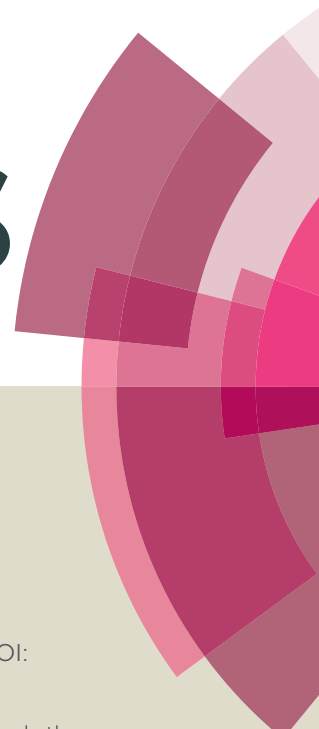


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Imidazolium-supported benzotriazole: An efficient and recoverable activating reagent for amide, ester and thioester bond formation in water⁵

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An efficient and recyclable imidazolium-supported benzotriazole reagent (Im-CH₂-BtH) as a novel synthetic auxiliary has been synthesized and its utility as carboxyl group activating reagent *via* the formation of stable imidazolium-supported acyl benzotriazoles was explored for the synthesis of amides, esters and thioesters in water under microwave conditions. The reagent was reused five times without any noticeable loss in activity. It is moisture insensitive and highly stable under thermal and aerobic conditions. The application of imidazolium-supported *N*-acetyl benzotriazole leads to synthesis of paracetamol on gram scale under greener conditions in 93% yield.

Introduction

Amide, ester and thioesters functionalities are highly desirable synthetic targets that form an integral component of numerous natural products and biologically active synthetic molecules. Amide bond itself accounts its presence in more than 25% of known drugs as per the Comprehensive Medicinal Chemistry (CMC) database analysis.¹ Amide and ester linkages are introduced as an essential component to synthetic drugs such as Procaine, Lidocaine, Tocainide to increase their metabolic stability.² These groups impose degradable character and good thermal and mechanical properties to biodegradable poly(ester amide)s (PEAs) polymers.³ Glycolamide esters of Aspirin,⁴ Ibuprofen,⁵ Niflumic acid,⁶ Scutellarin⁷ and Nimesulide⁸ have also been used as biolabile prodrugs due to their ability to undergo quick cleavage in human plasma. Similarly, thioesters have been extensively used in native chemical ligation for the synthesis of many biologically active small- and medium-sized peptides and proteins.⁹

Acid-activation as acyl halides, acyl azides, acylimidazoles, anhydrides, esters and acyl benzotriazoles, followed by nucleophilic substitution are among the most common strategies employed for construction of amide, ester and thioester bonds. *N*-Acylbenzotriazoles has surpasses most of the aforementioned reagents due to their relative stability, ease of formation, higher reactivity

and high yields of the *N*-, *S*- and *O*-acylated products.¹⁰ Katritzky's pioneer work on the applications of *N*-acylbenzotriazoles has led to the synthesis of libraries of novel peptides and peptidomimetics.¹¹ However, the *N*-acylbenzotriazole methodology suffers one or more hindrances in term of green chemistry perspective such as use of organic solvents in the acylation reaction, non-reusability of benzotriazole, and sometimes purification of the acylated product by column chromatography.¹² Efforts to overcome some of these drawbacks have been undertaken by Paio,^{13a} Showalter,^{13b} Fang^{13c} and Katritzky^{13d-e} leading to the synthesis of polymer-supported benzotriazole reagents. Although, polymer-supported benzotriazoles have overcome some of these limitations but they have their own issues such as low loading capacity, elaborate purification procedures, low swelling properties, limited solubility and scope of the reagents.¹³

In past decade, there has been a great attention on the synthesis of functionalized imidazolium-supported reagents and their use as alternative soluble support in solution-phase parallel synthesis¹⁴ and in facilitating the separation process (Figure 1).¹⁵

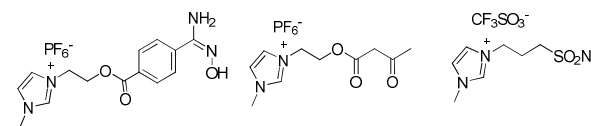


Figure 1 Some imidazolium-supported reagents used in organic synthesis

Tuneable chemical and physical properties, higher loading capacity, reactions under homogeneous conditions and use of conventional methods for the analysis of reaction progress has proved them as ideal support for the reagents¹⁶ in the synthesis of small molecule libraries,¹⁷ peptides,¹⁸ and oligosaccharides.¹⁹ With our interest in

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⁵ Dedicated to late Prof. A. R. Katritzky for his contribution to benzotriazole chemistry.

[†] Electronic Supplementary Information (ESI) available: ¹H & ¹³C NMR spectra of **4-6** and **8a-h**. Characterization data and ¹H NMR & ¹³C NMR spectra of **10aA-10hF**, **12aA-12gB**, **14aA-14gB**. DOI: 10.1039/x0xx00000x

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application of benzotriazole in acylation reactions and imidazolium-supported reagents we envisioned that supporting benzotriazole on imidazolium support can generate a soluble-supported benzotriazole auxiliary that can have high efficiency and can be easily recycled. In this article, we report synthesis of imidazolium-supported benzotriazole and its application as reusable carboxyl group activating reagent for amide, ester and thioester bond formation in aqueous media under microwave irradiation.

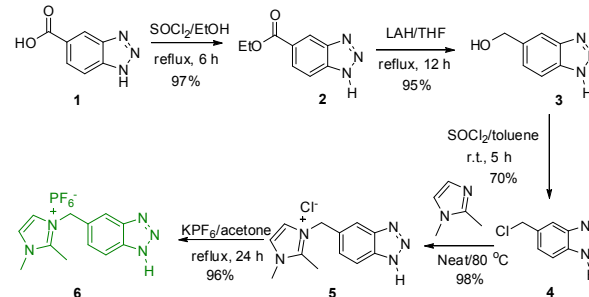
Results and discussion

Our work commenced with the synthesis of imidazolium-supported benzotriazole reagent connected via methylene linker (Im-CH₂-BtH, **6**) as depicted in Scheme 1. Esterification of commercially available benzotriazole-5-carboxylic acid (**1**), followed by reduction with lithium aluminium hydride (LAH) in THF yielded 5-hydroxymethylbenzotriazole (**3**).²⁰ Chlorination of **3** with thionyl chloride in toluene furnished 5-chloromethylbenzotriazole (**4**) in 70% as a single isomer. Reaction of **4** with 1,2-dimethylimidazole under solvent free heating condition afforded imidazolium methylene linked benzotriazole chloride salt (**5**), as a gummy product in 98% yield. Based on the ¹H NMR analysis, it was found that **5** is isomeric mixture of N¹- and N³-isomers with major amounts of N¹-isomer. It was used as such for the next step without further purification.

For tuning the solubility, the counter anion in **5** was exchanged with PF₆⁻ anion by reacting with KPF₆ in dry acetone under refluxing condition to yield methylene linked imidazolium benzotriazole potassium hexafluorophosphate (**6**) as a brown solid in 96% yield. Initially the exchange of Cl⁻ by PF₆⁻ was attempted in water at room temperature but the reaction never goes on completion and the product remains soluble along with **5** in water. On the other hand, the reaction goes to completion only on refluxing in dry acetone. The ¹H NMR of **6** indicated the presence of N¹- and N²-isomers in the ratio 2:1. Three characteristic singlet at δ 5.58, 3.76 and 2.64 for the methylene (2H), N-methyl (3H) and C-methyl (3H) protons were observed for N¹-isomer along with three singlets at δ 6.17, 3.66 and 2.44 for N²-isomer. Peaks for equivalent aromatic protons were observed in the region δ 7.37-8.07 in the ¹H NMR of **6**. We were successful in isolating N¹-isomer by recrystallization of the brown solid from methanol. Thus, the overall strategy provides a straight forward high yielding method for the synthesis of imidazolium-supported benzotriazole, avoiding protection and de-protection steps as usually required in polymer-supported benzotriazole synthesis.

The thermal stability profile of the synthesized reagent **6** was studied using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). The DSC experiment showed that the exothermic decomposition temperature of **6** is above 150 °C (Figure 2, left curve) with an initiation temperature of 151.81 °C and end point at 185.81 °C. We recommend the use of **6** well below its decomposition

temperature. It is worth mentioning that **6** has not shown any sign of decomposition or loss of reactivity even after storing for more than two month at room temperature. The TGA of **6** indicated the first weight loss to be around 254 °C and the full degradation centered around 366 °C (Figure 2, right curve) suggesting that **6** is thermally stable.



Scheme 1 Synthesis of imidazolium-supported benzotriazole (Im-CH₂-BtH) (**6**)

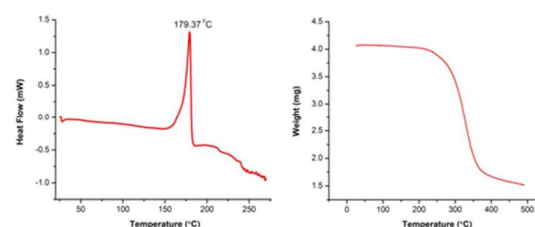


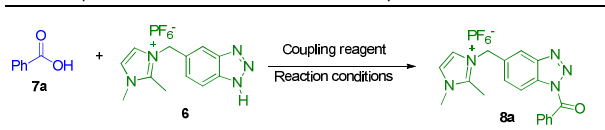
Figure 2 DSC and TGA curves for **6**.

After successful synthesis and characterization of **6**, we focused our attention to investigate the carboxylic acid activating capability of **6** to synthesize amides, esters and thioesters. Thus, we initially attempted the activation of benzoic acid (**7a**) with **6**. It is important to mention that initially the activation of **7a** was attempted with the reagent **5** (Im-CH₂-BtH, Cl⁻ salt), however due to difficulty in the weighing because of gummy nature of the reagent and comparatively lower reactivity, we switched to activation using **6** (Im-CH₂-BtH, PF₆⁻ salt).

Various coupling reagents viz. DCC, EDC.HCl, HBTU and HATU were screened in tetrahydrofuran (THF) and acetonitrile (CH₃CN) for the activation of benzoic acid (**7a**) with **6** (Table 1). Other polar solvents such as DMF and DMSO were discarded due to difficulty of removing them after the reaction. Among all the trials, DCC (1.2 eq.) in CH₃CN using a catalytic amounts of DMAP at room temperature gave best yield (75%) of imidazolium-supported N-benzoyl benzotriazole (**8a**) (Table 1, entry 3). A number of spots were visible on the TLC when the reaction was carried under refluxing conditions and subsequently leads to declination in the isolated yield of **8a** under similar experimental conditions (Table 1, entry 5) Interestingly due to high polarity of **8a**, the DCU was easily removed from the reaction mixture by simple washing with ethyl acetate and thereafter precipitation with methanol yielded **8a** as pure product. Catalytic amounts of DMAP was enough and

necessary for the reaction as its absence leads to tremendous decrease in the yield of **8a** (Table 1, entry 4).

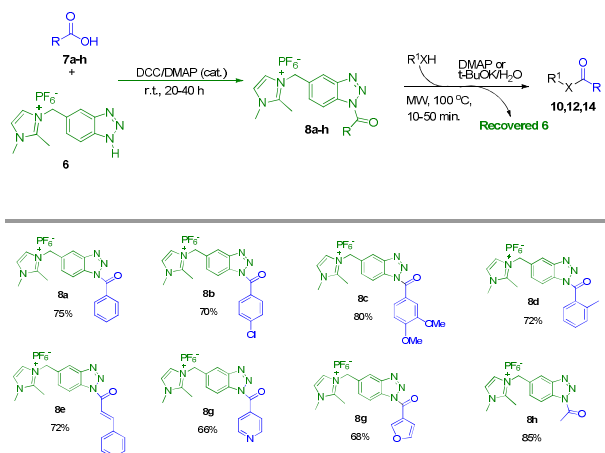
Table 1. Optimization of reaction conditions for the synthesis of **8a**



Entry	Coupling reagents	Solvent	Reaction conditions	Yield of 8a (%)
1	DCC (1.2 eq.) / DMAP (cat.)	THF	r.t., 26 h	50
2	DCC (2 eq.) / DMAP (cat.)	CH ₃ CN	r.t., 20 h	76
3	DCC (1.2 eq.) / DMAP (cat.)	CH ₃ CN	r.t., 20 h	75
4	DCC (1.2 eq.)	CH ₃ CN	r.t., 20 h	40
5	DCC (1.2 eq.) / DMAP (cat.)	CH ₃ CN	reflux, 8 h	55 ^a
5	EDC.HCl (1.5 eq.) / DMAP (cat.)	CH ₃ CN	r.t., 20 h	65
6	HBTU (1.5 eq.) / DMAP (cat.)	CH ₃ CN	r.t., 20 h	45
7	HATU (1 eq.) / DMAP (cat.)	CH ₃ CN	r.t., 20 h	52

^aA number of spots on TLC appeared on refluxing and subsequently the yield of **8a** decreased.

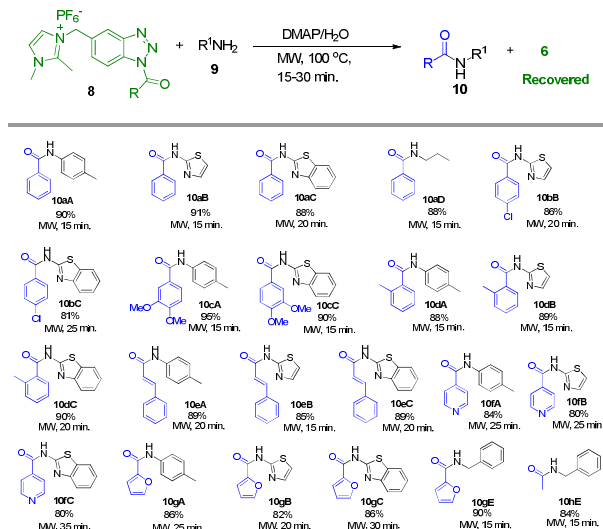
With these optimized conditions in hand, we studied the substrate scope of this reaction and successfully activated six more aromatic and heteroaromatic acids (**7b-g**) with imidazolium-supported benzotriazole auxiliary yielding their corresponding stable imidazolium-supported benzotriazole acyl reagents (Im-CH₂-Bt-COAr, **8b-g**) in 65–80% yields (Scheme 2) either in pure N¹-isomeric form or enriched N¹-isomer with small amounts of N³-isomer. Apart from aromatic and heteroaromatic acids, acetic acid also got efficiently activated by our synthesized reagent **6** yielding corresponding imidazolium-supported benzotriazole acetyl reagent (**8h**) in 85% isolated yield, under similar experimental conditions in 16 h. It is noteworthy that the loss in yield of **8** is solely during the isolation process due to its partial solubility in methanol.



Scheme 2 Synthesis of imidazolium-supported acyl benzotriazole reagents (Im-CH₂-Bt-COR) (**8**)

We next investigated benzoylation of *p*-toluidine (**9A**) with imidazolium-supported *N*-benzoyl benzotriazole (**8a**) using DMAP and K₂CO₃ as bases under classical and microwave conditions in a number of solvents such as CH₃CN, THF, EtOH and water. To our delight, the reaction in CH₃CN and water proceeded smoothly under microwave irradiation giving **10aA** in 85% and 90% yields, respectively (Scheme 3). On the other hand, it took 12–14 h for completion of reaction under reflux conditions in acetonitrile and water with almost comparable yields.

The substrate scope of other imidazolium-supported *N*-acyl benzotriazoles (**8b-g**) was checked under similar conditions with a variety of aliphatic, aromatic and heteroaromatic amines as *N*-nucleophilic substrates (**9A-E**). For all substrates, the reaction proceeded with quantitative conversion in water by applying 15–30 minutes of microwave irradiation, and 80–95% isolated yield of the corresponding amides (**10**) were obtained (Scheme 3). Interestingly, a simple extraction of the concentrated reaction mixture with ethyl acetate followed by washing with 1N HCl (to remove the un-reacted *N*-nucleophilic substrate and DMAP) yielded pure amides **10**, avoiding any use of column chromatography. Apart from aromatic and heteroaromatic *N*-nucleophiles, the acylation using **8** worked quite well with aliphatic amines such as propyl amine (**9D**) and benzyl amine (**9E**), yielding the corresponding amides **10aD** and **10gE** in 88% and 90% yields, respectively. Similarly the acetylation of benzyl amine (**9E**) with **8h** proceeded in 15 minutes under similar experimental conditions yielding **10hE** in 84% yield.

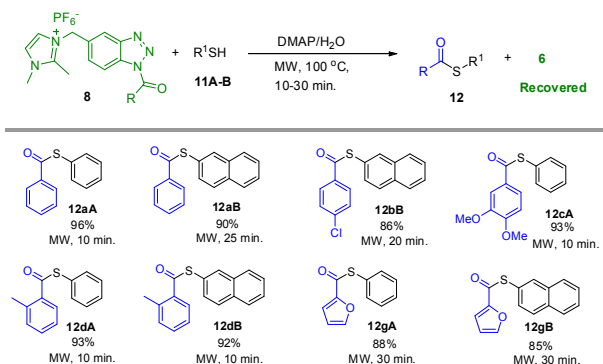


Scheme 3 Imidazolium-supported acyl benzotriazole (**8a-g**) mediated synthesis of amides (**10**) in aqueous media under MW irradiation.

We further utilized imidazolium-supported *N*-acyl benzotriazoles (**8a-g**) for the thioester bond formation by reacting with thiophenol (**11A**) and 2-naphthalenethiol (**11B**) under similar conditions (Scheme 4). Here again, DMAP was found to be the optimum base for the reactions in water and acetonitrile and the reaction worked

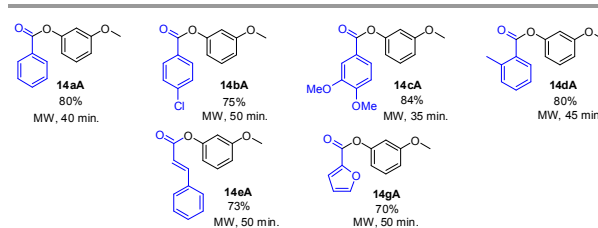
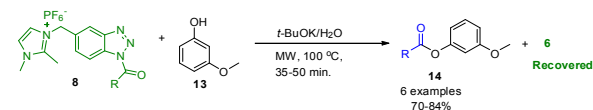
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comparatively slow with K_2CO_3 . Longer reaction time and lower yield of the product (**12aA**) was obtained under classical reflux conditions in water and acetonitrile. Both thiophenols reacted smoothly with **8a-g** and the reaction completed in 10-30 minute of microwave irradiation. Extraction of the concentrated reaction mixture with ethyl acetate followed by washing of organic filtrate with water (to remove DMAP) and recrystallization with hexanes yielded pure thioesters (**12**) in 85-96% yields.



Scheme 4 Imidazolium-supported acyl benzotriazole (**8a-g**) mediated synthesis of thioesters (**12**) in aqueous media under MW irradiation

After the success of amide and thioester bond formation in aqueous medium, we then turned our attention towards ester bond formation using imidazolium-supported *N*-acyl benzotriazoles (**8a-g**). When 3-methoxyphenol (**13**) was allowed to react with **8a** under the standardized condition for amide bond formation, corresponding ester **14a** was only formed in 26% yield. This may be attributed to the lower nucleophilicity of phenols compare to amines and thiols. However, use of *t*-BuOK instead of DMAP resulted in formation of **14a** in 80% isolated yield after 40 minutes of MW irradiation. Next, when other imidazolium-supported acyl benzotriazole (**8b-g**) were reacted with 3-methoxyphenol (**13A**) in water under microwave irradiation using *t*-BuOK as base to give corresponding esters **14aA-gA** (Scheme 5). Extraction of the concentrated reaction mixture with ethyl acetate followed by washing of organic filtrate with 2N NaOH yielded pure esters (**14aA-gA**) in 73-84% isolated yields.



Scheme 5 Imidazolium-supported acyl benzotriazole (**8a-g**) mediated synthesis of esters (**14**) in aqueous media under MW irradiation.

Recovery and reusability of imidazolium-supported benzotriazole reagent

Recoverability of Im-CH₂-BtH was studied in all the three cases of reactions. The insolubility of Im-CH₂-BtH (**6**) in ethyl acetate provided a simple procedure for separating it from crude reaction mixture. In case of amide and thioester synthesis, pure Im-CH₂-BtH (**6**) was obtained after washing of concentrated reaction mass with ethyl acetate followed by high vacuum drying whereas in case of ester synthesis an additional washing with water was required to remove *t*-BuOK to yield pure **6**. Comparison of the ¹H NMR of the recovered Im-CH₂-BtH (**6**) reagent with that of initially synthesized reagent (**6**) is shown in Figure 3. From the ¹H NMR it is very clear that the chemical structure of recovered **6** is identical to that of original compound.

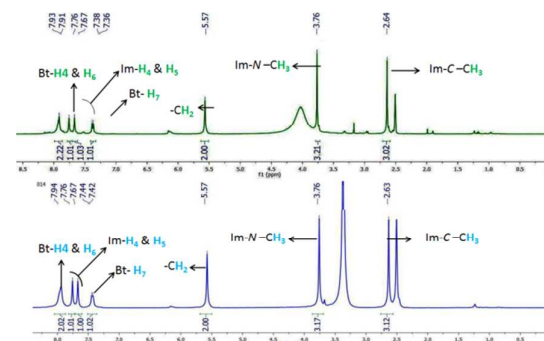
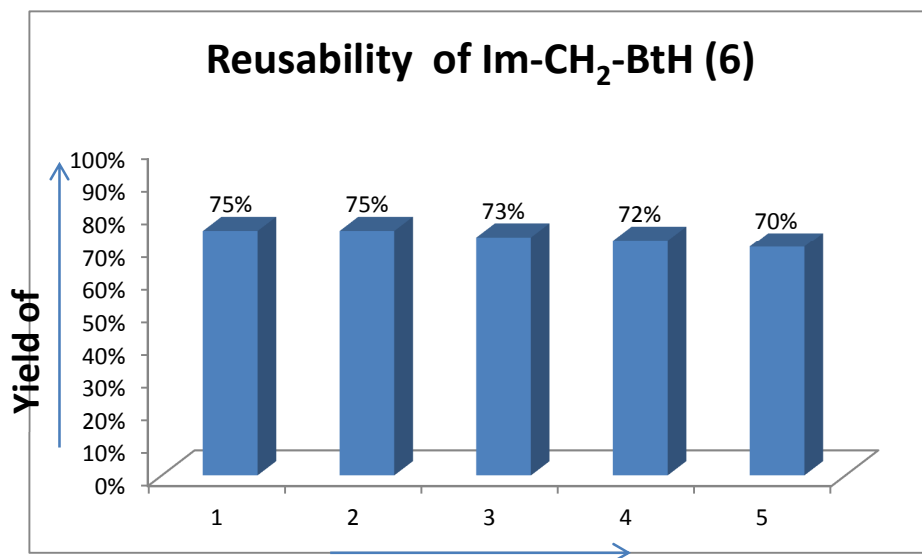


Figure 3 Comparison of ¹H NMR of **6** and recovered **6**.

The reusability of the recovered reagent (**6**) was evaluated towards the synthesis of **8a**. Delightfully the recovered reagent (**6**) has not shown any significant change in the chemical reactivity and for five cycles 75, 75, 73, 72 and 70% isolated yield of **8a** was obtained based on the amount of recovered Im-CH₂-BtH (**6**) (Figure 4). It is worth to mention that the recovery process is very simple and less arduous. However, due to inevitable loss of Im-CH₂-BtH (**6**) during the activation step, the amount of amide (**10aA**) formed in each subsequent cycle's decreases (percentage yield remain same) due to use of lesser amount of nucleophile in the subsequent cycles.

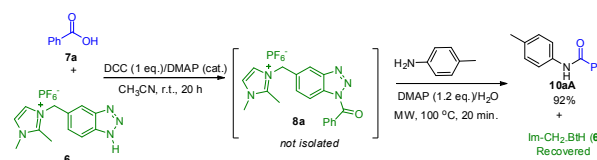
Figure 4 Recyclability and reusability of Im-CH₂-BtH (6)

One-pot and sequential synthesis of amide without isolating Im-CH₂-BtCOR

To overcome the loss in yield during the synthesis of imidazolium-supported acyl benzotriazole reagents (Im-CH₂-Bt-COR) (**8**) and to make the process more efficient and economical, we planned to perform the synthesis of amide (**10aA**) in one-pot fashion. It is important to mention that since the activation step does not proceed in water, therefore benzoic acid (**7a**) and Im-CH₂-BtH (**6**) were allowed to react in acetonitrile at room temperature for 20 h using DCC (1.2 eq.)/DMAP (5 mol %), after which *p*-toluidine (1.0 eq.), additional DMAP (1.2 eq.) were added to the same pot and the reaction mixture was subjected to microwave irradiation for 20 minutes. After the two sequential reactions in one-pot, the reagent Im-CH₂-BtH (**6**) was almost completely recovered (97% of its starting amount) by washing the concentrated and dried reaction mixture with ethyl acetate and decanting the organic filtrate to separate the product along with by-products such as DCU, DMAP and un-reacted acid from **6**. However, the isolation of the product **10aA** in 82% yield from this organic filtrate (ethyl acetate) required tedious separation procedure including acid-base work up followed by column chromatography.

In order to exploit the synthetic advantage of the reagent (Im-CH₂-BtCOR) to effectively undergo acylation in water, we also attempted the sequential synthesis of amide (**10aA**) by (i) carrying the activation step in acetonitrile in the usual manner at room temperature, (ii) removing the side products (DCU) by washing the concentrated and dried residue with ethyl acetate and (iii) using this concentrated residue for the benzylation of *p*-toluidine in water using DMAP (1.2 eq) under microwave irradiation. In this case,

amide (**10aA**) was isolated in 92% yield by usual work up procedure without employing column chromatography, along with almost recovery of Im-CH₂-BtH (**6**) (98% of its starting material). Thus, the step-wise synthetic strategy leads to the synthesis of amide (**10aA**) in comparable yields, with or without the isolation of Im-CH₂-BtCOPh.

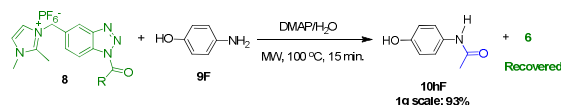
Scheme 6 Sequential synthesis of **10aA** without isolating Imidazolium-supported acyl benzotriazole (**8a**)

Application of imidazolium-supported acetyl benzotriazole (**8h**) for the synthesis of paracetamol

Lastly, we applied the chemical utility of imidazolium supported benzotriazole reagent towards the synthesis of paracetamol. Paracetamol (*N*-(4-hydroxyphenyl)acetamide) is a mild painkiller and reduces the temperature of patients with fever, and thus widely used OTC drug in many countries either in different pharmaceutical formulations, alone or in combination with other active pharmaceutical ingredients. Many synthetic routes have been explored for the paracetamol production but all those involve the acetylation of *p*-aminophenol using acetic anhydride at the final stage. We attempted to substitute corrosive acetic anhydride by imidazolium-supported *N*-acetyl benzotriazole **8h** for preparing paracetamol in a cleaner and safer way. **8h** effectively and selectively acetylated amino group of *p*-aminophenol (**9F**) using DMAP in water under microwave irradiation in 15 minutes yielding paracetamol (**10hF**) in 93% yield, along with the easy recovery of Im-CH₂-BtH (**6**) in pure form as described for other products. In order to evaluate the potential of this process on a larger scale, a one gram batch production of paracetamol from 3.95 g of **8h** and 1.0 g of *p*-aminophenol was successfully achieved under optimized conditions (Scheme 7).

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Scheme 7 Synthesis of paracetamol on gram scale using **6**.

Experimental

Materials and methods

All the chemicals were purchased from "Sigma-Aldrich", Alfa Aesar, and Spectrochem India Pvt. Ltd and were used without further purification. The solvents used were purchased from Merck (India) and were distilled and dried before use. Nuclear magnetic resonance spectra were recorded on Bruker Avance™ 400 spectrometer. All ^1H NMR experiments were reported in δ units, parts per million (ppm), and were measured relative to residual chloroform (7.26 ppm) or DMSO (2.5 ppm) in the deuterated solvent. All ^{13}C NMR spectra were reported in ppm relative to deuteriochloroform (77.0 ppm) or $[\text{D}_6]-\text{DMSO}$ (39.5 ppm). All coupling constants J were reported in Hz. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet and br s = broad singlet. Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. Mass spectra were recorded on an AB SCIEX TOF/TOF 5800 spectrometer. The reactions were carried in a CEM Discover BenchMate reactor in 10 mL pressure vials at 80 W. DSC was recorded on Perkin Elmer DSC 4000 at a heating rate of $10\text{ }^\circ\text{C}/\text{min}$. using nitrogen as the carrier gas in the range $0\text{ }^\circ\text{C}$ to $280\text{ }^\circ\text{C}$. Similarly, thermogravimetric analysis (TGA) was obtained using the Perkin Elmer TGA 4000 in the presence of nitrogen flow at a linear heating of $10\text{ }^\circ\text{C}/\text{min}$ starting from $25\text{ }^\circ\text{C}$ to $500\text{ }^\circ\text{C}$.

Synthesis of ethyl 1H-benzo[d][1,2,3]triazole-5-carboxylate (**2**)

To a solution of benzotriazole-5-carboxylic acid (0.1 mol) in ethanol (80 mL), thionyl chloride (0.3 mol) was added dropwise, at $0\text{ }^\circ\text{C}$. The reaction mixture was refluxed for about 6 h until the consumption of the starting material. The reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate and water ($3 \times 100\text{ mL}$). The combined organic layer was dried over Na_2SO_4 and concentration of the solvent yielded **2** in 97%. m.p: $106\text{--}108\text{ }^\circ\text{C}$ (Lit²⁰ m.p: $108\text{--}109\text{ }^\circ\text{C}$).

Synthesis of 1H-benzo[d][1,2,3]triazol-5-yl)methanol (**3**)

To a suspension of lithium aluminium hydride (0.09 mol) in dry THF (100 mL) in a round bottom flask, ethyl 1H-benzo[d][1,2,3]triazole-5-carboxylate (**2**) (0.03 mol) was slowly added from a dropping funnel at $0\text{ }^\circ\text{C}$ under an atmosphere of nitrogen. The reaction mixture was refluxed for 12 h. The reaction mixture was then quenched in ice-cold water, acidified with 1N HCl, filtered through celite,

extracted with ethyl acetate ($4 \times 100\text{ mL}$). Drying and concentrating the organic layer under reduced pressure afforded **3** in 95%. m.p: $147\text{--}149\text{ }^\circ\text{C}$ (Lit.²⁰ m.p: $149\text{--}150\text{ }^\circ\text{C}$).

Synthesis of 5-(chloromethyl)-1H-benzo[d][1,2,3]triazole (**4**)

Thionyl chloride (0.36 mol) was slowly added to a solution of (1H-benzo[d][1,2,3]triazol-5-yl)methanol (**3**) (0.026 mol) in toluene (100 mL), and the mixture was stirred vigorously for 5 h. The resulting solid was filtered and washed with hexanes to give pure **3**. White solid; yield: 70%; m.p: $162\text{--}163\text{ }^\circ\text{C}$; ^1H NMR (400 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$) δ 7.86 (s, 1H), 7.80 (d, $J = 8.5\text{ Hz}$, 1H), 7.41 (dd, $J = 8.6, 1.3\text{ Hz}$, 1H), 4.79 (s, 2H); ^{13}C NMR (100 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$) δ 143.3, 143.0, 140.3, 131.7, 120.1, 119.5, 51.0.

Synthesis of 3-((1H-benzo[d][1,2,3]triazol-5-yl)methyl)-1,2-dimethyl-1H-imidazol-3-ium Chloride (**5**)

A mixture of 1,2-dimethylimidazole (0.019 mol) and 5-(chloromethyl)-1H-benzo[d][1,2,3]triazole (0.017 mol) were heated at $80\text{ }^\circ\text{C}$ for 3 h. Upon completion of reaction, the reaction mixture was washed with ethyl acetate ($3 \times 25\text{ mL}$) yielding **5**. Brown gummy semi-solid ($\text{N}^1 + \text{N}^3$); yield: 98%; ^1H NMR (400 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$) δ 16.08 (s, 1H), 7.95 (s, 1H), 7.91 (d, $J = 8.5\text{ Hz}$, 1H), 7.81 (d, $J = 2.0\text{ Hz}$, 1H), 7.71 (d, $J = 1.9\text{ Hz}$, 1H), 7.43 (d, $J = 8.3\text{ Hz}$, 1H), 5.62 (s, 2H), 3.79 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$) δ 144.46, 144.08, 132.68, 131.21, 125.22, 122.63, 121.20, 117.69, 50.78, 33.68, 9.42.

Synthesis of 3-((1H-benzo[d][1,2,3]triazol-5-yl)methyl)-1,2-dimethyl-1H-imidazol-3-ium hexafluorophosphate (**6**)

In a round bottom flask, 3-((1H-benzo[d][1,2,3]triazol-5-yl)methyl)-1,2-dimethyl-1H-imidazol-3-ium chloride (**5**) (0.017 mol) was refluxed with potassium hexafluorophosphate (0.018 mol) in dry acetone (40 mL) for 24 h under an inert atmosphere of nitrogen gas. Upon completion of reaction, the excess potassium hexafluorophosphate was filtered off and the mother liquor was concentrated under reduced pressure, dried in high vacuum pump, precipitated with methanol to result compound **6**. Brown solid ($\text{N}^1 + \text{N}^2$ isomers); yield: 96%; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.07 (s, 1H), 7.96 (d, $J = 10.6\text{ Hz}$, 2H), 7.90 (s, 0.5H), 7.75 (s, 1H), 7.67 (s, 1H), 7.44 (d, $J = 7.6\text{ Hz}$, 1H), 7.37 (s, 1H), 6.17 (s, 1H, $\text{CH}_2\text{-N}^2$ -isomer), 5.58 (s, 2H, $\text{CH}_2\text{-N}^2$ -isomer), 3.76 (s, 3H, $\text{N-CH}_3\text{-N}^1$ -isomer), 3.66 (s, 1.5H, $\text{N-CH}_3\text{-N}^2$ -isomer), 2.64 (s, 3H, $\text{C-CH}_3\text{-N}^1$ -isomer), 2.44 (s, 1.5H, $\text{C-CH}_3\text{-N}^2$ -isomer); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 145.26, 139.68, 138.69, 132.36, 126.00, 123.16, 121.62, 116.02, 115.59, 51.55 ($\text{CH}_2\text{-N}^3$ -isomer), 51.02 ($\text{CH}_2\text{-N}^1$ -isomer), 35.22 ($\text{N-CH}_3\text{-N}^1$ -isomer), 33.71 ($\text{N-CH}_3\text{-N}^2$ -isomer), 11.35 ($\text{C-CH}_3\text{-N}^2$ -isomer), 9.88 ($\text{C-CH}_3\text{-N}^1$ -isomer).

Recrystallization in methanol yielded pure N^1 -isomer of **6**. White solid (N^1 -isomer); m.p: $172\text{--}173\text{ }^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 15.86 (s, 1H), 7.94 (s, 2H), 7.71 (d, $J = 34.9\text{ Hz}$, 2H), 7.43 (d, $J = 7.0\text{ Hz}$, 1H), 5.57 (s, 2H), 3.76 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 145.20,

140.39, 139.40, 131.61, 125.34, 123.15, 121.66, 116.04, 115.39, 51.15, 35.28, 9.97; HRMS (ESI-TOF) (m/z) calculated for $C_{12}H_{15}N_5^+$ 229.1327; found 229.1326 $[M+1-PF_6]^+$

General procedure for synthesis of imidazolium-supported acylbenzotriazole reagents (8a-h)

A 50 mL round bottom flask containing a mixture of DCC (1.2 mmol), carboxylic acid (1.2 mmol), **6** (1 mmol) and dimethylaminopyridine (5 mol %) in dry acetonitrile (10 mL) was stirred for 20-40 h. After the completion of reaction, the solvent was concentrated under reduced pressure, and the crude reaction mixture was washed with ethyl acetate (50 mL). The residue was dried for under high vacuum and washing of the residual solid with minimum amount of methanol yielded pure **8** in 65-80% yields. The products (**8a-h**) were analyzed by 1H & ^{13}C NMR and HRMS.

3-((1-Benzoyl-1H-benzo[d][1,2,3]triazol-5-yl)methyl)-1,2-dimethyl-1H-imidazol-3-ium hexafluorophosphate (8a): White solid (N^1 -isomer); yield: 75%; m.p: 164-166 °C; 1H NMR (400 MHz, DMSO- d_6 + $CDCl_3$) δ 8.37 (d, J = 8.6 Hz, 1H), 8.25 (s, 1H), 8.16 – 8.12 (m, 2H), 7.84 – 7.79 (m, 1H), 7.77 (dd, J = 4.8, 2.6 Hz, 2H), 7.68 (d, J = 2.1 Hz, 1H), 7.65 (t, J = 7.8 Hz, 2H), 5.68 (s, 2H), 3.82 (s, 3H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6 + $CDCl_3$) δ 166.06, 145.43, 133.64, 133.05, 131.30, 130.98, 130.33, 128.27, 122.79, 121.25, 119.21, 114.99, 50.26, 34.84, 9.48; HRMS (ESI-TOF) (m/z) calculated for $C_{19}H_{19}N_5O^+$ 333.1589; found 333.1614 $[M+1-PF_6]^+$.

3-((1-(4-Chlorobenzoyl)-1H-benzo[d][1,2,3]triazol-5-yl)methyl)-1,2-dimethyl-1H-imidazol-3-ium hexafluorophosphate (8b): Brown solid (N^1+N^3 -isomer); yield: 70%; m.p: 142-146 °C; 1H NMR (400 MHz, DMSO- d_6) δ 8.37 (dd, J = 9.8, 6.5 Hz, 1H), 8.27 (s, 1H), 8.15 (d, J = 8.3 Hz, 2H), 7.86 – 7.80 (m, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.70 (s, 1H), 7.60 (d, J = 8.3 Hz, 1H), 5.75 – 5.65 (m, 2H), 3.78 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 166.01, 145.40, 139.24, 133.77, 131.61, 131.10, 130.57, 129.14, 123.28, 121.75, 121.24, 119.65, 115.54, 114.58, 50.95, 50.59, 35.33, 10.19; HRMS (ESI-TOF) (m/z) calculated for $C_{19}H_{18}ClN_5O^+$ 367.1199; found 367.1219 $[M+1-PF_6]^+$.

3-((1-(3,4-Dimethoxybenzoyl)-1H-benzo[d][1,2,3]triazol-5-yl)methyl)-1,2-dimethyl-1H-imidazol-3-ium (8c): White Solid (N^1+N^3 -isomer); yield: 80%; m.p: 223-227 °C; 1H NMR (400 MHz, DMSO- d_6) δ 8.33 (dd, J = 15.0, 6.3 Hz, 1H), 8.28 (d, J = 11.0 Hz, 1H), 7.86 (dd, J = 8.5, 1.8 Hz, 1H), 7.83 – 7.73 (m, 2H), 7.71 (s, 2H), 7.23 (d, J = 8.7 Hz, 1H), 5.73 – 5.65 (m, 2H), 3.92 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 2.64 (d, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 165.66, 154.35, 148.77, 145.75, 145.41, 137.71, 133.74, 132.76, 132.37, 130.82, 127.38, 126.79, 123.36, 123.21, 121.73, 121.11, 119.61, 115.47, 114.47, 111.48, 56.43, 56.18, 50.90, 50.61, 35.34, 9.99; HRMS (ESI-TOF) (m/z) calculated for $C_{21}H_{23}N_5O_3^+$ 393.1800; found 393.1827 $[M+1-PF_6]^+$.

1,2-Dimethyl-3-((1-(2-methylbenzoyl)-1H-benzo[d][1,2,3]triazol-5-yl)methyl)-1H-imidazol-3-ium hexafluorophosphate (8d): White solid (N^1+N^3 -isomer); yield:

72%; m.p: 122-124 °C; 1H NMR (400 MHz, DMSO- d_6) δ 8.43 – 8.23 (m, 2H), 7.83 (dd, J = 17.4, 5.1 Hz, 1H), 7.78 – 7.64 (m, 3H), 7.59 (t, J = 8.4 Hz, 1H), 7.49 – 7.38 (m, 2H), 5.74 – 5.66 (m, 2H), 3.79 (s, 3H), 2.66 (s, 3H), 2.37 (2s, 3H total, for N^1+N^3 -isomers); ^{13}C NMR (100 MHz, DMSO- d_6) δ 168.09, 146.21, 145.81, 145.47, 138.03, 137.69, 134.05, 132.39, 131.61, 131.21, 130.62, 127.10, 125.93, 121.73, 121.25, 119.74, 115.36, 114.46, 51.06, 50.73, 35.34, 19.84, 10.00, 9.98; HRMS (ESI-TOF) (m/z) calculated for $C_{20}H_{21}N_5O^+$ 347.1746; found 347.1764 $[M+1-PF_6]^+$.

(E)-3-((1-Cinnamoyl-1H-benzo[d][1,2,3]triazol-5-yl)methyl)-1,2-dimethyl-1H-imidazol-3-ium hexafluorophosphate (8e): Brown solid (N^1 -isomer); yield: 72%; m.p: 214-216 °C; 1H NMR (400 MHz, DMSO- d_6) δ 8.36 (d, J = 8.5 Hz, 1H), 8.13 (s, 1H), 8.09 (s, 1H), 8.01 (dd, J = 16.3, 2.9 Hz, 1H), 7.82 (d, J = 3.7 Hz, 1H), 7.72 (dd, J = 27.4, 2.6 Hz, 4H), 7.56 (s, 1H), 7.46 (s, 2H), 5.62 (s, 2H), 3.81 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 163.84, 158.88, 149.04, 146.37, 145.48, 134.22, 133.94, 132.21, 131.17, 129.70, 123.34, 121.68, 119.75, 116.35, 115.39, 50.60, 35.35, 34.60, 10.02; HRMS (ESI-TOF) (m/z) calculated for $C_{21}H_{21}N_5O^+$ 359.1746; found 359.1767 $[M+1-PF_6]^+$.

3-((1-Isonicotinoyl-1H-benzo[d][1,2,3]triazol-5-yl)methyl)-1,2-dimethyl-1H-imidazol-3-ium hexafluorophosphate (8f): White solid (N^1+N^3 -isomer); yield: 65%; m.p: 181-184 °C; 1H NMR (400 MHz, DMSO- d_6) δ 9.23 (s, 1H), 8.92 (d, J = 2.7 Hz, 1H), 8.49 (d, J = 7.5 Hz, 1H), 8.44 – 8.24 (m, 2H), 7.89 – 7.58 (m, 4H), 5.75 – 5.67 (m, 2H), 3.79 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 165.72, 154.02, 151.91, 146.21, 145.26, 139.47, 138.14, 134.17, 131.87, 131.21, 128.30, 127.19, 123.89, 123.36, 121.74, 121.28, 119.69, 115.47, 114.49, 50.87, 50.59, 35.35, 9.99; HRMS (ESI-TOF) (m/z) calculated for $C_{18}H_{18}N_6O^+$ 334.1542; found 334.1561 $[M+1-PF_6]^+$.

3-((1-(Furan-2-carbonyl)-1H-benzo[d][1,2,3]triazol-5-yl)methyl)-1,2-dimethyl-1H-imidazol-3-ium hexafluorophosphate (8g): White solid (N^1+N^3 -isomer); yield: 68%; m.p: 220-224 °C; 1H NMR (400 MHz, DMSO- d_6) δ 8.34 (dd, J = 13.0, 8.6 Hz, 2H), 8.27 (s, 1H), 8.07 (d, J = 3.5 Hz, 1H), 7.86 – 7.74 (m, 2H), 7.69 (s, 1H), 6.94 (dd, J = 3.6, 1.6 Hz, 1H), 5.73 – 5.64 (m, 2H), 3.79 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 154.80, 151.00, 145.65, 145.36, 144.24, 137.97, 133.91, 132.40, 132.00, 131.13, 126.94, 125.63, 123.33, 121.72, 121.26, 119.75, 115.34, 114.42, 113.96, 50.88, 50.59, 35.33, 9.98; HRMS (ESI-TOF) (m/z) calculated for $C_{17}H_{17}N_5O_2^+$ 323.1382; found 323.1410 $[M+1-PF_6]^+$.

3-((1-Acetyl-1H-benzo[d][1,2,3]triazol-5-yl)methyl)-1,2-dimethyl-1H-pyrazol-2-ium (8h): White solid (N^1 -isomer); yield: 85%; m.p: 198-200 °C; 1H NMR (400 MHz, DMSO- d_6) δ 8.26 (d, J = 7.5 Hz, 1H), 8.21 (s, 1H), 7.75 (s, 2H), 7.69 (s, 1H), 5.66 (s, 2H), 3.77 (s, 3H), 2.94 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 170.26, 146.25, 145.85, 145.46, 137.85, 133.64, 130.99, 126.69, 123.33, 121.65, 121.14, 119.59, 115.06, 114.22, 50.70, 35.33, 23.61, 9.97.

General procedure for synthesis of amides, thioesters and esters (**10**, **12**, **14**) and recovery of reagent **6**

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In a microwave capped tube, *N*- *S*- or *O*--nucleophilic aromatic/heteroaromatic substrates (1.2 mmol), imidazolium supported *N*-acyl benzotriazole reagent (**8a-g**) (1 mmol) and DMAP (1.5 mmol) (*t*-BuOK for *O*-nucleophilic substrate) were mixed in water (2 mL). The tube was irradiated in a CEM microwave synthesizer for 10-50 minutes at 100 °C, 50 W and the progress of the reaction was monitored *via* TLC. After completion of the reaction, reaction mixture was concentrated in a 25 ml round bottom flask to give a gummy reaction mass. Subsequently, ethyl acetate (2 × 20 mL) was added to this mixture and stirred for 15 minutes and decanted. The product (amide, thioester and ester) got dissolved in organic filtrate leaving behind the regenerated reagent **6** as semi-solid (in case of *N*- & *S*-nucleophilic substrates. While in case of *O*-nucleophilic substrates, washing with water (5 mL) was required to remove *t*-BuOK to regenerate pure **6**.

For *N*-nucleophilic substrates, the organic filtrate was washed with 1N HCl, dried with Na₂SO₄ and concentrated to yield pure amides **10**.

For *S*-nucleophilic substrates, the organic filtrate was washed with water, concentrated and recrystallized with hexane to yield pure thioesters **12**.

For *O*-nucleophilic substrates, the organic filtrate was washed with 2N NaOH, dried with Na₂SO₄ and concentrated to yield pure esters **14**.

Reusability of 3-((1*H*-benzo[d][1,2,3]triazol-5-yl)methyl)-1,2-dimethyl-1*H*-imidazol-3-ium hexafluorophosphate (**6**)

After the first run of the reaction and work up procedure as mentioned above, regenerated semi-solid **6** was dried under vacuum for 10-12 h and was reused for the next cycle of the reaction, following the same procedures.

Procedure for one-pot synthesis of amide (**10aA**) without isolating Im-CH₂-BtCOR

A 25 mL round bottom flask containing a mixture of DCC (1.2 mmol), benzoic acid (1.2 mmol), **6** (1 mmol) and DMAP (5 mol %) in dry acetonitrile (8 mL) was stirred for 20 h at 20 °C. After the completion of reaction, *p*-toluidine (1.2 mmol), additional DMAP (1.2 mmol) were added to the same pot and the reaction mixture was subjected to microwave irradiation for 20 minutes. After the two sequential reactions in one-pot, reaction mixture was concentrated and dried under high vacuum for 5-6 h and the residue was washed with ethyl acetate (2 × 20 mL) and the organic filtrate was decanted to separate the product along with by-products such as DCU, DMAP and un-reacted acid from **6**. The un-dissolved semi-solid was dried under vacuum to give pure Im-CH₂-BtH (**6**) (97% of its starting amount). The organic filtrate was washed with 1N HCl and then with 2N NaOH. Purification of this residue by column chromatography over silica gel using EtOAc: hexane (1: 9, v/v) as eluent yielded **10aA** in 82% yield.

Procedure for sequential synthesis of amide (**10aA**) without isolating Im-CH₂-BtCOR

A 25 mL round bottom flask containing a mixture of DCC (1.2 mmol), benzoic acid (1.2 mmol), **6** (1 mmol) and DMAP (5 mol %) in dry acetonitrile (8 mL) was stirred for 20 h at 20 °C. After the completion of reaction, the mixture was concentrated and dried under vacuum and washed with ethyl acetate (2 × 20 mL) to remove DCU, DMAP and un-reacted acid. The residue was charged with *p*-toluidine (1.2 mmol), additional DMAP (1.2 mmol) and water (4 mL) and the mixture was subjected to microwave irradiation for 20 minutes. After completion of the reaction, reaction mixture was concentrated, dried and washed with ethyl acetate (2 × 20 mL). The organic filtrate was decanted and washed with 1N HCl, dried with Na₂SO₄ and concentrated to yield pure amide **10aA** in 92% yield. The left over residue was dried under vacuum to give pure Im-CH₂-BtH (**6**) (98% of its starting material).

Conclusions

In summary, we have synthesized and characterized imidazolium-supported benzotriazole reagent as a novel synthetic auxiliary and explored its utility as greener carboxyl group activating reagent for the synthesis of amides, esters and thioesters in aqueous microwave conditions *via* the formation of stable imidazolium-supported acyl benzotriazoles. The reagent is moisture insensitive and highly stable under thermal and aerobic conditions. The use of an aqueous medium and microwave energy in the acylation reaction, high yield of the amides, esters and thioesters in short reaction times, chromatography free purification and easy recyclability and reusability of imidazolium-supported benzotriazole makes it a greener, economical and environmentally friendly activating reagent. The other applications of this reagent are in progress.

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