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Trimethylsilyl azide-promoted acid-amine coupling: A facile one-pot route to amides from carboxylic acids and amines

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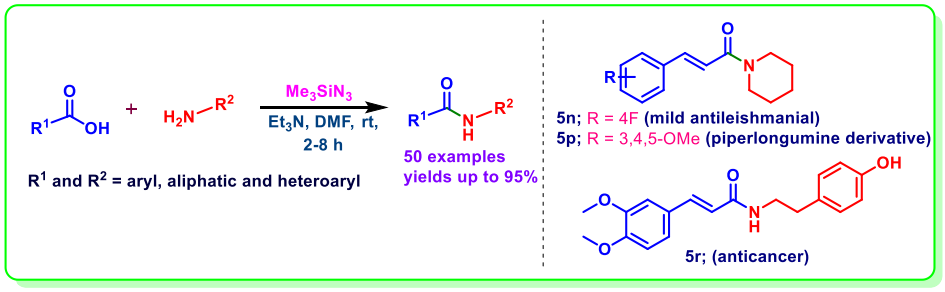
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Abstract

A versatile and efficient one-pot protocol has been developed for the synthesis of amides from easily accessible carboxylic acids and amines by employing trimethylsilyl azide as a promoter at room temperature. This reaction proceeds *via* an *in situ* generated acyl azide intermediates followed by the nucleophilic substitution of amines. Notably, most of the desired amides were obtained by simple filtration in excellent yields. The significant advantages like metal-free mild reaction conditions, higher yields, easily removable volatile byproducts, operational simplicity, and broad substrate scope make the transformation a useful contribution for the synthesis of biologically important amides.



Keywords: Amide coupling, amine, carboxylic acid, peptide, trimethylsilyl azide.

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Introduction

Amides are the basic and most important building blocks of organic molecules, widely found in many natural products and synthetic compounds,[1] playing a significant role in pharmaceuticals, agrochemicals and polymeric materials.[2-5] Also, the amide bond is an essential functional group because it constitutes the backbone of all peptides and proteins. According to the authoritative statistics reports from the leading pharmaceutical companies, nearly 25% of the drug molecules contain an amide bond linkage,[6] demonstrating its significance in synthetic organic chemistry. Therefore, the synthesis of amides is one of the hot topics in synthetic organic chemistry, which has received widespread attention, not only from the academic research aspect but also from the industrial perspective. So far, numerous strategies have been applied and reported for the synthesis of amides, such as the reaction of amines with carboxylic acid derivatives,[7,8] esters,[9,10] aldehydes[11,12] or alcohols,[24-26] rearrangement of aldoximes,[14,15] hydration of nitriles,[16] aminocarbonylation processes,[17,18] hydroamination of alkynes[19,20] transamidation,[21-25] Staudinger ligation,[26] and Staudinger-Vilarrasa reaction.[27] Recently, Benzoisothiazolone organo/Cu-cocatalyzed redox[28] and diselenide-catalyzed aerobic redox dehydration[29] protocols have developed for the amide/peptide bond formation. Moreover, several silane-based reagents have been reported[30-33] which suffered from high reaction temperatures, solid silane biproduct formation, limited substrate scope and excess usage of silane reagent. Although these existing silane-based protocols as well as other methods have met varying degrees of success, but they necessitate some limitations - usage of stoichiometric amounts of corrosive coupling reagents, expensive metal reagents, tedious work-up procedures, prolonged reaction times and high temperatures. In addition, labile substrates and their limited scope also restrict their broad utility.

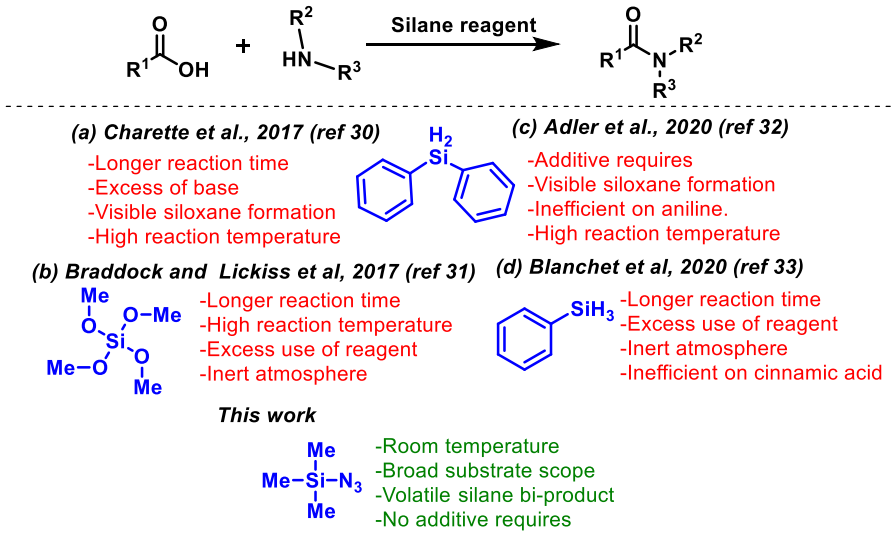


Figure 1 Recent silane-based amide coupling reactions.

On the other hand, industrial protocols currently engage with the stoichiometric use of acylation reagents, such as thionyl chloride, oxalyl chloride and phosphorus oxychloride[34-36] or coupling agents, for example 1,1'-carbonyldiimidazole (CDI), and 1-hydroxybenzotriazole (HOBt) for the activation of carboxylic acids.[37] Moreover, many efforts have been made to develop alternative coupling agents such as EDC.HCl., HATU and TBTU to form amides. However, most of these methods suffer from poor atom economy and the

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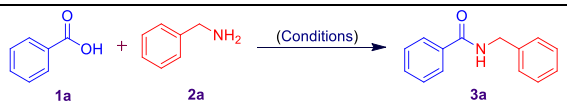
usage of expensive reagents.[1] In search of new approaches to circumvent such reagents, some metal-based catalysts,[4,5,38,39] and boron-based organocatalysts[40-42] were introduced to direct amide bond formations. In addition, numerous inorganic heterogeneous catalysts,[43-45] as well as polystyrene-bound 4-boronopyridinium salts[41] have also been utilized for the synthesis of amides. Nevertheless, limitations like difficulty in catalyst recovery, moderate reactivity, high temperature and the usage of extensive desiccating agents, such as molecular sieves, to uphold catalyst activity hindered these methodologies for industrial applications. Thus, it is always an attractive target for both synthetic as well as medicinal chemists to develop an efficient, mild, and inexpensive approach to synthesize amides using readily available materials in operationally simple way.

Based on the above observations and our ongoing interest in developing new synthetic methodologies for structurally/biologically interesting compounds,[46-48] herein, we introduced an efficient and straightforward one-pot approach for the synthesis of a variety of amides in excellent yields at room temperature in a shorter reaction time. This reaction occurs through the activation of carboxylic acid to the corresponding acid-azide using trimethylsilyl azide, followed by the nucleophilic attack of amines. This simple transformation might open a new window for the direct conversion of carboxylic acid with amines to their corresponding amides.

Results and Discussion

Initially, we commenced our investigation by examining the efficacy of various azides, bases and solvents in a model reaction of benzoic acid (**1a**) with benzylamine (**2a**) under a nitrogen atmosphere and the results are summarized in Table 1. Initially, an attempt has been made on the reaction of **1a** and **2a** with NaN_3 in the presence of triethylamine (Et_3N) in THF at room temperature. Unfortunately, the reaction failed to afford the desired product **3a** even after 24 h (entry 1, Table 1). Further, the same reaction was performed by replacing the NaN_3 with *p*-toluenesulfonyl azide; to our delight, product **3a** was formed in 15% (entry 2, Table 1). However, changing the base and reaction temperature did not enhance the yield of **3a** (entries 3 and 4, Table 1). Interestingly, in case of heating the desired product was formed in trace amount, which may be due to instability of the azide under heating conditions. Gratifyingly, when trimethylsilyl azide was used as an azide source, product **3a** was obtained in 78% within 3 h at room temperature (entry 5, Table 1). Increasing the stoichiometry of base (3 mmol) did not have a significant effect on the yield of **3a** (entry 6, Table 1), but decreasing the amount of base (1 mmol), reduced the yield of **3a** considerably (entry 7, Table 1). To further check the reaction efficacy and yield, also we performed the solvent screening. Some of the solvents were found to have a significant effect on the reaction outcome (entries 8-12, Table 1). DMF gave the best yield in a shorter time than other screened solvents (entry 9, Table 1). Then, a study about the influence of other bases such as K_2CO_3, *t*-BuOK, pyridine and DBU (entries 13-16, Table 1) for this transformation was done, and the results showed that organic bases provide product **3a** in higher yields than the inorganic bases. After a brief screening, it is concluded that the best molar ratio of substrates/reagents for this reaction is 1:1:1:2 for benzoic acid, amine, trimethylsilyl azide and Et_3N, respectively.

Table 1. Reaction optimization[a]



S. No	Azide	Base	Solvent	Time	Yield[b]
1	NaN_3	Et_3N	THF	24 h	-

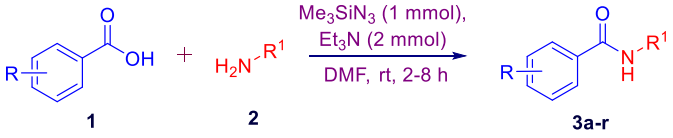
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2	*p*-Me(C_6H_4)SO_2N_3	Et_3N	THF	24 h	15%
3	*p*-Me(C_6H_4)SO_2N_3	K_2CO_3	THF	24 h	trace
4[c]	*p*-Me(C_6H_4)SO_2N_3	Et_3N	THF	24 h	trace
5	Me_3SiN_3	Et_3N	THF	3 h	78%
6[d]	Me_3SiN_3	Et_3N	THF	3 h	68%
7[e]	Me_3SiN_3	Et_3N	THF	3 h	45%
8	Me_3SiN_3	Et_3N	acetonitrile	3 h	79%
9	**Me_3SiN_3**	**Et_3N**	**DMF**	**2 h**	**90%**
10	Me_3SiN_3	Et_3N	DMSO	3 h	77%
11	Me_3SiN_3	Et_3N	$CHCl_3$	3 h	79%
12	Me_3SiN_3	Et_3N	EtOH	3 h	60%
13	Me_3SiN_3	K_2CO_3	DMF	6 h	75%
14	Me_3SiN_3	*t*-BuOK	DMF	6 h	73%
15	Me_3SiN_3	pyridine	DMF	2 h	80%
16	Me_3SiN_3	DBU	DMF	2 h	87%

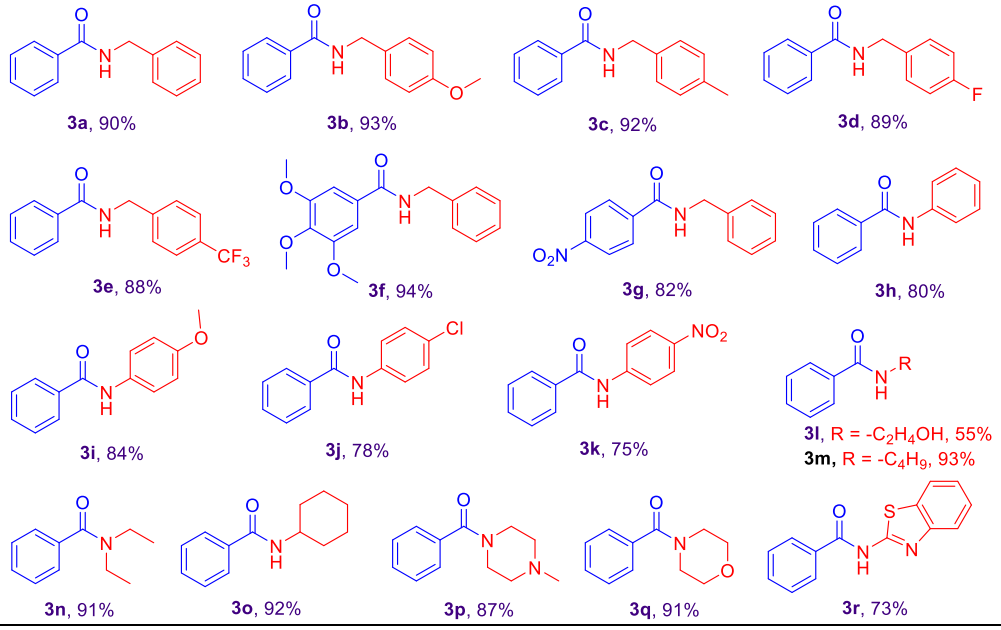
[a]Reactions were performed using benzoic acid (1 mmol), benzylamine (1 mmol) and base (2 mmol). [b]Isolated yield. [c]Reaction performed under reflux condition. [d,e]Reaction performed with 3 mmol and 1 mmol of the base, respectively.

Enduring to investigate the reaction scope, further explored the generality of this transformation towards various benzoic acids and amines under the optimized reaction conditions (Table 2). It is delighted to note that the present protocol is well compatible with the presence of electron-donating and electron-withdrawing functional groups on both substrates. Various substrates of different electronic nature were successfully converted to the corresponding amides in good to excellent yields with valuable functional group tolerance. Thus, the presence of methyl, methoxy, nitro, fluoro and chloro groups offered ample opportunity for further derivatization. Furthermore, the reaction conditions could be compatible with a wide range of amines such as benzyl, aliphatic, aromatic and heteroaromatic amines. As depicted in Table 2, with regard to the electronic properties of the substituents on the aromatic ring of benzylamines had a weak effect on reaction efficacy and delivered the corresponding products in excellent yields (**3a-g**, Table 2).

Table 2. Substrate scope using various benzoic acids with alkyl/arylamines[a]



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[a]Reactions performed using benzoic acids (1 mmol), amines (1 mmol), trimethylsilyl azide (1 mmol) and Et_3N (2 mmol) at room temperature for 2-8 h.

Interestingly, benzoic acids and aromatic amines bearing electron-withdrawing groups (**3g**, **3k** and **3j**, Table 2) gave the desired products in lower yields than those holding electron-donating groups (**3f** and **3i**, Table 2). It is worth mentioning that aromatic and heteroaromatic amines (**3h-k** and **3r**, Table 2) have taken more time (6-8 h) for the complete conversion compared to benzyl/aliphatic amines (2 h) during this coupling process, probably due to their weaker nucleophilicity. Moreover, aliphatic primary and secondary amines were well tolerated in this transformation and produced the corresponding amides in excellent yields (**3m-q**, 87%–94%, Table 2). However, reaction with ethanolamine was found to be clumsy and gave **3l** in considerable yield (55%) and didn't observe the ester formation. Importantly, diisopropylamine failed to give the desired amide, possibly due to steric hindrance. The efficacy of this protocol was also tested on an amino acid (glycine) with benzoic acid and benzyl amine, but unfortunately no desired product was observed, and the reaction mixture was found to be turbid. In addition, we tested the feasibility of the reaction with 2-aminobenzothaiazole, which underwent this transformation adequately to provide the desired amide in 73% of yield (**3r**, Table 2).

Cinnamamides are significant class of compounds with an array of biological activities such as herbicide,[49] insecticide[50,51] and antioxidant.[52] Therefore, it is envisioned to extend our protocol to the synthesis of cinnamamides, and the results are summarized in Table 3. Gratifyingly, the reactions preceded successfully with a series of cinnamic acids under the optimal reaction conditions and provided the corresponding cinnamamides in good to excellent yields. As shown in Table 3, the electronic nature of the cinnamic acids and benzylamines did not influence reaction efficiency, and all the desired amides were obtained in excellent yields. As expected, aromatic and heteroaromatic amines have taken more reaction time to complete conversion and yielded the corresponding amides in lower yields compared to the other amines (**5f**-**l**, Table 3).

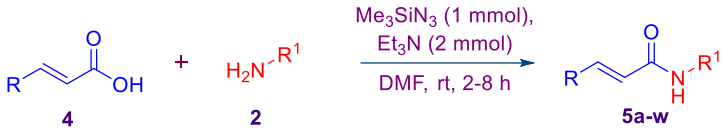
Notably, the reaction of 4-fluorocinnamic acid with piperidine provided the corresponding product **5n** in 88%, which is known to possess mild antileishmanial activity.[53] Further, 3,4,5-trimethoxycinnamic acid with piperidine under the optimal conditions provided the desired product **5p** in 95% which is known as piperlongumine derivative.[54] Moreover, hydroxyl-substituted amine was also smoothly suitable for this

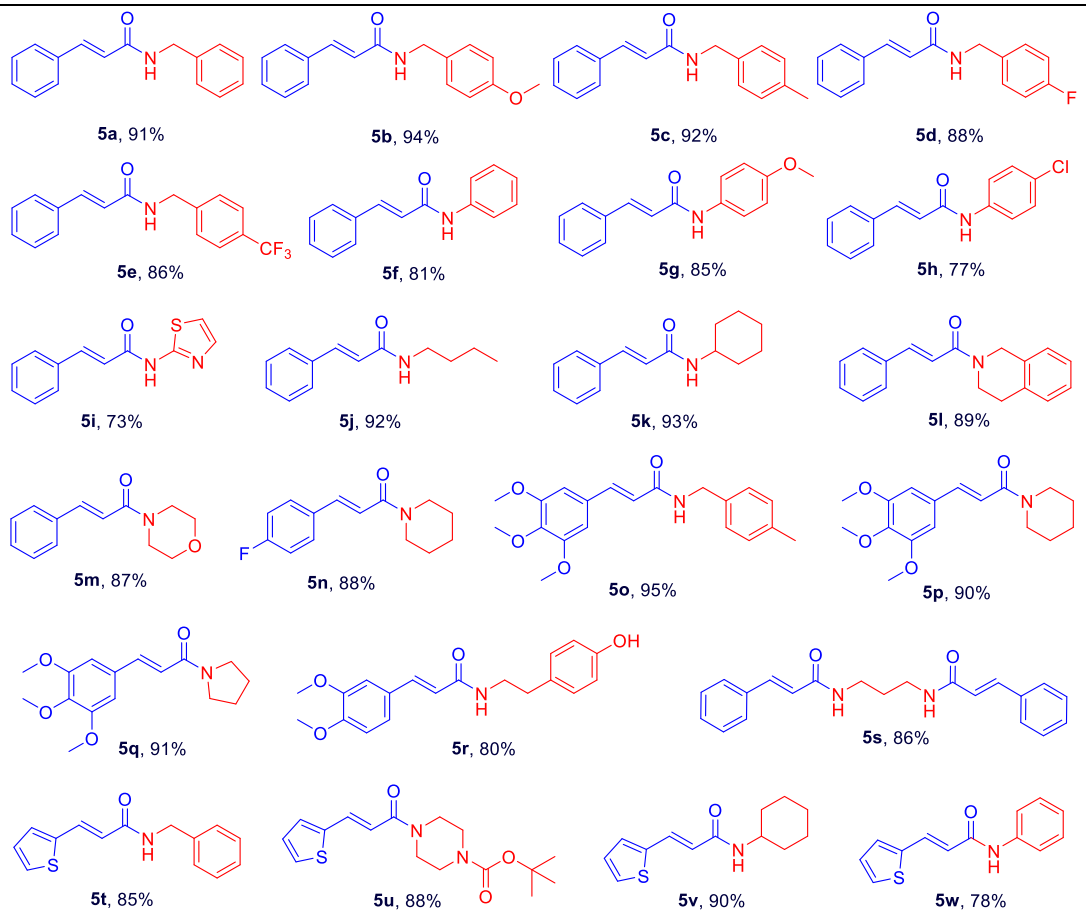
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transformation and delivered corresponding product **5r** in 73% yield, which shows anticancer activity.[55] Expectedly, the reaction of *trans*-cinnamic acid with 1,3-diaminopropane gave the corresponding diamide in 86% (**5s**, Table 3). Further explored this protocol on the heterocinnamic acid, (*E*)-3-(thiophen-2-yl)acrylic acid with a variety of amines (aliphatic, aromatic and boc-protected) and the reactions afforded desired products **5t-w** in good yields (Table 3). This protocol is however not efficient on phenylpropiolic acid and TLC of the reaction mixture shows no target compound.

To further explore the versatility of this protocol, it was thought worthwhile to apply the optimal set of reaction conditions to aliphatic and heteroaromatic acids as well. First, the reaction of propionic acid and 4-methoxyphenylacetic acid with a variety of amines such as aliphatic, aromatic and benzylamines were examined under the established conditions. The reaction underwent smoothly and delivered the corresponding amides (**7a-f**) in excellent yields as shown in Table 4.

Table 3. Substrate scope using various *trans*-cinnamic acids with alkyl/arylamines[a]





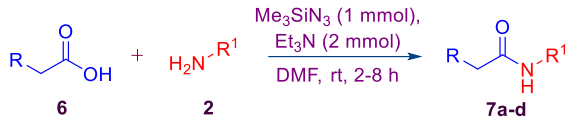
[a]Reactions performed using *trans*-cinnamic acids (1 mmol), amines (1 mmol), trimethylsilyl azide (1 mmol) and Et_3N (2 mmol) at room temperature for 2-8 h.

In fact, it is well-known that β-carboline derivatives are significant structural motifs in many biologically active small molecules, and they represent practically useful template in pharmaceutical research and

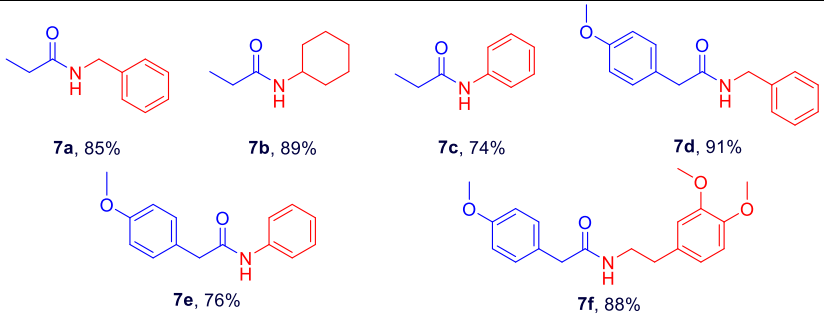
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development. Thus, in recent years great efforts have been directed toward the synthesis of biologically active β-carboline moieties.[56] In view of their importance, an attempt was made to apply this mild protocol for the synthesis of β-carboline derivatives using 9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid with various amines. These reactions of β-carboline acid were produced corresponding β-carboline amides in good yields (Table 5).

Table 4. Substrate scope using aliphatic acids with benzyl/aliphatic/aromatic amines[a]



6 **2** **7a-d**

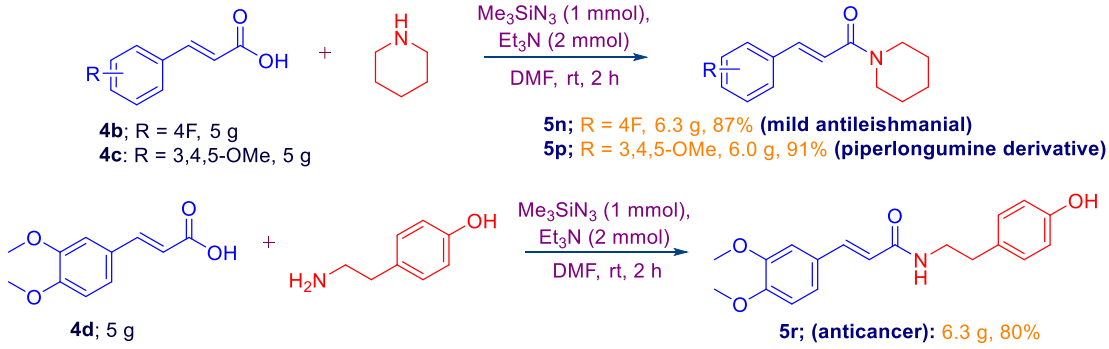


7a, 85% **7b**, 89% **7c**, 74% **7d**, 91%

7e, 76% **7f**, 88%

[a]Reactions performed using aliphatic acid (1 mmol), amines (1 mmol), trimethylsilyl azide (1 mmol) and Et_3N (2 mmol) at room temperature for 2-8 h.

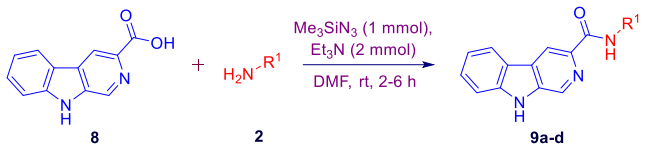
With an efficient procedure in hand for obtaining amides, it is decided to explore the synthetic feasibility of the current methodology. It can be believed that, amongst other silyl reagents, trimethylsilyl azide employed as a promoter in the preparation of amides could find useful applications in the large-scale synthesis of biologically active small molecules, from the perspective of economic and environmental considerations. For instance, gram-scale reactions were carried out by employing substrates **4b**, **4c** and **4d** (each 5 g) under the optimized reaction conditions. To our delight, reactions proceeded well and provided the corresponding bioactive amides **5n**, **5p** and **5r** in good yields (87%, 91% and 80% respectively), as shown in Scheme 1.



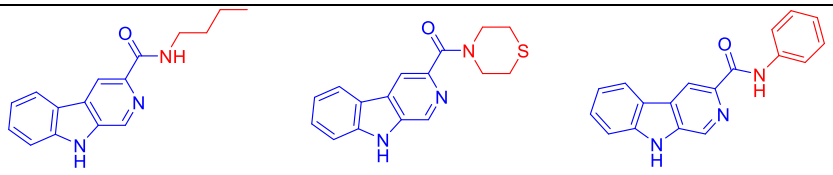
Scheme 1. Grams scale synthesis of fused derivatives **5n**, **5p and 5r**.

Table 5. Substrate scope using 9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid with alkyl/arylamines[a]

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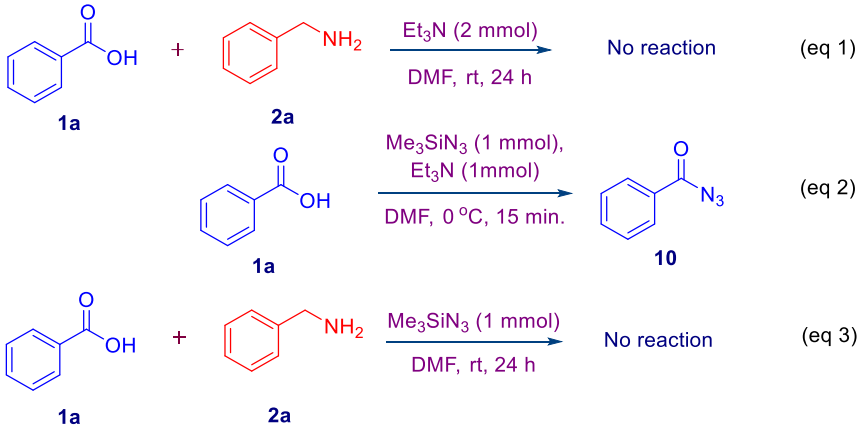
8 2 9a-d



9a, 88% **9b**, 85% **9c**, 72%

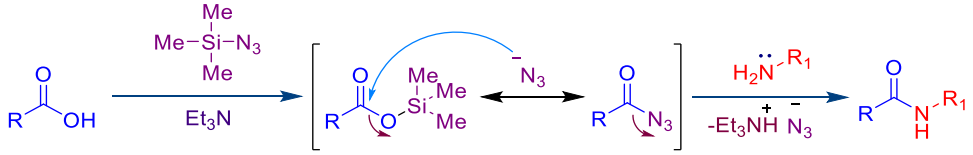
[a]Reactions performed using 9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (1 mmol), amines (1 mmol), trimethylsilyl azide (1 mmol) and Et_3N (2 mmol) at room temperature for 2-8 h.

In order to gain insights into the reaction mechanism, we performed some of the control experiments illustrated in Scheme 2. Initially, the reaction did not proceed with benzoic acid and benzylamine in the absence of trimethylsilyl azide under optimal reaction conditions (Scheme 2, eq 1). Next, when the benzoic acid reacted with trimethylsilyl azide in the absence of amine, delivered an isolable acid-azide **10** (Scheme 2, eq 2). Further, the reaction failed to deliver the corresponding amide in the absence of a base (Scheme 2, eq 3). This indicates the significance of trimethylsilyl azide and base for the current transformation to provide the amides.



Scheme 2. Control experiments.

Based on these control experimental outcomes and the related literature findings, a possible reaction mechanism has been proposed for the formation of amides outlined in Scheme 3. Initially, the carboxylic acid reacts with trimethylsilyl azide in the presence of Et_3N to form the corresponding azide intermediate, followed by the nucleophilic attack of amines to generate the desired amides.



Scheme 3. Plausible reaction mechanism.

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Conclusions

In summary, we have reported the utility of trimethylsilyl azide as a readily accessible and inexpensive promoter for the high yielding direct amidation protocol. In this transformation, we employed a variety of readily available alkyl, cinnamyl, aryl and hetero aryl carboxylic acids for the amide coupling with primary alkyl, cyclic, secondary amines and anilines. Gratifyingly, most of the amide products (**3a-k**, **3o**, **3r**, **5a-l**, **5k-w**, **7d-f** and **9a-c**) were isolated in good to excellent yields (up to 95%) by simple filtration and without need for any chromatographic purifications. This protocol was also efficiently applied in the gram-scale synthesis of bioactive amides **5n**, **5p** and **5r** in excellent yields. Overall, this metal-free and mild approach can be used as an alternative to the conventional approaches to the synthesis of biologically useful amides in drug discovery programs.

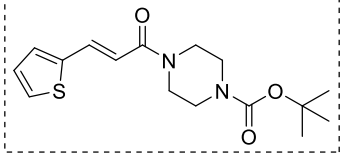
Experimental Section

General Information. All the starting materials, reagents and solvents were purchased from commercial suppliers and used without any further purification. All the reagents were handled and weighed in the air at room temperature. Thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F254 MERCK. TLC plates were visualized by exposure to UV light. Silica gel (60–120) column chromatography was performed by using indicated solvent system. ^{1}H and ^{13}C NMR spectra were recorded relative to tetramethylsilane and chemical shifts were reported in parts per million (δ). Melting points were recorded on an Electrothermal melting apparatus and are uncorrected. HRMS were performed on an ESI-QTOF mass spectrometer.

General experimental procedure for the one-pot synthesis of amides:
To a stirred solution of carboxylic acids **1**, **4**, **6** and **8** (1 mmol) in dry DMF (1 mL) were added Et_3N (2 mmol) and trimethylsilyl azide (1 mmol). The reaction mixture was stirred at room temperature for 10 min and was added amines **2** (1 mmol) at 0 °C. Then the reaction mixture was allowed to stir at room temperature for 2-8 h until complete consumption of starting materials as monitored by TLC, after the reaction was finished, ice-cold water was added to the reaction mixture. The obtained solids were filtered, washed with water and dried under *vacuum* to give most of the desired products (**3a-k**, **3o**, **3r**, **5a-l**, **5k-w**, **7d-f** and **9a-c**) in pure form. The crude products (**3l-n**, **5j** and **7a-c**) were purified by silica gel column chromatography using EtOAc/n-hexane or MeOH/DCM solvents as eluents. For the liquid compounds (**3p** and **3q**), after the reaction completion, ice-cold water (20 mL) was added to the reaction mixture and then extracted with DCM (2x20 mL). The combined organic layer washed with ice cold water (20 mL), saturated brine solution (20 mL) and evaporated under *vacuum* to give the desired amides in pure form as liquids. All the title compounds prepared were soluble in MeOH, DCM, $CHCl_3$ and EtOAC.

Note: All the final compounds **3**, **5**, **7** and **9** synthesized in this work are known in the literature (for analytical data, see ESI) except **5u**, **5v** and **9b.** The analytical data for **5u**, **5v** and **9b** are mentioned below.

(*E*)-*tert*-Butyl 4-(3-(thiophen-2-yl)acryloyl)piperazine-1-carboxylate (5u):

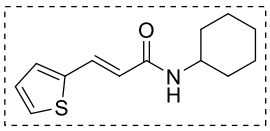


Isolated by filtration, White solid; Yield: 90%; mp: 132–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 14.9 Hz, 1H), 7.33 (d, *J* = 5.0 Hz, 1H), 7.23 (d, *J* = 3.3 Hz, 1H),

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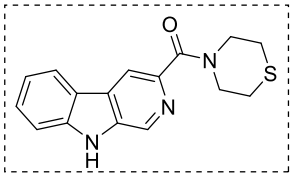
7.04 (dd, *J* = 3.8, 4.9 Hz, 1H), 6.65 (d, *J* = 14.9 Hz, 1H), 3.75 – 3.55 (m, 4H), 3.48 (s, 4H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.1, 154.4, 140.1, 136.0, 130.4, 127.9, 127.3, 115.2, 80.2, 45.3, 43.4, 41.9, 28.3; MS (ESI): *m/z* 323 $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{22}N_2O_3NaS$ *m/z* 345.1249 $[M + H]^+$, found 345.1259.

(*E*)-*N*-Cyclohexyl-3-(thiophen-2-yl)acrylamide (5v).



Isolated by filtration, White solid; Yield: 88%; mp: 212–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (d, *J* = 15.1 Hz, 1H), 7.29 (d, *J* = 5.1 Hz, 1H), 7.19 (d, *J* = 3.5 Hz, 1H), 7.02 (dd, *J* = 3.5, 5.0 Hz, 1H), 6.17 (d, *J* = 15.2 Hz, 1H), 5.45 (bs, 1H), 3.95 – 3.85 (m, 1H), 2.02 – 1.93 (m, 2H), 1.77 – 1.68 (m, 2H), 1.68 – 1.58 (m, 2H), 1.47 – 1.34 (m, 2H), 1.25 – 1.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO–d_6) δ: 164.0, 139.7, 131.4, 128.8, 127.2, 126.0, 120.6, 47.5, 32.3, 24.8, 24.2; HRMS (ESI) calcd for $C_{13}H_{18}NOS$ *m/z* 236.1104 $[M + H]^+$, found 236.1107.

(9*H*-Pyrido[3,4-*b*]indol-3-yl)(thiomorpholino)methanone (9b):



Isolated by filtration, White solid; Yield: 85%; mp: 240–242°C; ^{1}H NMR (300 MHz, DMSO–d_6) δ: 11.86 (s, 1H), 8.86 (s, 1H), 8.43 (s, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 7.66 – 7.54 (m, 2H), 7.27 (t, *J* = 7.9 Hz, 1H), 3. 94 (s, 2H), 3.77 (s, 2H), 2.76 – 2.61 (m, 4H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 168.1, 142.7, 140.8, 135.8, 131.9, 128.4, 127.8, 122.0, 120.6, 119.6, 115.3, 112.0, 49.5, 44.3, 27.2, 26.6; MS (ESI): *m/z* 298 $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{16}N_3OS$ *m/z* 298.1014 $[M + H]^+$, found 298.1010.

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Supplementary Material

All the analytical data and spectrums were included in the Supplementary Material file associated with this manuscript.

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