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단신 (Notes)

Microwave-acceleration of Carboxamides Formation Using Water Soluble Condensing Agent DMT-MM or DCC[a]

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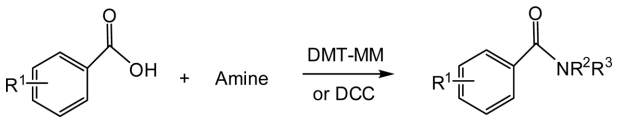
Amide linkages are present in key natural products and in many biologically active molecules. Therefore, the formation of amide bonds is important to both synthetic chemists and biologists. Approximately 66% of all preliminary screening reactions in industrial medicinal chemistry laboratories involve amide formation.[1] Although many methods have been developed for amide synthesis, a procedure for the direct coupling of amines with an acid in the presence of coupling agents without prior activation would be useful for building small-molecule libraries and for key steps in total syntheses.[2] Condensing agents such as carbodiimides[3] or other activating agents[4-12] are generally employed under dry conditions. However, the condensing agent 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholium chloride (DMT-MM) can be used to prepare carboxamides in alcohol or water.[13-14] This reaction is technically simple and relatively easy to implement, requiring only a mixing of acids, amines, and DMT-MM in MeOH or H_2O. The synthesis of DMT-MM is also relatively simple, and it can be prepared from CDMT (2-chloro-4,6 dimethoxy-1,3,5-triazine) and N-metheylmorphorine (NMM) in THF.[15]

The current report describes the application of microwave-induced acceleration to further improve the reaction conditions for amide synthesis using DMT-MM. High-speed synthesis using microwave technology has attracted considerable attention in organic chemistry.[16-18] Microwave irradiation provides advantages over conventional heating for chemical transformations, including accelerated reaction rates (and consequently reduced reaction times), higher yields, and cleaner reactions.[18] These advantages led us to evaluate the use of microwave irradiation for amidation reactions involving less reactive secondary and primary amines with acid in the presence of DMT-MM. We also compared the effectiveness of dicyclohexylcarbodiimide (DCC), a well-known condensing reagent,[3] when coupled with microwave irradiation versus classical thermal methods.

The reactions were performed by dissolving amines, carboxylic acids, and the condensing agent in solvent, followed by irradiation in a temperature-controlled microwave oven. For comparison, the same reactions were carried out under conventional heating conditions. The amidation of 2-phenylethylamine (a primary amine) with substituted benzoic acid in the presence of DMT-MM in MeOH gave a yield of over 90% products within 25 min at 110 °C with microwave irradiation. The reaction time with conventional heating was seven times that with microwave irradiation, and the yield was less than 10-20% of the yield with the microwave-assisted method. The reaction of piperidine (a secondary amine) with benzoic acid afforded a 91% yield within 30 min at 150 °C with microwave irradiation; note the higher reaction temperature and longer reaction time compared with those of the primary amine reaction.

Amidation of piperidine with substituted benzoic acid in the presence of DCC with pyridine in THF yielded more than 60% products within 25 min at 120 °C with microwave irradiation. Thus, DMT-MM was a much more effective coupling agent than DCC. Further increases in reaction temperature were limited by the potential of solvents for producing an explosive atmosphere within the micro-



***Scheme* 1.** Preparation of amides using condensing agent DMT-MM or DCC.

[a]This research was performed by undergraduate student's experimental project

***Table* 1.** Microwave-assisted Formation of Carboxamides Using Condensing Agent DMT-MM or DCC

Acid	Amine	Microwave irradiation			Conventional thermal heating (oil bath)		
		Time (min.)	Temp. (°C) (W)	Yield (%)	Time (hr.)	Temp. (°C)	Yield (%)
Benzoic acid[1]	2-phenylethylamine	25	110 (55 W)	99.0	3.5	Reflux	88.9
P-Nitrobenzoic acid[1]	2-phenylethylamine	25	110 (55 W)	92.6	3.0	Reflux	81.5
P-Methoxybenzoic acid[1]	2-phenylethylamine	25	110 (55 W)	91.7	3.0	Reflux	70.8
m-Methoxybenzoic acid[1]	2-phenylethylamine	25	110 (55 W)	96.0	3.0	Reflux	72.0
Benzoic acid[1]	Piperidine	30	150 (70 W)	91.7	11.5	Reflux	79.3
P-Nitrobenzoic acid[1]	Piperidine	30	150 (70 W)	75.6	24.0	Reflux	59.6
Benzoic acid[2]	Piperidine	25	120 (60 W)	63.0	10.0	Reflux	52.8
P-Methoxybenzoic acid[2]	Piperidine	25	120 (60 W)	60.0	12.0	Reflux	50.4

[1]Reaction with DMT-MM, solvent MeOH. [2]Reaction with DCC, solvent THF.

wave oven. Nevertheless, amide formation in THF at a low temperature (120 °C) still reached a yield of 60% within 25 min with microwave irradiation. Using conventional heating conditions, even with reaction times of more than 40- to 48-fold those used in the microwave experiments, the product yields were much lower (10-16%) than those obtained with the application of microwave irradiation.

EXPERIMENTAL

All ^{1}H NMR spectra were recorded on a Jeol 400 MHz Spectrometer and chemical shifts were recorded to tetramethylsilane (TMS) as an internal standard. Microwave-assistant reactions were performed with an initiator instrument (EXP EU, Biotage, 400W, 2450 MHz) Each microwave irradiation reaction was carried out in a 5 mm thickness Biotage vial sealed with a crimp cap. Reaction temperature were measured using infrared sensors on the outer surface of the traction vil. Products were purified by flash chromatography on 200-400 mesh ASTM 60 silica gel.

General method of formation of amides from substituted benzoic acid and 2-phenyethylamine or piperidine in presence of DMT-MM under microwave irradiation Acid (1.5 mmol), 2-phenylethylamine (1.65 mmol, 200 mg), DMT-MM (1.65 mmol, 457 mg) in MeOH (15 mL) were heated in microwave oven for 25 min. The end of reaction was checked with TLC. The solvent was removed under vacuum to give a crude product. The product was purified by column chromatography.

General Method of Formation of Amide From Substituted Benzoic Acid and 2-phenyethylamine or Piperidine in Presence of DMT-MM Under Thermal Heating

Acid (1.5 mmol), 2-phenylethylamine or piperidine (1.65 mmol), DMT-MM (1.65 mmol, 457 mg) in MeOH (15 mL) were refluxed for 3.5 hr. The end of reaction was checked with TLC. The solvent was removed under vacuum to give a crude product. The product was purified by column chromatography.

N-Phenethylbenzamide

Column chromatography: eluent, hexane : EA = 1 : 1, R_f 0.55, mp 112.4 °C (113-114 °C lit.[15]) yield = 88.9% (thermal reaction, reaction time 3.5 hr), yield = 99.0% (microwave irradiation reaction, reaction time 25 min.). ^{1}H NMR: 7.70 (10(CH), m, 10H), 6.14 (NH, s, 1H), 3.73 (NCH_2, t, 2H), 2.94 (NCH_2 $C\underline{H}_2$, t, 2H)

N-Phenethyl-4-nitrobenzamide

Column chromatography: eluent, hexane : EA = 3 : 2, R_f 0.59, mp 149 °C (149.5-150.5 °C lit.[15]) yield = 81.5% (thermal reaction, reaction time, 3.0 hr), yield = 92.6% (microwave irradiation reaction, reaction time 25 min.). ^{1}H NMR: 8.27, 8.25, 7.84, 7.82 (4(CH), dd, 4H), 7.33 (C_6H_5, m, 5H), 6.13 (NH, s, 1H), 3.76 (NCH_2, t, 2H), 2.96 ($NCH_2C\underline{H}_2$, t, 2H).

N-phenethyl-4-methoxybenzamide

Column chromatography: eluent, hexane : EA = 3 : 2, R_f 0.64, mp 118 °C (117.5-118.5 °C lit.[15]) yield = 70.8% (thermal reaction, reaction time, 3.0 hr), yield = 91.7% (microwave irradiation reaction, reaction time 25 min.). ^{1}H NMR: 8.27, 8.25, 7.84, 7.82 (4(CH), dd, 4H), 7.33 (C_6H_5, m, 5H), 6.13 (NH, s, 1H), 3.76 (NCH_2, t, 2H), 2.96 ($NCH_2C\underline{H}_2$, t, 2H)

N-Phenethyl-3-methoxybenzamide

Column chromatography: eluent, hexane : EA = 3 : 2, R_f 0.66, mp 112-113 °C (113-114 °C lit.[19]) yield = 72% (thermal reaction, reaction time, 3.0 hr), yield = 92.0% (microwave irradiation reaction, reaction time 25 min.). ^{1}H NMR: 7.5 (9(CH), m, 9H), 6.10(NH, s, 1H), 3.82 (OCH_3, s, 3H), 3.66 NCH_2, t, 2H) 2.88 ($NCH_2C\underline{H}_2$, t, 2H).

Phenyl-1-piperadinymethanone

Column chromatography: eluent, hexane : EA = 2 : 1, R_f 0.30, yield = 79.3% (thermal reaction, reaction time, 11.5 hr), yield = 91.7% (microwave irradiation reaction, reaction time 30 min.). ^{1}H NMR: 7.34 (5(CH), m, 5H), 3.66 (NCH_2, m, 2H), 3.29(NCH_2, m, 2H), 1.62 ($N(CH_2)_2(C\underline{H}_2)_2$, m, 4H), 1.46 ($(CH_2)_2C\underline{H}_2$, m, 2H).

4-Nitrophenyl-1-piperidinylmethanone

Column chromatography: eluent, hexane : EA = 2 : 1, R_f 0.23, yield = 59.6% (thermal reaction, reaction time, 24 hr), yield = 75.8% (microwave irradiation reaction, reaction time 30 min.). ^{1}H NMR: 8.27, 8.20, 7.57, 7.55 (4(CH), dd, 4H), 7.27 (NH, s, 1H), 3.73 (NCH_2, m, 2H), 3.29 (NCH_2, m, 2H), 1.70 ($N(CH_2)_2(C\underline{H}_2)_2$, m, 4H), 1.53 ($(CH_2)_2C\underline{H}_2$, m, 2H).

General Method of Formation of Amides from Substituted Benzoic Acid and Piperidine in in Presence of DCC Under Microwave Irradiation

Acid (2.5 mmol), piperidine (3 mmol), DCC (3.75 mmol) and pyridine (0.25 mmol) in dry THF (5 mL) were heated in a microwave oven at 120 °C (power 60 W) for 25 min. The end of reaction was checked with TLC. The solvent was removed under vacuum to give a crude product. The product was purified by column chromatography.

Phenyl-1-piperadinymethanone

Column chromatography: eluent, hexane : EA = 2 : 1, R_f 0.30, yield = 52.8% (thermal reaction, reaction time, 10 hr), yield = 63% (microwave irradiation reaction, reaction time 25 min.). ^{1}H NMR: 7.34 (5(CH), m, 5H), 3.66 (NCH_2, m, 2H), 3.29(NCH_2, m, 2H), 1.62 ($N(CH_2)_2(C\underline{H}_2)_2$, m, 4H), 1.46 ($(CH_2)_2C\underline{H}_2$, m, 2H).

4-Methoxybenzonyl-1-piperadinylmethanone

Column chromatography: eluent, hexane : EA = 2 : 1, R_f 0.23, yield = 50.4% (thermal reaction, reaction time 12 hr), yield = 60% (microwave irradiation reaction, reaction time 25 min.) ^{1}HNMR: 7.37, 7.35, 6.91, 6.89 (4(CH), dd, 4H), 3.82 (OCH_3, s, 3H), 3.45 ($N(CH_2)_2$, m, 4H), 1.67 ($N(CH_2)_2(C\underline{H}_2)_2$, m, 4H), 1.59 ($(CH_2)_2C\underline{H}_2$, m, 2H).

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