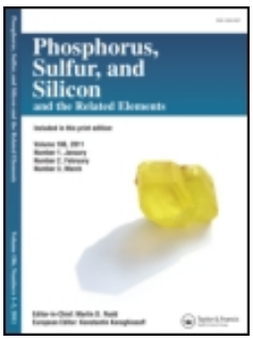

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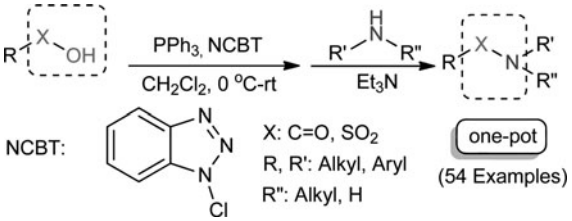
A ONE-POT, FAST, AND EFFICIENT AMIDATION OF CARBOXYLIC ACIDS, α-AMINO ACIDS AND SULFONIC ACIDS USING PPH_3/*N*-CHLOROBENZOTRIAZOLE SYSTEM

Hamed Rouhi-Saadabad and Batool Akhlaghinia
Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran

GRAPHICAL ABSTRACT



Abstract *Triphenylphosphine (PPh_3)/N-chlorobenzotriazole (NCBT), and amine (primary and secondary aliphatic amines and also substituted anilines) in CH_2Cl_2 efficiently converted carboxylic acids, α-amino acids, and sulfonic acids to the corresponding amides and sulfonamides at room temperature. Good to excellent yields, inexpensive, and fast reaction conditions are the important features of this procedure.*

Keywords Amidation; carboxylic acid; amino acid; sulfonic acid; triphenylphosphine; *N*-chlorobenzotriazole; one-pot synthesis

INTRODUCTION

Among the nitrogen-containing compounds, amides are important due to their vast application in synthesis and medicinal chemistry.[1] This functional group is also found in numerous naturally-occurring products (e.g., peptides and proteins).[2] Sulfonamides, as the other important functional groups in medicinal chemistry, are the first drugs which have been largely used as chemotherapeutic agents against various diseases.[3] They are often found in compounds with anticancer, antihypertensive, anti-inflammatory, antiallergic, antimigraine, and antiviral activities.[4] Due to the broad application of amides and sulfonamides, finding new, efficient, and practical methods for their synthesis is desirable.

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Address correspondence to Dr. Akhlaghinia, Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad 9177948974, Islamic Republic of Iran. E-mail: akhlaghinia@um.ac.ir
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/gpss.

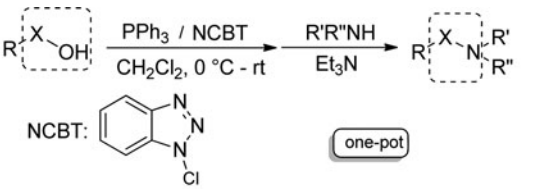
There are a multitude of well-known methods for efficient amide and sulfonamide bond formations. Direct condensation of carboxylic and sulfonic acids with amines has been used for the synthesis of amides and sulfonamides.[5] Requiring high temperatures and harsh reaction conditions have limited these methods. The most common method for the preparation of amides and sulfonamides is the reaction of acyl and sulfonyl halides with ammonia, primary, or secondary amines in the presence of a base.[3] Although, this is an efficient method, it needs the availability of acyl and sulfonyl halides. Acyl and some sulfonyl halides are moisture sensitive, require care in handling and[6] are difficult to store for long time.

The straightforward method for the synthesis of amides and sulfonamides is the reaction of activated carboxylic and sulfonic acids with amines.[7] In this regard, carboxamides and sulfonamides were prepared by the reaction of carboxylic and sulfonic acid derivatives with aromatic and aliphatic amines in the presence of $SOCl_2$,[8] $POCl_3$,[9] PCl_5,[10] or SO_2Cl_2.[11] Also, amidation of carboxylic and sulfonic acids, have been reported by using cyanuric chloride,[12] carbodiimides,[13] uronium salts,[14] triphosgene,[15] PPh_3/Cl_3CN,[16] and PPh_3/SO_2Cl_2,[17] as acid activators. Despite the efficiency of these methods, development a new, simple, fast, efficient, and highly profitable amidation method under mild reaction conditions is still highly desirable and demanded.

In the present study, we used PPh_3/ NCBT as an efficient mixed reagent system for a one-pot, fast, and efficient preparation of amides, α-amino acid amides, and sulfonamides.

RESULTS AND DISCUSSION

Following our interest in the chemistry of PPh_3 in functional group transformations,[18,6] we speculated on the possibility of using PPh_3 in conjunction with NCBT, as an *N*-halo reagent to activate carboxylic acids, α-amino acids, and sulfonic acids for a nucleophilic substitution at the carbonyl and sulfonyl groups to achieve amide and sulfonamide linkages (Scheme 1).



X: C=O

R = Ph, 4-MePh, 3,5-DiMePh, 4-MeOPh, 2-ClPh, 4-ClPh, 4-BrPh, 3,4-DiClPh, AcOPh, AcNHPh, 4-NO_2Ph, 3-NO_2Ph, PhCH=CH, 4-ClPhCH=CH, 3-NO_2PhCH=CH, 2,4-DiClPhOCH_2, $(Ph)_2CH$, 4-MeOPhCH_2, $CH_3(CH_2)_7CHCH(CH_2)_7CH_2$, $CH_3(CH_2)_3CH_2$, 3-Thiophene, AcNHCH$_2$, AcNHCH(CH_3), AcNHCH(CH_2Ph), AcNpyrrolidine, indole-3-CH_2CH(NHAc)

R'= PhCH_2, $CH_3(CH_2)_2CH_2$, $EtO(CH_2)_2CH_2$, Cyclohexyl, 4-MeOPhCH_2, 2-MeOPhCH_2, 2-ClPhCH_2, Et, *i*-Pr, 2-FuranCH_2, Ph, 4-BrPh, CH_3Ph.

R" = H, Et, *i*-Pr, Morpholine, Piperidine, pyrolidine

X: SO_2

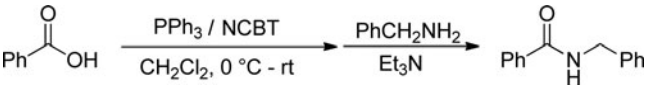
R = Me, Et, Ph, CH_3Ph, 4-ClPh.

R' = PhCH_2,Ph, Et, 4-BrPh, 4-MeOPhCH_2, Cyclohexyl, $CH_3(CH_2)_2CH_2$, .

R" = H, Et, Morpholine, Piperidine, pyrolidine

Scheme 1

Table 1 Conversion of benzoic acid to *N*-benzylbenzamide with PPh_3/NCBT/benzylamine system at 0°C to room temperature, under different reaction conditions



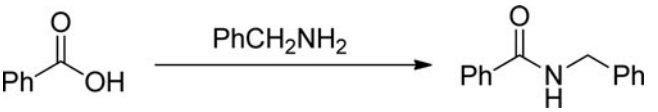
Entry	Solvent	Molar ratio PPh_3/NCBT/ RCO_2H/R'R"NH	Time (min)	Isolated yield (%)
1	CH_2Cl_2	1.25/1.25/1/2.5	30	95
2	CH_3CN	1.25/1.25/1/2.5	30	90
3	THF	1.25/1.25/1/2.5	45	80
4	$CHCl_3$	1.25/1.25/1/2.5	55	90
5	1,4-dioxane	1.25/1.25/1/2.5	95	70
6	acetone	1.25/1.25/1/2.5	70	85
7	*n*-hexane	1.25/1.25/1/2.5	95	60
8	CH_2Cl_2	0/0/1/2.5	120	0
9	CH_2Cl_2	0/1.25/1/2.5	120	0
10	CH_2Cl_2	1.25/0/1/2.5	120	0
11	none	1.25/1.25/1/2.5	120	10
12	CH_2Cl_2	1/1/1/1	100	70
13	CH_2Cl_2	1/1/1/1.5	90	80
14	CH_2Cl_2	1/1/1/2	50	80
15	CH_2Cl_2	1/1/1/2.5	40	90
16	CH_2Cl_2	1.25/1.25/1/3	30	95

In order to find out the most effective amidation, reaction of benzoic acid with benzylamine in the presence of PPh_3/NCBT was chosen as a model reaction. The best procedure was adding benzoic acid (1.0 mmol, 1 equiv.) and benzylamine (2.5 mmol, 2.5 equiv.) to the mixture of PPh_3/NCBT (1.25/1.25) in dry CH_2Cl_2 at room temperature. Since the intermediates and PPh_3 are reactive species and extremely sensitive to moisture, it is critical to use an anhydrous solvent. To neutralize the reaction mixture Et_3N (1 mmol) as a base, was then added dropwise into the suspension. The formation of *N*-benzylbenzamide was observed after 30 min and in high yield (monitored by TLC). As shown in Table 1 (entries 2–7), this reaction worked nicely in a number of common solvents including CH_3CN, THF, $CHCl_3$, 1,4-dioxane, acetone, and hexane. To prove the reaction was indeed involving PPh_3 and NCBT, we carried out several control experiments (Table 1, entries 8–10). The reaction of benzoic acid with benzylamine only led to formation of *N*-benzylbenzamide in trace amounts under solvent free conditions (Table 1, entry 11). Applying the other molar ratios of PPh_3/NCBT/benzoicacid/benzylamine led to formation of *N*-benzylbenzamide in low yield and in a longer reaction time (Table 1, entries 12–15). Using 1.25/1.25/1/3 molar ratio of PPh_3/NCBT/benzoicacid/benzylamine (Table 1, entry 16) gave the same result as entry 1.

To show the efficiency of this mixed reagent in amidation reaction, some of the reported amidation protocols were summarized in Table 2. As is apparent from Table 2, PPh_3/ NCBT mixed reagent is the most efficient reagent, for conversion of benzoic acid to *N*-benzylbenzamide.

After finding the optimal reaction conditions, we studied the methodology with an array of commercially available aromatic and aliphatic carboxylic acids with benzylamine (Table 3, entries 1–20). In comparison, aromatic carboxylic acids with electron deficient substituents were successfully reacted with benzylamine very rapidly than electron-rich

Table 2 Amidation of benzoic acid with benzyl amine by using different reagents



Entry	Reagent	Reaction condition	Time (h)	Yield (%)	References
1	*O,O′*-Di(2-pyridyl) thiocarbonate (DPTC)	Et_2O/ r.t.[a]	2	83	[19]
2	*p*-Nitrobenzenesulfonyl chloride	CH_3CN/r.t.[a]	40 min	98	[20]
3	I_2/trimethoxyphosphine $P(OMe)_3$	CH_2Cl_2/0 °C - r.t.[a]	3	94	[21]
4	PPh_3/trichloroacetonitrile (TCA)	CH_2Cl_2/r.t.[a]	3	73	[22]
5	Ion-supported $PPh_3/BrCCl_3$	THF/60 °C	6	99	[23]
6	PPh_3/hexachloroacetone (HCA)	CH_2Cl_2/-78 °C - r.t. [a]	1	95	[24]
7	PPh_3/azopyridine	CH_3CN/reflux	3.5	85	[25]
8	PPh_3/*N*-chlorobenzotriazole (NCBT)	CH_2Cl_2/0 °C - r.t. [a]	30 min	95	—

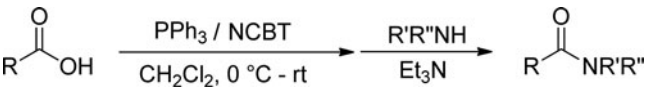
[a]r.t.: room temperature.

aromatic carboxylic acids (e.g., compare entry 4 and 10). We also determined that the reactions of aliphatic carboxylic acids with benzylamine proceeded very well to afford the corresponding amides in excellent yields (Table 3, entries 13–19). Next, other amines were also tried. Similarly, by using primary and secondary, cyclic and acyclic aliphatic amines, amidation reaction of benzoic acid furnished very rapidly as benzylamine (Table 3, entries 22–33). Those amines with lowered nucleophilicity, such as anilines (as demonstrated in Table 3), appear to require alternative reaction conditions to undergo efficient reaction with carboxylic acids. We therefore embarked on studies to establish conditions that would be suitable for efficient amidation of carboxylic acids with lower nucleophilic amines such as anilines. Extensive studies in our laboratory, employing various reaction time, solvents, and temperatures lead us to perform the amidation reactions in refluxing CH_3CN (Table 3, entries 34–37). Thiophene-3-carboxylic acid was also treated by this mixed reagent. Nucleophilic thiophene did not interfere with the reaction and the corresponding amide was obtained with quantitative yield (Table 3, entry 21).

α-Amino acid amides are important precursors in the synthesis of pharmaceutical compounds. Because of their importance, numerous protocols have been developed for their preparations.[51] Consequently, any new methodology that allows for the rapid, cost-effective synthesis of α-amino acid amides by using readily available reagents would be desirable. To improve and develop the applicability of the present method, synthesis of α-amino acid amides, were examined by using PPh_3/NCBT/amines system. At first, *N*-acetylated α-amino acids were prepared by the method reported previously,[52] to prevent any interference of amino groups. Acceptable results were obtained, when the above optimized reaction conditions were applied for the amidation of *N*-acetylated α-amino acids (Table 4). As shown in Table 4, the mixed reagent worked nicely in a series of *N*-acetylated α-amino acids such as glycine, alanine, phenylalanine, proline, and tryptophan. From the screening results, *N*-acetyl α-amino group did not change the reactivity of the carboxylic acids toward PPh_3/NCBT/amines system. This fact that, nucleophilic indole in tryptophan did not interfere the reaction is also noteworthy (Table 4, entry 5).

As we like to extend the applicability of the present methodology, after establishing the reaction conditions for the reaction of benzoic acid with benzylamine, in a series of experiments, we focused our attention on the synthesis of sulfonamides. We continued our

Table 3 Conversion of carboxylic acids to amides by using PPh_3/NCBT/amines system

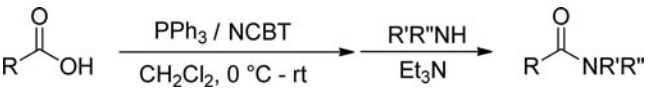


Entry	Carboxylic acid (RCOOH)	Amine (R'R"NH)	Time (min)	Isolated yield (%)	References
1	PhCOOH	$PhCH_2NH_2$	30	95	26
2	4-MeC_6H_4COOH	$PhCH_2NH_2$	45	95	26
3	3,5-$Me_2C_6H_3COOH$	$PhCH_2NH_2$	50	92	27
4	4-$MeOC_6H_4COOH$	$PhCH_2NH_2$	70	93	26
5	2-ClC_6H_4COOH	$PhCH_2NH_2$	35	85	28
6	4-ClC_6H_4COOH	$PhCH_2NH_2$	25	90	26
7	4-BrC_6H_4COOH	$PhCH_2NH_2$	25	93	23
8	3,4-$Cl_2C_6H_3COOH$	$PhCH_2NH_2$	20	90	29
9	4-$AcOC_6H_4COOH$	$PhCH_2NH_2$	40	90	30
10	4-$AcNHC_6H_4COOH$	$PhCH_2NH_2$	40	87	—
11	4-$NO_2C_6H_4COOH$	$PhCH_2NH_2$	15	95	23
12	3-$NO_2C_6H_4COOH$	$PhCH_2NH_2$	15	90	31
13	(*E*)-PhCH = CHCOOH	$PhCH_2NH_2$	90	92	26
14	4-ClPhCH = CHCOOH	$PhCH_2NH_2$	75	80	23
15	3-NO_2PhCH = CHCOOH	$PhCH_2NH_2$	60	89	32
16	2,4-$Cl_2C_6H_3OCH_2COOH$	$PhCH_2NH_2$	60	90	33
17	$(Ph)_2CHCOOH$	$PhCH_2NH_2$	85	84	34
18	4-$MeOPhCH_2COOH$	$PhCH_2NH_2$	120	91	34
19	$CH_3(CH_2)_7CH = CH(CH_2)_6\ CH_2COOH$	$PhCH_2NH_2$	90	87	35
20	$CH_3(CH_2)_3CH_2COOH$	$PhCH_2NH_2$	70	92	36
21	Thiophene-3-COOH	$PhCH_2NH_2$	100	94	37
22	PhCOOH	$CH_3(CH_2)_2CH_2NH_2$	20	85	38
23	PhCOOH	$EtO(CH_2)_2CH_2NH_2$	40	80	—
24	PhCOOH	Cyclohexyl-NH_2	30	80	39
25	PhCOOH	4-$MeOC_6H_4CH_2NH_2$	20	87	26
26	PhCOOH	2-$MeOC_6H_4CH_2NH_2$	20	92	40
27	PhCOOH	2-$ClC_6H_4CH_2NH_2$	35	87	41
28	PhCOOH	$(Et)_2NH$	40	92	42
29	PhCOOH	$(i\text{-}Pr)_2NH$	55	88	43
30	PhCOOH	morpholine	45	90	44
31	PhCOOH	piperidine	35	95	45
32	PhCOOH	pyrrolidine	40	85	46
33	PhCOOH	furan-2-CH_2NH_2	35	80	47
34[a]	PhCOOH	4-$MeC_6H_4NH_2$	100	85	48
35[a]	4-$NO_2C_6H_4COOH$	$PhNH_2$	60	90	40
36[a]	$CH_3(CH_2)_3CH_2COOH$	4-$BrC_6H_4NH_2$	110	92	49
37[a]	4-MeC_6H_4COOH	4-$MeC_6H_4NH_2$	120	80	50

[a]The reaction was performed in CH_3CN, reflux.

study on sulfonamides by examining the reaction of *p*-toluenesulfonic acid with benzylamine in the presence of PPh_3/NCBT system and by applying the same reaction conditions used above. As can be seen from Table 4, dry CH_2Cl_2 was found to be the most efficient solvent and it was employed as the preferred solvent for all subsequent sulfonamide preparation reactions (Table 5, entry 1). CH_3CN was acted as the same as CH_2Cl_2 (Table 5, entry 2). Reasonable yields were obtained when solvents such as THF, $CHCl_3$, 1,4-dioxane, acetone, and hexane were used (Table 5, entries 3–7). Both PPh_3/NCBT system and solvent play essential role in preparation of product (Table 5, entries 8–11). We also tested the

Table 4 Conversion of *N*-acetylated α-amino acids to α-amino acid amides by using PPh_3/NCBT/amines system



Entry*	Amino acid (RCOOH)	Amine (R'R"NH)	Time (min)	Isolated yield (%)	Reference
1	(AcNH)CH_2COOH	$PhCH_2NH_2$	60	95	[53]
2	(AcNH)(CH_3)CHCOOH	$PhCH_2NH_2$	70	90	[54]
3	(AcNH)($PhCH_2$)CHCOOH	$PhCH_2NH_2$	95	90	[53]
4	AcN-pyrolidine-2-COOH	$PhCH_2NH_2$	120	96	[55]
5	indole-3-CH_2CH(AcNH)COOH	$PhCH_2NH_2$	110	95	[56]

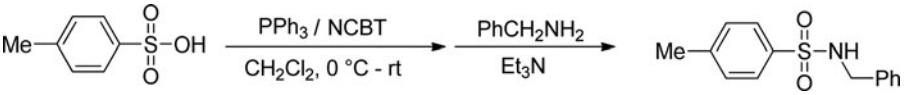
*Amino acids were *N*-acetylated and purified by the method reported in literature.[19]

influence of various molar ratios of PPh_3/NCBT/RSO_3H/R'R"NH on the model reaction, since it was expected, the reaction rate was decreased by decreasing the amount of PPh_3, NCBT, or R'R"NH (Table 5, entries 12–15). In this context, additional amount of benzylamine was applied and have found to have no influence on the reaction rate (Table 5, entry 16).

In order to investigate the scope of such amidation reactions in more detail, we tested the scope of our optimized protocol by applying it to various combinations of sulfonic acids and amines (Table 6).

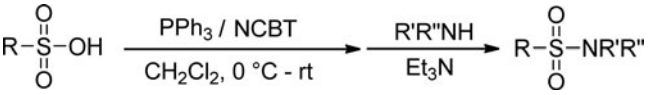
We were pleased to find the new protocol allows extending the method from aliphatic and aromatic sulfonic acids to the less-reactive aromatic sulfonic acids and amines (Table 6). Aliphatic sulfonic acids reacted smoothly with primary aliphatic amines as well as aromatic amines (Table 6, entries 1–3). Good yields were obtained in the amidation of aromatic sulfonic acids with primary, secondary aliphatic amines, too (Table 6, entries 4–10).

Table 5 Conversion of *p*-toluenesulfonic acid to *N*-benzyl-4methylbenzenesulfonamide with PPh_3/NCBT/benzylamine system at 0°C to room temperature, under different reaction conditions



Entry	Solvent	Molar ratio PPh_3/NCBT/RSO_3H/R'R"NH	Time (min)	Isolated yield (%)
1	CH_2Cl_2	1.25/1.25/1/2.5	80	90
2	CH_3CN	1.25/1.25/1/2.5	80	90
3	THF	1.25/1.25/1/2.5	90	90
4	$CHCl_3$	1.25/1.25/1/2.5	95	85
5	1,4-dioxane	1.25/1.25/1/2.5	95	75
6	acetone	1.25/1.25/1/2.5	120	85
7	*n*-hexane	1.25/1.25/1/2.5	100	70
8	CH_2Cl_2	0/0/1/2.5	180	0
9	CH_2Cl_2	0/1.25/1/2.5	180	0
10	CH_2Cl_2	1.25/0/1/2.5	180	0
11	none	1.25/1.25/1/2.5	180	10
12	CH_2Cl_2	1/1/1/1	180	40
13	CH_2Cl_2	1/1/1/1.5	150	80
14	CH_2Cl_2	1/1/1/2	95	70
15	CH_2Cl_2	1/1/1/2.5	90	80
16	CH_2Cl_2	1.25/1.25/1/3	80	90

Table 6 Conversion of sulfonic acids to sulfonamides by using PPh_3/NCBT/amines system



Entry	Sulfonic acid (RSO_3H)	Amine (R'R"NH)	Time (min)	Isolated yield (%)	References
1	$MeSO_3H$	$PhCH_2NH_2$	75	85	[57]
2	$EtSO_3H$	$PhNH_2$	70	90	[58]
3	$MeSO_3H$	4-$BrC_6H_4NH_2$	85	90	[59]
4	$PhSO_3H$	4-$MeOC_6H_4CH_2NH_2$	90	80	[60]
5	$PhSO_3H$	cyclohexyl-NH_2	95	80	[61]
6	4-$MeC_6H_4SO_3H$	$PhCH_2NH_2$	80	90	[62]
7	4-$MeC_6H_4SO_3H$	$(Et)_2NH$	85	92	[63]
8	4-$MeC_6H_4SO_3H$	piperidine	90	85	[64]
9	4-$MeC_6H_4SO_3H$	pyrrolidine	90	80	[65]
10	4-$MeC_6H_4SO_3H$	morpholine	95	80	[66]
11	4-$MeC_6H_4SO_3H$	4-$BrC_6H_4NH_2$	90	92	[67]
12	4-$ClC_6H_4SO_3H$	$CH_3(CH_2)_2CH_2NH_2$	70	85	68

Treatment of *p*-toluenesulfonic acid with *p*-bromoaniline afforded *N*-(*p*-bromophenyl)-4-methylbenzenesulfonamide in high yield (Table 6, entry 11). In the end, in a similar fashion, *N*-butyl-4-chlorobenzenesulfonamide was formed in excellent yield from the reaction of *p*-chlorobenzenesulfonic acid with *n*-butyl amine (Table 6, entry 12). We observed that excellent yields of the sulfonamides could be obtained in most cases without excessive reaction time.

FT-IR spectroscopy of the column chromatography purified products revealed an absorption band at 3412–3223 or 3295–3220 cm^{-1} due to NH vibration stretching of carboxamide and sulfonamide respectively. A strong absorption band at 1661–1607 cm^{-1} due to carbonyl group confirmed the formation of carboxamide. N-H bending vibration and C-N stretching vibration were also appeared as medium bands at 1570–1515 and 1349–1213 cm^{-1} respectively. Presence of sulfone group (SO_2) was established by appearance of two strong absorption bands at 1346–1340 and 1165–1135 cm^{-1} (due to asymmetric and symmetric stretching vibration of sulfone) and S-N vibration stretching was revealed as a medium absorption band at 765–725 cm^{-1}. A broad signal at 7.1–5.76 and 7.1–4.65 ppm is assigned to NH proton of carboxamide and sulfonamide respectively which are exchangeable with D_2O (see Supplemental Materials). In the ^{13}C NMR spectra, the quaternary carbon of carboxamides showed an up-field shift as compared to the carbonyl carbon of carboxylic acids. All of the products were known compounds and characterized by the FT-IR spectroscopy, mass spectrometry and comparison of their melting points with known compounds.The structure of selected products was further confirmed by ^1H NMR and ^{13}C NMR spectroscopy.

EXPERIMENTAL

General

The products were purified by column chromatography. The purity of the products was determined by TLC on silica gel polygram STL G/UV 254 plates (Merck, Germany). Melting points of the products were determined with an Electrothermal Type 9100 melting point apparatus (UK). The Fourier transform infrared (FT-IR) spectra were recorded on an

Avatar 370 FT-IR Therma Nicolet spectrometer (USA). The nuclear magnetic resonance (NMR) spectra were provided on Brucker Ultrashield Avance III instruments (Germany) at 400 and 100 MHz, respectively, for ^{1}H and ^{13}C NMR spectroscopy, in $CDCl_3$ and DMSO-d_6. TMS was used as an internal standard. Chemical shifts are given in ppm relative to TMS. 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. Mass spectra were recorded with a CH7A Varianmat Bremem instrument (Germany) at 70 eV; in m/z (rel%). Elemental analyses were performed using an Elementar, Vario EL III, and Thermofinnigan Flash EA 1112 Series instrument. Silica gel in the size of 40–73 μm that used for column chromatography was purchased from Merck, Germany. NCBT was prepared and purified by the method described in the literature.[69] The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra of the products (Figures S1–S18).

Typical Procedure for Conversions of Carboxylic Acids to Amides. *N*-benzylbenzamide (Table 3, Entry 1)

To a cold solution of PPh_3 (0.327 g, 1.25 mmol) in CH_2Cl_2 (3 mL), freshly prepared NCBT (0.188 g, 1.25 mmol) was added with continuous stirring. Benzoic acid (0.122 g, 1 mmol) was then added and stirring was continued for 15 min. Benzylamine (0.267 g, 2.5 mmol) was added and the temperature was raised up to room temperature. The white suspension was neutralized by triethylamine (0.139 mL). Stirring was continued for 30 min at room temperature. The progress of the reaction was followed by TLC. Upon completion of the reaction, the concentrated residue was passed through a short silica-gel column using *n*-hexane–ethyl acetate (8:1) as eluent. *N*-Benzylbenzamide was obtained with 95% (0.201 g) yield after removing the solvent under reduced pressure.

Typical Procedure for Conversions of *N*-Acetylated α-Amino Carboxylic Acids to Amides. 2-Acetamido-*N*-benzyl-3-phenylpropanamide (Table 4, Entry 3)

To a cold solution of PPh_3 (0.327 g, 1.25 mmol) in CH_2Cl_2 (3 mL), freshly prepared NCBT (0.188 g, 1.25 mmol) was added with continuous stirring. 2-Acetamido-3-phenylpropanoic acid (0.207 g, 1 mmol) was then added and stirring was continued for 15 min. Benzylamine (0.267 g, 2.5 mmol) was added and the temperature was raised up to room temperature. The white suspension was neutralized by triethylamine (0.139 mL). Stirring was continued for 95 min at room temperature. The progress of the reaction was followed by TLC. Upon completion of the reaction, the mixture was filtered and residue was concentrated and passed through a short silica-gel column using *n*-hexane–ethyl acetate (3:1) as eluent. 2-Acetamido-*N*-benzyl-3-phenylpropanamide was obtained with 90% (0.266 g) yield after removing the solvent under reduced pressure.

Typical Procedure for Conversion of Sulfonic Acids to Sulfonamides. *N*-benzyl-4-methylbenzenesulfonamide (Table 6, Entry 6)

To a cold solution of PPh_3 (0.327 g, 1.25 mmol) in CH_2Cl_2 (3 mL), freshly prepared NCBT (0.188 g, 1.25 mmol) was added with continuous stirring. *p*-Toluenesulfonic acid (0.172 g, 1 mmol) was then added and stirring was continued for 15 min at room temperature. Benzylamine (0.267 g, 2.5 mmol) was added. The white suspension was neutralized by

triethylamine (0.139 mL). Stirring was continued for 80 min at room temperature. The progress of the reaction was followed by TLC. Upon completion of the reaction, the concentrated residue was passed through a short silica-gel column using *n*-hexane–ethyl acetate (3:1) as eluent. *N*-Benzyl-4-methylbenzenesulfonamide was obtained with 90% (0.236 g) yield after removing the solvent under reduced pressure.

Characterization Data of New Compounds

4-Acetamido-*N*-benzylbenzamide (Table 3, Entry 10)

White solid; mp 126–128 °C, yield: 87%; IR (KBr): $\bar{\upsilon}$ = 3395 (NH), 3070, 3039, 2920, 1670(C=O), 1649 (C=O), 1553, 1515, 1489, 753, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.62 (s, 1H, NH), 7.69–7.36 (m, 9H, ArH), 7.28 (s, J = 2 Hz, 1H, NH), 6.32 (s, 1H, NH), 4.43 (d, J = 4.4 Hz, 2H, CH_2), 2.06 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz; DMSO-d_6): δ = 168.3 (C=O), 167.1 (C=O), 134.6, 129.4, 128.9, 128.8, 128.7, 128.5, 127.7, 127.1, 45.7, 24.5 ppm; MS (EI, 70 eV), $C_{16}H_{16}N_2O_2$ (268.31 $g.mol^{-1}$): *m/z* (%) = 268 (M^+, 10%), 224 (M−CH_3CO, 8%), 162 (M-$PhCH_2NH$, 22%), 106 ($PhCH_2NH$, 75%), 91 ($PhCH_2$, 70%) 77 (Ph, 72%) 43 (CH3CO, 70%); elemental anal. (%), calcd for $C_{16}H_{16}N_2O_2$ (268.31): C 71.62, H 6.01, N 10.44; found: C 72.02, H 6.23, N 10.67.

N-(3-Ethoxypropyl) Benzamide (Table 3, Entry 23)

Red wine oil; yield: 80%; IR (neat): $\bar{\upsilon}$ = 3311 (NH), 3068, 2955, 2925, 2868, 1643 (C=O), 1539, 1113, 747 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 7.77-7.75 (m, 2H), 7.46-7.21 (m, 3H), 7.21 (brs, 1H), 3.60-3.41 (m, 6H), 2.11-2.02 (m, 2H), 1.37-1.21 (m, 3H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$): δ = 167.1 (C=O), 134.7, 131.1, 128.4, 126.8, 70.4, 66.5, 39.3, 28.8, 15.3 ppm; MS (EI, 70 eV), $C_{12}H_{17}NO_2$ (207.27 $g.mol^{-1}$): *m/z* (%) = 207 (M^+, 15%), 178 (M-Et, 5%), 162 (M-EtO, 20%), 148 (M-$EtOCH_2$, 100%), 106 (PhCO, 75%), 60 ($EtOCH_2$, 25%), 45 (EtO, 72%), 28 (Et, 58%); elemental anal. (%), calcd for $C_{12}H_{17}NO_2$ (207.27): C 69.54, H 8.27, N 6.76; found: C 69.01, H 7.98, N 6.39.

CONCLUSION

In summary, we presented here a fast, one-pot, and novel amide and sulfonamide bond formation strategy from carboxylic acids, α-amino acids, and sulfonic acids using PPh_3/NCBT/amines system. The reaction has been shown good functional group tolerance and high yielding. We envisaged that the present protocol would therefore be suitable for less nucleophilic amines such as anilines. In addition, we have identified suitable reaction conditions that are successful for amidation of α-amino acids of which are biologically active compounds and possess therapeutically useful properties. Compared to other amide and sulfonamide formation methods, it took place under very mild reaction conditions, and the reaction rate was extremely fast. The chemistry is easily executed. We hope that this method may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry programs.

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SUPPLEMENTARY INFORMATION

Supplemental data for this article can be accessed on the publisher's website at http://dx.doi.org/10.1080/10426507.2015.1024313.

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