

View Article Online View Journal

RSC Advances

This article can be cited before page numbers have been issued, to do this please use: K. Pandey, M. K. Muthyala, S. Sunita Choudhary and A. Kumar, *RSC Adv.*, 2015, DOI: 10.1039/C4RA14856H.



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This Accepted Manuscript will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the <u>Ethical guidelines</u> still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



www.rsc.org/advances

Graphical Abstract

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



ARTICLE TYPE

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

Khima Pandey, Manoj Kumar Muthyala, Sunita Choudhary and Anil Kumar^{*a}

Received (in XXX, XXX) Xth XXXXXXXX 20XX, Accepted Xth XXXXXXXX 20XX 5 DOI: 10.1039/b000000x

A novel imidazolium salt-supported Mukaiyama reagent (2chloropyridinium 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 10 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 ¹⁵ 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 ²⁰ 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 rearrangement⁶
- ²⁵ 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
- ³⁰ 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-
- ³⁵ 1,2-dihydroquinoline (EEDQ),⁹ the boron reagent B(OCH₂CF₃)₃,¹⁰ nano-Mgo¹¹ 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-2-40 chloropyridinium iodide (Mukaiyama reagent) (1) is an efficient activating agent for the formation of esters,¹³ carboxamides,¹⁴
- activating agent for the formation of esters,¹⁵ carboxamides,¹⁴ ketenes,¹⁵ lactones¹⁶ and lactams¹⁷ from carboxylic acids. Despite its great success, it is also associated with some issues of solubility, stability and purification of coupled products.¹⁸ In
- ⁴⁵ 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 50 example, Xu et. al.¹⁹ have synthesized a novel N-ethyl-2bromopyridinium tetrafluoroborate as an excellent coupling reagent for peptide synthesis with high activity and a low level of racemisation. The Tye,²⁰ Taddei²¹ and Swinnen²² groups have independently developed polymer-supported Mukaiyama 55 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 60 2-chloropyridinium salts, low loading capacity, high cost and slower reaction rates makes these approaches less attractive. Nagashima²³ and Matsugi²⁴ 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 65 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 saltsupported reagents have gained considerable interest as a promising alternative soluble support for reagents owing to their 70 high loading capacity, tuneable solubility, homogeneity and easy monitoring of the reaction by various analytical techniques such as NMR, IR and mass spectroscopy.²⁶



Fluorous-supported Mukaiyama reagents

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

Solid-supported Mukaiyama reagents

75

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 (2-80 chloropyridinium salt) and its application in amide bond formation. To the best of our knowledge this is the first report of Published on 13 January 2015. Downloaded by Brigham Young University on 15/01/2015 04:26:30

the synthesis of an imidazolium salt-supported Mukaiyama reagents.

Result and discussion

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

- 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-hydroxybenzaldehyde (12) as shown in Scheme 1. Reaction of 12 with 1-20 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 $_{25}$ with aqueous KPF₆ resulted in corresponding imidazolium saltsupported 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 saltsupported Mukaiyama reagent 15 in good yield (55%). It is
- ³⁰ believed that sequential *in situ* formation of imidazolium saltsupported triflic acid ester followed by quaternization of 2chloropyridine 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 ¹H NMR,
- $_{35}$ 13 C NMR and HRMS (Supporting information). Presence of two singlets at 3.73 ppm (N*CH*₃) and 5.92 ppm (Ph*CH*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
- ⁴⁰ ¹H NMR spectrum of **15** clearly indicated that the 2chloropyridne has been tagged with imidazolium ion. Similarly, the number of peaks in the ¹³C NMR spectrum of **15** were well in

agreement with the proposed sturcture. Presence of the peaks at m/z 502.4 [M-CF₃SO₃]⁺ and 506.3 [M-PF₆]⁺ in the mass spectrum ⁴⁵ 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 ⁵⁰ 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, ⁵⁵ 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 ⁶⁰ lead to the formation of the ester as a by-product.

Table 1: Optimization of reaction conditions for amide bond formation

0 ₂ N-	-СООН + H ₂ N-С-Вг 17	15, Et ₃ N, solvent	O ₂ NBr 18a			
Entry	Solvent	Time (h)	Yield (%)			
1	DCM	2	72 (62) ^a			
2	CH ₃ CN	2	55			
3	CH ₃ CN	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						

65 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). 70 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 75 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). 80 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 85 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 90 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

structure of imidazolium salt-supported pyridone 20 was confirmed by ¹H NMR, ¹³C NMR and IR spectroscopy

(Supporting information). It is worth to mention that recovered

¹⁰ IL-supported pyridone (20) can be easily converted to reagent 15 by reacting with phosphorus oxychloride followed by anion

metathesis with sodium trifluoromethanesulfonate.^{24a}

heteroamines. All the amides were obtained in excellent purity after simple workup without additional chromatography. The melting point and ¹H NMR data for the synthesized amides were in agreement with the reported data in the literature. The by-5 product imidazolium salt-supported pyridone 20 was easily removed from the reaction mixture by simple washing. The

Table 2: S

Published on 13 January 2015. Downloaded by Brigham Young University on 15/01/2015 04:26:30.

: Substrate	scope for amide formation R^{0}	n using reagent 15 H ⁺ R'NH ₂ 17	$2 \xrightarrow{15 20} 0$ $NEt_3, THF, R_2 atm, reflux 18a$	√ [.] R' + - p	
Entry	R	Rʻ	Product	Time (h)	Yield (%) ^a
1	C_6H_5	C_6H_5	HN 18a	3	87
2	C_6H_5	4-CH ₃ C ₆ H ₄		2	93
3	C ₆ H ₅	4-BrC ₆ H ₄	HNBr 18c	3	70
4	$C_{6}H_{5}$	C ₆ H ₅ CH ₂		3	68
5	4-NO ₂ C ₆ H ₄	C ₆ H ₅		3	90
6	4-NO ₂ C ₆ H ₄	4-CH ₃ C ₆ H ₄		3	95
7	$4\text{-NO}_2C_6H_4$	4-BrC ₆ H ₄	O_2N HN Br Br $I8g$	2	84
8	$4-NO_2C_6H_4$	$C_6H_4CH_2$	O ₂ N- 18h	3	90
9	4 - $CH_3OC_6H_4$	C_6H_5		3	92
10	C_6H_5	$4\text{-}CH_3OC_6H_4$		3	95
11	3,4,5-(CH ₃ O) ₃ C ₆ H ₄	4-CH ₃ C ₆ H ₄	H_3CO H_3CO H_3CO H_3CO H_3CO H_8k	5	60

ARTICLE TYPE

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx



It is believed that the reaction proceeds through initial activation of carboxylic acid (16) by IL-supported 2-chloropyridinium ⁵ 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)



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

Experimental

General

Published on 13 January 2015. Downloaded by Brigham Young University on 15/01/2015 04:26:30

The NMR (¹H and ¹³C) spectra were recorded on 300 MHz and 400 MHz spectrometer in CDCl₃ and DMSO- d_6 . The chemical shifts were expressed in ppm and coupling constants (*D* in Hz

- ¹⁵ 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-F₂₅₄ plates. Melting points were ²⁰ 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 25 otherwise specified

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

4-Hydroxybenzaldehyde (8.00 g, 65 mmol), 1-bromo-3-

chloropropane (6.46 mL, 65 mmol) and potassium carbonate ³⁰ (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 \times 2). The organic layer was dried with anhydrous sodium ³⁵ 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 ⁴⁰ 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 ⁴⁵ 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%); ⁵⁰ mp: 53-55 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ 158.4, 133.4, 128.7, 114.6, 65.0, 64.3, 41.5, 32.3.

55 General procedure for the synthesis of imidazolium saltsupported 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 $_{60}$ (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 5 and washed with water and dried in vacuum to get pure **14**.

Yield: 11.37 g, 97%; mp: 115 °C; ¹H 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 ¹⁰ (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); ¹³C 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-15 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 N₂ atmosphere. Triflic anhydride (6.40 mL, 38 mmol) was added drop wise over 5 min. After complete addition, the resulting ²⁰ 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; ¹H NMR (300 MHz, DMSO- d_6) ²⁵ 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 = ³⁰ 6.3 Hz, 2H); ¹³C 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-PF₆]⁺.

Representative procedure for the amide bond formation ³⁵ 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

- ⁴⁰ (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 \times 2) from viscous mixture and washed
- ⁴⁵ with 2M HCl solution (5.0 mL \times 3) and saturated bicarbonate solution (5.0 mL \times 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%).
- ⁵⁰ *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; ¹H NMR (400 MHz, CDCl₃) 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* = ⁵⁵ 7.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) 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; ¹H NMR (400 MHz, CDCl₃) δ 7.96 ⁶⁰ (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); ¹³C NMR (101 MHz,

2H), 7.18 (d, J = 8.2 Hz, 2H), 2.36 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) 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; ⁶⁵ mp: 196-198 °C (lit.³¹ 200-202 °C); IR (KBr, cm⁻¹): 3322, 2935, 1644, 1588, 1530, 1360, 830; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ 165.6, 137.0, 134.6, 132.1, 128.9, 127.0, 121.7, 117.1.
- ⁷⁰ *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; ¹H NMR (300 MHz, CDCl₃) 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 ⁷⁵ (d, *J* = 5.6 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) 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; ¹H NMR (400 MHz, CDCl₃) ⁸⁰ 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); ¹³C NMR (101 MHz, CDCl₃) 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: ⁸⁵ 200-203 °C (lit.²⁸ 201-203 °C); IR (KBr, cm⁻¹): 3317, 2924, 2854, 1651, 1597, 1528, 1350, 1319, 849; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 163.4, 149.7, 140.6, 135.1, 134.6, 90 129.7, 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; ¹H NMR (300 MHz, CDCl₃) δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.33 – 7.21 (m, 5H), 95 6.62 (s, 1H), 4.56 (d, *J* = 5.7 Hz, 2H), ¹³C NMR (75 MHz, CDCl₃) 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; ¹H 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); ¹³C NMR (101 MHz, CDCl₃) δ 163.9, 149.2, 140.4, 137.8, 131.4, 129.1, 123.2, 122.4, 116.5.

¹⁰⁵ *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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C
¹¹⁰ NMR (101 MHz, CDCl₃) δ 165.6, 156.6, 135.0, 131.7, 131.0, 128.7, 127.0, 122.1, 114.2, 55.5.

Published on 13 January 2015. Downloaded by Brigham Young University on 15/01/2015 04:26:30

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; ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, J = 8.8 Hz, 2H), 7.80 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 5 7.18 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H), 2.36 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) 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, ¹⁰ 2924, 1682, 1643, 1589, 841, 756; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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.

¹⁵ *N-Butylbenzamide* (**181**): Yield 82%; Colourless liquid; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ ²⁰ 167.7, 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; ¹H NMR (300 MHz, CDCl₃) 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), 25 2.32 (q, *J* = 7.5 Hz, 2H), 1.18 (dd, *J* = 9.0, 6.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) 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, 30 3055, 2962, 1674, 1597, 1551; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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.

³⁵ *N-Phenylnicotinamide* (**180**): Yield 63%; off white solid; mp: 112-115 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ 164.2, 152.1, 147.9, 137.6, 135.6, 130.9, ⁴⁰ 129.0, 125.0, 123.7, 120.7.

N-(*Quinoline-6-yl*)*benzamide* (**18p**): Yield 59%; yellow solid; mp: 155-158 °C; ¹H NMR (400 MHz, CDCl₃) 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,

⁴⁵ 1H), 7.48 (t, J = 7.4 Hz, 2H), 7.38 (dd, J = 8.2, 4.2 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) 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; ¹H NMR

⁵⁰ (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); ⁵⁵ ¹³C 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 ⁶⁰ IL-supported pyridone **20** (168 mg, 0.347 mmol) and phosphorus oxychloride (95 μ L, 1.04 mmol) was added dropwise at room temperature. The reaction mixture was then heated at 80 °C for 8 h. After completion of the reaction, the volatile impurities were removed under reduced pressure. To the residue was added dry ⁶⁵ 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 ⁷⁰ washing with ethyl acetate (5 mL \times 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 ⁷⁵ 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 ⁸⁰ Mukaiyama reagent.^{24a}

Acknowledgements

The authors sincerely acknowledge the financial support from Council of Scientific and Industrial Research (CSIR), New Delhi (01(115)/13/EMR-II) for this research. KP thanks UGC, New 85 Delhi for junior research fellowship (JRF) and MMK and SC thank CSIR, New Delhi for providing senior research fellowship

Notes

(SRF).

^aDepartment of Chemistry, Birla Institute of Technology and Science, 90 Pilani, Rajasthan, India, PIN-333031. Phone: +91-1596-245652. Fax:

+91-1596-244183.

E-mail: anilkumar@pilani.bits-pilani.ac.in.

†Electronic Supplementary Information (ESI) available: [Copies of ¹H and ¹³C NMR spectra for compounds 13, 14, 15, 18a-p and 19]. See 95 DOI: 10.1039/b000000x/

References

105

(a) B. Rogge, Y. Itagaki, N. Fishkin, E. Levi, R. Rühl, S.-S. Yi, K. Nakanishi and U. Hammerling, *J. Nat. Prod.*, 2005, **68**, 1536-1540;
 (b) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451-3479;
 (c) S. Ahmed, J. H. Mondal, N. Behera and D. Das,

Langmuir, 2013, **29**, 14274-14283; (d) C. Yu and K. Mosbach, *J. Org. Chem.*, 1997, **62**, 4057-4064.

(a) D. Fattori, M. Porcelloni, P. D'Andrea, R.-M. Catalioto, A. Ettorre, S. Giuliani, E. Marastoni, S. Mauro, S. Meini, C. Rossi, M. Altamura and C. A. Maggi, *J. Med. Chem.*, 2010, **53**, 4148-4165;
 (b) K. Lee, C. W. Park, W.-H. Jung, H. D. Park, S. H. Lee, K. H. Chung, S. K. Park, O. H. Kwon, M. Kang, D.-H. Park, S. K. Lee, E. E. Kim, S. K. Yoon and A. Kim, *J. Med. Chem.*, 2003, **46**, 3612-3622.

75

- F. Damkaci and P. DeShong, J. Am. Chem. Soc., 2003, 125, 4408-4409.
- 4. M. P. Cassidy, J. Raushel and V. V. Fokin, *Angew. Chem. Int. Ed.*, 2006, **45**, 3154-3157.
- T. Ribelin, C. E. Katz, D. G. English, S. Smith, A. K. Manukyan, V. W. Day, B. Neuenswander, J. L. Poutsma and J. Aubé, *Angew. Chem. Int. Ed.*, 2008, 47, 6233-6235.
- M. Hashimoto, Y. Obora, S. Sakaguchi and Y. Ishii, J. Org. Chem., 2008, 73, 2894-2897.
- (a) T. M. U. Ton, C. Tejo, S. Tania, J. W. W. Chang and P. W. H. Chan, J. Org. Chem., 2011, **76**, 4894-4904; (b) V. Prasad, R. R. Kale, B. B. Mishra, D. Kumar and V. K. Tiwari, Org. Lett., 2012, **14**, 2936-2939; (c) S. Muthaiah, S. C. Ghosh, J.-E. Jee, C. Chen, J. Zhang and S. H. Hong, J. Org. Chem., 2010, **75**, 3002-3006; (d) S.
- 15 C. Ghosh, J. S. Y. Ngiam, C. L. L. Chai, A. M. Seayad, T. T. Dang and A. Chen, *Adv. Synth. Catal.*, 2012, **354**, 1407-1412.
- J. Xiao, G. Yuan, W. Huang, A. S. C. Chan and K. L. D. Lee, J. Org. Chem., 2000, 65, 5506-5513.
- B. Zacharie, T. P. Connolly and C. L. Penney, J. Org. Chem., 1995, 60, 7072-7074.
- R. M. Lanigan, P. Starkov and T. D. Sheppard, J. Org. Chem., 2013, 78, 4512-4523.
- 11. V. K. Das, R. R. Devi and A. J. Thakur, *Appl. Catal.*, *A*, 2013, **456**, 118-125.
- 25 12. (a) G. Quéléver, S. Burlet, C. Garino, N. Pietrancosta, Y. Laras and J.-L. Kraus, *J. Comb. Chem.*, 2004, **6**, 695-698; (b) C. A. G. N. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827-10852.
- 13. T. Mukaiyama, M. Usui, E. Shimada and K. Saigo, *Chem. Lett.*, 1975, **4**, 1045-1048.
- 30 14. E. Bald, K. Saigo and T. Mukaiyama, Chem. Lett., 1975, 4, 1163-1166.
 - 15. R. L. Funk, M. M. Abelman and K. M. Jellison, *Synlett*, 1989, **1989**, 36-37.
- 16. T. Mukaiyama, M. Usui and K. Saigo, Chem. Lett., 1976, 5, 49-50.
- 35 17. H. Huang, N. Iwasawa and T. Mukaiyama, Chem. Lett., 1984, 13, 1465-1466.
 - H. L. Bradlow and C. A. Vanderwerf, J. Org. Chem., 1951, 16, 1143-1152.
- 19. P. Li and J.-C. Xu, Tetrahedron, 2000, 56, 8119-8131.

Published on 13 January 2015. Downloaded by Brigham Young University on 15/01/2015 04:26:30

- 40 20. E. Convers, H. Tye and M. Whittaker, *Tetrahedron Lett.*, 2004, 45, 3401-3404.
- D. Donati, C. Morelli, A. Porcheddu and M. Taddei, J. Org. Chem., 2004, 69, 9316-9318.
- 22. S. Crosignani, J. Gonzalez and D. Swinnen, *Org. Lett.*, 2004, **6**, 4579-4582.
- 23. T. Nagashima, Y. Lu, M. J. Petro and W. Zhang, *Tetrahedron Lett.*, 2005, **46**, 6585-6588.
- (a) Y. Sugiyama, Y. Kurata, Y. Kunda, A. Miyazaki, J. Matsui, S. Nakamura, H. Hamamoto, T. Shioiri and M. Matsugi, *Tetrahedron*, 2012, **68**, 3885-3892; (b) M. Matsugi, S. Nakamura, Y. Kunda, Y.
- Sugiyama and T. Shioiri, *Tetrahedron Lett.*, 2010, **51**, 133-135.
 25. R. Berger, G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, *Chem. Soc. Rev.*, 2011, **40**, 3496-3508.
- 26. (a) N. V. Plechkova and K. R. Seddon, *Chem. Soc. Rev.*, 2008, 37, 123-150; (b) M. Pucheault and M. Vaultier, in *Ionic Liquids*, ed. B.
- Kirchner, Springer Berlin Heidelberg, 2010, vol. 290, pp. 83-126.
 27. (a) M. K. Muthayala, B. S. Chhikara, K. Parang and A. Kumar, ACS Comb. Sci., 2011, 14, 60-65; (b) M. K. Muthayala and A. Kumar,
- ACS Comb. Sci., 2011, 14, 5-9; (c) M. K. Muthyala, S. Choudhary
 and A. Kumar, J. Org. Chem., 2012, 77, 8787-8791; (d) M. Kumar
 Muthyala, S. Choudhary, K. Pandey, G. M. Shelke, M. Jha and A. Kumar, Eur. J. Org. Chem., 2014, 2014, 2365-2370.
- 28. J. Gao and G.-W. Wang, J. Org. Chem., 2008, 73, 2955-2958.
- 29. Z. Zhang, Y. Yu and L. S. Liebeskind, *Org. Lett.*, 2008, **10**, 3005-3008.
- V. K. Haridasan, A. Ajayaghosh and V. N. R. Pillai, J. Org. Chem., 1987, 52, 2662-2665.
- L. Kumar, T. Mahajan and D. D. Agarwal, *Green Chem.*, 2011, 13, 2187-2196.
- 70 32. C. L. Allen, S. Davulcu and J. M. J. Williams, Org. Lett., 2010, 12, 5096-5099.
- A. R. Katritzky, C. Cai and S. K. Singh, J. Org. Chem., 2006, 71, 3375-3380.

- 34. Y. Wu, S. Wang, L. Zhang, G. Yang, X. Zhu, Z. Zhou, H. Zhu and
- S. Wu, Eur. J. Org. Chem., 2010, 2010, 326-332.
- 35. J. Pharm. Pharmacol., 1960, 12, 82-86.
- 36. L.-F. Liu, H. Liu, H.-J. Pi, S. Yang, M. Yao, W. Du and W.-P. Deng, *Synth. Commun.*, 2011, **41**, 553-560.
- 37. D. Fajkusova and P. Pazdera, Synthesis, 2008, 2008, 1297-1305.