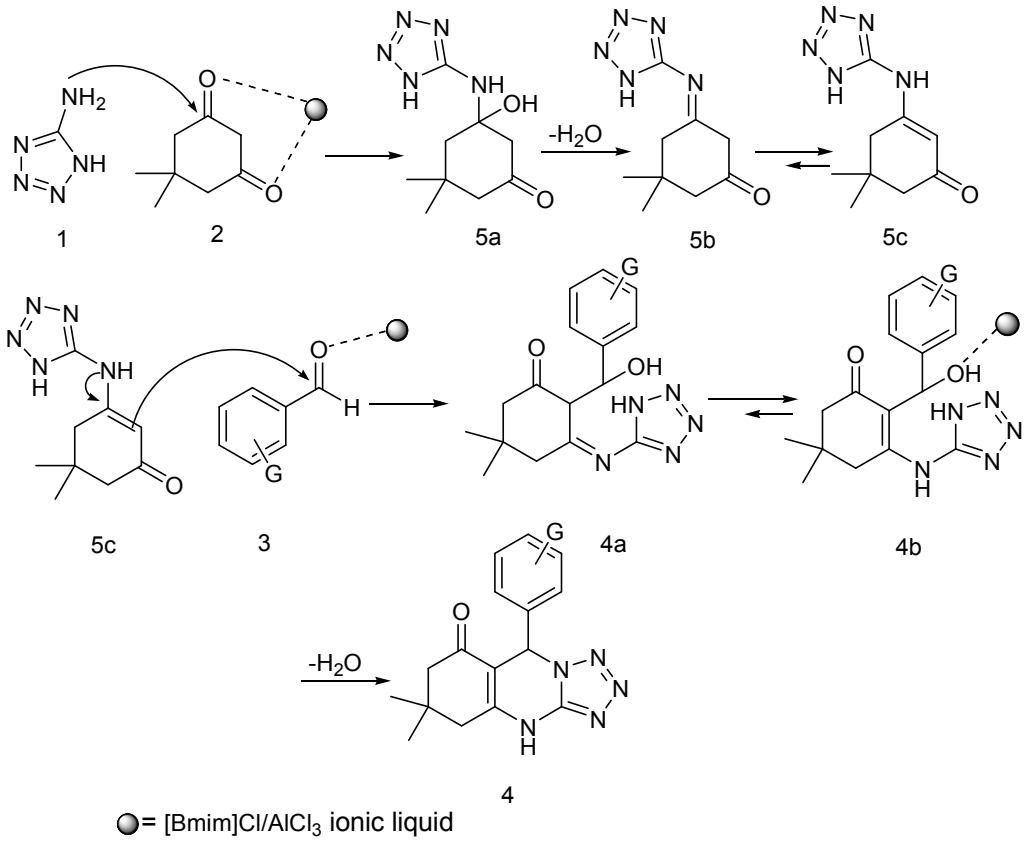
Due to the success of the above-mentioned pilot reaction, we explored the scope and limitations of this promising reaction by varying the structures of the benzaldehyde component. As demonstrated in Table 2, the reactions proceed very cleanly under mild conditions, and no undesirable side reactions were observed under these reaction conditions. Diverse starting material was tested in this study. In almost all of the cases, this protocol gave excellent results at 80°C. The generality of this three-component one-pot synthesis of tetrazolo[1,5-a]quinazoline derivatives is well illustrated with structurally diverse aldehydes. The reaction proceeded smoothly and equally well for electron-withdrawing as well as electron-donating aldehydes to afford the corresponding products in high to excellent yields. All known products have been reported previously in the literature and were characterized by comparison of their spectral (IR and NMR) and physical data with those of authentic samples. [23-28].

Table 2. Synthesis of tetrahydrotetrazolo[1,5-a]quinazolines using [Bmim]Cl/$AlCl_3$.

Entry	Ar	Time (min)	Yield (%)[a]	Melting Point (°C)	Reported Melting Point(°C) [Ref]
1	C_6H_5	30	92	>270	>270 [28]
2	4-Br-C_6H_4	35	95	250-253	246–249[28]
3	4-NO_2-C_6H_4	40	91	248-250	248-250 [28]
4	2-NO_2-C_6H_4	40	92	262-264	262-264 [28]
5	2-Cl-C_6H_4	30	93	>270	>270 [28]
6	4-Cl-C_6H_4	35	95	257-258	259–260 [23]
7	2-Me-C_6H_4	30	90	276–277	277–279[23]
8	3-Me-C_6H_4	30	92	231–232	232–233 [23]
9	2,4-Cl_2-C_6H_3	40	94	>270	280–281[23]
10	3-Br-C_6H_4	30	95	241-242	243-244 [23]
11	3-NO_2-C_6H_4	30	95	>270	>270 [28]

[a]Yields refer to isolated pure products

The proposed mechanism for the reaction is shown in Scheme 2. Initially, intermolecular enamine formation from 5-aminotetrazole (1) and dimedone (2) promoted by the [Bmim]Cl/$AlCl_3$ ionic liquid occurs. The amino groups of third nucleophilic center in 5- aminotetrazole attack the carbonyl group of dimedone with elimination of H_2O leading to enamine intermediates (5a-c). After this step, the other NH group of the 5- aminotetrazole attacks the carbonyl group of aldehyde (3), which is itself activated by the catalyst to form intermediate (4a-b). Finally, the six-membered ring products 4 are afforded via intramolecular cyclization of (4b).



Scheme 2. The proposed reaction mechanism for the synthesis of product.

Conclusion

In summary, we have developed a new, efficient and green procedure for the synthesis of tetrahydrotetrazolo[1,5-*a*]quinazoline derivatives by using a 1-Butyl-3-Methylimidazolium Tetrachloroaluminate [Bmim]Cl/$AlCl_3$ ionic liquid. The protocol has several advantages over previously reported methods for the synthesis of heterocyclic compound containing tetrahydrotetrazolo[1,5-*a*]quinazolines. These include the use of a one-pot MCR strategy, an environmentally-benign [Bmim]Cl/$AlCl_3$ ionic liquid, a simple and easy work-up, mild reaction conditions, a clean procedure, short reaction times, high-to-excellent yields and high atom economy.

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