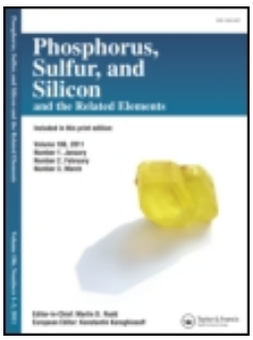

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Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: 1042-6507 (Print) 1563-5325 (Online) Journal homepage: http://www.tandfonline.com/loi/gpss20

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To cite this article: Sara S. E. Ghodsinia & Batool Akhlaghinia (2016) A high-yielding, expeditious, and multicomponent synthesis of urea and carbamate derivatives by using triphenylphosphine/trichloroisocyanuric acid system, Phosphorus, Sulfur, and Silicon and the Related Elements, 191:1, 1-7, DOI: 10.1080/10426507.2015.1085038

To link to this article: http://dx.doi.org/10.1080/10426507.2015.1085038

PHOSPHORUS, SULFUR, AND SILICON
2016, VOL. 191, NO. 1, 104–110
http://dx.doi.org/10.1080/10426507.2015.1085038

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A high-yielding, expeditious, and multicomponent synthesis of urea and carbamate derivatives by using triphenylphosphine/trichloroisocyanuric acid system

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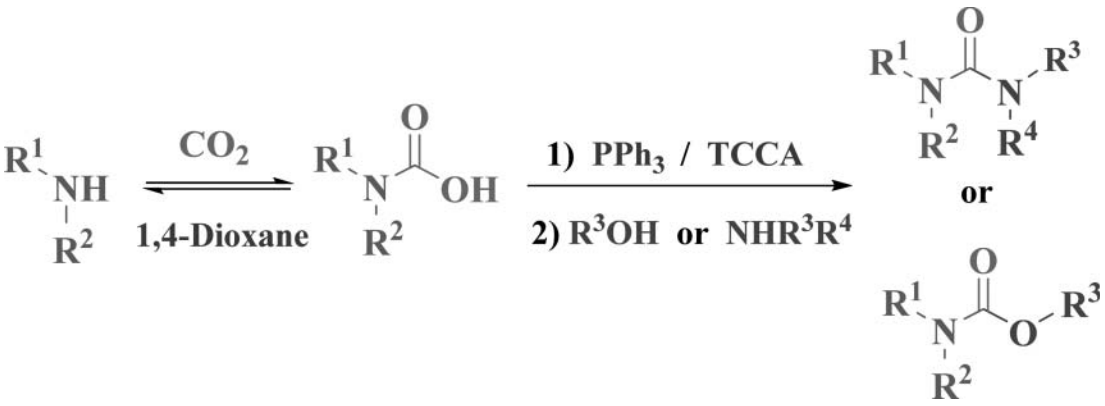
ABSTRACT

An efficient method for the synthesis of urea and carbamate derivatives from amines and alcohols is described by using triphenylphosphine (PPh_3)/trichloroisocyanuric acid system. The protocol allows for the preparation of symmetrical, unsymmetrical di, tri-, and tetra-substituted ureas and carbamates and is tolerant of a wide range of functional groups. To optimize the reaction conditions, experimental variables including temperature, the concentration of amine and alcohol, solvent, and reaction time were studied. Satisfactory yields were obtained at the optimized conditions. The present methodology is experimentally simple, mild, and represents a valuable alternative to the existing methods.

ARTICLE HISTORY
Received 18 April 2015
Accepted 17 August 2015

KEYWORDS
Triphenylphosphine; trichloroisocyanuric acid; urea; carbamate; amine; alcohol

GRAPHICAL ABSTRACT



Introduction

N-containing compounds such as urea and carbamate derivatives, as an important class of carbonyl compounds, are significant subunits present in numerous naturally occurring compounds. They have interesting applications in organic chemistry, medicinal chemistry, agriculture, petrochemicals, biology, and material science.[1-5] Several substituted ureas, which can be used as intermediates for the production of carbamates,[5-7] possess a marked inhibitory effect on HIV-1 protease, p38 MAP kinase,[8-12] microbial alkaline protease,[13] and several other classes of enzymes.[14] It was found that trace amounts of urea derivatives enhances the photoreduction of nitrobenzene by catalyzing the proton transfer step.[15] Thus, to satisfy their demand, numerous synthetic methods have been developed for the formation of the urea and carbamate linkages by convenient and safe methodologies. Traditional synthesis of urea and carbamates derivatives involves the reaction of amines with phosgene and phosgene derivatives,[16-28] carbonyl-imidazoles,[29-31] carbon monoxide,[32-34] isocyanate (which are often generated in situ in the presence of alcohols via the Hofmann,[35] Curtius,[36] Lossen,[37] and Schmidt[38] rearrangements or the reductive carbonylation of nitroaromatic compounds[39]),[40-43] acid anhydrides,[44] and chloroformates.[45-49] Also, other methods have been developed involving the reaction of amines with reagents which originate from CO_2 reacting with ammonium,[50] ethylene oxide or ethanol,[51] and alkyl halides[52] such as urea,[53] ethylene carbonate,[54] or diethyl carbonate.[55]

However, some of the reported methods suffer from the use of costly and toxic chemicals directly or indirectly, limited substrate scope, harsh reaction conditions, multiple-step preparations or the lack of readily available starting materials. (For instance, using phosgene and phosgene derivatives as highly toxic reagents which is not environmental friendly opens many worrying toxicological and environmental problems.[17]

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Preparation of carbamates and ureas by using costly, toxic, and limited number of commercially available isocyanates suffers from limited substrate scope and multiple-step reaction.[56] In addition, in some cases, various kinds of metal and nonmetal catalysts,[34,57-65] were used which have tremendous toxicological and environmental problems although different alternative methods that do not involve the use of toxic reagents have also been reported (such as phosgene-free synthesis of carbamates over zeolite-based catalysts,[66] one-pot synthesis of substituted ureas from the corresponding amines using Mitsunobu's reagent,[67] synthesis of urea derivatives from amines and CO_2 in the absence of catalyst and solvent[68]). Thus, an alternative environmentally benign synthetic method for the preparation of ureas and carbamates is demanded. Carbon dioxide as a nontoxic, noncorrosive, inflammable, abundant, and cheap carbon source is particularly attractive in urea and carbamate synthesis. Urea and carbamate linkages can be obtained from the reaction of carbon dioxide with amines followed by the treatment of produced carbamic acid with amines and alcohols, respectively. Carbon dioxide easily combines with amines at ambient temperature and atmospheric pressure to produce carbamic acids.[69-71] A few reports exist on direct synthesis of ureas and carbamates from CO_2 and amines.[57,72-79]

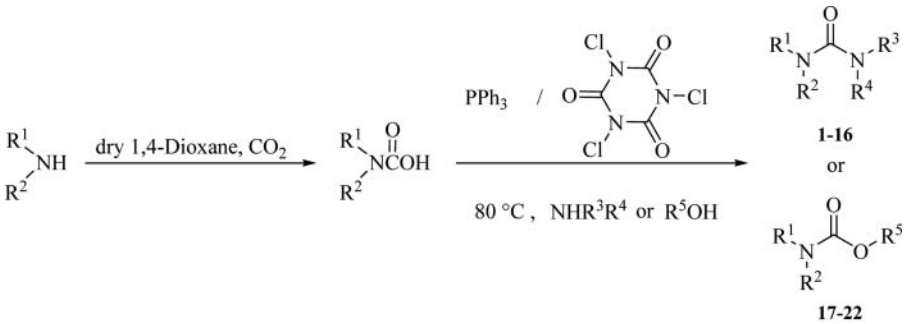
Herein, we aimed to successfully prepare urea and carbamate derivatives from carbamic acids (which was prepared in situ from the reaction between amines and CO_2 as the carbonyl source) by using triphenylphosphine/trichloroisocyanuric acid/amine (or alcohol) system.

Results and discussion

Our own interest in the synthesis of ureas and carbamates stems from our recent studies in application of triphenylphosphine/*N*-halo reagents systems,[80-93] and the other reports[94-99] in organic synthesis. Here, we have utilized triphenylphosphine/trichloroisocyanuric acid system in preparation of symmetrical, unsymmetrical di, tri-, and tetra-substituted ureas and carbamates (Scheme 1).

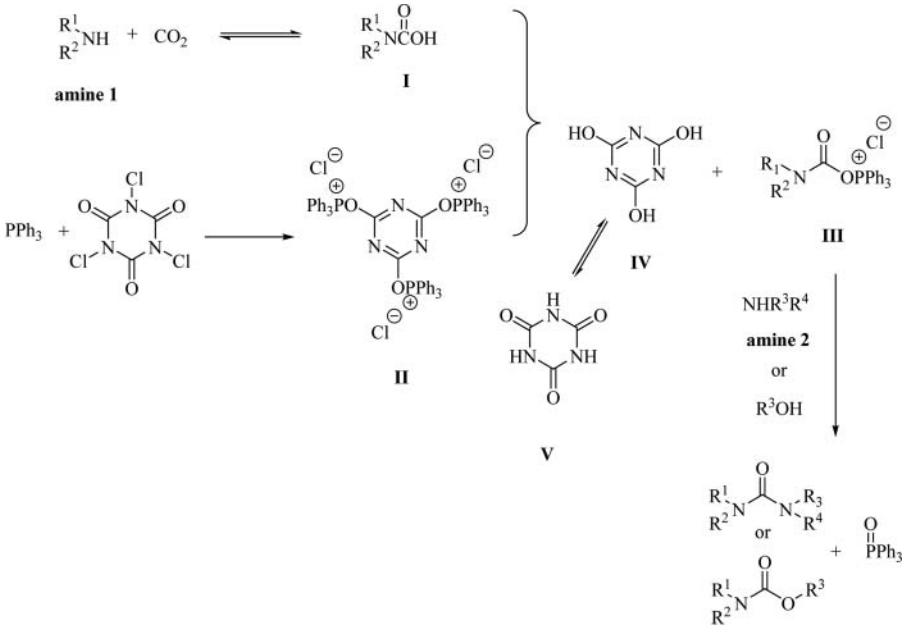
To begin with, we investigated the preparation of 1-benzyl-3-phenylurea as a model reaction by using triphenylphosphine/trichloroisocyanuric acid system. In this study, we tested the effect of different molar ratios of reactants as well as solvents at different temperatures on the reaction rate. The obtained results are summarized in Table 1. Since the intermediates and PPh_3 are reactive species and extremely sensitive to moisture, it is critical to use an anhydrous solvent. At first, benzyl carbamic acid was prepared by passing gaseous carbon dioxide through a solution of benzyl amine in 1,4-dioxane at ambient temperature. By adding 0.3:1 mixture of TCCA:PPh_3 in 1,4-Dioxane to the reaction mixture which was followed by addition of aniline, 1-benzyl-3-phenylurea was prepared. On the basis of our previous studies,[90,92] the optimized molar ratios of TCCA: PPh_3 was selected as 0.3:1. Applying 0.3:1:1:1 molar ratio of TCCA:PPh_3: benzyl amine:aniline in 1,4-dioxane at 80°C produced the desired product in 95% isolated yield (Table 1, entry 1). To investigate the effect of temperature on model reaction rate, the aforementioned condition was performed at room temperature, 90°C and reflux (Table 1, entries 2–4). According the data from Table 1, the reaction has not progressed at room temperature whereas higher temperature (90°C and reflux) have no any influence on the reaction rate. We tried many other solvents like, CH_3CN, DMF, DMSO, THF, toluene, and CH_3NO_2 in preparation of 1-benzyl-3-phenylurea by applying 0.3:1:1:1 molar ratio of TCCA:PPh_3:benzyl amine:aniline. Performing the reaction in CH_3CN, DMF, and DMSO produced the desired product in low yields after longer reaction times (Table 1, entries 5–7) while in THF, toluene and CH_3NO_2 no product was obtained even after long period of time (Table 1, entries 8–10). Additional amount of aniline has not any influence on the reaction rate (Table 1, entry 11).

Passing gaseous CO_2 through **amine 1** solution generated unstable carbamic acid **I**.[68,72] On the other hand, the initial attack at the halogen in TCCA by triphenylphosphine leads to the halogen–phosphonium salt **II**. The reaction of halogen-phosphonium salt with carbamic acid **I** yields the activated species **III** and [1,3,5]triazine-2,4,6-triol (**IV**), which is in equilibrium with [1,3,5]triazinane-2,4,6-trione (**V**). As soon as **III** is formed, a nucleophilic attack occurs between **III** and **amine 2**/or alcohol to form triphenylphosphine oxide and corresponding urea/or carbamate. To elucidate the reaction path more clearly, we attempted to isolate and identify the **IV** and **V** (Scheme 2). FTIR spectrum of two tautomeric forms [1,3,5]



R^1= Benzyl, Phenyl, *p*-Tolyl, *o*-Pyridyl, Cyclohexyl, Pyrrolidine, *tert*-Butyl
R^2= H, Pyrrolidine
R^3= Benzyl, Phenyl, *n*-Butyl, *tert*-Butyl, *o*-Chlorobenzyl, *o*-Methoxybenzyl, Morpholine, Pyrrolidine
R^4= H, Morpholine, Pyrrolidine
R^5= Benzyl, 1-Heptyl, 1-Phenylethyl, Phenyl

Scheme 1. Synthesis of urea and carbamate derivatives.



Scheme 2. Proposed mechanism of urea and carbamate synthesis.

triazine-2,4,6-triol (**IV**) and [1,3,5] triazinane-2,4,6-trione (**V**) showed a broad absorption band at 3350–3100 cm^{-1} due to OH and NH stretching vibration of **IV** and **V**. Presence of C=N and C=O was confirmed by the appearance of absorption bands at 1613 and 1755–1713 cm^{-1}, respectively.

With the best conditions in hand, a variety of structurally divergent aliphatic and aromatic amines were selected to explore the generality and scope of the present mixed reagent in the preparation of symmetrical, unsymmetrical di, tri-, and tetra-substituted ureas. The obtained results are summarized in Table 2. As can be seen in Table 2, the reaction was highly tolerant of the amine 1 and amine 2 structure. The optimized reaction conditions (0.3:1:1:1 molar ratio of TCCA:PPh_3:amine 1:amine 2 in dry 1,4-dioxane at 80°C) were used for all reactions and the corresponding ureas were prepared within 2.5–5.5 h with good to excellent yields.

According the results of Table 2, primary aliphatic amines have more reactivity than aromatic amines and tertiary amines toward benzyl carbamic acids (compare entries 2, 3 with entries 1, 4). The difference in reactivity can be attributed to low nucleophilicity of aromatic amine and the steric hindrance of tertiary amine. Steric effects play an essential role in the reaction of amine 2 with carbamic acid. For instance, 2-chloro benzylamine and 2-methoxy benzylamine react more slowly than *n*-butyl amine with phenyl carbamic acid (compare entries 6,7 with entry 8). Also, morpholine and pyrrolidine as two secondary amine, show low reactivity than *n*-butyl amine (compare entries 9, 10 with entry 8).

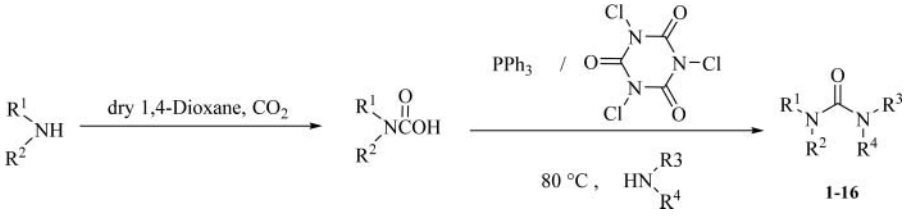
Seeking to widen the applicability of the present protocol, we envisioned an alternative approach to add to the existing methods of carbamate synthesis. After establishing the methodology for ureas, we examined the preparation of benzyl phenyl carbamate by using triphenylphosphine/ trichloroisocyanuric acid system. Benzyl phenylcarbamate was synthesized from the reaction between benzyl carbamic acid (which was prepared by passing gaseous carbon dioxide through a solution of benzyl amine in 1,4-dioxane at ambient temperature) and benzyl alcohol in 1,4-dioxane at 80°C, using a 0.3:1:1:1 molar ratio of TCCA:PPh_3:benzyl amine:benzyl alcohol in high yields (97%).

Under the optimized reaction conditions established, various kinds of carbamates were prepared through the reaction of various kinds of structurally diverse primary and secondary alcohols and phenol with variety of carbamic acids using TCCA:PPh_3 system, to afford the corresponding carbamates in

Table 1. Synthesis of 1-benzyl-3-phenylurea (**1**) by using triphenylphosphine/trichloroisocyanuric acid system in various solvents, different molar ratios of reactants, and different temperatures.

Entry	Molar ratio TCCA/PPh_3/benzyl amine/aniline	Solvent	Temp. (°C)	Time (h)	Isolated yield (%)
1	0.3/1/1/1	1,4-Dioxane	80	4	95
2	0.3/1/1/1	1,4-Dioxane	90	4	90
3	0.3/1/1/1	1,4-Dioxane	Reflux	4	90
4	0.3/1/1/1	1,4-Dioxane	r.t.	10	0
5	0.3/1/1/1	CH_3CN	Reflux	5	60
6	0.3/1/1/1	DMF	90	5	55
7	0.3/1/1/1	DMSO	90	5	60
8	0.3/1/1/1	THF	Reflux	10	0
9	0.3/1/1/1	Toluene	100	10	0
10	0.3/1/1/1	CH_3NO_2	Reflux	10	0
11	0.3/1/1/1.5	1,4-Dioxane	80	4	95

Table 2. Preparation of structurally different symmetrical and unsymmetrical ureas by using triphenylphosphine/trichloroisocyanuric acid system.



Entry	R^1	R^2	R^3	R^4	Time (h)	Isolated yield (%)	References
1	Benzyl	H	Phenyl	H	4	95	107
2	Benzyl	H	Benzyl	H	3	92	108
3	Benzyl	H	*n*-Butyl	H	2.5	98	109
4	Benzyl	H	*tert*-Butyl	H	4.5	90	100
5	Phenyl	H	Phenyl	H	4	95	110
6	Phenyl	H	*o*-Chlorobenzyl	H	3.5	90	—
7	Phenyl	H	*o*-Methoxybenzyl	H	3	92	111
8	Phenyl	H	*n*-Butyl	H	2	95	109
9	Phenyl	H	$R^3 = R^4 =$	Morpholine	5	95	112
10	Phenyl	H	$R^3 = R^4 =$	Pyrrolidine	5	98	113
11	*p*-Tolyl	H	Benzyl	H	3	98	114
12	*p*-Tolyl	H	*o*-Chlorobenzyl	H	4	95	—
13	*p*-Tolyl	H	$R^3 = R^4 =$	Pyrrolidine	5.5	98	115
14	*o*-Pyridyl	H	*tert*-Butyl	H	3	88	116
15	Cyclohexyl	H	*n*-Butyl	H	3	98	117
16	$R^1 = R^2 =$	Pyrrolidine	$R^3 = R^4 =$	Pyrrolidine	5.5	98	118

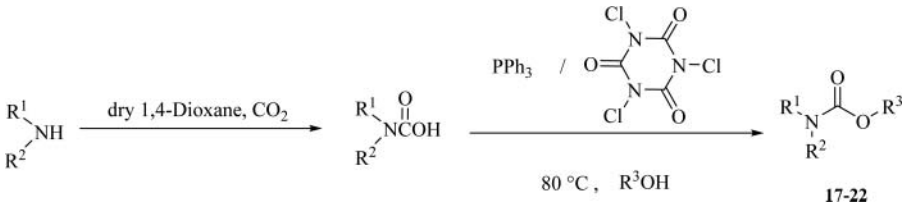
high yields as mentioned in Table 3. Again, steric effects have essential effect in the reaction of alcohol with carbamic acid. As can be seen from Table 3, primary alcohols react faster than secondary ones (compare entry 2 with entry 3). Similarly, because of low nucleophilicity of phenol, the reaction of phenol with carbamic acids was completed in longer reaction time (compare entries 4, 6 with entry 1).

In our experiments, completion of the reaction was confirmed by the disappearance of the amine/or alcohol on TLC, followed by the disappearance of NH_2/or OH stretching frequencies at 3500 and 3300/or 3400–3300 cm^{-1} in the Fourier transform infrared (FTIR) spectra. It is worthy to note that all the products listed in Tables 2 and 3 could be simply purified by flash column chromatography and characterized using FTIR, NMR, and mass spectrometry (MS). Absorption bands at 3383–3302/or 3364–3274 and 1689–1627/or 1716–1636 cm^{-1} corresponding to NH and carbonyl groups of urea/or carbamate, respectively, confirmed the formation of corresponding products (see "Supplemental Materials" file). In the ^{1}H NMR and ^{13}C NMR spectra, signals at 8.66–7.18 and 156.8–156.7 ppm due to the NH and quaternary carbon atom of urea, respectively.

No side reactions/products (e.g., symmetrical urea in the case of unsymmetrical urea synthesis and urea in the case of carbamate synthesis) were observed during the course of the reaction; thus, we believe that the present methodology opens new possibilities for the synthetic organic chemistry and could be an important addition to the existing methodologies.

The efficiency of the present protocol was compared with the previously reported methods in the literature. The results are shown in Table 4. It can be seen from Table 4 that, most of the reported methods suffer from using environmentally hazardous, high corrosive and high cost chemicals, harsh reaction conditions, multiple-step procedures, tedious work-up, long reaction times to achieve reasonable yields and limited substrate scope.

Table 3. Preparation of structurally different carbamate by using triphenylphosphine / trichloroisocyanuric acid system.



Entry	R^1	R^2	R^3	Time (h)	Isolated yield (%)	References
1	Phenyl	H	Benzyl	3	97	119
2	Phenyl	H	1-Heptyl	2.5	98	120
3	Phenyl	H	1-Phenylethyl	4	95	121
4	Phenyl	H	Phenyl	4.5	90	122
5	*tert*-Butyl	H	Benzyl	3.5	95	123
6	*tert*-Butyl	H	Phenyl	4	92	124

Table 4. Comparison of various methods and catalysts in 1-benzyl-3-phenylurea synthesis.

Entry	Substrates and reagents	Explanations	Catalysts	Time (h)	Isolated yield (%)
1	RNH_2, CO_2, DBU, PBu_3, DBAD, N_2[74]	Low yield, multiple-step reaction, expensive reagent (DBU, DBAD)	—	1	68
2	Cyanamides, benzyl alcohol, DCE (solvent)[100]	Long reaction time, multiple-step reaction, low yield	$FeCl_3$	4.5	86
3	Cyanamides, dibenzyl ether, Aceticacid (Solvent) [101]	Tedious work-up, using of toxic cyanamides, limited substrate scope	$BF_3.Et_2O$	2	94
4	*N*′-Phenyl urea, benzaldehyde, triethylsilane, trifluoroacetic acid, toluene (solvent)[102]	Long reaction time, highly corrosive reagent (TFA)	—	18	97
5	RNH_2, 2,2,2-trichloroethyl-*N*-phenyl carbamate, THF (solvent)[103]	Harsh reaction conditions, high-pressure conditions, long reaction time	—	30	97
6	R_2NH, nitrobenzene, CO, Et_3N[104]	Hightemperature (150–160°C), low yield, mixed products (nonselective products), harsh reaction conditions	Se	1.5	14.4
7	*N*-benzyl-*N*′-phenylthiourea, thiophosgene in water, acetone (solvent)[105]	Using of toxic thiophosgene which is not environmental friendly, low yield, harsh reaction conditions	—	2	75
8	RNH_2, 4-nitrophenyl-*N*-benzylcarbamate, Et_3N, dichloromethane (solvent)[106]	Long reaction times, using costly and limited number of commercially available 4-nitrophenyl-*N*-benzylcarbamate	—	6	83
9	RNH_2 or R_2NH, CO_2, TCCA, PPh_3, dry 1,4-dioxane (solvent)	Excellent yield, short reaction time, using low-priced reagents and experimental convenience, mild reaction conditions, easy work-up, low-pressure	—	1	95

Experimental

General

The products were purified by column chromatography. The purity determinations of the products were accomplished by TLC on silica gel polygram STL G/UV 254 plates (Merck, Germany). The melting points of products were determined with an Electrothermal Type 9100 melting point apparatus (UK). The FTIR spectra were recorded on an Avatar 370 FTIR Therma Nicolet spectrometer (USA). The nuclear magnetic resonance (NMR) spectra were provided on Brucker Avance 300 and 400 MHz instruments in DMSO-d_6. Coupling constants *J* are given in Hz. Abbreviations used for ^{1}H NMR signals are: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, and *m* = multiplet. Elemental analyses were performed using a Thermo Finnegan Flash EA 1112 Series instrument. Mass spectra were recorded with a CH7A Varianmat Bremem instrument (Germany) at 70 eV; in *m*/*z* (rel%). All of the products were known compounds and characterized by the IR, MS, and comparison of their melting points with known compounds. The structures of the novel products were further confirmed by ^{1}H NMR, ^{13}C NMR spectroscopy, and elemental analysis data. The full characterization data and sample IR, mass spectra and ^{1}H and ^{13}C NMR spectra are presented in the Supplemental Materials (Figures S1–S69).

Typical experimental procedure for preparation of 1-benzyl-3-phenylurea (Table 2, entry 1)

Benzylamine (0.107 g, 1 mmol) was taken in dry 1,4-dioxane (10 mL) and gaseous CO_2 was bubbled through it for 20–30 min at room temperature. To a cold solution of triphenylphosphine (0.262 g, 1 mmol) in dry 1,4-dioxane (2 mL) trichloroisocyanuric acid (0.076 g, 0.3 mmol) was added with continuous stirring. The resultant white suspension was added slowly in 2–3 small portions to the produced benzyl carbamic acid which was followed by addition of aniline (0.093 g, 1 mmol). The reaction temperature was raised to 80°C with stirring. After completion of the reaction (4 h) as confirmed by TLC, the reaction mixture was then poured into 15 mL distilled water and extracted with ethyl acetate (3 × 10). The organic layer was separated and dried over anhydrous sodium sulfate and then passed through a short silica-gel column using *n*-hexane-ethyl acetate (1:1) as the eluent. 1-Benzyl-3-phenylurea was obtained with 95% yield (0.214 g) after removing the solvent under reduced pressure.

Typical experimental procedure for preparation of benzyl phenyl carbamate (Table 2, entry 1)

Aniline (0.093 g, 1 mmol) was taken in dry 1,4-dioxane (10 mL) and gaseous CO_2 was bubbled through it for 20–30 min at room temperature. To a cold solution of triphenylphosphine (0.262 g, 1 mmol) in dry 1,4-dioxane (2 mL) trichloroisocyanuric acid (0.076 g, 0.3 mmol) was added with continuous stirring. The resultant white suspension was added slowly in two to three small portions to the produced phenyl carbamic acid, which was followed by addition of benzyl alcohol (0.108 g, 1 mmol). The reaction temperature was raised to 80°C with stirring. After completion of the reaction (3.5 h) as confirmed by TLC, the reaction mixture was then poured into 15 mL distilled water and extracted with ethyl acetate (3 × 10). The organic layer was separated and dried over anhydrous sodium sulfate and then passed through a short silica-gel column using *n*-hexane-ethyl acetate (1:1) as the eluent. Benzyl phenyl carbamate was obtained with 97% yield (0.205 g) after removing the solvent under reduced pressure. The characterization data of known urea derivatives and carbamates is presented in the Supplemental Materials.

Conclusion

A new, convenient and efficient protocol for the formation of C—O, and C—N bonds essential to numerous organic syntheses is described. The present method generates urea and carbamate derivatives in good to excellent yields. The elegance of

this process lies in its mild reaction conditions, substrate versatility, high yields, short reaction times, using low-priced reagents and experimental convenience.

Funding

The authors gratefully acknowledge the partial support of this study by Ferdowsi University of Mashhad Research Council.

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