Tetrahedron Letters 56 (2015) 1392–1396

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Mechanistic insights into Brønsted acid-induced nucleophilic substitution of aliphatic imidazole carbamate with halide ions

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ARTICLE INFO

Article history:
Received 17 December 2014
Revised 11 January 2015
Accepted 12 January 2015
Available online 30 January 2015

Keywords:
Nucleophilic substitution
Brønsted acid
Alcohol
Alkyl halide
Imidazole carbamate

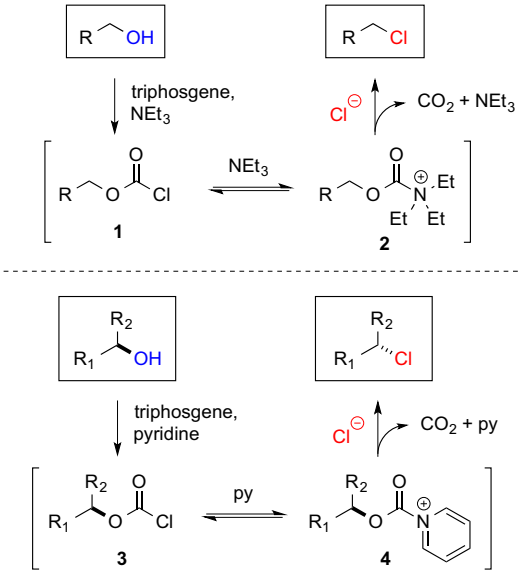
ABSTRACT

Herein we report interesting reactivity of imidazole carbamate towards nucleophilic substitution with halide ions under Brønsted acidic conditions. Depending upon reaction conditions, halide ions could readily attack the carboxyl position and trigger decarboxylative alkyl halide formation. Alternatively, halide ions were also found to competitively undergo nucleophilic acyl substitution, which ultimately results in the generation of carbonate dimerization product.

Introduction

Alcohols constitute one of the most synthetically useful organic compounds. One of the fundamental reactions involving alcohols as a starting material is their conversion to alkyl halides. Alkyl halides are ubiquitous functional groups due to their versatile reactivity.[1–4] They are widely employed as a source of a carbon electrophile. However, the reactivity of these functional groups can be reversed into a carbon nucleophile upon insertion of a metallic species into the carbon-halogen bonds.

Recently, our group became interested in developing new synthetic methods to access alkyl chlorides. More specifically, we aim for mild strategies that are amenable for a late-stage application in total synthesis of complex natural products. We discovered that activation of unreactive aliphatic alcohols using a mixture of triphosgene and amine bases in dichloromethane readily produced the corresponding alkyl chlorides in high yields.[5,6] As shown in Scheme 1, we identified that triethylamine is most suitable for substrates containing primary alcohols,[5] whereas chlorination of secondary alcohols required the use of pyridine.[6] Through systematic studies, the mechanism of these de novo chlorination reactions was proposed to involve an intermediacy of putative triethylammonium carbamate ion **2** or pyridinium carbamate ion **4**,[7–12] respectively. These species were presumably produced upon nucleophilic acyl substitution of chloroformate intermediate **1** and **3** with their respective amine bases. This mode of hydroxyl-activation enhances the electrophilicity of the carboxyl carbon, enabling nucleophilic substitution by chloride ions via an inversion of stereochemistry.



Scheme 1. Triphosgene-amine base promoted chlorination of alcohols.

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http://dx.doi.org/10.1016/j.tetlet.2015.01.098
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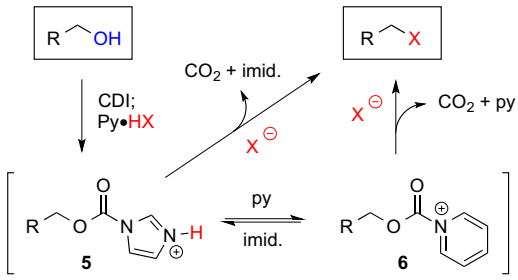


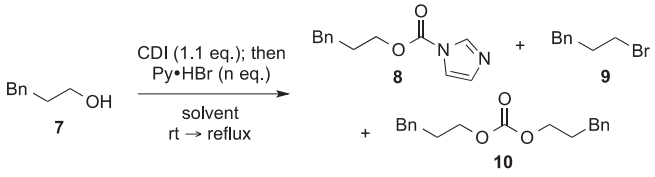
Scheme 2. Alkyl halides formation via imidazolium carbamate intermediates.

The propensity of triethylammonium carbamate ion **2** and pyridinium carbamate ion **4** to undergo decarboxylative nucleophilic substitution with chloride ions led us to investigate analogous electrophilic systems that can be specifically harnessed towards nucleophilic attack by other halide ions. Naturally, such reactive intermediates must be generated under chloride ion-free conditions, which essentially rules out the use of triphosgene to activate the starting alcohols. These considerations led us to formulate a hypothesis as depicted in Scheme 2. We envisioned that aliphatic alcohols could be reacted with carbonyl diimidazole (CDI) to give imidazole carbamate adduct, that would be further activated in situ with pyridinium halides, prompting proton transfer that should generate imidazolium carbamate ion **5**. This reactive intermediate would subsequently undergo nucleophilic substitution with halide ions at the carboxyl position to produce the target alkyl halides, while releasing carbon dioxide and imidazole as byproducts. It is also conceivable that imidazolium carbamate ion **5** participated in a reversible nucleophilic acyl substitution with free pyridine, which would be liberated during proton transfer, to form pyridinium carbamate ion **6**.[13,14] The ensuing nucleophilic attack of this reactive species by halide ions should also readily produce the intended alkyl halides.

Results and discussion

Table 1 depicts the results of our initial experiments, in which we employed 3-phenyl-1-propanol **7** as a model substrate to aim for the production of alkyl bromide **9**. The typical protocol in these studies involved treatment of alcohol **7** with 1.1 equiv of CDI for one hour at room temperature, followed by the addition of pyridinium bromide. The reaction was then brought to reflux for 24 h. Upon aqueous workup, the crude mixtures were subjected to GC–MS analyses.

Table 1
Initial investigation



Entry	Solvent	Py·HBr (equiv)	Conc. (mM)[a]	% **7**:**8**:**9**:**10**[b]			
1	THF	3.0	100	0	95	5	0
2	DCM	3.0	100	0	100	0	0
3	Toluene	3.0	100	0	100	0	0
4	DMF	3.0	100	0	100	0	0
5	**MeCN**	**3.0**	**100**	**0**	**72**	**28**	**0**
6	MeCN	3.0	50	10	79	11	0
7	MeCN	3.0	250	0	86	11	3
8	MeCN	3.0	500	3	72	7	18
9	MeCN	4.0	100	0	69	31	0
10	MeCN	5.0	100	6	59	35	0
11	MeCN	7.0	100	0	44	56	0
12	**MeCN**	**10.0**	**100**	**8**	**11**	**73**	**8**

The best reaction conditions were highlighted in bold texts.
[a] Reaction concentration was based on 3-phenyl-1-propanol.
[b] Ratios were determined by GC–MS analysis of the crude mixtures assuming that these compounds elicited identical GC responses.

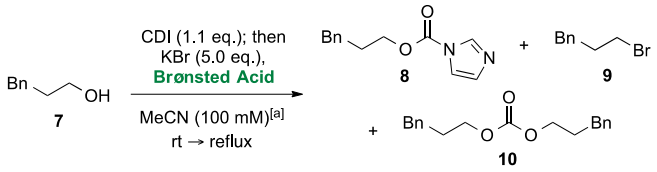
We began by screening various solvents for the reaction. As indicated in entries 1–5, commonly used polar and non-polar solvents, such as tetrahydrofuran, dichloromethane, toluene and dimethylformamide, only yielded imidazole carbamate adduct **8**. In fact, alkyl bromide **9** was not (or barely) detected in the crude reaction mixtures with these solvents. Interestingly, when the reaction was performed in acetonitrile, GC–MS analyses of the crude reaction revealed formation of alkyl bromide **9** in 28% conversion. These findings were quite unexpected, considering the fact that our previously reported chlorination reactions, which were proposed to have involved participation of analogous reactive intermediates as shown in Scheme 1, were most efficient when performed in dichloromethane.[5,6]

Our study then continued with the investigation on the effect of reaction concentration. The above preliminary reactions were performed in 100 mM concentration with respect to starting alcohol **7**. As shown in entries 5–8, changing the reaction concentration did not improve the production of alkyl bromide **9**. However, we observed that the formation of symmetrical carbonate **10** appeared to become more prominent at higher reaction concentrations. Interestingly, this carbonate formation did not appear to originate from the initial step when alcohol **7** was treated with CDI. Further reaction optimization then involved varying the amount of pyridinium bromide salts. As shown in entries 9–12, increasing the molar equivalence of pyridinium bromide directly correlates to the increasing production of the alkyl bromide. In fact, the use of 10 equiv of pyridinium bromide readily generated product **9** in 73% conversion yield as determined by GC–MS analyses.

Although we were able to considerably improve the conversion yield of alkyl bromide **9**, the use of 10 equiv of pyridinium bromide was not ideal due to the challenge in removing excess pyridine from crude reaction mixtures during aqueous workup. Furthermore, limited commercial availability of other pyridinium halide salts would simply restrict this chemistry to bromination. These concerns led us to explore analogous reaction conditions. As shown in Table 2, we proposed the use of a Brønsted acid to activate imidazole carbamate adduct **8** in the presence of potassium bromide, which supplied the bromide ions. A typical protocol for these new activation conditions is as follows: starting alcohol **7** was initially treated with 1.1 equiv of CDI in anhydrous acetonitrile for one hour at room temperature. Then, potassium bromide, Brønsted acid and other additives were sequentially added. The reaction was then stirred at reflux for 24 h, followed by aqueous workup and GC–MS analyses of the crude mixtures.

As indicated in Table 2, entries 1 and 2, we initially employed 2.0 equiv of Brønsted acid, such as pyridinium triflate and pyridinium tosylate. These conditions were found to be ineffective to activate imidazole carbamate intermediate **8**, as the crude reaction mixture only contained a negligible amount of alkyl bromide **9**. Increasing the molar concentration of these pyridinium salts to 4.0 equiv also failed to improve the product output. Interestingly, formation of carbonate byproduct **10** became more competitive under these conditions. We also explored the compatibility of pyridinium sulfate in this reaction. Interestingly, the use of 2.0 equiv of this acid, that is, 4.0 molar equivalents of the pyridinium ions, readily afforded alkyl bromide **9** in 71% conversion (entry 6). A further increase in the product formation to 81% yield was observed when both 4 Å molecular sieves and a catalytic dibenzo-18-crown-6 were introduced to the reaction mixture (entry 7).[15–17]

Table 2
Alternative bromination reaction conditions



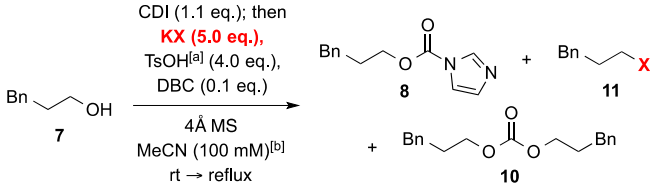
Entry	Brønsted acid	Equiv	Additive[b]	% 7:8:9:10[c]			
1	Py·TfOH	2.0	—	1	88	4	7
2	Py·TsOH	2.0	—	3	96	1	0
3	Py·TfOH	4.0	—	0	71	22	7
4	Py·TsOH	4.0	—	11	13	36	30
5	$Py_2{\cdot}H_2SO_4$[d]	1.0	4 Å MS	13	77	7	3
6	$Py_2{\cdot}H_2SO_4$[d]	2.0	4 Å MS	14	9	71	6
7	**$Py_2{\cdot}H_2SO_4$[d]**	**2.0**	**4 Å MS, DBC**	**6**	**11**	**81**	**2**
8	TsOH[d]	2.0	4 Å MS, DBC	0	36	64	0
9	**TsOH[d]**	**4.0**	**4 Å MS, DBC**	**0**	**0**	**100**	**0**
10	CSA	2.0	DBC	0	56	44	0
11	**CSA**	**4.0**	**DBC**	**2**	**0**	**98**	**0**

The best reaction conditions were highlighted in bold texts.
[a] Reaction concentration was based on 3-phenyl-1-propanol.
[b] Dibenzo-18-crown-6 (DBC, 0.1 equiv) was added. 4 Å molecular sieves were oven-dried prior use.
[c] Ratios were determined by GC–MS analysis of the crude mixtures assuming that these compounds elicited identical GC responses.
[d] These Brønsted acids were azeotroped with toluene prior use.

Although pyridinium sulfate enabled a reasonably high conversion of alcohol **7** to the alkyl bromide **9**, the ability of this reaction to reach completion was quite inconsistent due to the perplexing regeneration of starting alcohol **7** and formation of its corresponding carbonate adduct **10**. It is assumed that the forward progress of this bromination reaction was most likely controlled by the extent of proton transfer between the pyridinium salts and imidazole carbamate **8**. We proposed that perhaps the use of a stronger Brønsted acid would help push protonation of the imidazole carbamate moiety, which is the driving force behind the ensuing decarboxylative nucleophilic substitution by bromide ions. To test this hypothesis, we explored the use of organic acids, such as camphorsulfonic acid (CSA) or *p*-toluenesulfonic acid (TsOH).[18] Indeed, a substantial improvement was immediately observed. As shown in entries 8–11, the use of 2.0 equiv of CSA or TsOH readily improved the production of alkyl bromide **9**. Increasing their concentration to 4.0 equiv resulted in the formation of the target product essentially in quantitative conversion yields.

The propensity for putative imidazolium carbamate, viz. **5**, to undergo nucleophilic substitution with bromide ions in the absence of any pyridinium salts suggested that an intermediacy of pyridinium carbamate intermediate **6**, which was critical for our previously reported chlorination reaction,[5,6] was not essential in this bromination reaction. Furthermore, our successful attempt in supplying the bromide ions with potassium bromide salt naturally prompted us to investigate the ability of other halide ions to intercept the participating imidazolium carbamate species. As shown in Table 3, entries 1–4, a series of potassium fluoride, chloride, bromide and iodide salts were subsequently employed in this carbon-halogen bond forming reaction. Not surprisingly, the use of potassium fluoride failed to furnish any alkyl fluoride product, as GC–MS analyses of the crude mixture only indicated the presence of unreacted imidazole carbamate adduct **8**. In contrast, the reaction with potassium chloride yielded an interesting mixture of products. In addition to the target alkyl chloride, unreacted imidazole carbamate **8** and symmetrical carbonate **10** were detected in the crude mixture. More critically, starting alcohol **7** was also regenerated in a significant quantity. Potassium bromide and potassium iodide proved to be the most suitable salts, enabling

Table 3
Preparative scale reaction with various potassium salts[20]



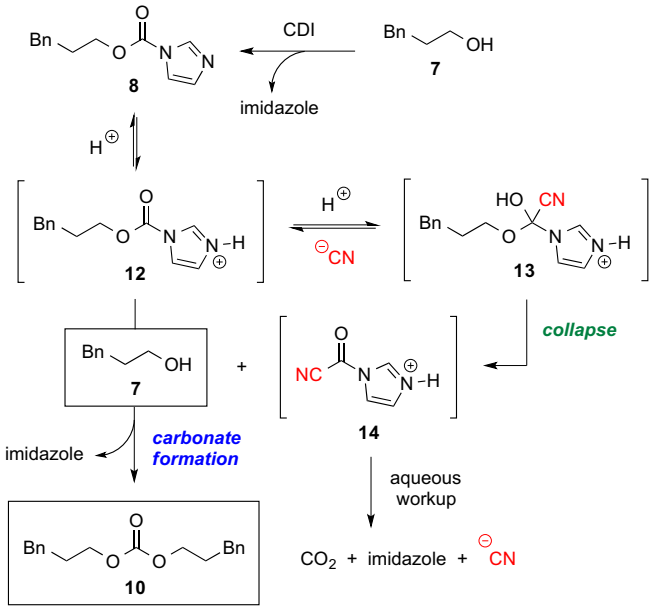
Entry	KX	% 7:8:11:10[c]				Isolated yield of 11[d]
1	KF	0	100	0	0	0
2	KCl	31	36	27	6	11
3	KBr	1	0	96	3	56
4	KI	0	0	100	0	92
5	KCN	8	0	0	92	0

[a] TsOH was azeotroped with toluene prior use.
[b] Reaction concentration was based on 3-phenyl-1-propanol.
[c] Ratios were determined by GC–MS analysis of the crude mixtures assuming that these compounds elicited identical GC responses.
[d] Isolated yield after flash column chromatography.

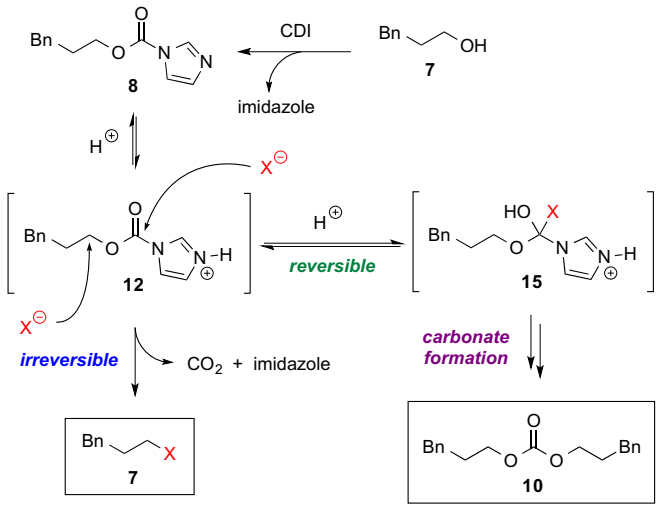
a complete conversion of alcohol **7** to the intended 1-bromo-3-phenylpropane and 1-iodo-3-phenylpropane, respectively.[19]

The regeneration of starting alcohol **7** and its subsequent dimerization to carbonate **10** under certain reaction conditions was quite puzzling. The initial treatment of alcohol **7** with CDI always resulted in a rapid and full conversion to imidazole carbamate **8**. Thus, it is reasonable to conclude that the presence of alcohol **7** in the crude mixtures, which was detected up to 31% recovery yield, was not due to its incomplete carbamoylation with CDI. The likelihood for the production of starting alcohol **7** from adverse hydrolysis of imidazole carbamate **8** during the course of the reaction was also remote. Our reactions were performed in anhydrous acetonitrile and inert atmosphere. In addition, activated 4 Å molecular sieves were added into the reaction mixtures to help maintain scrupulous anhydrous conditions, and the Brønsted acids were carefully azeotroped with toluene prior use.

A surprising result that ultimately led us to gaining some mechanistic insights into the competitive formation of starting alcohol **7** and its carbamate adduct **10** was acquired when we employed

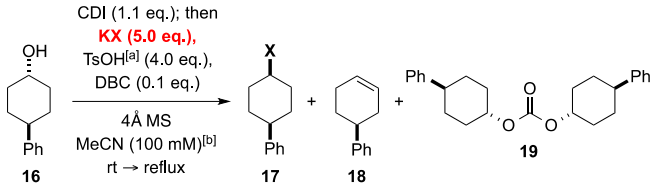


Scheme 3. Cyanide ion-mediated formation of starting alcohol **7** and symmetrical carbonate **10**.



Scheme 4. Proposed reaction mechanism for nucleophilic substitution of imidazolium carbamate with halide ions.

Table 4
Bromination and iodination of *trans*-4-phenylcyclohexanol[16]



Entry	KX	% **16**:**17**:**18**:**19**[c]			
1	KBr	27	4	5	64
2	KI	0	53	31	16

[a] TsOH was azeotroped with toluene prior use.
[b] Reaction concentration was based on 3-phenyl-1-propanol.
[c] Ratios were determined by GC–MS analysis of the crude mixtures assuming that these compounds elicited identical GC responses.

potassium cyanide as the source of nucleophile. As illustrated in Table 3, entry 5, the use of cyanide ions did not yield any formation of the intended carbonitrile homologation product. Instead, the reaction almost exclusively afforded carbonate dimerization product **10** along with a small amount of alcohol **7**. The proposed reaction mechanism for this transformation is depicted in Scheme 3. Upon carbamoylation of starting alcohol **7** with CDI, in situ protonation of the resulting imidazole carbamate adduct **8** generated imidazolium ion **12**. This activated cationic species then underwent nucleophilic acyl substitution with cyanide ions via putative tetrahedral intermediate **13**. The ensuing collapse of this tetrahedral species produced both alcohol **7**, which was readily detected in the crude mixtures, and acyl imidazolium ion **14**, which presumably decomposed via hydrolysis upon aqueous workup. The newly regenerated starting alcohol **7** then intercepted any residual imidazolium carbamate ion **12**, which eventually afforded the observed symmetrical carbonate **10**.

Based on these experimental results, the overall mechanism for our bromination and iodination reaction is proposed in Scheme 4. Protonation of the carbamoylation product **8** to the corresponding imidazolium carbamate ion **12** will promote nucleophilic substitution at two possible competitive electrophilic sites. An attack at the carboxyl position by halide ions irreversibly formed the target alkyl halides, driven by the release of carbon dioxide and imidazole. In the meantime, imidazolium carbamate **12** was also susceptible to an attack by halide ions at the carbonyl position to give a putative tetrahedral intermediate **15**. This nucleophilic acyl addition pathway was presumably reversible. The extent of this equilibrium and the propensity of tetrahedral intermediate **15** to collapse would consequently contribute to the regeneration of starting alcohol **7**, en route to forming the observed carbonate **10** via reaction mechanism analogous to that depicted in Scheme 3.

The selectivity between nucleophilic substitutions by halide ions at the carboxyl versus carbonyl positions was prominent when a secondary alcohol was used as a starting material. For example, as shown in Table 4, entry 1, treatment of *trans*-4-phenyl-cyclohexanol **16** with the optimized bromination conditions predominantly led to a mixture of regenerated starting alcohol **16** and its carbonate dimerization product **19**. This observation suggested that the steric barrier exhibited by the secondary carboxyl carbon of the corresponding imidazolium carbamate intermediate could not be overcome by the incoming bromide ions, thus preventing the key decarboxylative nucleophilic substitution to occur. Consequently, the alternative nucleophilic acyl substitution pathway became competitive. This process liberated the starting secondary alcohol **16**, which then readily reacted with the remaining putative imidazolium carbamate ions to afford the observed carbonate **19**.

Interestingly, the use of potassium iodide with *trans*-4-phenylcyclohexanol substrate **16** mainly produced a mixture of the intended secondary alkyl iodide **17** and elimination product **18**. It appeared that in this case, the strong nucleophilicity of iodide ions readily promoted the substitution reaction at the carboxyl carbon to produce the observed secondary alkyl iodide **17** despite the steric barrier imposed by the secondary imidazolium carbamate intermediate. Formation of 4-phenylcyclohexene **18** most likely originated from the instability of alkyl iodide **17** and its susceptibility to undergo elimination. This was evidenced by an attempt to isolate compound **17** using silica-gel column chromatography, which only resulted in its decomposition to byproduct **18**.

Conclusion

In conclusion, we have discovered an unusual reactivity of imidazolium carbamate intermediates towards nucleophilic substitution with halide ions. Our experimental data suggested that the mechanism of this reaction proceeded via two competitive pathways: decarboxylative alkyl halide formation involving a nucleophilic attack at the carboxyl position, or nucleophilic acyl substitution, which leads to regeneration of the starting alcohol and dimerization to carbonate byproduct. Further synthetic utilities of these imidazolium carbamate ions in other useful bond-forming processes are currently being explored in our laboratory. The results will be reported in due course.

Acknowledgments

Generous financial support from Louisiana State University (LSU) is greatly appreciated. R.K. thanks the Office of Research and Economic Development at LSU for the Council of Research Award. We thank Professor George Stanley for kindly allowing us to use the GC–MS instrument in his laboratories.

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19. The modest isolation yield for 1-bromo-3-phenylpropane was most likely due to volatility of the product.
20. *A typical reaction protocol:* 3-Phenyl-1-propanol **7** (2.0 mmol) or *trans*-4-phenylcyclohexanol (2.0 mmol) was dissolved in anhydrous acetonitrile (20 mL). Carbonyldiimidazole (2.2 mmol) was then added. The reaction was stirred for one hour at room temperature, at which alcohol **7** was fully consumed. Then, potassium halide salts (10 mmol), freshly azeotroped *p*-toluenesulfonic acid (8.0 mmol), and dibenzo-18-crown-6 (0.2 mmol) were sequentially added. After allowing the mixture to stir at gentle reflux for 24 h, the reaction was quenched with Dl H_20 and extracted with ethyl acetate. The organic layers were then combined, dried with sodium sulfate, and concentrated under vacuum. The crude material was analyzed by GC–MS and then purified by silica-gel column chromatography. *1-Chloro-3-phenylpropane:* ^{1}H NMR (400 MHz, $CDCl_3$); δ (ppm) = 7.32–7.19 (5H, m), 3.53 (2H, t, J = 6.5 Hz), 2.78 (2H, t, J = 7.3 Hz), 2.11 (2H, qn, J = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$); δ (ppm) = 140.70, 128.55, 128.49, 126.13, 44.23, 34.03, 32.77. *1-Bromo-3-phenylpropane:* ^{1}H NMR (400 MHz, $CDCl_3$); δ (ppm) = 7.37–7.24 (5H, m), 3.44 (2H, t, J = 6.6 Hz), 2.83 (2H, t, J = 7.2 Hz), 2.22 (2H, qn, J = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$); δ (ppm) = 140.58, 128.59, 128.54, 126.20, 34.21, 34.02, 33.13. *1-Iodo-3-phenylpropane:* ^{1}H NMR (400 MHz, $CDCl_3$); δ (ppm) = 7.37–7.24 (5H, m), 3.24 (2H, t, J = 6.8 Hz), 2.78 (2H, t, J = 7.2 Hz), 2.18 (2H, qn, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$); δ (ppm) = 140.45, 128.60, 128.54, 126.22, 36.27, 34.94, 6.42. *Bis(3-phenylpropyl) carbonate:* ^{1}H NMR (400 MHz, $CDCl_3$); δ (ppm) = 7.41–7.28 (10H, m), 4.27 (4H, t, J = 6.5 Hz), 2.82 (4H, t, J = 7.4 Hz), 2.14–2.07 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$); δ (ppm) = 155.40, 141.10, 128.57, 128.51, 126.17, 67.29, 32.02, 30.36.