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Dithiocarbamate and DBU-promoted amide bond formation under microwave condition

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ABSTRACT

Dithiocarbamate and DBU-promoted amide bond formation under microwave condition has been reported. The versatility of this synthetic protocol has been demonstrated with various carboxylic acids and different dithiocarbamates. The products thus obtained have been characterized by mp, IR, ^{1}H NMR, and mass spectroscopy.

The stable amide bond is not only common in naturally occurring materials like peptides and proteins but is also found in many synthetic substances.[1] This makes the amide function important to synthetic chemists especially in peptides and lactam synthesis, in which the formation of amide bond is crucial. Some derivatives of amides exhibit biological properties such as anticancer, antihistamine, antifungal, and antibacterial.[2–5] Recently, it has been observed that many potent kinase inhibitors contain *N*-aryl amide bonds and this kind of bond plays a crucial role for enzyme inhibition as observed in the cases of Imatinib and ZM-447439 (Fig. 1).[6,7] In connection with a drug discovery program, we needed an efficient route to the synthesis of various *N*-phenyl amides.

In the last decade, microwaves (MWs) have been used to simplify and improve reaction conditions for many classic organic reactions. Microwave irradiation often leads to a remarkable decrease in reaction time, increased yields, and easier workup matching with green chemistry protocols.[8–10]

The microwave-assisted syntheses of amides had already been investigated.[11] However, in these studies a limited number of amines and carboxylic acids were combined to afford the corresponding amides.

Only acids and amines with no additional functionality were used. In short, the chemical diversity covered in the amides generated was rather poor.

The condensation reaction between isocyanates and carboxylic acids is a well-known method for practical synthesis of N-substituted amides.[12] The major drawback of these reactions is the use of toxic isocyanate. Apart from handling these toxic agents, the synthesis of isocyanates requires handling of highly toxic phosgene. Moreover, the disadvantage with isocyanates is that they are unstable if stored for a longer period. Following our studies toward the development of a new route for the synthesis of organic compounds, our interest remains in dithiocarbamate-mediated reactions.[13] Herein, we report a highly efficient microwave-assisted one-pot synthesis of amides using various substituted acids and substituted dithiocarbamates (Scheme 1). These dithiocarbamates are easy to synthesize in larger quantities by using readily available anilines.[14]

The initial experiment was performed with commercially available 4-fluoro benzoic acid and *S*-methyl-*N*-aryl dithiocarbamate by using DBU as a base in DMF at 60 °C for 3 min in microwave. The desired *N*-phenylbenzamide was isolated in good yield (entry1). Several organic bases like pyridine, DABCO, and DMAP as well as inorganic bases were screened to optimize the methodology. But it was observed that the DMF and DBU combination gave the best results under microwave conditions.

With this efficient transformation under mild conditions, we successfully explored this methodology with respect to different acids and dithiocarbamates (Table 1). This reaction was quite successful in the cases of aromatic, alicyclic, and heterocyclic acids.

In summary, we have reported an efficient synthesis of an amide bond formation via microwave condition employing dithiocarbamate as an amine source.

General procedure: To the solution of acid (1 mmol) in 2 ml of DMF were added the corresponding dithiocarbamate (1.1 mmol)

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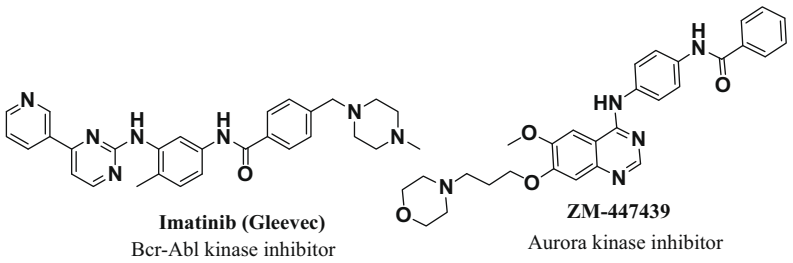
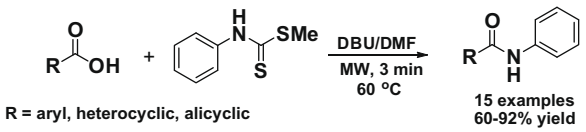


Figure 1. Kinase inhibitor with *N*-phenyl amide bond.



Scheme 1.

and DBU (1 mmol) and were irradiated in a CEM microwave system (300 W) using a 10 mL vial that contained a stir bar at 60 °C for 3 min. The reaction mixture was cooled to rt and the reaction was quenched with cold water. The solid obtained was filtered, washed with water, and dried under vacuum to obtain the corresponding pure amide. The physical data of these synthesized compounds are reported below.

Table 1
Synthesis of *N*-phenyl amides

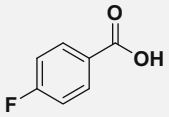
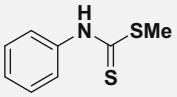
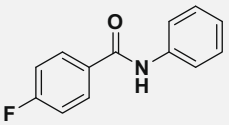
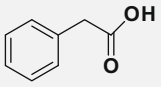
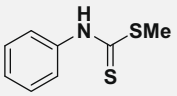
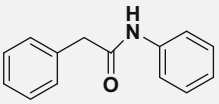
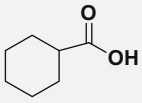
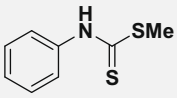
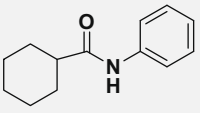
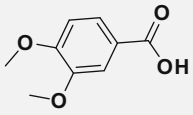
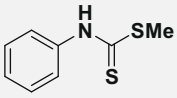
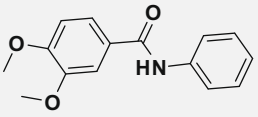
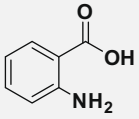
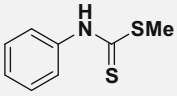
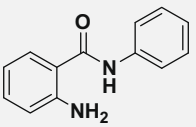
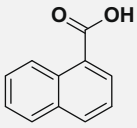
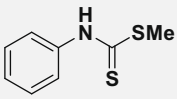
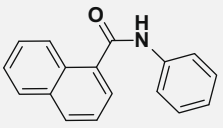
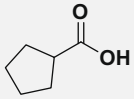
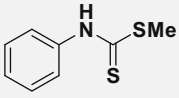
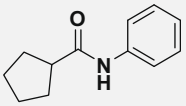
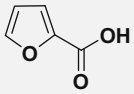
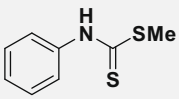
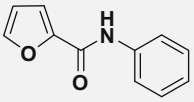
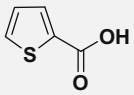
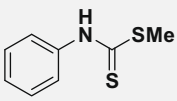
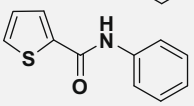
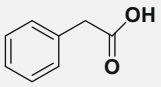
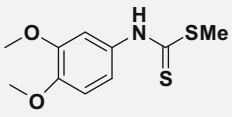
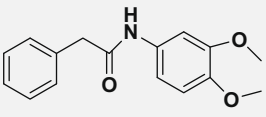
Entry	Acid	Dithiocarbamate	Amide	Yield (%)
1				92
2				88
3				82
4				76
5				68
6				78
7				70
8				72
9				76
10				83

Table 1 (*continued*)

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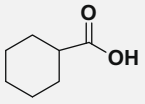
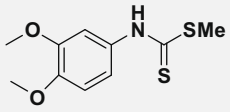
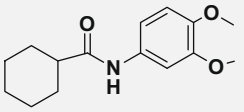
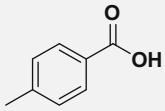
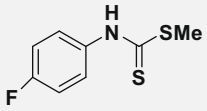
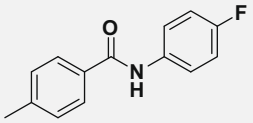
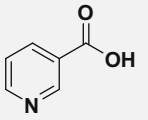
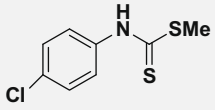
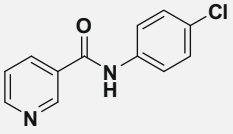
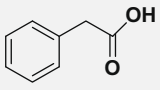
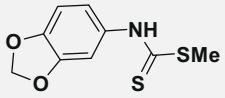
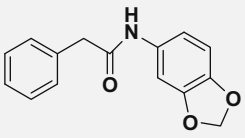
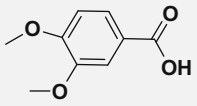
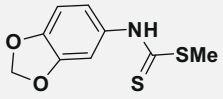
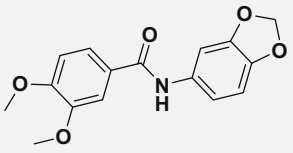
11				76
12				78
13				60
14				78
15				72

4-Fluoro-N-phenylbenzamide (entry 1): mp: 180–181 °C (Lit[15] 180–181 °C); IR (KBr, cm^{-1}): 3340, 3055, 2918, 1651, 1597, 1529, 1504; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.16 (s, 1H, NH), 8.04–7.9 (m, 2H), 7.77–7.70 (m, 2H), 7.39–7.34 (m, 4H), 7.12–7.09 (m, 1H); Mass (ESI) = 216 $[M+H]^+$.

N,2-Diphenylacetamide (entry 2): mp: 116–117 °C (Lit[16] 116–118 °C); IR (KBr, cm^{-1}): 3282, 3194, 3136, 1957, 1815, 1658; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.12 (s, 1H. NH), 7.58 (m, 2H), 7.33–7.22 (m, 7H), 7.05–7.02 (m, 1H), 3.6 (s, 2H); Mass (ESI) = 212 $[M+H]^+$.

N-Phenylcyclohexanecarboxamide (entry 3): mp: 136–137 °C (Lit[17] 137–139 °C); IR (KBr, cm^{-1}): 3275, 3190, 2931, 2850, 1658, 1597; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.76 (s, 1H, NH), 7.59 (m, 2H), 7.26 (m, 2H), 7.0–6.98 (m, 1H), 2.34–2.28 (m, 1H), 1.80–1.63 (m, 5H), 1.45–1.31 (m, 2H), 1.31–1.18 (m, 3H); Mass (ESI) = 204 $[M+H]^+$.

3,4-Dimethoxy-N-phenylbenzamide (entry 4): mp: 175–176 °C; IR (KBr, cm^{-1}): 3317, 3271, 2960, 2939, 1647, 1598 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.03 (s, 1H, NH), 7.74 (m, 2H), 7.62 (m, 2H), 7.34 (m, 2H), 7.10–7.07 (m, 2H), 3.84 (s, 6H); Mass (ESI) = 258 $[M+H]^+$.

2-Amino-N-phenylbenzamide (entry 5): mp: 255–256 °C (Lit[18] 255 °C); IR (KBr, cm^{-1}): 3331, 3244, 3097, 2929, 1892, 1685; ^1H NMR (400 MHz, DMSO-d_6): δ = 13.03 (s, 1H, NH), 7.95–7.85 (m, 2H), 7.49–7.24 (m, 9H); Mass (ESI) = 213 $[M+H]^+$.

N-Phenyl-1-naphthamide (entry 6): mp: 164–165 °C (Lit[19] 165 °C); IR (KBr, cm^{-1}): 3286, 3047, 2960, 2862, 1653, 1595, 1525, 1500; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.54 (s, 1H, NH), 8.19–8.17 (m, 1H), 8.07–8.05 (m, 1H), 8.03–8.01 (m, 1H), 7.81–7.78 (m, 2H), 7.74–7.70 (m, 1H), 7.63–7.60 (m, 3H), 7.37–7.34 (m, 2H), 7.12–7.10 (m, 1H); Mass (ESI) = 248 $[M+H]^+$.

N-Phenylcyclopentanecarboxamide (entry 7): mp: 147–148 °C (Lit[20] 152 °C); IR (KBr, cm^{-1}): 3280, 3250, 3192, 3078, 2962, 2866, 1948, 1654, 1541; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.80 (s, 1H, NH), 7.59–7.56 (m, 2H), 7.29–7.25 (m, 2H), 8.03–8.00 (m, 1H), 2.80–2.72 (m, 1H), 1.87–1.50 (m, 8H); Mass (ESI) = 190 $[M+H]^+$.

N-Phenylfuran-2-carboxamide (entry 8): mp: 130–132 °C (Lit[21] 125–126 °C); IR (KBr, cm^{-1}): 3280, 3140, 3059, 1656, 1598, 1581, 1529; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.13 (s, 1H, NH), 7.92 (s, 1H), 7.75–7.72 (m, 2H), 7.35–7.31 (m, 3H), 7.11–7.07 (m, 1H), 6.70–6.69 (m, 1H); Mass (ESI) = 188 $[M+H]^+$.

N-Phenylthiophene-2-carboxamide (entry 9): mp: 136–138 °C (Lit[22] 139–140 °C); IR (KBr, cm^{-1}): 3305, 3084, 1631, 1595, 1535, 1514; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.19 (s, 1H, NH). 8.02–8.01 (m, 1H), 7.85–7.84 (m, 1H), 7.71–7.68 (m, 2H), 7.73–7.70 (m, 2H), 7.37–7.21 (m, 1H), 7.12–7.10 (m, 1H); Mass (ESI) = 204 $[M+H]^+$.

N-(3,4-Dimethoxyphenyl)-2-phenylacetamide (entry 10): mp: 148–149 °C (Lit[23] 147 °C); IR (KBr, cm^{-1}): 3284, 3062, 3026, 2993, 2968, 2835, 1658, 1519; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.99 (s, 1H, NH), 7.32–7.30 (m, 5H), 7.25–7.22 (m, 1H), 7.08–7.05 (m, 1H), 6.86–6.82 (m, 1H), 3.70 (s, 6H), 3.59 (s, 2H); Mass (ESI) = 272 $[M+H]^+$.

N-(3,4-Dimethoxyphenyl)cyclohexanecarboxamide (entry 11): mp: 146–147 °C; IR (KBr, cm^{-1}): 3302, 3162, 2924, 2848, 1651, 1604, 1529, 1514; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.60 (s, 1H, NH), 7.05–7.03 (m, 1H), 6.89–6.86 (m, 1H), 6.82–6.80 (d, J = 8 Hz, 1H), 3.73 (s, 6H), 2.25–2.20 (m, 1H), 1.78–1.63 (m, 5H), 1.40–1.18 (m, 5H); Mass (ESI) = 264 $[M+H]^+$.

N-(4-Fluorophenyl)-4-methylbenzamide (entry 12): mp: 185–186 °C (Lit[24] 186–188 °C); IR (KBr, cm^{-1}): 3265, 3104, 3030,1693, 1531; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.20 (s, 1H, NH), 7.95–7.93 (m, 2H), 7.80–7.78 (m, 2H), 7.35–7.30 (m, 2H), 7.20–7.15 (m, 2H), 2.40 (s, 3H); Mass (ESI) = 230$[M+H]^+$.

N-(4-Chlorophenyl)nicotinamide (entry 13): mp: 171–172 °C (Lit[25] 169.5–170 °C); IR (KBr, cm^{-1}): 3217, 3132, 3061, 3035, 1718, 1695, 1530; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.50 (s, 1H, NH), 8.75–8.72 (m, 1H), 8.16–8.14 (m, 1H), 8.07–8.05 (m, 1H), 7.96–7.92 (m, 2H), 7.70–7.67 (m, 1H), 7.42–7.38 (m, 2H); Mass (ESI) = 233 $[M+H]^+$.

N-(Benzo[d][1,3]dioxol-5-yl)-2-phenyl acetamide (entry 14): mp: 141–143 °C(Lit[26] 146 °C); IR (KBr, cm^{-1}): 3263, 3028, 2914, 1654, 1537, 1504; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.04 (s, 1H, NH), 7.32–7.21 (m, 6H), 6.96–6.94 (m, 1H), 6.83–6.80 (m, 1H), 5.96 (s, 2H), 3.58 (s, 2H); Mass (ESI) = 256 $[M+H]^+$.

N-(Benzo[d][1,3]dioxol-5-yl)-3,4-dimethoxybenzamide (entry 15): mp: 159–161 °C; IR (KBr): 3280, 3001, 2879, 2837, 1645, 1600; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.95 (s, 1H, NH), 7.58–7.55 (m, 1H), 7.50–7.48 (m, 1H), 7.42–7.40 (m, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.06–7.02 (m, 1H), 6.88–6.85 (m, 1H), 6.0 (s, 2H), 3.83 (s, 6H); Mass (ESI) = 302 $[M+H]^+$.

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