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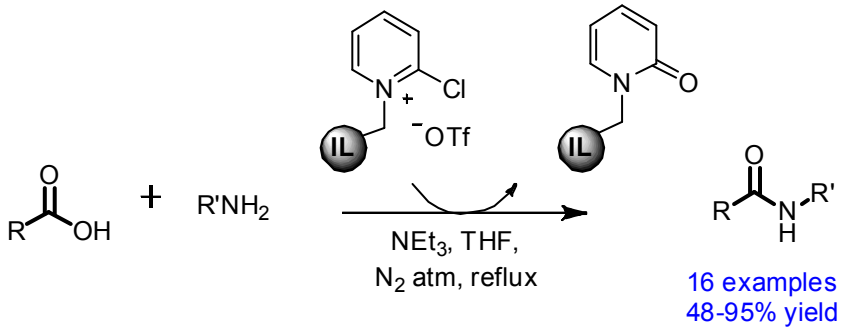
Graphical Abstract

A novel imidazolium salt-supported Mukaiyama reagent has been synthesized and utilized as coupling agent for synthesis of amides.



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ARTICLE TYPE

Imidazolium Salt-supported Mukaiyama Reagent: An Efficient Condensation Reagent for Amide Bond Formation

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A novel imidazolium salt-supported Mukaiyama reagent (2-chloropyridinium salt) has been developed and explored as an efficient coupling agent for the amide bond formation. The use of ionic liquid-supported reagent enabled isolation of the amide products by simple extraction with organic solvents in high purity and avoiding column chromatography purification.

Introduction

The amide bond is an significant building unit in many natural and synthetic compounds.[1] Amide bond has a unique role in peptides and proteins. Molecules possessing amide bonds have shown wide range of biological properties.[2] Establishing synthetic methods for amides are immensely important pursuit in organic synthesis. The most prevalent strategy for amide bond formation relies heavily upon the interconversion of activated carboxylic acid derivatives with an amine. However, other methodologies to access amide functionality have been also developed like Staudinger reaction,[3] hydrative amide syntheses with alkynes,[4] the Schmidt reaction,[5] Beckmann rearrangement[6] and amidation of aldehydes catalyzed by transition metals and hypervalent iodine reagents.[7] Although these methods are highly efficient but has an innate drawback of using expensive transition metals, hazardous oxidants, longer reaction time and waste generation. Formation of amide bonds from carboxylic acids is not a spontaneous process at ambient temperature and generally it relies on activation of a carboxylic acid using a coupling reagent. To address these challenging problems several coupling and activating reagents such as 2-chloropyridinium salts, dicyclohexylcarbodiimide (DCC),[8] 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ),[9] the boron reagent $B(OCH_2CF_3)_3$,[10] nano-Mgo[11] and 1-[bis(dimethylamino)-methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU) have been described in literature for this reaction.[12] Among these coupling reagents, *N*-methyl-2-chloropyridinium iodide (Mukaiyama reagent) (**1**) is an efficient activating agent for the formation of esters,[13] carboxamides,[14] ketenes,[15] lactones[16] and lactams[17] from carboxylic acids. Despite its great success, it is also associated with some issues of solubility, stability and purification of coupled products.[18] In most of the reactions using Mukaiyama reagent, cumbersome chromatographic separation is mandatory to separate the product from the by-product, *N*-alkylpyridone. Over the last couple of years different approaches have been reported to address these problems associated with Mukaiyama reagents (Figure 1). For example, Xu *et. al.*[19] have synthesized a novel *N*-ethyl-2-bromopyridinium tetrafluoroborate as an excellent coupling reagent for peptide synthesis with high activity and a low level of racemisation. The Tye,[20] Taddei[21] and Swinnen[22] groups have independently developed polymer-supported Mukaiyama reagents (**2** & **3**) and demonstrated their application for the synthesis of carbodiimide, guanylation of primary amines, synthesis of amide & esters and generation of ketenes for Staudinger cycloaddition reactions, respectively. Although polymer-supported reagents have addressed some of the issues of 2-chloropyridinium salts, low loading capacity, high cost and slower reaction rates makes these approaches less attractive. Nagashima[23] and Matsugi[24] groups have independently reported fluorous tagged Mukaiyama reagents **4** and **5**, respectively for the amide bond formation. The reactivity of reagent **5** was found to be dependent on the length of the fluorous tag in molecule.[24b] In the case of fluorous-supported synthesis, special solvent requirements and cost are serious concerns.[25] Onium salt-supported reagents have gained considerable interest as a promising alternative soluble support for reagents owing to their high loading capacity, tuneable solubility, homogeneity and easy monitoring of the reaction by various analytical techniques such as NMR, IR and mass spectroscopy.[26]

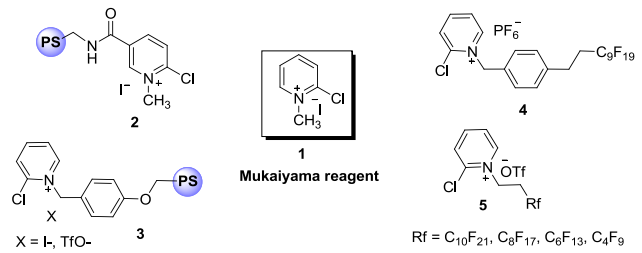


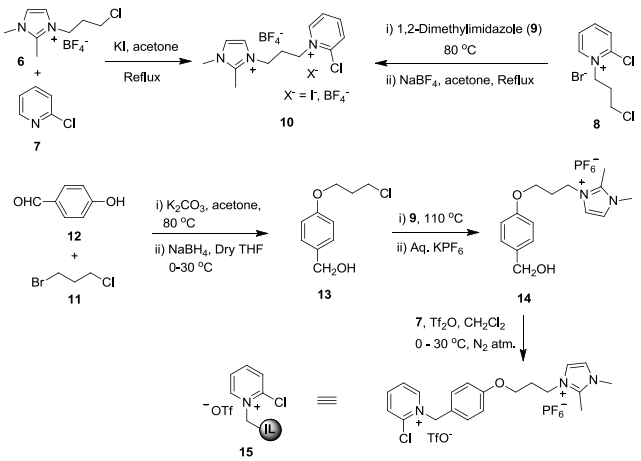
Fig. 1: Some solid-supported and fluorous-supported Mukaiyama reagents

In continuation to our interest towards ionic liquid-supported reagents in organic synthesis,[27] herein we report the synthesis of novel imidazolium salt-supported Mukaiyama reagent (2-chloropyridinium salt) and its application in amide bond formation. To the best of our knowledge this is the first report of

the synthesis of an imidazolium salt-supported Mukaiyama reagents.

Result and discussion

Our initial investigation to synthesize an imidazolium salt-supported Mukaiyama reagent by the reaction of 1-(3-chloropropyl)-2,3-dimethylimidazolium tetrafluoroborate (**6**) with 2-chloropyridine (**7**) in the presence of KI or by the reaction of 2-chloro-1-(3-chloropropyl)pyridin-1-ium bromide (**8**) with 1,2-dimethylimidazole (**9**) followed by anion exchange (Scheme 1) failed to give a substantial amount of imidazolium salt-supported Mukaiyama reagent **10**.

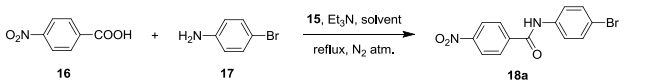


Scheme 1: Synthesis of imidazolium salt-supported Mukaiyama reagent **10** and **15**.

We envisioned the reaction of imidazolium salt-supported benzyl alcohol **14** with 2-chloropyridine (**7**) and triflic anhydride would afford us the desired imidazolium salt-supported Mukaiyama reagent.[22] Synthesis of **14** was achieved from 4-hydroxy-benzaldehyde (**12**) as shown in Scheme 1. Reaction of **12** with 1-bromo-3-chloropropane (**11**) in the presence of potassium carbonate gave monoalkylated aldehyde, which on subsequent reduction resulted into the monoalkylated benzyl alcohol **13**. Reaction of **13** with 1,2-dimethylimidazole (**9**) at 110 °C gave the corresponding chloride salt. Anion exchange of the chloride salt with aqueous KPF_6 resulted in corresponding imidazolium salt-supported benzyl alcohol (**14**). Reaction of **14** and **7** in the presense of triflic anhydride under nitrogen atmosphere in dichloromethane for 10 h resulted in the imidazolium salt-supported Mukaiyama reagent **15** in good yield (55%). It is believed that sequential *in situ* formation of imidazolium salt-supported triflic acid ester followed by quaternization of 2-chloropyridine gave **15** (IL-supported Mukaiyama reagent). This reaction proved to be convenient and fast compared to our earlier attempts. The structure of reagent **15** was confirmed by ^{1}H NMR, ^{13}C NMR and HRMS (Supporting information). Presence of two singlets at 3.73 ppm (NCH_3) and 5.92 ppm (PhCH_2), two doublets at 7.60 ppm and 7.64 ppm for the imidazolium protons along with characteristic double doublet at δ 9.27 for the *ortho*-protons adjacent to nitrogen of pyridinium and other peaks in the ^{1}H NMR spectrum of **15** clearly indicated that the 2-chloropyridne has been tagged with imidazolium ion. Similarly, the number of peaks in the ^{13}C NMR spectrum of **15** were well in agreement with the proposed sturcture. Presence of the peaks at *m/z* 502.4 $[M\text{-}CF_3SO_3]^+$ and 506.3 $[M\text{-}PF_6]^+$ in the mass spectrum of **15** conformed the formation of **15**.

In order to explore synthetic applicability of the reagent, coupling of 4-nitrobenzoic acid (**16**) and 4-bromoaniline (**17**) was performed without additive in DCM as a prototype reaction. DCM was the first solvent of choice and this proved to work efficiently showing completion of reaction within 2 h. However, the choice of DCM was not optimal, because many carboxylic acids are insoluble in it, while it is too volatile for parallel synthetic use. Various solvents were screened to circumvent the issue. Among the various solvents evaluated for the reaction, THF proved to be the best choice in terms of yield and reaction time (Table 1, entry 4). Although the reagent was soluble in acetonitrile the yield of product was less even after longer reaction times. In methanol, the yield of the desired product was poor, probably because the nucleophilicity of the methanol also lead to the formation of the ester as a by-product.

Table 1: Optimization of reaction conditions for amide bond formation



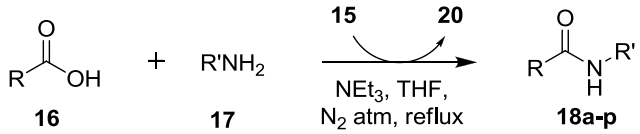
Entry	Solvent	Time (h)	Yield (%)
1	DCM	2	72 (62)[a]
2	CH_3CN	2	55
3	CH_3CN	4	65
4	**THF**	**2**	**85**
5	Methanol	2	43
6	H_2O	2	20 (53)[b]

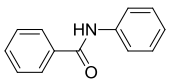
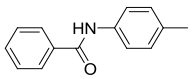
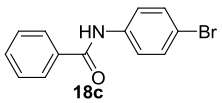
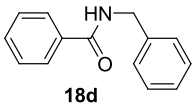
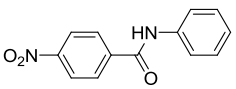
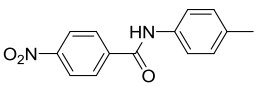
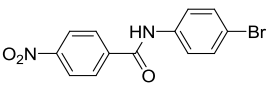
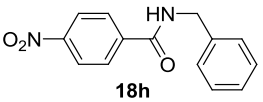
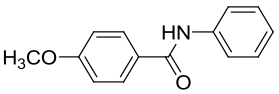
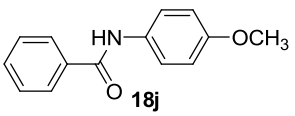
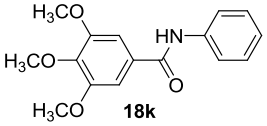
[a] room temperature, [b] stirring for 5 h

Having identified optimum reaction conditions, the scope of reagent was examined by employing different substituted carboxylic acids and amines and results are summarized in table 2. For the synthesis of amide, a mixture of benzoic acid (**16**), imidazolium salt-supported Mukaiyama reagent (**15**), triethylamine were suspended in THF and amine (**17**) was added to mixture. The reaction mixture was refluxed for an optimal time. It was observed that aromatic amines having electron donating substituents like methyl and methoxy group furnished better yields of product as compared to aniline with electron withdrawing bromo substituents (Table 2, entries 2, 3 & 6, 7). On the other hand aromatic acid with electron donating as well as withdrawing groups showed excellent reactivity (Table 2, entries 1, 5 & 2, 6). However, 3,4,5-trimethoxybenzoic acid gave a lower yield even after longer reaction time (Table 2, entry 11). Aliphatic acid, propionic acid also furnished low yield of corresponding *N*-phenylpropionamide (Table 2, entries 13). The lower yield in case of 3,4,5-trimethoxybenzoic acid and propionic acid may be attributed to their lower reactivity towards first step of substitution. *n*-Butylamine also coupled with benzoic acid giving good yield of *N*-butylbenzamide (Table 2, entry 12). The heterocyclic amine, 2-aminobenzothiazole and 6-aminoquinoline also coupled with benzoic acid to give desired amide in moderate to good yield (48-59%) in 4-6 h using **15** as coupling reagent (Table 2, entry 14, 16). Nicotinic acid also coupled with aniline affording good yield of the desired product in 4h. The longer reaction time taken by heteroaromatic acids and amines is attributed to lesser reactivity of acid and lower nucleophilicity of

heteroamines. All the amides were obtained in excellent purity after simple workup without additional chromatography. The melting point and ^{1}H NMR data for the synthesized amides were in agreement with the reported data in the literature. The by-product imidazolium salt-supported pyridone **20** was easily removed from the reaction mixture by simple washing. The structure of imidazolium salt-supported pyridone **20** was confirmed by ^{1}H NMR, ^{13}C NMR and IR spectroscopy (Supporting information). It is worth to mention that recovered IL-supported pyridone (**20**) can be easily converted to reagent **15** by reacting with phosphorus oxychloride followed by anion metathesis with sodium trifluoromethanesulfonate.[24a]

Table 2: Substrate scope for amide formation using reagent **15**



Entry	R	R'	Product	Time (h)	Yield (%)[a]
1	C_6H_5	C_6H_5	 **18a**	3	87
2	C_6H_5	4-$CH_3C_6H_4$	 **18b**	2	93
3	C_6H_5	4-BrC_6H_4	 **18c**	3	70
4	C_6H_5	$C_6H_5CH_2$	 **18d**	3	68
5	4-$NO_2C_6H_4$	C_6H_5	 **18e**	3	90
6	4-$NO_2C_6H_4$	4-$CH_3C_6H_4$	 **18f**	3	95
7	4-$NO_2C_6H_4$	4-BrC_6H_4	 **18g**	2	84
8	4-$NO_2C_6H_4$	$C_6H_4CH_2$	 **18h**	3	90
9	4-$CH_3OC_6H_4$	C_6H_5	 **18i**	3	92
10	C_6H_5	4-$CH_3OC_6H_4$	 **18j**	3	95
11	3,4,5-$(CH_3O)_3C_6H_4$	4-$CH_3C_6H_4$	 **18k**	5	60

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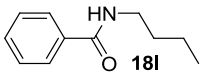
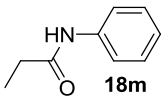
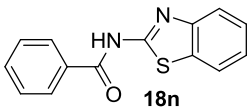
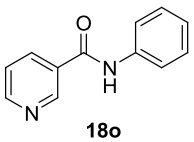
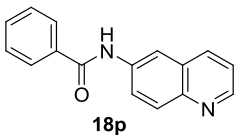
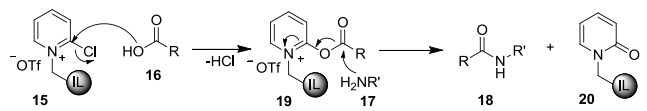
12	C_6H_5	C_4H_9	 **18l**	4	82
13	C_2H_5	C_6H_5	 **18m**	2.5	56
14	C_6H_5	C_7H_4NS	 **18n**	4	48
15	C_5H_4N	C_6H_5	 **18o**	4	63
16	C_6H_5	C_9H_6N	 **18p**	6	59

[a]Isolated yield.

It is believed that the reaction proceeds through initial activation of carboxylic acid (**16**) by IL-supported 2-chloropyridinium triflate to give intermediate ester (**19**) which on subsequent reaction with amine (**17**) by nucleophilic attack furnishes amide (**18**) as product and IL-supported pyridone (**20**) as by-product (Scheme 2)



Scheme 2: Plausible mechanism for the amide formation using reagent **15**

Experimental

General

The NMR (^{1}H and ^{13}C) spectra were recorded on 300 MHz and 400 MHz spectrometer in $CDCl_3$ and DMSO-d_6. The chemical shifts were expressed in ppm and coupling constants (J) in Hz. The IR spectra were recorded on ABB Bomen MB3000 FTIR spectrophotometer. The progress of the reaction was determined on thin-layer chromatography (TLC) performed on Merck-precoated silica gel 60-F_{254} plates. Melting points were determined on open capillary tube on MPA-120G EZ-Melt automated melting point apparatus and are uncorrected. 1,2-Dimethylimidazole, 2-chloropyridine, trifluoromethanesulfonic acid and other reagents and solvents were purchased from commercial sources and used without further purification unless otherwise specified

General procedure for the synthesis of (4-(3-chloropropoxy)phenyl)methanol (13)

4-Hydroxybenzaldehyde (8.00 g, 65 mmol), 1-bromo-3-chloropropane (6.46 mL, 65 mmol) and potassium carbonate (9.05 g, 65 mmol) were taken in dry acetone (25 mL) in a 250 mL round bottom flask. The reaction mixture was refluxed for 12 h. After completion of reaction, acetone was evaporated and residue was washed with water (20 mL) and extracted by ethyl acetate (15 mL × 2). The organic layer was dried with anhydrous sodium sulphate and evaporated under reduced pressure to get crude product. Crude product was purified by column chromatography on silica (60-120 mesh) using hexane and ethyl acetate as eluent (9:1, *v/v*) to get 7.86 g of pure 4-(3-chloropropoxy)benzaldehyde. It was further dissolved in dry THF (15 mL) at 0 °C, then sodium borohydride (2.24 g, 59 mmol) was added in pinches. After addition the resulting mixture was stirred at room temperature for 3 h. On completion of reaction, methanol was evaporated and water (15 mL) was added to the viscous residue. The solution was neutralized to pH 7 by 2N HCl and extracted in ethyl acetate (15 mL × 2). The organic layer was washed with brine water and dried with anhydrous sodium sulfate and concentrated under reduced pressure to get pure product as white solid.

(4-(3-Chloropropoxy)phenyl)methanol (**13**): Yield: 6.80 g (86%); mp: 53-55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 4.65 (d, J = 5.9 Hz, 2H), 4.14 (t, J = 5.8 Hz, 2H), 3.78 (t, J = 6.3 Hz, 2H), 2.31 – 2.20 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 133.4, 128.7, 114.6, 65.0, 64.3, 41.5, 32.3.

General procedure for the synthesis of imidazolium salt-supported benzyl alcohol (14)

A mixture of **13** (6.00 g, 30 mmol) and 1,2-dimethylimidazole (2.87 g, 30 mmol) was heated at 110 °C for 3 h to give thick viscous liquid. The viscous liquid was washed with ethyl acetate (3 × 20 mL) to remove unreacted starting materials to give pure

chloride salt (8.56 g, 96%). Ion exchange of chloride was performed using (20 mL) aqueous potassium hexafluorophosphate (6.37 g, 35 mmol) solution at room temperature for 1 h. The resulting solid precipitate was filtered and washed with water and dried in vacuum to get pure **14**.

Yield: 11.37 g, 97%; mp: 115 °C; ^{1}H NMR (300 MHz, DMSO) δ 7.65 (d, *J* = 2.0 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.05 (t, *J* = 5.6 Hz, 1H), 4.41 (d, *J* = 5.6 Hz, 2H), 4.29 (t, *J* = 6.8 Hz, 2H), 3.97 (t, *J* = 5.9 Hz, 2H), 3.73 (s, 3H), 2.55 (s, 3H), 2.19 (p, *J* = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 157.4, 144.9, 135.3, 128.4, 122.9, 121.4, 114.4, 64.5, 62.9, 45.3, 35.1, 29.1, 9.5.

General procedure for the synthesis of imidazolium salt-supported Mukaiyama reagent (15)

A mixture of **14** (11.00 g, 27 mmol) and 2-chloropyridine (14 g, 135 mmol) was suspended in 20 mL DCM at 0 °C under N_2 atmosphere. Triflic anhydride (6.40 mL, 38 mmol) was added drop wise over 5 min. After complete addition, the resulting reaction mixture was allowed to stir at room temperature for 10 h. Reaction was monitored by TLC. On completion, the reaction mixture was filtered and thoroughly washed with 20% DCM-Methanol solution (20.0 mL) to furnish pure **15**.

Yield (9.68 g, 55%); mp 120 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.27 (dd, *J* = 6.2, 1.3 Hz, 1H), 8.65 (td, *J* = 8.1, 1.5 Hz, 1H), 8.40 (dd, *J* = 8.2, 1.0 Hz, 1H), 8.21 – 8.14 (m, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 5.90 (s, 2H), 4.28 (t, *J* = 6.9 Hz, 2H), 4.02 (t, *J* = 5.9 Hz, 2H), 3.73 (s, 3H), 2.55 (s, 3H), 2.20 (p, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.2, 148.2, 148.1, 146.8, 144.9, 131.0, 130.8, 127.3, 124.8, 122.8, 121.4, 115.4, 64.7, 62.4, 45.2, 35.2, 29.0, 9.5.; ESI-MS (*m/z*): 502.4 [M-OTf]$^+$ and 506.3 [M-PF_6]$^+$.

Representative procedure for the amide bond formation using 15

A mixture of 4-nitrobenzoic acid (0.030 g, 0.17 mmol) and imidazolium salt-supported Mukaiyama reagent 15 (0.1404 g, 0.21 mmol) was suspended in THF (5.0 mL) under nitrogen atmosphere. To this reaction mixture were added triethylamine (0.044 g, 0.43 mmol) and 4-bromoaniline (0.030 g, 0.17 mmol) in sequence. The resulting reaction mixture was allowed to reflux for 2 h. After completion of reaction, THF was evaporated to obtain viscous mixture. Product was extracted with 30% ethyl acetate: hexane (10 mL × 2) from viscous mixture and washed with 2M HCl solution (5.0 mL × 3) and saturated bicarbonate solution (5.0 mL × 3) in order to remove any unreacted amine and by-products. The organic layer was washed with brine and dried over sodium sulphate and concentrated in vacuum to get pure amide **18g** in 0.048 g (84%).

N-Phenylbenzamide **(18a):** Yield 87%; Pale yellow solid; mp: 157-159 °C (lit.[29] 162-164 °C); IR (KBr, cm^{-1}): 3298, 3075, 1670, 1556, 1450, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.2 Hz, 2H), 7.84 (s, 1H), 7.67 (d, *J* = 7.7 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 137.9, 135.0, 131.8, 129.1, 128.8, 127.0, 124.6, 120.2.

N-p-Tolylbenzamide **(18b):** Yield 93%; Crystalline solid; mp: 158-160 °C(lit.[30] 158 °C); IR (KBr, cm^{-1}): 3319, 2910, 1649, 1580, 1521, 1404, 1315, 812; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.90 – 7.85 (m, 2H), 7.57 – 7.52 (m, 3H), 7.50 – 7.44 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 135.4, 135.0, 134.2, 131.7, 129.5, 128.7, 127.0, 120.4, 20.94.

N-(4-Bromophenyl)benzamide **(18c):** Yield 70%; Off-white solid; mp: 196-198 °C (lit.[31] 200-202 °C); IR (KBr, cm^{-1}): 3322, 2935, 1644, 1588, 1530, 1360, 830; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.82 (s, 1H), 7.61 – 7.56 (m, 3H), 7.52 (dd, *J* = 12.2, 5.3 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 137.0, 134.6, 132.1, 128.9, 127.0, 121.7, 117.1.

N-Benzylbenzamide **(18d):** Yield 68%; Yellow crystalline; mp: 102-103 °C (lit.[32] 100-101 °C); IR (KBr, cm^{-1}): 3325, 3055, 2924, 1643, 1551, 1319, 800, 694; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.2 Hz, 2H), 7.53 – 7.46 (m, 1H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.35 (d, *J* = 4.1 Hz, 2H), 7.32 – 7.28 (m, 4H), 6.49 (s, 1H), 4.64 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 138.2, 134.4, 131.5, 128.8, 128.6, 127.9, 127.6, 126.9, 44.1.

4-Nitro-N-phenylbenzamide **(18e):** Yield 90%; Yellow solid; mp: 210-212 °C (lit.[33] 211 °C); IR (KBr, cm^{-1}): 3317, 3078, 2924, 1651, 1597, 1528, 1350, 1319, 856; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.6 Hz, 2H), 8.07 (d, *J* = 8.5 Hz, 2H), 7.84 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 149.3, 140.8, 138.5, 129.1, 128.6, 124.4, 123.2, 120.9.

4-Nitro-N-p-tolylbenzamide **(18f):** Yield 95%; Yellow solid; mp: 200-203 °C (lit.[28] 201-203 °C); IR (KBr, cm^{-1}): 3317, 2924, 2854, 1651, 1597, 1528, 1350, 1319, 849; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.6 Hz, 2H), 7.82 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 149.7, 140.6, 135.1, 134.6, 129.7, 128.2, 124.0, 120.4, 20.9.

N-Benzyl-4-nitro benzamide **(18h):** Yield 90%; Off-white solid; mp: 137-138 °C (lit.[33] 136-137 °C); IR (KBr, cm^{-1}): 3279, 2924, 1628, 1597, 1535, 1342, 872; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.33 – 7.21 (m, 5H), 6.62 (s, 1H), 4.56 (d, *J* = 5.7 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 149.6, 139.9, 137.4, 128.9, 128.2, 127.9, 127.9, 123.8, 44.4.

N-(4-Bromophenyl)-4-nitrobenzamide (**18g**): Yield 84%; Yellow solid; mp: 236-238 °C (lit.[28] 238-240 °C); IR (KBr, cm^{-1}): 3296, 2839, 1659, 1597, 1529, 1389, 1342, 840, 825; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.42 – 8.33 (m, 2H), 8.22 – 8.14 (m, 2H), 7.80 – 7.72 (m, 2H), 7.61 – 7.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 149.2, 140.4, 137.8, 131.4, 129.1, 123.2, 122.4, 116.5.

N-(4-Methoxyphenyl)benzamide **(18i):** Yield 95%; Off-white solid; mp: 154-157 °C (lit.[29] 156-157 °C); IR (KBr, cm^{-1}): 3325, 3047, 2839, 1643, 1612, 1026, 825; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.0, 1.5 Hz, 2H), 7.74 (s, 1H), 7.59 – 7.54 (m, 3H), 7.53 – 7.48 (m, 2H), 6.97 – 6.88 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 156.6, 135.0, 131.7, 131.0, 128.7, 127.0, 122.1, 114.2, 55.5.

4-Methoxy-N-p-tolylbenzamide **(18j):** Yield 97%; White solid; mp: 186-188 °C (lit.[34] 169-170 °C); IR (KBr, cm^{-1}): 3340, 2916, 2839, 1651, 1605, 1520, 841, 818; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 2H), 7.80 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 162.4, 135.5, 133.9, 129.5, 128.8, 127.2, 120.3, 113.9, 55.4, 20.9.

3,4,5-Trimethoxy-N-phenylbenzamide **(18k):** Yield 60%; Yellow solid; mp: 139-140 °C (lit.[35] 137-139 °C); IR (KBr, cm^{-1}): 3249, 2924, 1682, 1643, 1589, 841, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.68 – 7.63 (m, 2H), 7.41 – 7.35 (m, 2H), 7.17-7.15 (m, 1H), 7.08 (s, 2H), 3.91 (s, 3H), 3.90 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 153.3, 141.2, 137.9, 130.4, 129.1, 124.6, 120.3, 107.9, 104.5, 60.9, 56.3.

N-Butylbenzamide **(18l):** Yield 82%; Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 2H), 7.50 – 7.45 (m, 1H), 7.40 (dd, *J* = 8.6, 7.2 Hz, 2H), 6.48 (s, 1H), 3.44 (dd, *J* = 13.0, 7.2 Hz, 2H), 1.60 (dt, *J* = 14.9, 7.5 Hz, 2H), 1.40 (dq, *J* = 14.5, 7.3 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 134.8, 131.2, 128.4, 126.9, 39.8, 31.7, 20.1, 13.7.

N-Ethylbenzamide **(18m):** Yield 56%; Off-white solid; mp: 110-114 °C (lit.[36] 106-108 °C); IR (KBr, cm^{-1}): 3294, 2978, 2932, 1666, 1605, 1551; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.9 Hz, 2H), 7.23 (dd, *J* = 15.5, 7.4 Hz, 2H), 7.02 (t, *J* = 7.3 Hz, 1H), 2.32 (q, *J* = 7.5 Hz, 2H), 1.18 (dd, *J* = 9.0, 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 137.9, 128.9, 124.1, 119.7, 30.7, 29.7, 9.6.

N-(Benzo[d]thiazol-2-yl)benzamide **(18n):** Yield 48%; Off-white solid; mp: 188-191 °C (lit.[37] 188-190 °C); IR (KBr, cm^{-1}): 3225, 3055, 2962, 1674, 1597, 1551; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.66 (s, 1H), 8.22 (d, *J* = 6.4 Hz, 1H), 8.09 (d, *J* = 6.5 Hz, 1H), 7.85 (s, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.52 – 7.39 (m, 3H), 7.33 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 147.4, 133.1, 131.9, 130.0, 128.9, 128.4, 128.0, 126.2, 124.0, 121.4, 120.4.

N-Phenylnicotinamide **(18o):** Yield 63%; off white solid; mp: 112-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.91 (s, 1H), 8.67 (s, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 3H), 7.16 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 152.1, 147.9, 137.6, 135.6, 130.9, 129.0, 125.0, 123.7, 120.7.

N-(Quinoline-6-yl)benzamide **(18p):** Yield 59%; yellow solid; mp: 155-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 2.8 Hz, 1H), 8.50 (s, 1H), 8.47 (s, 1H), 8.12–8.05 (m, 2H), 7.94 (d, *J* = 7.4 Hz, 2H), 7.72 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.38 (dd, *J* = 8.2, 4.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 149.5, 145.6, 135.9, 134.6, 133.8, 132.0, 130.1, 128.8, 127.14, 123.5, 121.6, 116.6, 107.4.

IL-supported pyridone **(19):** White solid; mp: 70-72 °C; IR (KBr, cm^{-1}): 3140, 2932, 1659, 1582, 1535, 1250, 841, 771; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 – 7.75 (m, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.40 (m, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.40 (d, *J* = 9.1 Hz, 1H), 6.23 (t, *J* = 7.2 Hz, 1H), 5.02 (s, 2H), 4.28 (t, *J* = 6.8 Hz, 2H), 3.97 (t, *J* = 5.9 Hz, 2H), 3.73 (s, 3H), 3.34 (s, 3H), 2.19 (p, *J* = 6.3 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.8, 158.0, 144.9, 140.4, 139.4, 130.2, 129.8, 122.8, 121.4, 120.3, 114.9, 105.9, 64.6, 50.9, 45.2, 35.1, 29.1, 9.5.

Representative procedure for the regeneration of 15 from 20

A 10 ml clean oven dried round bottom flask was charged with IL-supported pyridone **20** (168 mg, 0.347 mmol) and phosphorus oxychloride (95 µL, 1.04 mmol) was added dropwise at room temperature. The reaction mixture was then heated at 80 ^{O}C for 8 h. After completion of the reaction, the volatile impurities were removed under reduced pressure. To the residue was added dry acetonitrile (5 mL) and sodium triflouromethansulfonate (80 mg). The reaction mixture was again refluxed for 12 h. After complete anaion metathesis, the reaction mixture was filtered through a thin pad of silica to remove solid impurity and the filtrate was concentrated to get viscous product. The viscous liquid on washing with ethyl acetate (5 mL × 3) resulted into desired reagent **15**.

Conclusion

In conclusion, we have developed a shelf stable and efficient imidazolium salt-supported Mukaiyama reagent. This reagent is utilized for amide bond formation between carboxylic acids and amines. The significance of this protocol is evading column chromatography, shorter reaction time and good to excellent yields of amides. The isolated by-product imidazolium salt-supported pyridone **19** can be further utilized in regeneration of Mukaiyama reagent.[24a]

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