Groebke-Blackburn-Bienaymé Multicomponent Reaction Catalysed by Reusable Brϕnsted-Acidic Ionic Liquids

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Abstract: In the present work, the use of Brϕnsted acidic ionic liquids (BAIL) as catalysts for Groebke-Blackburn-Bienaymé (GBB) multicomponent reactions was systematically investigated. A series of four 1-(butyl-4-sulfonic)-3-methylimidazolium salts bearing different anions was easily prepared and screened as acidic catalysts for this transformation. The best reaction conditions were stablished as 20 mol% of catalyst [$(SO_3H)^4C_4C_1Im$][OTf] in refluxing EtOH or MeOH under conventional heating and in sealed tube at 150ºC for 1-4 hours under microwave heating, affording a series of imidazo-fused heterocycles in moderate to excellent yields (42-93%). The homogeneous BAIL catalyst could be recycled and reused in four consecutive reaction cycles, despite of a laborious recovery procedure employed. This approach represents the first example of a task-specific reusable homogeneous Brϕnsted acidic catalyst in GBB reactions and opens new opportunities for the exploration of acidic ionic liquid phases as catalysts for this fascinating multicomponent reaction.

Introduction

The exploration of chemical space in order to find bioactive molecules and lead compounds for drug development has been mostly carried out based on scaffolds of known bioactive small molecules, either synthetic or natural products.[1–3] Undoubtedly, Nature is a wonderful source of inspiration but lead-like chemical space can also be prospected using synthetic approaches that enable the combinatorial variation of chemical features to explore complex and functionally diverse scaffolds. However, according to MacLellan and Nelson,[4] exploration of chemical space has been somewhat timid as only 0.25% of known molecular scaffolds gives rise to all compounds known to date. In order to boost the exploration of lead-like chemical space, chemists must develop new efficient synthetic approaches to prepare chemical libraries of potential biologically active molecules.

Multicomponent reactions (MCR) are very atom-efficient transformations between three or more reactants in the same reaction flask, useful for the rapid and efficient generation of chemical libraries with high levels of molecular complexity and diversity.[5] In theory, through the careful combination of specific sets of reagents in tricomponent reaction (3-CR), tetra component (4-CR) or even higher order multicomponent reactions (planned as isolated or sequential approaches),[6–8] organic chemists are able to reach specific regions in the vastness of chemical space and ultimately find druggable lead-like scaffolds.

The Groebke-Blackburn-Bienaymé (GBB) reaction[9–11] is an isocyanide-based multicomponent reaction related to the Ugi 4-CR,[12] useful for the synthesis of imidazo-fused heterocycles.[13,14] This fascinating multi-bonding-forming and highly atom-efficient reaction can be catalysed by different catalysts, either acidic or basic, displaying a broad substrate scope regarding the amidines (2-aminoazines), aldehydes and isocyanides used as starting materials.[15] When 2-aminopyridines are used as amidine components, the products are imidazo[1,2-*a*]pyridines,[16] heterocyclic compounds recognized as privileged scaffolds for drug discovery and development, displaying several interesting biological properties.[17,18] Representative examples include Alpidem (anxiolytic), Saripidem (sedative) and Zolpidem (hypnotic). In general, GBB reactions can be efficiently catalysed by different Lewis acids such as $Sc(OTf)_3$,[19–23] $Yb(OTf)_3$,[24–26] $In(OTf)_3$,[27–30] $Gd(OTf)_3$,[31] $InCl_3$,[32] $BiCl_3$,[33,34] $RuCl_3$,[35] $FeCl_3$,[36] $ZnCl_2$,[37] $ZrCl_4$,[38,39] $CeCl_3.7H_2O$,[40] and $LaCl_3.7H_2O$,[41] among others. In addition, the use of ordinary Brϕnsted acids, such as $HClO_4$,[42–44] PTSA,[45,46] AcOH,[47,48] HCl,[49,50] TFA,[51] NH_4Cl,[52] $ClCH_2CO_2H$,[53] as well as SiO_2/H_2SO_4,[54] are also reported in the literature.

Acidic ionic liquids are task-specific ionic liquids (TSILs) able to catalyse organic reactions due to their Lewis and/or Brϕnsted acidic properties.[55] More specifically, Brϕnsted-acidic ionic liquids (BAILs) are ionic compounds bearing ionizable protons which can be directly bound to both the cation and/or the anion. More commonly, the acidic functional groups (*e.g.* SO_3H, CO_2H) are

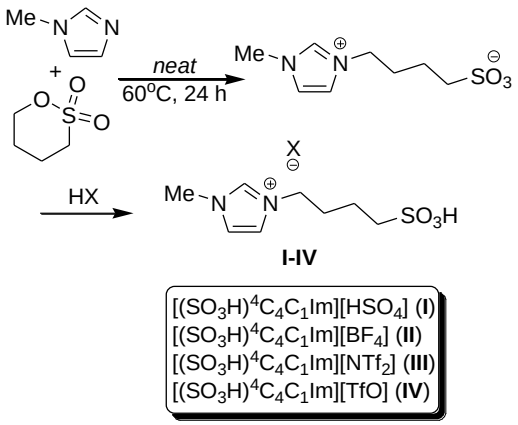
attached to the alkyl side chain of the cation. BAILs have been described as efficient acidic catalysts for several organic transformations, including multicomponent reactions.[56] Recently, we reviewed the use of sulfonic acid-functionalized TSILs as homogeneous and heterogeneous catalysts for MCRs.[57] For example, enantioselective Biginelli MCR for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones can be efficiently catalysed by chiral TSIL composed by a functionalized dialkyl imidazolium cation and a chiral phosphoric acid anion, in a very efficient asymmetric counter anion-directed catalytic approach.[58] Also, BAILs have been recently reported as catalysts for the multicomponent synthesis of dihydropyrido[2,3-*d*]pyrimidines,[59] 5-dihydro-2*H*-pyrrol-2-ones,[60] and dihydropyrano[2,3-*c*]pyrazoles,[61] among several other important heterocyclic scaffolds.[57]

The combination of the synthetic advantages of multicomponent reactions (*i.e.* atom-efficiency, high molecular diversity and complexity, waste reduction, and operational simplicity) with the fine-tuned properties of ionic liquids can offer many possibilities for the development of eco-friendly heterocyclic synthetic approaches.[62] Nevertheless, the use of ionic liquids in GBB reactions, either as reaction media or catalyst, is relatively rare and only few examples describing the use of guanidinium ionic liquids and ordinary 1-butyl-3-methylimidazolium bromide are reported in the literature.[63,64]

In line with our interest in the development of sustainable multicomponent synthesis and the exploration of TSILs as catalysts for challenging organic transformations, we describe herein the first approach on the use of homogenous Brϕnsted-acidic ionic liquids as reusable catalysts for Groebke-Blackburn-Bienaymé multicomponent reaction applied to the synthesis of imidazo-fused heterocycles (*e.g.* imidazo[1,2-*a*]pyridines and imidazo[1,2-*b*]thiazoles).

Results and Discussion

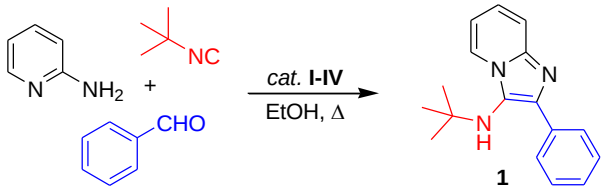
Our initial efforts were directed towards the preparation of the Brϕnsted acidic ionic liquid catalysts based on the 1-(butyl-4-sulfonic)-3-methylimidazolium cation – $[(SO_3H)^4C_4C_1Im][X]$ **I-IV**, where X = HSO_4^-, BF_4^-, NTf_2^- and TfO^- – using standard procedures described in the literature.[65–68] Firstly, 1-methylimidazole reacted with 1,4-butanesultone to give the corresponding zwitterion in nearly quantitative yield. Further neutralization with equimolar amounts of different acids furnished the catalysts **I-IV** (Scheme 1).



Scheme 1. Preparation of Brϕnsted-acidic ionic liquid catalysts **I-IV**.

The catalytic activity of I-IV was evaluated using a GBB model reaction between 2-aminopyridine, benzaldehyde and tert-butyl isocyanide to afford the imidazo[1,2-a]pyridine 1 (Table 1). The uncatalysed reaction in refluxing EtOH during 24 hours furnished 1 in only 16% yield (entry 1). However, when the Br□nsted-acidic ionic liquids catalysts I-IV (different loadings) were introduced into the reaction medium, the desired product 1 was obtained in variable higher yields. The best catalyst loading was 20 mol%, as indicated by the control experiments carried out with catalyst I (entries 2-4). The nature of the anion seemed to have negligible impact on the reaction productivity, since all reactions using 20 mol% of catalysts I-IV led to 1 in the yield range from 63 to 68% (entries 4-7).

Table 1. Optimization of the BAIL-catalysed GBB reaction conditions.[a]



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Entry	Catalyst	Loading (mol%)	Time (h)	Yield (%)[b]
1	—	—	24	16
2	$[(SO_3H)^4C_4C_1Im][HSO_4]$ (**I**)	5	4	55
3	$[(SO_3H)^4C_4C_1Im][HSO_4]$ (**I**)	10	4	57
4	$[(SO_3H)^4C_4C_1Im][HSO_4]$ (**I**)	20	4	63
5	$[(SO_3H)^4C_4C_1Im][BF_4]$ (**II**)	20	4	64
6	$[(SO_3H)^4C_4C_1Im][NTf_2]$ (**III**)	20	4	69
7	$[(SO_3H)^4C_4C_1Im][OTf]$ (**IV**)	20	4	68
8	$[(SO_3H)^4C_4C_1Im][HSO_4]$ (**I**)	20	15	65
9	$[(SO_3H)^4C_4C_1Im][HSO_4]$ (**I**)	20	24	68
10	**$[(SO_3H)^4C_4C_1Im][OTf]$ (IV)**	**20**	**24**	**71**

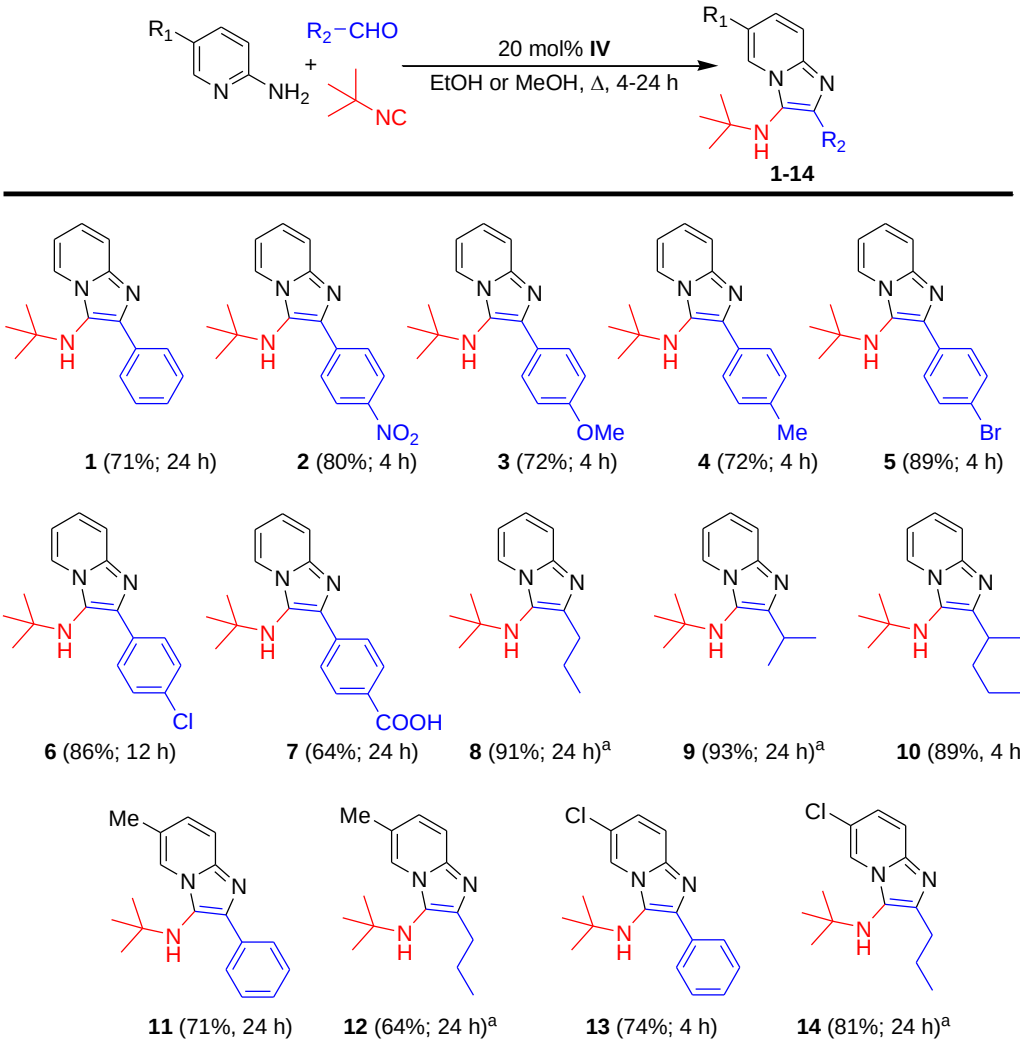
[a] ***Reagents and conditions:*** 2-aminopyridine (1.0 mmol), *tert*-butyl isocyanide (1.0 mmol), benzaldehyde (1.0 mmol), catalysts $[(SO_3H)^4C_4C_1Im][X]$ **I-IV** (different loadings in mol%), absolute EtOH (6 mL), reflux; [b] Isolated yields.

Higher yields were observed when catalysts **III** and **IV**, bearing $[NTf_2]$ and [OTf] as counter anions, respectively, were used in refluxing EtOH for 4 or 24 hours (entries 6 and 10). Given the high cost of bis(trifluoromethane)sulfonamide superacid ($HNTf_2$) used in the preparation of **III**, catalyst **IV** was selected to proceed with the study of the substrate scope.

With optimal conditions stablished for the model BAIL-catalysed GBB reaction (Table 1; method A), substrate scope was further investigated in order to explore the reactivities of the carbonyl compound (aldehyde) and the 2-aminoazine components, using the commercially available *tert*-butyl isocyanide.

Due to the reasons mentioned so far, the catalyst $[(SO_3H)^4C_4C_1Im][OTf]$ (**IV**) was chosen for the construction of the chemical library of imidazo[1,2-*a*]pyridines **1-14** shown in Scheme 2. Several aromatic *para*-substituted benzaldehydes, bearing different electron-withdrawing and electron-donating groups, led to the expected imidazo[1,2-*a*]pyridines in good to excellent yields (**1-7**; 64-89%). For example, when 2-aminopyridine, *tert*-butyl isocyanide and *p*-nitrobenzaldehyde were refluxed in EtOH with 20 mol% of **IV** for 24 h, the product **2** was obtained in 80% yield. Similarly, the reaction with *p*-anisaldehyde under similar conditions led to **3** in 72% yield. The reactivity of aliphatic aldehydes was also assessed. However, the reactions using the volatile butyraldehyde or isobutyraldehyde were carried out in refluxing MeOH (temperature *ca.* 65ºC) in order to avoid loss of starting materials by evaporation and, as a consequence, lowering the yields. Indeed, the reaction of 2-aminopyridine, *tert*-butyl isocyanide and butyraldehyde or isobutyraldehyde in refluxing MeOH with 20 mol% of catalyst **IV** for 24 hours led to the imidazo[1,2-*a*]pyridines **8** and **9** in excellent yields (91% and 93%, respectively). Likewise, the reaction with aliphatic cyclohexane carboxaldehyde led to the desired product **10** in 89% yield.

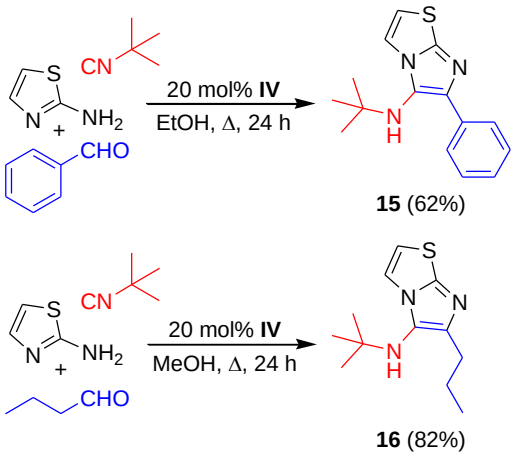
The variation of the 2-aminoazine component was further examined. We focused our attention on the use of 5-substituted 2-aminopyridines, and the reaction of 6-amino-3-picoline (2-amino-5-methylpyridine) with *tert*-butyl isocyanide and benzaldehyde or butyraldehyde, under standard conditions described so far, led to imidazo[1,2-*a*]pyridines **11** and **12** in 71% and 64% yields, respectively. When 2-amino-5-chloropyridine was reacted with *tert*-butyl isocyanide and benzaldehyde or butyraldehyde, the expected products **13** and **14** were obtained in slightly higher yields (74% and 81%, respectively).



Scheme 2. Substrate scope for the BAIL-catalysed GBB 3-CR for the synthesis of imidazo[1,2-*a*]pyridines (**1-14**). ***Reagents and conditions:*** Method A: 2-aminoazine (1.0 mmol), *tert*-butyl isocyanide (1.0 mmol), aldehyde (1.0 mmol), 20 mol% of $[(SO_3H)^4C_4C_1Im][OTf]$ (**IV**), absolute EtOH or MeOH (6 mL), reflux, 4-24 hours (isolated yields); [a] refluxing MeOH was used in these reactions**.**

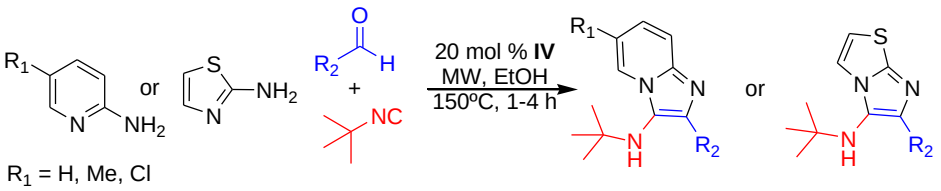
The use of 2-aminothiazole as amidine component to access imidazo[2,1-*b*]thiazoles was further explored. The synthesis of this heterocyclic scaffold via GBB methodology has been relatively less exploited, compared to the widely studied imidazo[1,2-*a*]pyridines.[15] Electron-poor 2-aminoazines, such as 2-aminothiazole and others, have been described as less efficient nucleophiles for GBB reactions, often leading to lower conversions and long reaction times.[11,69] We have recently demonstrated that $Gd(OTf)_3$ can be an efficient catalyst for the GBB synthesis of imidazo[2,1-*b*]thiazoles under microwave heating, and the reaction productivity seem to be mainly related to the aldehyde reactivity, being aliphatic aldehydes more reactive than aromatic aldehydes.[31] The same behaviour was observed in the preliminary study of the BAIL-catalysed GBB reaction between 2-aminothiazole, *tert*-butyl isocyanide and benzaldehyde or butyraldehyde. When the reactions were carried out using 20 mol% of catalyst **IV** in refluxing alcohol, the imidazo[2,1-*b*]thiazoles **15** or **16** were isolated in 62% and 82% yield, respectively (Scheme 3). Notably, longer reaction times did not improve the yields obtained for compounds **15** or **16**.

Over the last years, microwave-assisted multicomponent reactions have gained popularity as alternative approaches for conventional thermal synthetic methodologies.[70,71] Using microwave irradiation as unconventional heating source may benefit the reaction outcome because of uniform dielectric heating distribution coefficients, upon the right choice of high polar solvents. This often results in higher conversions, increasing in reaction rates and shortening of reaction times as well as lower byproduct formation, thus overall increasing yield and efficiency.[72,73]



Scheme 3. Synthesis of imidazo[2,1-*b*]thiazoles **15** and **16** using BAIL-catalysed GBB 3-CR. ***Reagents and conditions:*** Method A: 2-aminothiazole (1.0 mmol), *tert*-butyl isocyanide (1.0 mmol), aldehyde (1.0 mmol), 20 mol% of $[(SO_3H)^4C_4C_1Im][OTf]$ (**IV**), absolute EtOH or MeOH (6 mL), reflux, 24 hours (isolated yields).

Table 2. GBB 3-CR catalysed by catalyst $[(SO_3H)^4C_4C_1Im][OTf]$ (**IV**) under microwave heating.[a]



Entry	Aminoazole	Aldehyde (R_2)	Time (h)	Product (yield)[b]
1	2-aminopyridine	C_6H_5	1	**1** (83%)
2	2-aminopyridine	4-OMe-C_6H_4	1	**3** (86%)
3	2-aminopyridine	4-Me-C_6H_4	1	**4** (86%)
4	2-aminopyridine	4-COOH-C_6H_4	2	**7** (67%)
5	2-amino-5-methylpyridine	C_6H_5	1	**11** (74%)
6	2-amino-5-methylpyridine	nC_3H_7	1	**12** (54%)
7	2-amino-5-chloropyridine	C_6H_5	1	**13** (79%)
8	2-aminothiazole	C_6H_5	3	**15** (58%)
9	2-aminothiazole	4-NO_2-C_6H_4	3	**17** (56%)
10	2-aminothiazole	4-OMe-C_6H_4	3	**18** (59%)
11	2-aminopyridine	*trans*-crotonaldehyde	4	**19** (42%)
12	2-aminopyridine	*trans*-cinnamaldehyde	4	**20** (86%)

[a] ***Reagents and conditions:*** Method B: 2-aminoazole (1.0 mmol), *tert*-butyl isocyanide (1.0 mmol), aldehyde (1.0 mmol), 20 mol% of $[(SO_3H)^4C_4C_1Im][OTf]$ (**IV**), absolute EtOH (1,5 mL), 150ºC, 1-4 h; all reactions were performed in a sealed tube under microwave irradiation using MONOWAVE 300. [b] Isolated yields

As some of the reactions showed in Schemes 2 and 3 led to the desired imidazo-fused heterocycles in moderate yields (lower than 75%), the catalytic efficiency of catalyst **IV** in GBB 3-CR reactions under microwave heating was further investigated (Table 2, method B). Based on a previous study of our group on the $Gd(OTf)_3$-catalysed GBB reaction under microwave heating,[31] we started with the model reaction between 2-aminopyridine, benzaldehyde and *tert*-butyl isocyanide using 20 mol% of **IV** in EtOH at 150ºC (MW) for 1 hour (Table 2, entry 1). This reaction led to the desired product **1** in 83% yield, higher than 71% yield observed

when thermal conventional heating was used (Scheme 2). In general, higher yields were obtained when using the optimized conditions for the microwave-assisted GBB 3-CR catalysed by **IV**. However, moderate yields were obtained for imidazo[1,2-*a*]pyridine **12** and imidazo[2,1-*b*]thiazoles **15**, **17** and **18** (entries 6 and 8-10, respectively). At this point, we also explored the reactivity of unsaturated aldehydes such as *trans*-crotonaldehyde and *trans*-cinnamaldehyde which upon reaction with 20 mol% of **IV** in EtOH at 150ºC (MW) for 4 hours led to the expected products **19** and **20** in 42% and 86% yield, respectively (entries 11 and 12). It must be highlighted that all GBB reactions carried out in the microwave reactor were faster than those performed under conventional heating.

Next, we examined the reactivity of the isocyanide component in the BAIL-catalysed microwave-assisted reactions (method B). At this point, it is worthy to mention that Boltjes and Dömling recently published a comprehensive survey on the reactants, catalysts and reaction conditions for GBB 3-CR.[15] The isocyanide scope is quite broad and, despite the fact that approximately a hundred different isocyanides have been investigated so far, this component does not seem to impose limitations to the method. In our tests, no significant conversion differences were observed when tertiary (*tert*-butyl), secondary (cyclohexyl) or primary (1-pentyl) isocyanides were used in combination with 2-aminopyridine and benzaldehyde. Thus, the expected imidazo[1,2-*a*]pyridines **1**, **21** and **22** were obtained in 83%, 87% and 88% isolated yields, respectively (Figure 1). Similarly, the use of benzyl isocyanide and 2-morpholinoethyl isocyanide led to products **23** and **24** in good yields (83% and 85%, respectively). The reactivity of α-acidic isocyanides was also studied with methyl and ethyl isocyanoacetates, which furnished **25** and **26** in 70% and 83% yields, respectively. It worthy to mention that reaction of 2-aminopyridine, benzaldehyde and methyl isocyanoacetate was carried out using methanol as solvent (instead of ethanol) to avoid transesterification side products.

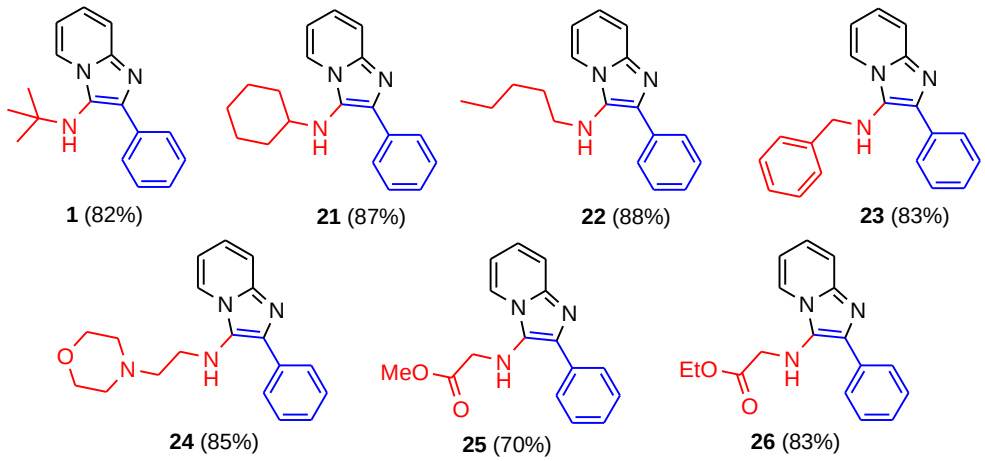


Figure 1. ***Reagents and conditions:*** Method B: 2-aminopyridine (1.0 mmol), isocyanide (1.0 mmol), aldehyde (1.0 mmol), 20 mol% of $[(SO_3H)^4C_4C_1Im][OTf]$ (**IV**), absolute EtOH (1,5 mL), MW, 150ºC, 1-2 h (isolated yields). Compound **25** was prepared using MeOH as solvent.

The recovery and reuse of the catalyst was also evaluated for the model reaction of 2-aminopyridine, *tert*-butyl isocyanide and benzaldehyde using 20 mol% of **IV** in EtOH at 150ºC under microwave heating (Table 3). After completion of the reaction, the solvent was removed under reduced pressure and the crude mixture was then dissolved in dichloromethane (10 mL) and extracted with ultrapure water (3 x 5 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the imidazo[1,2-*a*]pyridine **1** in 83% yield (first cycle). The combined aqueous extracts, containing the catalyst $[(SO_3H)^4C_4C_1Im][OTf]$ (**IV**), were then concentrated firstly using rotatory evaporator followed by drying under high vacuum at 60ºC overnight at pressures ~ 10^{-2} mbar. ^{1}H NMR analysis of the recovered catalyst **IV** confirmed its suitable purity to be used in the next reaction cycles. Using this optimized protocol, the catalyst **IV** could be reused at least in four consecutive cycles, although a drop in the yield of **1** was observed in the third cycle (entry 3). It is noteworthy that this recycling procedure is somewhat tedious, with the need of long drying process of catalyst under reduced pressure. Also, it seems that part of the acidic ionic liquid **IV** is lost throughout the steps, thus resulting in lower yields of the desired product over consecutive reaction cycles.

Several different homogeneous Brϕnsted acids have been reported to be efficient catalysts for GBB multicomponent reactions applied to the synthesis of imidazo[1,2-*a*]pyridines (Table 4). Ordinary inorganic acids such as $HClO_4$[42,43] and HCl[50] can be used as catalysts for GBB 3-CR, either at room temperature or under microwave heating (entries 1, 2 and 6). However, it must be recognized the explosive nature of perchloric acid and the disadvantage of the non-green dioxane used in HCl-catalysed reactions. Similarly, GBB reactions catalysed by simple organic acids such as PTSA[45,46] and AcOH[48] are also described elsewhere, although in stoichiometric quantities or at high catalyst loadings (entries 3-5).

Very recently, de la Sovera et al.[51] described the use of TFA as catalyst for GBB reactions to explore the synthetic utility of 5-hydroxymethylfurfural as carbonyl component. Thus, a series of (5-hydroxymethylfuran-2-yl)imidazo[1,2-*a*]pyridines was obtained in variable yields, when 20 mol% of TFA was used in EtOH at 60ºC for 2 hours (entry 7).

The merit and innovation of our method relies on the practical implementation of the Brϕnsted-acidic ionic liquid [$(SO_3H)^4C_4C_1Im$][OTf] (**IV**) as catalyst for GBB 3-CR. The preparation of the BAIL catalyst is straightforward and the reaction can be conveniently carried out under thermal or microwave heating. Moreover, catalyst **IV** can be recycled and reused in consecutive reaction cycles with no significant loss in activity (Table 4, entry 10). These features are unprecedented for a homogeneous acidic catalyst in this multicomponent reaction.

Finally, we scaled up to a gram-scale the reaction between 2-aminopyridine, *tert*-butyl isocyanide and benzaldehyde, which efficiently furnished pure imidazo[1,2-*a*]pyridine **1** in 85% isolated yield, after two consecutive recrystallization steps using dichloromethane and petroleum ether (Scheme 4).

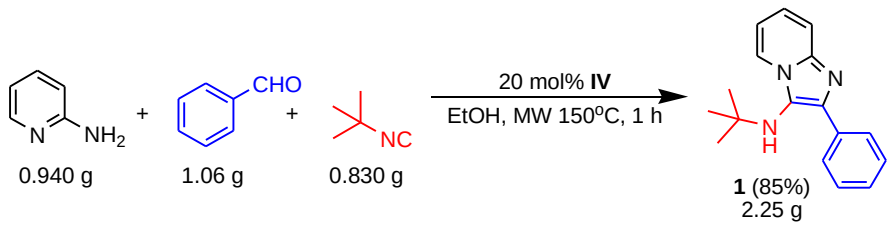
Table 3. Recyclability of the catalyst [$(SO_3H)^4C_4C_1Im$][OTf] (**IV**) used in GBB 3-CR under microwave heating for the synthesis of imidazo[1,2-*a*]pyridine **1**.[a]

Entry	Cycle	Yield (%)[b]
1	First	83
2	Second	81
3	Third	73
4	Forth	72

[a] ***Reagents and conditions:*** Method B: 2-aminopyridine (1.0 mmol), *tert*-butyl isocyanide (1.0 mmol), benzaldehyde (1.0 mmol), 20 mol% of [$(SO_3H)^4C_4C_1Im$][OTf] (**IV**), absolute EtOH (1,5 mL), 150ºC, 1 h; all reactions were performed in a sealed tube under microwave irradiation using MONOWAVE 300 reactor. [b] Isolated yields

Table 4. Synthesis of imidazo[1,2-*a*]pyridines by GBB 3-CR catalysed by different homogeneous Brϕnsted acidic catalysts.

Entry	Catalyst	Conditions	Examples (yield range)	Reference
1	5 mol% $HClO_4$	MeOH, r.t., 0.5-24 h	13 examples (30-80%)	Tber et al.[42]
2	5 mol% $HClO_4$	MeOH, r.t., 4 h	22 examples (22-70%)	Arnould et al.[43]
3	52 mol% PTSA	MeOH, r.t., 2 h	10 examples (88-97%)	Shaabani et al.[45]
4	20 mol% PTSA	MeOH, r.t., 18 h	7 examples (65-93%)	Tyagi et al.[46]
5	1 - 2 eq. AcOH	MeOH, r.t., 18 h	17 examples (24-80%)	Hieke et al.[48]
6	4 N HCl	Dioxane, MW, 100ºC, 20 min	9 examples (yields not given)	Salunke et al.[50]
7	20 mol% TFA	EtOH, 60ºC, 2 h	14 examples (8-87%)	de la Sovera et al.[51]
8	1 eq. NH_4Cl	MeOH, r.t., 3 h	10 examples (60-96%)	Ahmad et al.[52]
9	25 mol% $ClCH_2CO_2H$	MeOH, MW, 100ºC, 1h	16 examples (61-98%)	Basavanag et al.[53]
10	20 mol% [$(SO_3H)^4C_4C_1Im$][OTf] **IV**	MeOH or EtOH, reflux, 4-24 h (method A) or EtOH, MW, 150ºC 1-4 h (method B)	22 examples (42-93%) **Reuse: 4 cycles**	Present work



Scheme 4. BAIL-catalysed GBB 3-CR in gram-scale. ***Reagents and conditions:*** 2-aminopyridine (10.0 mmol), *tert*-butyl isocyanide (10.0 mmol), benzaldehyde (10.0 mmol), 20 mol% of [$(SO_3H)^4C_4C_1Im$][OTf] (**IV**), absolute EtOH (15mL), 150ºC, MW, 1 hour

Conclusion

In this study, we described for the first time the Groebke-Blackburn-Bienaymé tricomponent reaction catalysed by reusable Brϕnsted-acidic ionic liquids. A series of four 1-(butyl-4-sulfonic acid)-3-methylimidazolium-based salts, bearing different anions such as HSO_4^-, BF_4^-, NTf_2^- and TfO^-, was synthesized and screened as acidic catalyst for the title reaction. The 1-(butyl-4-sulfonic acid)-3-methylimidazolium trifluoromethane sulfonate (**IV**) was selected as the most efficient catalyst. The optimized method was applied to the synthesis of a series of imidazo[1,2-*a*]pyridines and imidazo[1,2-*b*]thiazoles in moderate to excellent yields (ranging from 42% to 93%), either under thermal or microwave heating. As expected, the substrate scope regarding the aminoazole, the aldehyde and the isocyanide seems to be quite broad, in accordance with general findings from other systematic investigations.[15] In addition, the homogeneous Brϕnsted-acidic ionic liquid **IV** could be recycled and reused in four reaction cycles, although with a slightly decline in the reaction productivity.

This seems to be a result of tedious and laborious recycling procedures for the recovery of the catalyst that hampered reaction efficiency in consecutive cycles. In this scenario, one can take advantage from the heterogenization of the Brϕnsted-acidic ionic liquid phase, making the recycling process straightforward and easier.[74–76] The direct linkage of the imidazolium cation to a polystyrene resin, using standard techniques applied to the synthesis of polymer-supported Brϕnsted-acidic ionic liquid phases (PS-BAILs),[75] is now under investigation in our laboratory. The new PS-BAILs thus obtained may be useful catalysts for GBB 3-CR in order to access expanded chemical libraries comprising of different imidazo-fused heterocycles (mainly through the variation of the 2-aminoazine component). Further results will be published in due course.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Experimental Section

General Methods. All reagents used in this study were obtained from common commercial suppliers and used without further purification, unless otherwise stated. ***Caution:*** isocyanides are harmful reagents! All reactions must be carried out inside the fume hoods with appropriate ventilation. The ultrapure water used in this work was Millipore Milli-Q (*ca*. 18 MΩ). Melting points of all compounds were determined using a Buchi 545 MP apparatus and are uncorrected. Column chromatography was performed using silica gel (pore size 60 Å, 230-400 mesh). Thin layer chromatography (TLC) analyses were carried out using silica gel plates 60 F254 from Merck®, and UV-light, vanillin or *p*-anisaldehyde solutions for visualization. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at room temperature on Bruker DPX300, DPX400 or AV400 spectrometers, using D_2O, DMSO-d_6, CD_3OD or $CDCl_3$ as solvents. Chemical shifts (δ) are expressed in ppm and referenced to the residual solvent peak; coupling constants are expressed in hertz (Hz). High resolution mass spectrometry (HRMS) analyses were carried out using a Bruker MicroTOF 61 spectrometer [electrospray ionization method, ESI(+)]. Microwave experiments were performed using MONOWAVE 300 reactor (Anton Paar®), operating at 2.455 GHz frequency with continuous irradiation power from 0 to 300 W. The reactions were carried out in borosilicate glass vials sealed with Teflon septum (manufacturer design). All described reaction times reflect the irradiation time at the set reaction temperature (variable power).

General procedure for the Groebke-Blackburn-Bienaymé reaction catalysed by [$(SO_3H)^4C_4C_1$Im][OTf] (IV) under conventional heating (Method A). A mixture of 2-aminoazine (1.00 mmol), aldehyde (1.00 mmol), isocyanide (1.00 mmol) and the catalyst [$(SO_3H)^4C_4C_1$Im][OTf] (**IV**) (20 mol%) was dissolved in absolute EtOH or MeOH (6 mL) and refluxed for the time specified in Schemes 2 and 3. Upon completion of the reaction, as indicated by TLC analysis of the crude mixture (eluent: hexane/EtOAc 1:1 v/v), the mixture was concentrated by removal of the solvent under reduced pressure, followed by the addition of water (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product which was purified by column chromatography (eluent: 0-50% v/v EtOAc in hexane; gradient elution), furnishing the imidazo-fused heterocycles in the yields shown in Schemes 2 and 3.

General procedure for the Groebke-Blackburn-Bienaymé reaction catalysed by [$(SO_3H)^4C_4C_1$Im][OTf] (IV) under microwave heating (Method B). In G10 vial (Anton Paar design), a mixture of 2-aminoazine (1.00 mmol), aldehyde (1.00 mmol), isocyanide (1.00 mmol) and the catalyst [$(SO_3H)^4C_4C_1$Im][OTf] (**IV**) (20 mol%) was dissolved in absolute EtOH (3 mL). The vial was sealed with a Teflon septum and the reaction mixture was stirred (600 rpm) at 150ºC under microwave heating (variable power), during the time specified in Table 2. Upon completion of the reaction, as indicated by TLC analysis (eluent: hexane/EtOAc 1:1 *v/v*), the mixture was concentrated by removal of the solvent under reduced pressure, followed by the addition of water (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product which was purified by column chromatography (eluent: 0-50% v/v EtOAc in hexane; gradient elution), furnishing the imidazo-fused heterocycles shown in Table 2 and Figure 1.

General procedure for the recycling of catalyst [$(SO_3H)^4C_4C_1$Im][OTf] (IV). The recycling of the catalyst was carried out as following: after the reaction being carried out, either under conventional or microwave heating, the aqueous layer was concentrated in rotavapor (removing of water required temperatures of *ca.* 60ºC for approximately 2-3 hours) and the recovered ionic liquid was then dried *in vacuo* (pressure ~ 10^{-2} mbar) overnight at 60ºC. ^{1}H RMN analysis of the recovered catalyst [$(SO_3H)^4C_4C_1$Im][OTf] (**IV**) showed no degradation and suitable purity to be used in the next reaction cycle.

See Supporting Information for full characterization data and copies of NMR spectra of all compounds in this study.

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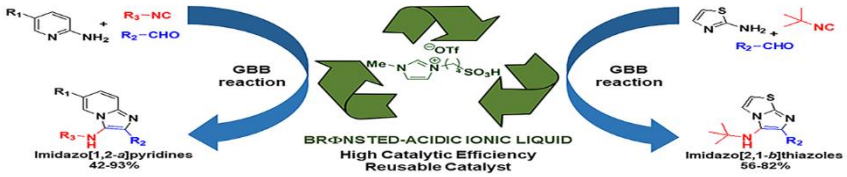

Groebke-Blackburn-Bienaymé multicomponent reactions can be efficiently catalysed by Brϕnsted acidic ionic liquids for the synthesis of imidazo[1,2-*a*]pyridines and imidazo[2,1-*b*]thiazoles in moderate to excellent yields (42-93%), either under thermal or microwave heating. The homogeneous acidic catalyst can be recycled and reused in four consecutive reaction cycles.