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REGULAR ARTICLE

A potential greener protocol for peptide coupling reactions using recyclable/reusable ionic liquid [C_4-DABCO][$N(CN)_2$]

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Abstract. Development of greener methodologies in synthetic organic chemistry has brought awareness in recent decades due to the ecological performance of green solvent media and catalytic systems. Here, we carried out the peptide bond formation reaction in one of the environmentally secure solvents, 'ionic liquids' in the presence of coupling reagent and in the absence of external base at room temperature, affording dipeptides in good to excellent yields.

Keywords. Base free; green chemistry; ionic liquid; peptides synthesis.

1. Introduction

The peptide synthesis has drawn significant importance due to the most resourceful carbon-nitrogen bond formation with the advantages like milder reaction conditions, atom efficiency, tolerability to various functional groups as well as its varied applications in a number of pharmaceutical, agrochemical and other industries.[1,2] Peptide synthesis deals with the amide bond formation of amino acids in protein chemistry and encourages the researchers for advanced synthesis in a smarter manner like as nature does in living systems.[3] Mimicking the natural protocol for the peptide synthesis, the development of speedy and proficient synthesis protocols has been a feature in the pharmaceutical prospective of peptides to be realized and would likely be welcomed.[4–6] There were 55 peptide-based drugs developed and a further 200 in clinical phases up to 2016. Many more research works are going on which signify the pharmaceutical importance of peptide chemistry (Figure 1).[7]

The amide linkage is the universal feature in small synthetic or natural molecules and proteins which play a vital role in practically all biological processes.[8,9] Literature survey showed that in both solution and solid phase, the C-terminal modified peptide fragments (protected and/or activated) can be readily stitched together in segment condensations for the assembly of large peptides or small proteins.[10,11]

The elementary reaction to synthesize the dipeptide is the coupling of two amino acids. This reaction proceeds in homogeneous conditions in the presence of a base such as NEt_3, K_2CO_3, $NaHCO_3$, etc., and a coupling agent such as DCC, EDC, etc., along with some promoters which increase the reaction rate.[12]

Literature survey reveals the use of imidazole-based or incorporated ionic liquids for the synthesis of peptides at room temperature or at elevated temperatures. Galy *et al.*,[13a] recently reported the ionic liquid-assisted peptide synthesis at room temperature, but the reaction time for peptide coupling was quite long (24 h). Kühl *et al.*,[13b] reported peptide ligation reaction showing different side chain reactions using 1-ethyl-3-methylimidazolium acetate as an ionic liquid. Petiot *et al.*,[13c] synthesized hydrophilic poly(ethylene glycol)-ionic liquid medium for the peptide synthesis and Seitkalieva *et al.*,[13d] reported peptide extraction through ionic liquid of imidazolium-type.

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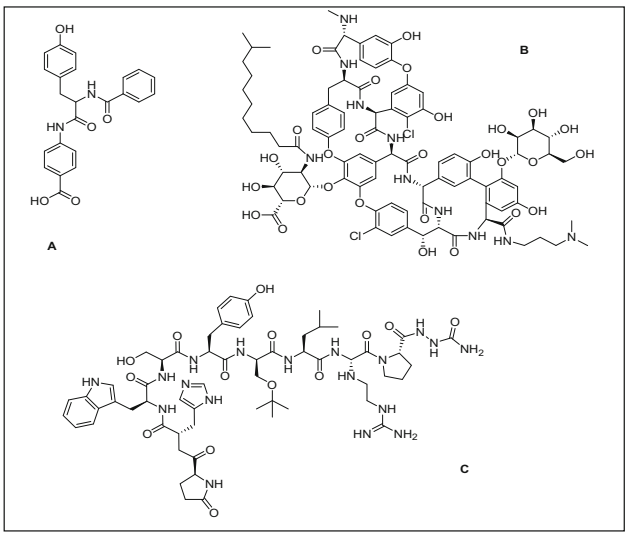


Figure 1. Some biologically active peptide molecules. [A] Bentiromide (exocrine pancreatic insufficiency screening); [B] Dalbavancin (antibiotic); [C] Goserelin (anticancer).

Similarly, Vallette *et al.,* [14a] and Chan *et al.,* [14b–c] carried out peptide synthesis by the use of neutral ionic liquids. But these methods have some shortcomings such as the use of the external base, elevated reaction temperature, low reaction yield, adverse effect on environment leading to pollution. [15,16] The role of coupling agent in peptide bond formation is proved to be unfavorable when the coupling reaction is carried out in aqueous condition. [17] Base catalyzes the hydrolysis of amino acid ester, which is used as a coupling partner, thus inhibiting the reaction progress. [18,19] It is, therefore, of prime importance to build up recyclable and reusable homogeneous reaction conditions, which will formulate the reaction more atom-economic.

It is becoming progressively more essential to replace environmentally harmful volatile organic solvents in the chemical manufacturing processes. Amongst the various alternative solvents such as water, polyethylene glycol and supercritical fluids, a potential alternative is the room-temperature ionic liquids (RTILs) to carry out the organic reactions. [20,21] Since these liquids are salts of different cations and anions, we can design them simply by changing the cation or anion, known as "Designer Solvents" in recent decades. [22,23] The impressive effects of ionic liquids on any reaction are due to the interaction of cations and anions with solutes molecules and hence they are of prime interest in the scholarly research and industrial sectors. [24–27] The much lower melting points of room temperature ionic liquids compared to inorganic salts can be partially attributed to the bulky cationic groups. These liquids have a lower vapour pressure, non-flammable, high chemical and thermal stability, superior ionic conductivity and afford superior solubility for an extensive range of compounds (both organic and inorganic). [28–30] Ionic liquids can be considered as promising and novel alternatives for organic solvents in synthetic organic chemistry due to easy preparation and recyclability, and their properties can be tuned by varying the alkyl group and anion. [31,32] Therefore, the main objective of our work was to synthesize the dipeptide moieties in greener and cheaper reaction conditions. In search of greener methodologies, we mainly focused on the use of ionic liquids that were liquid at room temperature and basic in nature. Use of basic ionic liquid nullifies the requirement of organic solvent and external base for peptide coupling.

2. Experimental

All reagents and solvents were purchased from Sigma Aldrich and Alfa Aesar and used without further purification unless otherwise stated. All reported yields are isolated yields. Peptide coupling reactions were performed on oven-dried glassware at open air. ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz spectrometers at room temperature, respectively. Chemical shifts are reported in parts per million (ppm, δ). Column chromatography was performed on silica gel (200–300 mesh). Thin layer chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel $60F_{254}$ (Merck) and was visualized under 254 nm UV light.

2.1 *Procedures*

2.1a *Preparation of [C_4-DABCO][$N(CN)_2$]*: In a round bottom flask, a mixture of DABCO (5 g; 44.57 mmol) and n-butyl bromide (6.10 g; 44.57 mmol) in 30 mL ethyl acetate was added and stirred at room temperature, overnight. After overnight stirring, neutral ionic liquid [C_4-DABCO][Br] was obtained as white solid. The reaction mixture was washed with ethyl acetate four times for complete removal of n-butyl bromide and other organic compounds. It was then subjected to vacuum to obtain the pure solid [C_4-DABCO][Br]. On the other hand, silver dicyanamide ($AgN[CN]_2$) was prepared by mixing the equimolar amount of silver nitrate (7.33 g, 43.13 mmol) and sodium dicyanamide (3.84 g, 43.13 mmol) in water. Freshly prepared silver dicyanamide was added to the [C_4-DABCO][Br] in water and stirred overnight at room temperature. Water was removed in vacuum to obtain the pure [C_4-DABCO][$N(CN)_2$] as a colourless liquid. Yield = 98%.

2.1b *Preparation of [EMIM][BF_4]*: In a round bottom flask, a mixture of 1-methyl imidazole (4.1 g; 50 mmol) and ethyl bromide (5.45 g, 50 mmol) was stirred at 80 °C in neat condition for 10 h. After that, neutral ionic liquid [EMIM][Br] was obtained as white solid. The reaction mixture was washed with ethyl acetate four times for complete removal of n-ethyl bromide and other organic compounds. It was then subjected

to vacuum to obtain the pure solid [EMIM][Br]. After that, sodium tetrafluoroborate (5.3 g, 48.17 mmol) was added to the [EMIM][Br] in acetone and stirred overnight at room temperature to obtain [EMIM][BF_4]. The solution was filtered and acetone was removed in vacuum to obtain the pure [EMIM][BF_4] as a colorless liquid.

2.1c *Preparation of [EMIM][OH]*: In a round bottom flask, a mixture of 1-methyl imidazole (4.1 g; 50 mmol) and ethyl bromide (5.45 g, 50 mmol) was stirred at 80 °C in neat condition for 10 h. After that, neutral ionic liquid [EMIM][Br] was obtained as white solid. The reaction mixture was washed with ethyl acetate four times for complete removal of n-ethyl bromide and other organic compounds. It was then subjected to vacuum to obtain the pure solid [EMIM][Br]. After that, potassium hydroxide (2.7 g, 48.15 mmol) was added to [EMIM][Br] to get [EMIM][OH]. The solution was filtered and acetone was removed in vacuum to obtain the pure [EMIM][BF_4] as a colorless liquid and [EMIM][OH] as a brown liquid.

2.1d *Preparation of [BMIM][BF_4]*: In a round bottom flask, a mixture of 1-methyl imidazole (4 g; 48.78 mmol) and n-butyl bromide (6.7 g; 48.78 mmol) was stirred at 80 °C in neat condition for 10 h. After that, neutral ionic liquid [BMIM][Br] was obtained as white solid. The reaction mixture was washed with ethyl acetate four times for complete removal of n-butyl bromide and other organic compounds. It was then subjected to vacuum to obtain the pure solid [BMIM][Br]. After that, sodium tetrafluoroborate (5 g, 45.66 mmol) was added to the [BMIM][Br] in acetone and stirred overnight at room temperature to obtain [BMIM][BF_4]. The solution was filtered and and acetone was removed in vacuum to obtain the pure [BMIM][BF_4] as colorless liquid.

2.1e *Preparation of [BMIM][OH]*: In a round bottom flask, a mixture of 1-methyl imidazole (4 g; 48.78 mmol) and n-butyl bromide (6.7 g; 48.78 mmol) was stirred at 80 °C in neat condition for 10 h. After that, neutral ionic liquid [BMIM][Br] was obtained as white solid. The reaction mixture was washed with ethyl acetate four times for complete removal of n-butyl bromide and other organic compounds. It was then subjected to vacuum to obtain the pure solid [BMIM][Br]. After that, potassium hydroxide (2.5 g, 44.75 mmol) was added to [BMIM][Br] to get [BMIM][OH]. The solution was filtered and and acetone was removed in vacuum to obtain the pure [BMIM][OH] as dark brown liquid.

2.1f *Preparation of [OMIM][OH]*: In a round bottom flask, a mixture of 1-methyl imidazole (4 g; 48.78 mmol) and n-octyl bromide (9.42 g; 48.78 mmol) was stirred at 80 °C in neat condition for 10 h. After that, neutral ionic liquid [OMIM][Br] was obtained as white solid. The reaction mixture was washed with ethyl acetate four times for complete removal of n-octyl bromide and other organic compounds. It was then subjected to vacuum to obtain the pure solid [OMIM][Br]. After that, potassium hydroxide (2.65 g, 47.25 mmol) was added to the [OMIM][Br] in acetone and stirred overnight at room temperature to obtain [OMIM][OH]. The solution was filtered and acetone was removed in vacuum to obtain the pure [OMIM][OH] as dark brown liquid.

2.1g *Preparation of [BMIM][$N(CN)_2$]*: In a round bottom flask, a mixture of 1-methyl imidazole (4 g; 48.78 mmol) and n-butyl bromide (6.7 g; 48.78 mmol) was stirred at 80 °C in neat condition for 10 h. After that, neutral ionic liquid [BMIM][Br] was obtained as white solid. The reaction mixture was washed with ethyl acetate four times for complete removal of n-butyl bromide and other organic compounds. It was then subjected to vacuum to obtain the pure solid [BMIM][Br]. On the other hand, silver dicyanamide ($AgN[CN]_2$) was prepared by mixing equimolar amount of silver nitrate (7.72 g, 45.66 mmol) and sodium dicyanamide (4.07 g, 45.66 mmol) in water. Freshly prepared silver dicyanamide was added to the [BMIM][Br] in acetone and stirred overnight at room temperature. The solution was filtered and acetone was removed in vacuum to obtain the pure [BMIM][$N(CN)_2$] as colourless liquid.

All the ionic liquids are reported in the literature and were synthesized and characterized following the existing procedures.[33]

2.2 *General reaction procedure for peptide synthesis*

In a 50 mL round bottom flask, a mixture of N-benzoyl glycine (1 mmol, 0.179 g), glycine methyl ester hydrochloride (1.5 mmol, 0.188 g), EDC.HCl (1 equiv.) in [C_4-DABCO][$N(CN)_2$] (3 mL) was added and stirred at room temperature for 4 h. After completion of the reaction (by TLC monitoring), the reaction mixture was extracted with diethyl ether (3 × 10 mL) and the organic layer was washed with distilled water (20 mL), dried over anhydrous Na_2SO_4 and the organic layer was evaporated in vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes (1:1) as eluent to get the corresponding peptide.

3. Results and Discussion

In continuation of our work on peptide synthesis and applications of room temperature ionic liquids,[34,35] we have designed and synthesized a series of ionic liquids based on imidazole and DABCO and demonstrated their applications on peptide synthesis (Figure 2). One of the most important agents in peptide synthesis is the coupling reagent which is necessary to couple the amine and acid group of two amino acid residues in presence of a base.[36,37] The mostly used coupling reagents in peptide synthesis are DCC, EDC.HCl, DIC, etc. Ionic liquids based on imidazolium cations are likely to be unstable under basic condition.[38] Superior acidity at C-2 position of imidazole results in deprotonation

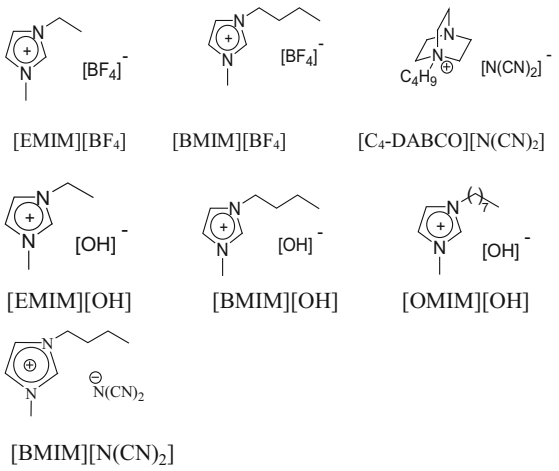
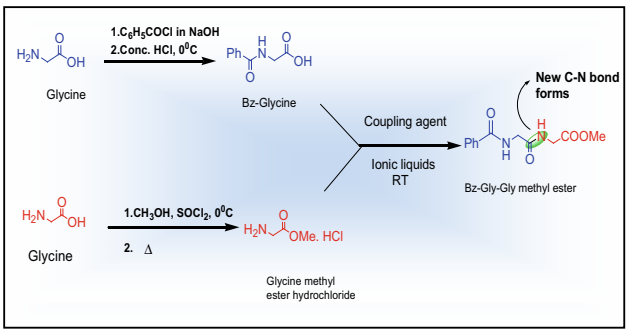


Figure 2. Ionic liquids used in this study.



Scheme 1. General reaction conditions for synthesis of dipeptide.

leading to the formation of N-heterocyclic carbenes which may lead to complexation and/or breakdown side reactions.[39] From this point, the ionic liquid/base combination could be detrimental for carrying out organic transformation. Therefore, our concern was to develop a base and organic media-free green protocol for the peptide synthesis. In our work, peptide synthesis was carried out in basic ionic liquids in the absence of any external base. We carried out peptide synthesis in five different basic ionic liquids; namely, i) 1-butyl-1,4-diazabicyclo[2.2.2]octane dicyanamide, [C_4-DABCO][$N(CN)_2$], ii) 1-butyl-3-methylimidazolium hydroxide, [BMIM][OH], iii) 1-ethyl-3-methylimidazolium hydroxide, [EMIM][OH], iv) 1-octyl-3-methylimidazolium hydroxide [OMIM][OH], and v) 1-butyl-3-methylimidazolium dicyanamide [BMIM][$N(CN)_2$] (Figure 2).[40] Peptide synthesis was also carried out in neutral ionic liquids [EMIM][BF_4] and [BMIM][BF_4] but in the presence of an external base.

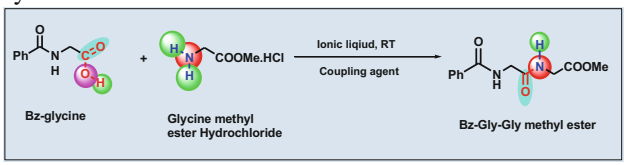
The reaction of N-benzoyl glycine and glycine methyl ester hydrochloride in presence of EDC.HCl in neutral ionic liquids [EMIM][BF_4] and [BMIM][BF_4] did not proceed at all even after 12 h (Table 1, entries 1-2). The same reaction in four basic ionic liquids [EMIM][OH], [BMIM][OH], [C_4-DABCO][$N(CN)_2$] and [OMIM][OH] afforded dipeptides in 40%, 65%, 98% and 78%, respectively (Table 1; entries 3–6). The same reaction in basic ionic liquid [C_4-DABCO][$N(CN)_2$] in the absence of coupling agent did not afford any dipeptide indicating the necessity of a coupling agent (Table 1; entry 7). From this outcome, [C_4-DABCO][$N(CN)_2$] was found to be the most excellent and suited basic ionic liquid for peptide synthesis at room temperature. The efficiency of the DABCO-based ionic liquids in peptide synthesis, as compared to other ionic liquids, is due to the presence of two nitrogen atoms at the bicyclo ring of DABCO and dicyanamide anion has high value of conductivities.[41] High viscosity of the ionic liquid is a detrimental factor for their use as an alternative solvent in organic synthesis. The ionic liquids based on dicyanamide anion, however, exhibit much lower viscosity than ionic liquids with other anions and these ionic liquids are considered as effective solvents for organic reactions due to the high complexing capability of dicyanamide anion.[42] To the best of our knowledge, no such observations are reported so far for carrying out peptide synthesis in basic ionic liquid.

Amino acids with different electron rich substituent were used to construct the dipeptide moiety in the absence of an external base and organic media-free environment (Table 2). Under this reaction condition, each amino acid with various electron rich groups reacts to afford the dipeptide in reasonably higher yields. The coupling of Bz-glycine and glycine methyl ester hydrochloride afforded Bz-Gly-Gly-methyl ester with a promising yield of 80% in 4 h (Table 2, entry 1). However, there are some amino acids giving poor yields of dipeptides which may due to the presence of more bulky phenyl rings (Table 2, entries 5,6,11-15). Good to excellent results of peptide coupling were obtained for amino acids with less bulky substituent (Table 2, entries 2-4,7-10) under this reaction condition.

In order to show the useful application of the solvent system consisting of ionic liquids and EDC.HCl, it is very important to recycle and reuse the catalytic system. It was seen that the catalytic system could be recovered and reused up to four times without any significant loss in its activity (Table 3).

To perform the recyclability test, in a 50 mL round bottom flask, a mixture of N-Bz glycine (1 mmol, 0.179 g), glycine methylester hydrochloride (1.5 mmol, 0.188 g), EDC.HCl (1 mmol, 0.192 g) in [C_4-DABCO][$N(CN)_2$] (3 mL) were added and stirred at room temperature for 4 h (Table 3, entry 1). After completion of the reaction (by TLC monitoring), the resulting mixture was

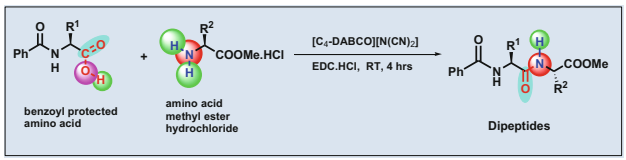
Table 1. Optimization of the base and the solvent system for the peptide synthesis.[a]



Entry	Solvent (IL)	Coupling agent	Time (h)	Yield[b](%)
1	[EMIM][BF_4]	EDC.HCl	12	n.r.
2	[BMIM][BF_4]	EDC.HCl	12	n.r.
3	[EMIM][OH]	EDC.HCl	4	40
4	[BMIM][OH]	EDC.HCl	4	65
5	[C_4-DABCO][$N(CN)_2$]	EDC.HCl	4	98
6	[OMIM][OH]	EDC.HCl	4	78
7	[C_4-DABCO][$N(CN)_2$]	–	12	n.r.
8	[BMIM][$N(CN)_2$]	EDC.HCl	12	50

[a]Reaction conditions: benzoyl glycine (1 mmol), glycine methyl ester hydrochloride (1.5 mmol), EDC.HCl (1 mmol), ionic liquid (3 mL) at room temperature.
[b]isolated yield.

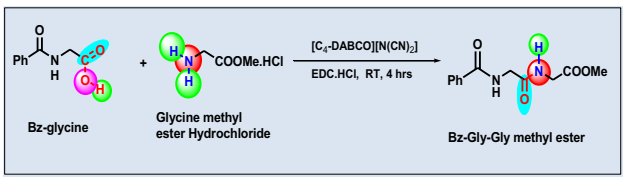
Table 2. Effect of substituent on peptide synthesis.[a]

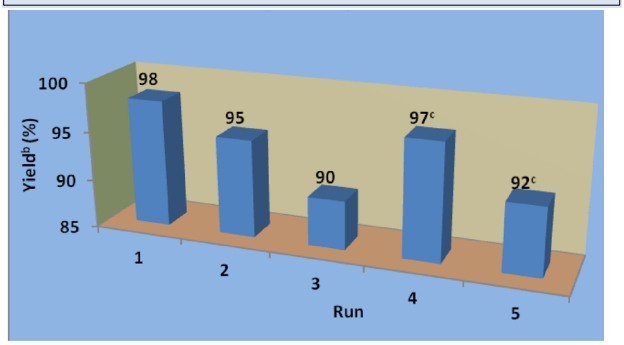


Entry	R^1	R^2	Yield[b](%)
1	-H	-H	98
2	$-CH_3$	$-CH_3$	85
3	-H	$-CH_3$	81
4	$-CH_3$	-H	83
5	$-CH_2$-Ph	-H	76
6	$-CH_2$-Ph	$-CH_3$	75
7	$-CH(CH_3)_2$	-H	79
8	$-CH(CH_3)_2$	$-CH_3$	77
9	$-CH_2-CH(CH_3)_2$	-H	75
10	$-CH_2-CH(CH_3)_2$	$-CH_3$	79
11	-H	$-CH_2$-Ph	76
12	$-CH_3$	$-CH_2$-Ph	74
13	$-CH_2$-Ph	$-CH_2$-Ph	70
14	$-CH(CH_3)_2$	$-CH_2$-Ph	72
15	$-CH_2-CH(CH_3)_2$	$-CH_2$-Ph	71

[a]Reaction conditions: benzoyl protected amino acid (1 mmol), amino acid methyl ester hydrochloride (1.5 mmol), EDC.HCl (1 mmol), [C_4-DABCO][$N(CN)_2$] (3 mL) at room temperature. [b]isolated yield.

Table 3. Recyclability test of the peptide synthesis.[a]





[a]Reaction conditions: benzoyl glycine (1 mmol), glycine methyl ester hydrochloride (1.5 mmol), EDC.HCl (1 mmol), [C_4-DABCO][$N(CN)_2$] (3 mL) at room temperature.
[b]isolated yield.
[c]time 5 h.

extracted with diethyl ether (3 × 10 mL) and the ether layer was separated and the catalytic medium was reused for next four runs (Table 3, entries 2-5). Any attempt to wash the catalytic medium by water was avoided as the ionic liquid [C_4-DABCO][$N(CN)_2$] was prepared in water and hence it is completely miscible with water.

4. Conclusions

This communication has summarized the development of a highly efficient ionic liquid-mediated peptide synthesis protocol. It is comprehensible that the ionic

liquids are similar in function with many other solvents in solution phase strategy.[43] Peptide coupling reactions were successfully carried out in an 'organic solvent and external base' free condition, affording peptides in good to excellent yields at room temperature. Due to the dual function, "alternative green solvent and base" of basic ionic liquids, it is believed that their use in organic transformation, peptide synthesis in particular, will gain more attention in near future.

Supplementary Information (SI)

General experimental procedure, NMR & MS spectra for all compounds with full characterization data are available as Supplementary Information at www.ias.ac.in/chemsci.

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