

One-Pot Synthesis of Disubstituted Urea from Carbon Dioxide, Propylene Oxide, and Amines Catalyzed by Imidazolium-Tetraiodoindate

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In this article, synthesis of 1,3-disubstituted urea (DSU) from three component reagent systems comprising amine, carbon dioxide, and propylene oxide is described. DSU is synthesized in the presence of a variety of ionic liquids (ILs) with/without promoters. Among used ILs, 1-butyl-3-methylimidazolium tetraiodoindate^{III} (represented as [Bmim][InI₄]) is found to give the highest DSU product. A serious experiment clearly indicates that the tetraiodoindate anion plays an important role for the selective production of the DSU. Based on the *in situ* infrared spectroscopic studies, a plausible reaction mechanism for producing dicyclohexylurea from cyclohexylamine is proposed. The synthesis and characterization of [Bmim][InI₄] are given in details. Moreover, the effect of reaction variables such as time, temperature, pressure, and the molar ratio of substrate to catalyst is also studied.

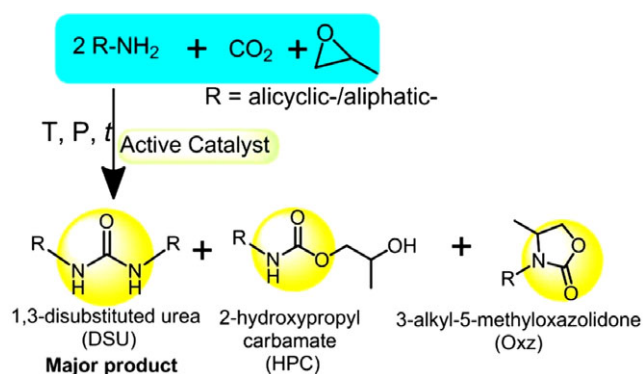
Keywords: Disubstituted urea, Amines, Carbon dioxide, Propylene oxide, Ionic liquid-based catalyst

Introduction

Natural events and human activities are believed to be contributing to increasing greenhouse gases in the environment, and the emission of these greenhouse gases is responsible for global warming. Among the utilization of various greenhouse gases, carbon dioxide (CO₂) is recognized as attractive and environmentally benign feedstock for producing various types of chemicals^{1–4} for industrial interests, and is of great importance to create further a high degree of sustainability in chemical processing and production. CO₂ is abundantly in nature, cheap, and safe building blocks in the organic synthesis. However, the inert nature of CO₂ has restricted to increase the range of its applications and thus efficient catalytic process, especially with amines, remains a significant challenge.^{5–10} The products such as urea and its derivatives have widely been used as intermediates for biologically active compounds, pesticides,¹¹ herbicides,¹² medicines,^{13–15} and so on. Other kinds of representative and important products such as 1,3-disubstituted ureas (DSUs), oxazolidinones, and carbamates¹⁶ are important N-containing chemical products.^{17–21} Furthermore, aforementioned urea products having a variety of applications such as pharmaceuticals, agricultural chemicals, and in dye chemistry²² are useful chemical

intermediates and regarded as raw materials of polyurethanes. A number of methodologies for the synthesis of ureas have been reported. However, these strategies mainly used toxic and corrosive phosgene as a carbonyl source.^{23–26} As alternatives, oxidative carbonylation^{27–29} and reductive carbonylation^{30–32} were also used but these processes could also be suffered from the possible explosion depended on the ratio of O₂/CO and harmful nature of CO, respectively. The use of CO₂ as a carboxylating agent among various approaches is safe and attractive in a combination of epoxide, which can facilitate the reaction under the milder condition.

Recently, ionic liquids (ILs) have attracted much attention due to their tunable properties according to the needs.^{33–35} However, the application of ILs just as the solvent is much expensive with respect to industrial viewpoint. The use of ILs as active catalysts for the efficient organic transformation reactions have resulted in opening a new level of application fields.^{24–26,29–32,36,37} Accordingly, there have been numerous reports on the dramatic enhancement in their catalytic activities just by incorporating metal salts into ILs.^{32,38,39} As mentioned earlier, the CO₂ fixation could be accomplished by using many catalysts but most of them still suffer from the harsh reaction conditions, *e.g.*, above 180°C of the reaction temperature or longer reaction



Scheme 1. Synthesis of DSU from one-pot cascade coupling reaction of three components (amine, CO₂, and PO).

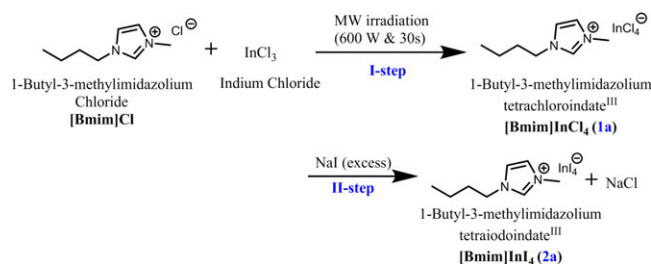
time for more than 6–12 h.^{40–44} To solve this problem, propylene oxide (PO) is added as a third agent for lowering the activation barrier which renders the reaction conditions milder. However, this protocol has resulted in the production of a large amount of amino alcohol as a by-product. Thus, a new catalyst system needs to be designed to increase urea as a main product by minimizing amino alcohols.

Herein, we report a facile synthesis of 1,3-disubstituted urea as a major product from one-pot cascade coupling reaction of three components of amine, CO₂, and PO (Scheme 1) in the presence of indium-based ILs used as catalysts. A hitherto unreported indium-based IL, 1-butyl-3-methylimidazolium tetraiodoindate^{III} ([Bmim][InI₄]) prepared from 1-butyl-3-methylimidazolium tetrachloroindate^{III} ([Bmim][InCl₄]) and sodium iodide (NaI), is evaluated. Based on the *in situ* Fourier transform infrared (FT-IR) spectroscopy studies, a plausible reaction mechanism for producing DSU, especially dicyclohexylurea (DCU) from cyclohexylamine (CHA) through the 2-hydroxypropyl carbamates (HPC) as an intermediate catalyzed by [Bmim][InI₄] is proposed.

Experimental

Materials. All amines, 1-butyl-3-methylimidazolium chloride, indium halides, and alkali metal salts were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA) and used as such without any further purification (General considerations, Section S1 in Appendix S1, Supporting Information). All solvents were of analytical grades and distilled in the presence of appropriate drying agents under a nitrogen atmosphere prior to use. Over 99% purity of CO₂ cylinder was purchased from Gaskor Co. Ltd, Seosan, South Korea. The liquid CO₂ was transported into a gas reservoir through a HSK-600 liquid pump and was gasified at room temperature (RT).

Synthesis of [Bmim][InI₄] Ionic Liquid Used as a Catalyst. Synthetic route to [Bmim][InI₄] IL used as an active catalyst is shown in Scheme 2. The route commences from [Bmim][Cl] and indium chloride (InCl₃) to [Bmim][InCl₄]



Scheme 2. A synthetic route to [Bmim][InI₄] (2a) ionic liquid as an active catalyst.

IL (I-step), which was prepared by following the microwave-assisted method reported by Kim *et al.*³⁹ (Section S2 in Appendix S1). The InCl₃ (25.0 mmol) and [Bmim]Cl (23.9 mmol) were mixed together in 20 mL of the glass vial. Then, the vial containing mixture was subjected to microwave (MW) radiation at 600 W (two times for 15 s irradiation) in a household MW oven until the solid mixture resulted in a crude mixture of liquid. A small quantity of unreacted InCl₃ was filtered using a syringe filter to afford colorless single-phase liquid with 98% yield. The viscosity of [Bmim][InCl₄] was measured as 27 mPa, which is well in accordance with the literature.⁴⁵ ¹H NMR (CD₃OD, 25°C, 300 MHz): δ 9.08 (s, 1H), 7.66–7.60 (d, *J* = 18.8 Hz, 2H), 4.31–4.27 (t, *J* = 6.7 Hz, 2H), 3.99 (s, 3H), 1.93–1.84 (m, 2H), 1.43–1.34 (m, 2H), 0.98–0.94 (t, *J* = 6.7 Hz, 3H). Anal. Calcd for C₈H₁₅Cl₄InN₂: C, 24.27; H, 3.82; N, 7.08. Found: C, 24.25; H, 3.85; N, 7.07.

Then, [Bmim][InCl₄] was converted to [Bmim][InI₄] (II-step). For the preparation of [Bmim][InI₄], a solution of [Bmim][InCl₄] in toluene was treated with 5 equiv of NaI (excess) and refluxed overnight at 100°C. After the reaction, a yellow liquid phase was extracted, followed by evaporation to give a yellowish crude solid. The crude solid was dissolved again in toluene and the insoluble part was removed by filtration. The concentrated final filtrate was recrystallized.

Pentane to get a beige powder of [Bmim][InI₄] with 90% yield (Section S3 in Appendix S1). ¹H NMR (CD₃OD, 25°C, 300 MHz): δ 8.98 (s, 1H), 7.64–7.57 (d, *J* = 21.1 Hz, 2H), 4.26–4.21 (t, *J* = 7.3 Hz, 2H), 3.90 (s, 3H), 1.93–1.83 (m, 2H), 1.45–1.32 (dq, *J* = 14.7, 7.4 Hz, 2H), 1.00–0.96 (t, *J* = 7.4 Hz, 3H). Anal. Calcd for C₈H₁₅I₄InN₂: C, 12.62; H, 1.99; N, 3.68. Found: C, 12.64; H, 2.02; N, 3.55.

General Procedure for the Synthesis of 1,3-Disubstituted Urea. All the experiments related to the coupling reaction of three components (amine, CO₂, and PO) were conducted in a 100-mL high-pressurized stainless steel reactor equipped with a magnetic stirrer and an electrical heater. The reactor was charged with an amine (86.1 mmol), PO (42.9 mmol), 15 mL of THF/toluene as a solvent, and the required amount of IL used as a catalyst (0.43 mmol) without a promoter (2.2 mmol). The reactor was kept to

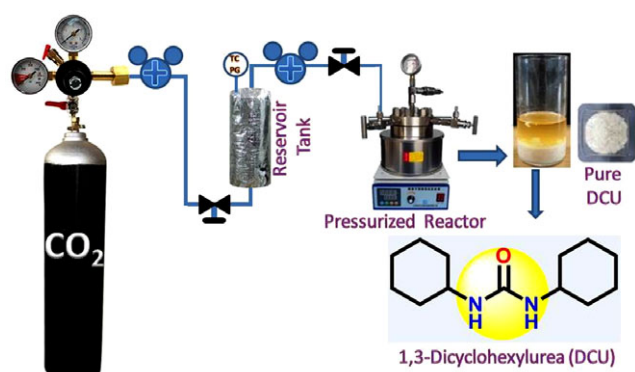


Figure 1. Process diagram for disubstituted urea from amine, propylene oxide, and CO₂.

homogenize the reaction mixture at 500 rpm of stirring speed for at least 5 min at RT. (It was observed that this step was required for obtaining reproducible result.) After that, 1.0 MPa of CO₂ was purged into the reactor to deoxygenate the reaction mixture three times. The reactor was then pressurized again up to 1.0 MPa of CO₂ and heated up to the desired temperature with vigorous stirring. The reactor was further pressurized up to 8.3 MPa when the temperature reached up to 150°C. Throughout the entire reaction time, the final pressure of CO₂ into the reactor (8.3 MPa) was maintained by using a gas reservoir equipped with a back-pressure regulator and a pressure transducer. At the end of the coupling reaction, the reaction mixture was allowed to cool down and was filtered to separate out the solid product DSU. The obtained solid product, DSU, was washed with water to remove possible remaining carbamate salt, and then washed with THF or toluene several times, followed by drying in a vacuum oven overnight. To the filtrate, an external standard (isooctane) was added and the solution was analyzed by gas chromatography (GC) for quantitative analysis of other products (Oxz, AmA, and HPC). Quantitative analyses were made on an Agilent 6890N gas chromatograph equipped with a flame ionization detector (FID) and qualitative analyses on an Agilent 6890N-5975 Mass spectrometer-gas chromatograph (MSD-GC) equipped with HP-5 column (30 m × 0.32 m × 0.25

μm). The dried DSU was weighed to calculate the isolated yield (Figure 1).

Results and Discussion

Evaluation of Indium Chloride and IL-based Catalysts.

Indium chloride and IL-based catalysts were evaluated in cascade coupling reaction of three components, CHA, CO₂, and PO (molar ratio of CHA/PO = 2) and the results are summarized in Table 1. The cascade coupling reaction of three components was carried out without a catalyst. It could be seen that there was no formation of DCU product, except a lot of by-products, cyclohexylamino-propan-2-ol (AmA) with 49.8% yield, Oxz (4.9%) and an intermediate HPC (5.1%) at 59.8% CHA conversion. An addition of indium chloride to the reaction system could lead a small amount of DCU (5.3%) without any significant change in CHA conversion (60.3%) (entry 2). In a separate reaction, it could be observed that [Bmim][Cl] gave a higher conversion of CHA (86.3%) while DCU yield was low as 2.7% (entry 3). Indium-based IL [Bmim][InCl₄] gave a signal for the formation of DCU with a higher yield than other catalysts such as InCl₃ and [Bmim]Cl, and was 18.9% yield of DCU at CHA conversion (80.1%) (entry 4). Although a considerable amount of undesirable product, AmA (47.6%) was also present in the product mixture. The intrinsic nature and low solubility of DCU in most of the organicsolvents make this process advantageous, *i.e.*, easy to separate DCU from the product mixture. The reason for using [Bmim][InCl₄] as the catalyst for this reaction was that it had been substantiated the coupling reaction of CO₂ and PO to produce propylene carbonate (PC). Upon the postulation that the formation of PC might be the first step for producing DCU, the activity of [Bmim]₂[ZnBr₂Cl₂] used as a catalyst for the same reaction was tested because it is also a well-known catalyst for producing PC. Unexpectedly, it showed very low activity toward the formation of DCU, delivering only 6.0% yield. However, it produced a considerable amount of HPC and 3-cyclohexyl-5-methyloxazolidone (Oxz) in 8.4 and 27.5%, respectively (entry 5). The formation of Oxz is explained from an intramolecular dehydrative cyclization reaction from HPC.^{46–48}

Table 1. InCl₃ and ILs catalyzed one-pot reaction of three components (CHA, CO₂, and PO).^a

Entry	Catalyst	CHA conversion (%)	Yield (%)			
			DCU ^b	HPC ^c	Oxz ^c	AmA ^c
1	None	59.8	0	5.1	4.9	49.8
2	InCl ₃	60.3	5.3	4.6	1.7	48.7
3	[Bmim]Cl	86.3	2.7	7.9	27.1	48.5
4	[Bmim][InCl ₄]	80.1	18.9	5.3	8.2	47.6
5	[Bmim] ₂ [ZnCl ₂ Br ₂]	83.5	6.0	8.4	27.5	41.4

^a Reaction conditions: CHA = 86.1 mmol, PO = 42.9 mmol, catalyst = 0.43 mmol, THF used as solvent = 15 mL, *T* = 150°C, *P*(CO₂) = 8.3 MPa, *t* = 2 h.

^b Isolated yield.

^c GC yield.

Table 2. DCU formation from the reaction of CHA with PC.^a

Entry	Catalyst	CHA conversion (%)	Yield (%)			
			DCU ^b	HPC ^c	Oxz ^c	AmA ^c
1	None	64.0	0.8	11.3	30.3	21.6
2	[Bmim][InCl ₄]	72.6	55.6	4.5	0.0	12.5
3	[Bmim] ₂ [ZnCl ₂ Br ₂]	78.8	20.2	6.3	36.0	16.2

^a Reaction conditions: CHA = 86.1 mmol, PC = 42.9 mmol, catalyst = 0.43 mmol, THF used as solvent = 15 mL, *T* = 150°C, *t* = 2 h.

^b Isolated yield.

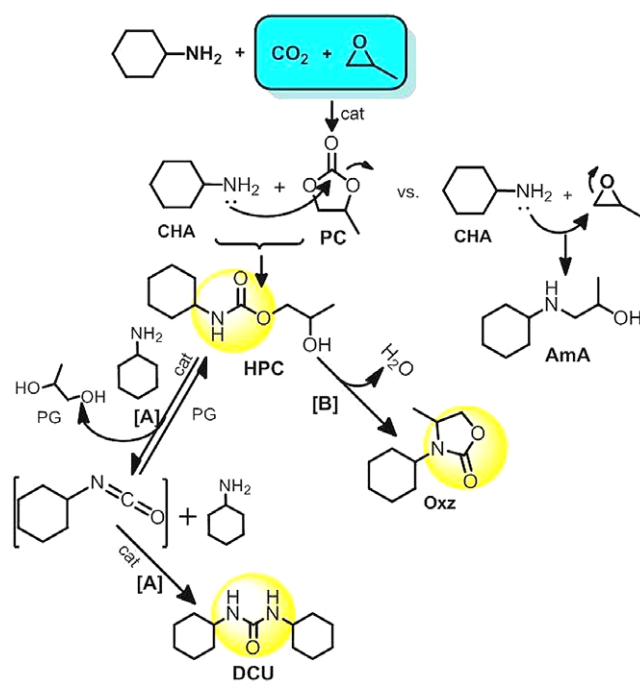
^c GC yield.

Understanding Toward the Reaction Pathway for the Formation of DCU. To correlate the hypothesis that PC would be a first step for producing DCU, a series of separate reactions was performed by reacting CHA with PC (molar ratio of CHA/PC = 2) in the absence of catalyst and in the presence of the two kinds of catalysts, [Bmim][InCl₄] and [Bmim]₂[ZnCl₂Br₂] without CO₂ pressure. The results summarized in Table 2 show that a trace amount of DCU yield (0.8%) without other product Oxz was formed in the absence of catalyst. While, [Bmim][InCl₄] delivered 55.6% yield of DCU at 72.6% CHA conversion whereas, [Bmim]₂[ZnCl₂Br₂] produced only 20.2% yield of DCU with a considerable amount of Oxz (36.0%). The obtained results indicated that the DCU was formed through the PC pathway and it was much facilitated in the presence of [Bmim][InCl₄]. The synthesis of DSUs from amines and an alkylene carbonate different from our reactant system had already been described in the literature.^{49–51}

Moreover, [Bmim][InCl₄]-catalyzed reaction of CO₂ and epoxide to form PC is well described in the previous literature in terms of activities and mechanistic studies.³⁹ In case of DCU formation from one-pot cascade coupling reaction of three components (CHA, CO₂, and PO), it could be understood that *in situ* formed PC might firstly react with CHA to generate HPC through a nucleophile attack of amino group on carbonyl carbon of PC, and the additional attack of a CHA at the carbonyl group of HPC would be required during the reaction, which was likely to be facilitated by the presence of [Bmim][InCl₄] by the certain roles of [Bmim]⁺ and [InCl₄]⁻. The AmA, an undesired by-product in this reaction, is supposed to be formed by direct attack of an amino group of CHA at a propylene group of PO or PC.⁵² Therefore, leading the reaction to PC through HPC pathway rather than AmA is very important (Scheme 3). For this purpose, a modification of catalyst was undertaken so that it could lead to pathway [A] for improving the productivity of DCU. Zhao *et al.*⁴⁴ clearly ascribed that the decrease of the yield of carbamates at high temperatures was that it is a reversible and exothermic reaction; there is equilibrium during conversion of CHA into carbamate salt and its equilibrium constant decreases as temperature increases. According to Aguirre *et al.*⁵³ and Gallou *et al.*,⁵⁴ carbamates also dissociate into isocyanate and alcohol in the presence of a amine. The *in situ*

generated isocyanate then reacts with the amine nucleophile to form DSU. Both carbamate dissociation and urea formation were shown to be equilibrium. This translates into equilibrium between carbamate (HPC), CHA, urea (DCU), and alcohol (PG) (Scheme 3).

Effect of Adding Promoters. To see the effect of various promoters on the catalytic behavior of [Bmim][InCl₄] catalyst, one-pot cascade coupling reaction of three components (CHA, CO₂, and PO) was carried out by adding various promoters and the results are summarized in Table 3. Among various promoters, it could be seen that NaI with [Bmim][InCl₄] exhibited the most promoting effect on increasing DCU yield (46.5%) by minimizing yield 28.2% of AmA (entry 4). It was mentioned earlier that [Bmim][InCl₄] itself could show only the 18.9% yield of DCU. On comparing both the results obtained with and without a promoter, DCU yield with promoter increased almost three times higher DCU yield than that obtained without a promoter. On the contrary, other promoters showed rather a



Scheme 3. Reaction pathway for the formation of DCU as main and other products (HPC, Oxz, and AmA).

Table 3. Effect of promoters on the DCU formation using [Bmim][InCl₄] as a catalyst.^a

Entry	Promoter	CHA conversion (%)	Yield (%)			
			DCU ^b	HPC ^c	Oxz ^c	AmA ^c
1	NaNO ₂	62.7	4.7	3.2	4.6	49.9
2	K ₂ CO ₃	77.4	22.0	2.8	4.2	48.2
3	KOAc	64.3	5.7	4.4	4.1	49.7
4	NaI	88.8	46.5	10.7	3.3	28.2
5 ^d	NaI	76.9	21.2	5.9	30.7	17.2
6	Al ₂ O ₃	25.1	2.5	19.9	0.3	2.2
7	CaCO ₃	73.3	12.1	9.6	3.9	47.3
8	ZnO	73.8	6.9	15.3	1.6	49.7

^a Reaction conditions: CHA = 86.1 mmol, PO = 42.9 mmol, [Bmim][InCl₄] = 0.43 mmol, promoter = 2.1 mmol, *P*(CO₂) = 8.3 MPa, THF used as solvent = 15 mL, *T* = 150°C, *t* = 2 h.

^b Isolated yield.

^c GC yield.

^d Toluene used as a solvent.

negative effect, just delivering a large amount of AmA as a by-product. Interestingly, the use of toluene as solvent delivered a lower yield of DCU (entry 5).

Since the [Bmim][InCl₄]-NaI catalyst system showed the best performance, therefore various alkali metal halides were also evaluated, and the results are presented in Figure 2. It could be seen that CHA conversion and DCU yield were largely influenced by the halide anions than alkali metal cation. It is interesting to note that the influence on DCU yield was in the following order I⁻ > Br⁻ > Cl⁻ regardless of alkali metal cations, Na⁺, K⁺, Rb⁺, and Cs⁺.

The high nucleophilicity and leaving ability of iodide ion (I⁻) might play important role in enhancing the catalytic activity toward the formation of DCU. It is also noteworthy to mention that the presence of NaI leads the productivity yield of DCU (from 18.9 → 46.5%) by reducing the formation of AmA significantly (from 47.6 → 28.2%). This dramatic synergistic effect is likely attributed to the *in situ* formation of active species, [Bmim][InI₄].

Catalytic Activities of [InI₄]⁻ with Various Counter-Cations. After looking the promoting effect of NaI and the activity of [Bmim][InCl₄] in separate cascade coupling reaction of three components (CHA, CO₂, and PO), a mixture of [Bmim][InCl₄] (**1a**) and NaI was refluxed in toluene overnight (details are provided in Scheme 2) to prepare [Bmim][InI₄] (**2a**). An elemental analysis of the solid product revealed to be [Bmim][InI₄] (**2a**) wherein all chlorides were replaced by iodides. The ¹H NMR spectrum of **2a** in methanol-*d*₄ indicated up-field shifts of protons of a methyl group at C (3) position and proton of C (2) in imidazolium, respectively (Section S3, Appendix S1). This is possibly due to the relatively electron donating environment arising from the existence of I⁻ compared to Cl⁻ in **1a**. Instead of using THF as solvent in the case of dual catalyst system

(**1a** + NaI), the catalytic activity of **2a** was tested using toluene as a solvent since it was used in the synthetic procedure and found to be well-dissolved **2a**. The results as summarized in Table 4 show that the catalytic activity of **2a** is even higher (entry 1) than that obtained from the dual catalyst system comprising **1a** and NaI in THF (entry 4, - Table 3), producing 63.1% of DCU yield with the considerably reduced amount of AmA (5.4%). This result strongly suggests that **2a**, indeed, acts as active species for producing DCU in the three component coupling reaction and can dramatically facilitate the pathway [A] (Scheme 3). The lower activity of **2a** in THF than in toluene could be ascribed to lower solubility of **2a** in THF. When we have a close look at Tables 3 and 4 especially with respect to the solvent system (THF and toluene), it is interesting to note that THF is the best solvent for the dual catalyst system **1a** + NaI whereas toluene for **2a**. The reason for lower activity in toluene with the dual catalyst system might be ascribed due to the difference in the rate for the formation of active species, *i.e.*, DCU formation rate in the presence of **2a** from the metathesis reaction of **1a** with NaI in toluene would be faster than in THF, however, concurrently resulting in faster formation of NaCl and it might act as a poison by driving reverse reaction to produce **1a** again. This effect is, indeed, endorsed by entry 3 in Table 4, which showed the decreased activity (19.8% of DCU yield) upon adding NaCl to the **2a**-catalyzed reaction and this result almost corresponded to the 21.2% yield of DCU from the dual catalyst system (**1a** + NaI) in toluene (entry 5 in Table 3). Other solvents such as methylene chloride, MeOH, DMF, NMP, acetonitrile, or chloroform did not show any significant or enhancing effect in this reaction.

To study the promoting effect of iodide ion, the catalytic activities of analogue compounds containing iodides such as [Bmim]I and InI₃ were tested (entries 4 and 5, Table 4). When [Bmim]I was used as a catalyst, no DCU was formed and cyclic carbamates (Oxz) was predominantly formed.

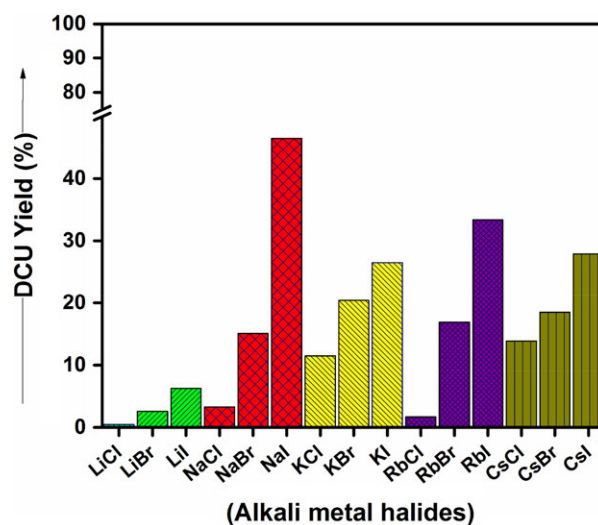
**Figure 2.** Effect of alkali metal halides on DCU yield.

Table 4. Catalytic activities of various iodide-containing compounds.^a

Entry	Catalyst	CHA conversion (%)	Yield (%)			
			DCU ^b	HPC ^c	Oxz ^c	AmA ^c
1	[Bmim][InI ₄] (2a)	82.9	63.1	11.4	2.0	5.4
2	[Bmim][InI ₄]/THF	78.5	33.2	4.0	15.8	25.4
3	[Bmim][InI ₄]+NaCl	78.2	19.8	16.1	30.5	11.7
4	[Bmim]I	58.9	0	8.2	50.7	0
5	InI ₃	81.0	39.3	2.2	4.7	34.8
6	Na[InI ₄]	75.7	28.5	4.5	30.9	11.7
7 ^d	[C ₂ mim][InI ₄]	77.9	42.5	19.5	0.5	15.4
8 ^e	[C ₆ mim][InI ₄]	79.5	31.1	27.3	2.4	18.6
9 ^f	[C ₁₀ mim][InI ₄]	82.0	34.0	22.6	3.4	21.9
10 ^g	[TBA][InI ₄]	76.9	15.7	7.8	40.8	12.6
11 ^h	[Chol][InI ₄]	73.7	23.6	4.8	9.4	35.9
12 ⁱ	[C ₄ Py][InI ₄]	80.8	43.3	5.0	23.8	8.6
13 ^j	[TBP][InI ₄]	80.2	43.5	4.6	22.4	9.7

^a Reaction conditions: CHA = 86.1 mmol, PO = 42.9 mmol, catalyst = 0.43 mmol, toluene used as a solvent = 15 mL, $T = 150^{\circ}\text{C}$, $P(\text{CO}_2) = 8.3 \text{ MPa}$, $t = 2 \text{ h}$.

^b Isolated yield.

^c GC yield.

^d C₂mim = 1-ethyl-3-methylimidazolium.

^e C₆mim = 1-hexyl-3-methylimidazolium.

^f C₁₀mim = 1-decyl-3-methylimidazolium.

^g TBA = tetra-*n*-butylammonium.

^h Chol = cholinium.

ⁱ C₄Py = tetra-*n*-butylpyridinium.

^j TBP = tetra-*n*-butylphosphonium.

However, InI₃ alone showed fairly good activities toward DCU (39.3% yield) but the productivity was still lower than **2a**. To understand the effect of imidazolium cation, which might be an important factor in enhancing the catalytic activity, it is interesting to compare the activity of **2a** with Na[InI₄], which is isolobal with **2a**. However, Na[InI₄] delivered only 28.5% of DCU (entry 6), supporting the important role of imidazolium cation that makes more stable intermediates through hydrogen bonding.

To compare catalytic activities of other ILs containing [InI₄]⁻, various [Q][InI₄] (Q = C_{*n*}mim, TBA, Chol, C₄Py, TBP, *n* = 2, 6, 10) were synthesized and their activities were tested (entries 7–13). Although [C₂mim][InI₄], [C₄Py][InI₄], and [TBP][InI₄] showed fairly good activity (about 43% of DCU yield), none of them was found to show better activity than **2a**. Studies on the influence of alkyl chain length (alkyl = C₂, C₄, C₆, and C₁₀) of 1-alkyl-3-methylimidazolium cation evidenced that by increasing the alkyl chain, the selectivity and conversion decreased.⁵⁵ The change of substituted alkyl group on the imidazole ring mainly resulted in the change in IL viscosity: a previous study reported that an increase in the van der Waals forces primarily contributed to the increase in viscosity of the ILs.⁵⁶ In agreement with this statement, in the [C_{*n*}mim][InI₄] series, viscosity increases as the number of carbon atoms in the linear alkyl group is increased.⁵⁷ However, in our work, [C_{*n*}mim][InI₄] series showed a more complicated

behavior, resulting in the disordered reactivity: there was no linear relationship between reactivity and the substituted number of carbon atoms, while **2a** showed the best reactivity for DCU formation.

Proposed Reaction Mechanism for Generating DCU.

To check a mechanistic pathway for the formation of DCU, a separate reaction of CO₂ and PO was carried out for the formation of PC, which would be an intermediate for HPC, in the presence of **1a** or **2a**. It was expected that **2a** would deliver a higher yield of PC than **1a** because **2a** was found to be more active for DCU production, however, **2a** gave the lower PC yield as shown in Table 5. Nevertheless this unexpected result was well in accordance with the previous report, which explained that the relatively lower activity for the formation of PC in the presence of [Bmim][InI₃Cl] could be rationalized by the lower Lewis acidity resulting from the decreased electronegativity of [Bmim][InI₃Cl] compared with [Bmim][InCl₄].³⁹

Therefore, the reason for three times higher activity of **2a** than **1a** toward the DCU formation in the three components coupling reaction was elucidated by a separate experiment, *i.e.*, DCU generation from the reaction of HPC with CHA. For this purpose, HPC was firstly prepared by refluxing 1:1 mixture of CHA and PC in methylene chloride for 24 h. The crude product was then purified with column to obtain the HPC (Section S8 in Appendix S1).⁴⁶ With this HPC as a substrate, three kinds of different reactions were

Table 5. Catalytic activities of various catalysts for the formation of PC from CO₂ and PO.^a

Entry	Catalyst	PC yield (%) ^b
1	None	0
2	[Bmim][InCl ₄] (1a)	75.8
3	[Bmim][InI ₄] (2a)	53.9

^a Reaction conditions: PO = (42.9 mmol), catalyst (0.22 mmol), toluene used as a solvent = 15 mL, *T* = 150°C, *P* (CO₂) = 8.3 MPa, *t* = 2 h.

^b Isolated yield.

performed by reacting HPC with CHA in the presence of **1a**, **2a**, and none. The results summarized in Table 6 showed that **1a** and **2a** delivered DCU in 21.1 and 40.5% yield, respectively; however, no DCU yield could be observed in the absence of a catalyst. These results strongly indicate that even though **2a** does not catalyze as much as **1a** for PC, the **2a** has enough ability to catalyze the DCU formation from a nucleophilic reaction of CHA on HPC, which might be a driving force for DCU from one-pot coupling reaction of the three components. From a series of aforementioned experimental results using **1a** and **2a**, it became clear that the DCU was formed through a couple of cascade reactions consisting of (1) formation of PC from CO₂, and PO, (2) HPC from CHA and PC, and finally (3) DCU from CHA and HPC, and each step is assisted by the active catalyst, [Bmim][InI₄] **2a**.

Based on the experimental results, a mechanism for producing DCU from HPC and CHA catalyzed by **2a** is proposed in Scheme 4. The mechanism for generating PC from CO₂, and PO using **1a** is not discussed in details here because it was already well studied by Kim *et al.*^{38,39} Thus we assume that **2a** would follow the similar way as **1a**. The initial active catalyst, **2a**, interacted firstly with HPC through an oxygen atom to form Int-A with the liberation of I⁻ from indium center, which was balanced with the carbocation. This carbocation was readily attacked by an amino group in CHA and generated Int-B with liberation of one molecule of propylene glycol (PG) from Int-A, and this step would be the rate-determining step. Following the attack of I⁻ on the indium center regenerated the initial active catalyst with the formation of the DCU. Reminding that **1a** could deliver only 1/3 and 1/2 of DCU yield obtained by using **2a** in the respective reaction of three components and a separate reaction of HPC and CHA (Table 6), the high activity toward the formation of DCU using **2a** might be due to the fact that I⁻ in **2a** could act as a switching ligand, *i.e.*, good leaving and nucleophilic while intrinsic nature of Cl⁻ in **1a** could not show these characteristics, and this proposed mechanism is conceivable.

For supporting the above proposed reaction mechanism, a series of *in situ* FT-IR spectroscopic studies was carried out. Figure 3(a)–(d) show the IR spectra of [Bmim][InI₄], CHA, HPC, and 1:1:1 mixture of HPC:CHA:[Bmim][InI₄],

Table 6. Catalytic activities of the formation of DCU from HPC and CHA.^a

Entry	Catalyst	CHA conversion (%)	DCU yield (%) ^b
1	None	<0.5	0
2	[Bmim][InCl ₄] (1a)	22.3	21.1
3	[Bmim][InI ₄] (2a)	42.9	40.5

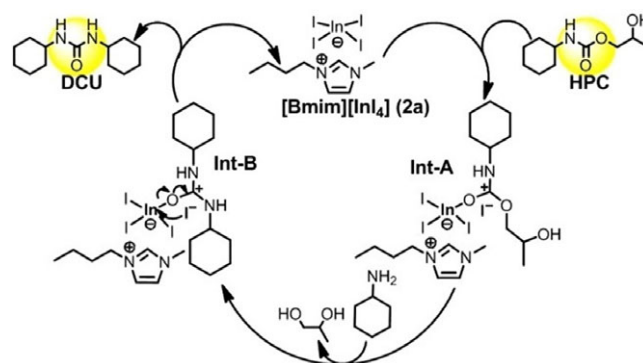
^a Reaction conditions: CHA = 4.9 mmol, HPC = 4.9 mmol, catalyst = 0.025 mmol, *T* = 150°C, *t* = 2 h, toluene used as a solvent = 15 mL.

^b Isolated yield.

respectively. The characteristic peak at 1733 cm⁻¹ in **2c** can be assigned to the C=O stretching frequency of the HPC. Interestingly, the 1:1:1 mixture at RT resulted in the appearance of a new peak at 1687 cm⁻¹ at the sacrifice of an original carbonyl peak of the HPC. This red shift should be caused by the coordination of carbonyl group of HPC to indium (see Int-A in Scheme 4), thereby weakening the C=O bond strength. Figure 3(e) shows the 1:1:1 mixture at RT and Figure 3(f)–(i) represent spectral changes as a function of temperatures from 70 to 150°C, respectively, and Figure 3(j) shows IR spectrum of authentic DCU. It is evident that there is a blue shift in the carbonyl peak with increasing temperature, probably due to the electron donating effect through a recoordination of I⁻ (see Int-B in Scheme 3).

Interestingly, this carbonyl band splits into three peaks at 150°C (h). Such a split was also observed in the previous study by Shang *et al.*⁵⁸ Surprisingly, after 30 min at this temperature, the three peaks disappeared and a new set of three peaks were generated at 1628, 1575, and 1530 cm⁻¹, which might be assigned to urea, indeed, when comparing them with an authentic DCU, they were found to be identical.

Influence of Variables on Reaction Parameters. Based on the understanding of active catalyst, the influence of the reaction time on the catalytic activity, given in terms of CHA conversion and products yield, was studied by varying the reaction time (from 0.5 to 4 h) and keeping all other

**Scheme 4.** Plausible reaction mechanism for DCU from HPC and CHA catalyzed by [Bmim][InI₄](**2a**).

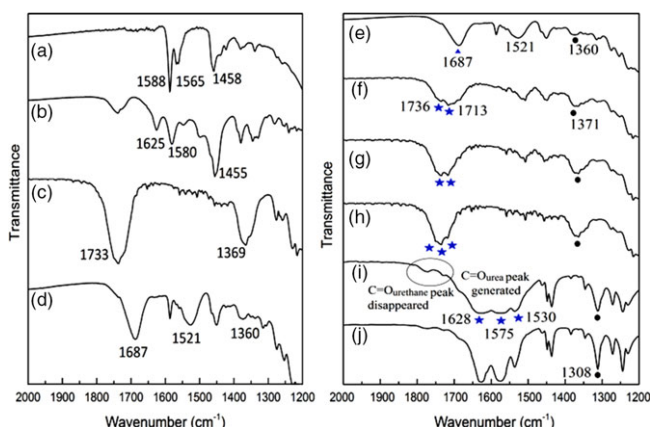


Figure 3. FT-IR spectra of (a) [Bmim][InI₄], (b) cyclohexylamine (CHA), (c) 2-hydroxypropyl cyclohexylcarbamate (HPC), (d) the 1:1:1 mixture of HPC:CHA:[Bmim][InI₄], (e) the 1:1:1 mixture at 30°C, (f) at 70°C, (g) at 110°C, (h) at 150°C, (i) after 30 min, and (j) authentic DCU.

variables constant and the results are presented in Figure 4. As a function of reaction time (Figure 4), the CHA conversion increased when reaction time increased. DCU yield increased gradually up to 65.8%. Figure 5 shows the effect of reaction temperature (from 110 to 190°C) on the product composition. When we look at the temperature effect (Figure 5), the DCU yield increased rapidly with the gradual increase of CHA conversion as a function of temperature. As mentioned earlier, preventing the formation of AmA and leading to HPC forming route (pathway A) is very important for high yield of DCU. Moreover, based on the *in situ* IR spectroscopic studies (Figure 3), it was demonstrated that HPC is an important intermediate that could be transformed into DCU. When we have a close look at the compositional changes of DCU, HPC, Oxz, and AmA as a function of reaction time and temperature (Figures 4

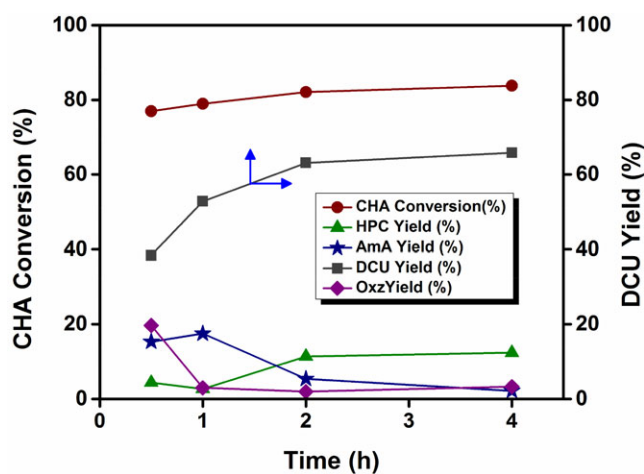


Figure 4. Effect of reaction time on CHA conversion and product yield. Reaction conditions: CHA = 86.1 mmol, PO = 42.9 mmol, [Bmim][InI₄] = 0.43 mmol, toluene used as solvent = 15 mL, P (CO₂) = 8.3 MPa, T = 150°C.

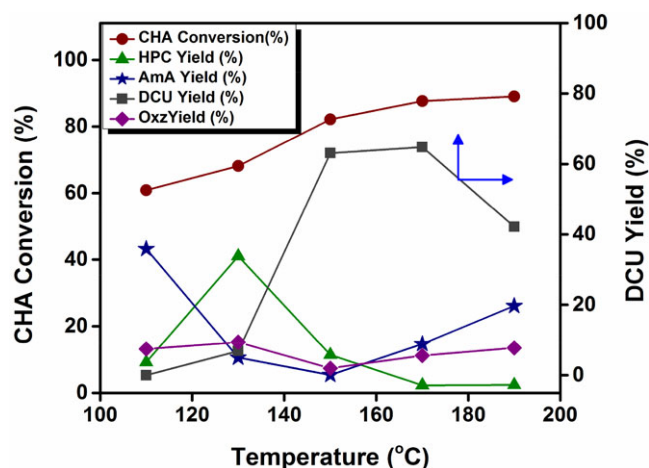


Figure 5. Effect of temperature on CHA conversion and product yield. Reaction conditions: CHA = 86.1 mmol, PO = 42.9 mmol, [Bmim][InI₄] = 0.43 mmol, toluene used as solvent = 15 mL, P (CO₂) = 8.3 MPa, t = 2 h.

and 5), the formation of DCU vs. others (HPC, Oxz, AmA) is inverse proportion relationship, *i.e.*, the less formation of AmA results in more formation of HPC, in turn, leading to enhancing yield of DCU as this reaction conditions changes to optimal status (2 h, 150°C). The formation of AmA, however, increased with elevated temperature above 150°C and accordingly, DCU yield decreased, which is likely due to that the rate of direct attack of CHA at PO becomes faster than that of PC formation at high reaction temperature, which in turn, leads to less formation of HPC and DCU (Figure 5). The highest DCU yield was achieved up to 65.8% at 4 h and 150°C.

The one-pot cascade coupling reaction of three components was carried out by varying the pressure (from 8.27 to 9.65 MPa) and keeping other variables constant and the results are presented in Figure 6. It could be seen that DCU yield was highest in the pressure range of 8.27–9.65 MPa

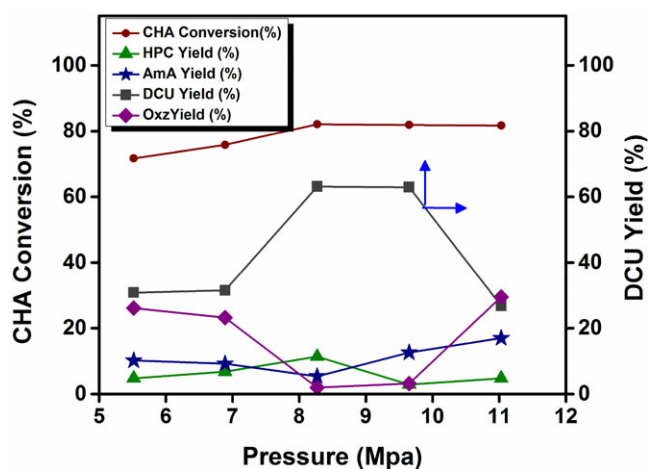


Figure 6. Effect of CO₂ pressure on CHA conversion and product yield. Reaction conditions: CHA = 86.1 mmol, PO = 42.9 mmol, [Bmim][InI₄] = 0.43 mmol, toluene used solvent = 15 mL, T = 150°C, t = 2 h.

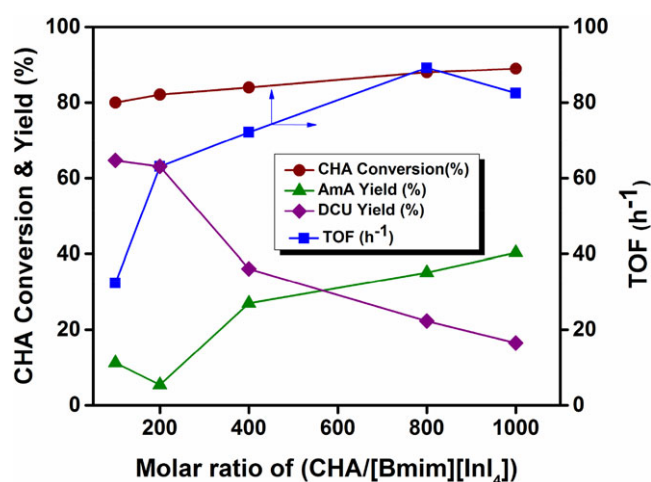


Figure 7. Effect of molar ratio (CHA/[Bmim][InI₄]) on CHA conversion and product yield. Reaction conditions: CHA = 86.1 mmol, PO = 42.9 mmol, toluene used solvent = 15 mL, $T = 150^{\circ}\text{C}$, $P(\text{CO}_2) = 8.3 \text{ MPa}$, $t = 2 \text{ h}$.

but thereafter a sharp decrement was observed due to the augmented formation of AmA and Oxz. This pressure dependence is rather difficult to explain but it is likely that there is a certain optimal pressure range in the three-component reaction that can suppress the formation of AmA and Oxz. The effect of varying molar ratio (CHA/**2a**) on the product compositional change was studied at 150°C and 8.3 MPa of CO_2 pressure for 2 h and the result is presented in Figure 7. The DCU yield decreased continuously with the increase in the molar ratio. The highest turnover frequency was found to be 89.2 h^{-1} at a molar ratio of 800.

To broaden the scope of the one-pot cascade coupling reaction of three components (substrate, CO_2 , and PO), various alicyclic and aliphatic amines were also examined by using **2a** as a catalyst and the results are summarized in Table 7.

Alicyclic amines such as cyclopentyl amine (entry 1), cycloheptylamine (entry 2), and cyclododecyl-amine (entry 3) were converted to their corresponding DSU products with good yields; however, aliphatic amines such as an *n*-butylamine (entry 4) could give only about 14% yield of DSU. When increasing the temperature and pressure up to 200°C and 10.0 MPa, respectively, the DSU yield also increased to 47% (entry 5). The aliphatic heptylamine could give only 36.1% yield of its corresponding product (entry 6), even at high temperature and pressure up to 200°C and 10.0 MPa. These results indicate that the **2a**-catalyzed three component reaction is more advantageous toward alicyclic than aliphatic amines. It is also important to note that the more electron-donating substituents in the alicyclic amine, the better yield of corresponding DSU, were obtained (entries 1–3), probably due to the increased basicity in the amino group, thereby leading to improved nucleophilic attack to PC and HPC. All alicyclic DSU products were isolated as white powder whereas aliphatic DSUs were found to be in a liquid state after reaction so the yields were calculated with GC calibration method using an external standard.

Table 7. Coupling reaction of three components with various substrates.^a

Entry	Substrate	Product	DSU yield (%) ^b
1			45.4
2			54.4
3			65.1
4			14.0 ^c
5 ^d			47.0
6 ^d			36.1

^a Reaction conditions: substrates (amines) = 86.1 mmol, PO = (42.9 mmol), [Bmim][InI₄] (**2a**) = (0.43 mmol), toluene used as a solvent = 15 mL, $T = 150^{\circ}\text{C}$, $P(\text{CO}_2) = 8.3 \text{ MPa}$, $t = 2 \text{ h}$.

^b Isolated yield.

^c GC yield.

^d $T = 200^{\circ}\text{C}$, $P(\text{CO}_2) = 10.0 \text{ MPa}$.

Conclusion

A new approach for the synthesis of DSU from one-pot cascade coupling reaction of three components (amine, CO_2 , and PO) is proven. In this research work, 1,3-disubstituted urea with acceptable yield (65.8%) is synthesized successfully in the presence of indium-based IL [Bmim][InI₄]. Furthermore, DSU products obtained from the alicyclic amines can easily be separated out from the reaction mixture. The separation of DSU products makes the process easy and more advantageous. It is noteworthy to mention that the *in situ* formation of HPC, an important intermediate in the coupling reaction of three components (CHA, CO_2 , and PO), was authenticated and was supported by the *in situ* FT-IR spectroscopy studies. A plausible reaction mechanism for the formation of DCU from CHA via HPC as an intermediate is proposed. Synthesis of DSU products by utilizing CO_2 as feedstock is in favor of a benign way to diminish the greenhouse gases in the environment. Overall, it is concluded that this developed new approach, one-pot cascade coupling reaction of three components (amine, CO_2 , and PO) for the formation of DSU products, can be well exploited industrially.

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Supporting Information. Additional supporting information such as General Considerations; Synthesis procedures, ^1H NMR, ^{13}C NMR and FT-IR spectra of 2-hydroxypropyl carbamate (HPC) and different ionic liquid based catalysts; GC-MS data and Elemental analysis of DSU products are available in the online version of this article.

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Graphical abstract

One-Pot Synthesis of Disubstituted Urea from Carbon Dioxide, Propylene Oxide, and Amines Catalyzed by Imidazolium-Tetraiodoindate

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