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Microwave-promoted solvent-free synthesis of *N*-(diphenylmethylene)glycine alkyl esters

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Abstract

The efficient synthesis of *N*-(diphenylmethylene) glycine alkyl esters was achieved for the first microwave irradiation under solvent-free condition, using PEG or quaternary ammonium salts as phase transfer catalysts (PTCs). Under the optimum conditions, *N*-(diphenylmethylene) glycine alkyl esters were obtained in excellent yields in most cases.

Keywords: Microwave; Solvent-free; *N*-(Diphenylmethylene)glycine alkyl esters

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Since the past three decades, *N*-(diphenylmethylene) glycine esters have received considerable attention due to their wide use to make biologically active substances [1]. For instance, they served as good substrates for asymmetric alkylation, Mannich-type reaction and aldol reaction to make all kinds of natural and unnatural α-amino acids [2]. Several methods have been reported to prepare *N*-(diphenylmethylene) glycine alkyl esters [3–6]. Due to it's attractive as an industry process, we are interested in Eils et al.'s route [7], in which benzophenone imine directly reacted with α-substituted acetate esters. However, this methodology has some limitations such as not high yields, tedious aqueous workup and toxic solvents (*N*-methylpyrrolidone, CH_3CN, DMF, or DMSO). As far as green chemistry concerned, there is a rapid need to develop a simple and efficient method for the synthesis of these compounds.

Recently the use of microwave irradiation has become an increasingly popular and useful technique to accomplish various organic reaction types including nucleophilic substitution, cycloaddition, and organometallic reaction in an efficient way. One of the most popular application is to form C–N bond [8]. Many studies have reported the *N*-alkylation of amines [9], however, to our best knowledge, the *N*-alkylation of imines under microwave irradiation condition has not been reported. Herein, we report an environment-friendly solvent-free method with high efficiency to synthesize *N*-(diphenylmethylene) glycine alkyl esters using microwave irradiation.

In the initial experiment, we investigated the nucleophilic reaction of *t*-butyl chloroacetate and benzophenone imine (Scheme 1). Under solvent-free condition, when Et_3N was used as base, although it was a homogeneous reaction, the conversion was low after oil bath heating of 24 h at 90 °C. When K_2CO_3 was used, as a heterogeneous

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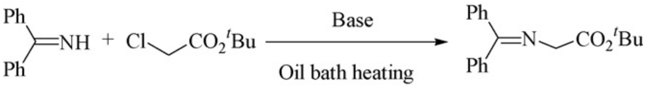


Scheme 1. The nucleophilic reaction under oil bath heating.

reaction, PTC was needed. With the help of PEG-400, 44% yield was obtained after 24 h oil bath heating at 130 °C. Considering that long-time heating was not efficient, we introduced the microwave irradiation into this transformation. It was found that the yield could be improved to 90% under solvent-free condition by microwave irradiation for 30 min at 650 W. Inspired by this result, we screened several parameters such as microwave power, temperature and reaction time. It was found that 700 W, 120 °C and irradiating for 20 min were the optimal conditions. When the reaction time was longer than 20 min, trace of benzophenone was detected; given stronger irradiation or higher temperature, deeper color appeared and the yields decreased.

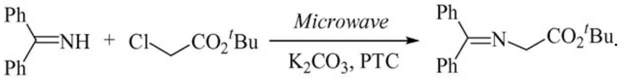
With optimized conditions in hand, we further assessed several PTCs and attempted to probe their roles in this kind of reaction. The results are summarized in Table 1. It was found that the heterogeneous reaction could not occur without PTC (Table 1, entry 7). Quaternary ammonium salts have also been tested to be effective PTCs in this transformation, although the yields were slightly lower than those obtained by using PEG-400 (entries 3–6). With the increase of the molecular weight of PEG, the yields decreased dramatically (entry 1 vs entry 2). PEG-400 is the best catalyst in this kind of microwave irradiation solvent-free *N*-alkylation reaction.

To probe the generality of the methodology, a number of α-halogen esters were examined with benzophenone imine under optimal conditions. With use of the general procedure, a variety of *N*-(diphenylmethylene) glycine esters were easily prepared (Table 2, entries 1–6 and 9). The yield decreased when R^3 was phenyl group (entry 7). Not surprisingly, corresponding product yields decreased when disubstituted esters were used, which could be attributed to steric hindrance (entry 8). The influence of the substituent X (Cl, Br) was also studied and change from chloride to bromide did not have obvious impact on the yields of the products.

All the products were characterized by comparing their physical and spectral (^{1}H NMR) data [10]with those of the authentic compounds reported in literature. Compounds **1** and **2** were prepared respectively according to Ref. [11].

In conclusion, a fast and efficient method for the preparation of *N*-(diphenylmethylene) glycine esters has been developed via solvent-free microwave-promoted *N*-alkylation of benzophenone imine. Shorter reaction time, environment benign and excellent yields are some advantages compared the conventional heating. Moreover, it represents the first successful synthesis of *N*-alkylation of imine using microwave irradiation to date.

Table 1
The effect of PTCs on *N*-alkylation of imine and *t*-butyl chloroacetate under using microwave irradiation[a]



Entry	Catalyst[b]	Yield[c] (%)
1	PEG-400	98
2	PEG-1000	78
3	TBAB	90
4	TMAI	90
5	BTEAC	85
6	CTAB	87
7	–	NR[d]

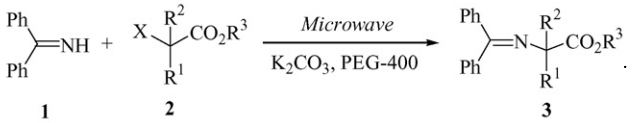
[a] Reaction conditions: *t*-butyl chloroacetate (5 mmol), benzophenone imine (5 mmol), K_2CO_3 (6 mmol), quaternary ammonium salts (0.5 mmol) or PEG (0.5 mmol), 700 W, 120 °C, 20 min.

[b] PEG: polyethylene glycol; TBAB: tetrabutyl ammonium bromide; TMAI: tetramethyl ammonium iodide; BTEAC: benzyltriethyl ammonium chloride; CTAB: cetyltrimethyl ammonium bromide.

[c] Isolated yields.

[d] No reaction.

Table 2
N-Alkylation of imine and α-halogen esters using microwave irradiation[a]



Entry	Product	X	R^1	R^2	R^3	Yield[b] (%)
1	**3a**	Cl	H	H	Me	97
2	**3a**	Br	H	H	Me	98
3	**3b**	Cl	H	H	Et	94
4	**3c**	Cl	H	H	*i*-Pr	93
5	**3d**	Cl	H	H	*n*-Bu	91
6	**3e**	Cl	H	H	*t*-Bu	98
7	**3f**	Br	H	H	Ph	80
8	**3g**	Cl	H	Ph	Et	69
9	**3h**	Br	H	Me	Et	93

[a] Reaction conditions: **1** (5 mmol), **2** (5 mmol), K_2CO_3 (6 mmol), PEG-400 (0.5 mmol), 700 W, 120 °C, 20 min.
[b] Isolated yields.

Acknowledgments

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[10] The general procedure of nucleophilic reaction: a mixture of α-halogen esters (5 mmol), PEG-400 (0.5 mmol), K_2CO_3 (6 mmol) and benzophenone imine (5 mmol) was placed in a 50 mL glass vessel, and then heated in the MW reactor for 20 min at 120 °C. Upon completion of the reaction (monitored by TLC), water (10 mL) and ethyl acetate (20 mL) were added, and the organic material was extracted, washed by water and dried over Na_2SO_4. The ethyl acetate was removed in vacuum leaving the crude product which was washed by hexane to give white solid as pure product. In the cases of **3f** and **3g**, recrystallization in ethanol was the good method for purification. **3a**: mp 41–42 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δppm): 3.7 (s, 3H, CH_3), 4.2 (s, 2H, NCH_2C), 7.47–8.0 (m, 10H, ArH). **3b**: mp 50–52 °C, ^{1}H NMR (400 MHz, $CDCl_3$, δppm): 1.26 (t, 3H, $J = 6.8$ Hz, CH_3), 4.17 (s, 2H, NCH_2C), 5.07 (q, 2H, CH_2-methyl), 7.10–7.70 (m, 10H, ArH). **3c**: mp 66–68 °C, ^{1}H NMR (400 MHz, $CDCl_3$, δppm): 1.24 (d, 6H, $J = 6.0$ Hz, CH_3), 4.18 (s, 2H, NCH_2C), 5.10 (m, 1H, methyl-CH-methyl), 7.20–7.70 (m, 10H, ArH). **3d**: mp 99–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δppm): 0.94 (t, 3H, $J = 7.2$ Hz, CH_3), 1.35–1.43 (m, 2H, methlene-CH_2-methyl), 1.62–1.67 (m, 2H, methlene-CH_2-ethyl), 4.06 (s, 2H, NCH_2C), 4.20 (t, 2H, $J = 6.4$ Hz, CO_2-CH_2-propyl), 7.30–7.70 (m, 10H, ArH). **3e**: mp 111–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δppm): 1.46 (s, 9H, CH_3), 4.12 (s, 2H, NCH_2C), 7.20–7.70 (m, 10H, ArH). **3f**: mp 76–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δppm): 4.06 (s, 2H, NCH_2C), 7.10–7.90 (m, 15H, ArH). **3g**: mp 64–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δppm): 1.19 (t, 3H, $J = 7.2$ Hz, CH_3), 4,14 (q, 2H, CH_2-methyl), 5.13 (s, 1H, NCHC), 7.10–7.90 (m, 15H, ArH). **3h**: mp 52–54 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δppm): 1.25 (t, 3H, $J = 7.2$ Hz, methylene-CH_3), 1.42 (d, 3H, $J = 6.8$ Hz, NC-CH_3), 4.10 (q, 1H, N-CH-methyl), 4.10 (q, 2H, CH_2-methyl), 7.40–7.90 (m, 10H, ArH).
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