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Short communication

SHORT COMMUNICATION

Benzylation of *N*-phenyl-2-phenylacetamide under microwave irradiation

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Abstract: *N*-Phenyl-2-phenylacetamide was alkylated with benzyl chloride in the presence of powdered potassium hydroxide under microwave irradiation in a solvent-free system. The reactions were also performed in the presence of phase-transfer catalysts. The formation of *N*-, *O*- and *C*-products of alkylation was followed by gas chromatography. The *N*-product was found to be the main product under microwave irradiation. The *O*-product was obtained in higher yields when an excess of base and benzyl chloride was used.

Keywords: alkylation; amides; phenylacetamides; phase-transfer conditions; microwave irradiation.

INTRODUCTION

N-Substituted 2-phenylacetamides are very interesting compounds because of their structural similarity to the lateral chain of natural benzylpenicillin.[1] Selective *O*-alkylation of *N*-substituted 2-phenylacetamides is of practical importance in penicillin chemistry, not only for use in chemical transformations of natural benzylpenicillin into 6-aminopenicillanic acid, but also because of the possibility of direct transformation of the imino ether into a new semi-synthetic penicillin. On the other hand, *N*-alkylation yields *N*,*N*-disubstituted 2-phenylacetamides, which are important intermediates in the production of herbicides and tertiary amines.[2]

Alkylation of *N*-substituted 2-phenylacetamides under neutral and basic conditions has been reviewed recently.[2] Alkylation of *N*-phenyl-2-phenylacetamide (**1**, Scheme 1) has also been studied.[3–6] Work *et al.*[3] showed that when **1** is alkylated with benzyl chloride in the presence of sodium amide, only the *C*-product is formed. Torosyan *et al.*[4] alkylated **1** with benzyl chloride under phase-transfer conditions and obtained only the *N*-product in 48 % yield. Benzylation of

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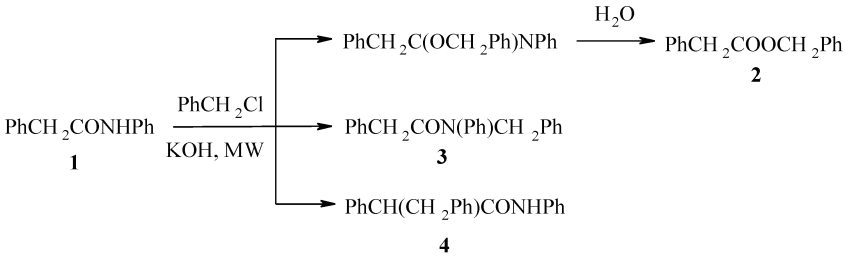
N-phenyl-2-phenylacetamide with benzyl chloride in the presence of powdered KOH was performed in the presence of various phase-transfer catalysts, solvents and temperatures.[5] The *N*-product was found to be the main product in most of the employed systems. In an excess of potassium hydroxide and benzyl chloride at reflux temperature in toluene, an almost quantitative yield of the *N*-product was obtained after 4 h of heating. When **1** was alkylated with ethyl bromide under phase-transfer conditions, in addition to the *N*-product, the *O*-product was also detected.[6]



Scheme 1. Alkylation of *N*-phenyl-2-phenylacetamide (**1**) with benzyl chloride in the presence of KOH under microwave irradiation. Product **2** is the *O*-product (benzyl ester of phenylacetic acid, PAA), product **3** is the *N*-product (*N*-benzyl-*N*-phenyl-2-phenylacetamide) and product **4** is the *C*-product (*N*-phenyl-2,3-diphenylpropanamide) of alkylation.

Microwave irradiation has become an important method in organic synthesis which is applicable to a wide range of reactions with short reaction times and high yields. Reactions in the absence of solvent (solvent-free synthesis) under microwave irradiation also offer several advantages. The absence of solvent reduces the risk of explosion and simplifies the work-up procedure.[7] Such procedures are often examples of green chemistry.

Fast solvent-free alkylation of amides and lactams under microwave irradiation was reported.[8] Under PTC/OH conditions in a very short time (2.5 min), *N*-alkylation was achieved in high yield but phenylacetamides were not used. Conveniently, the author used amides which can be easily *N*-alkylated, such as *N*-methylacetamide, *N*-phenylacetamide, *N*-phenylbenzamide, caprolactam and valerolactam. To the best of our knowledge, no other study of other reaction products of alkylation of amides under microwave irradiation has hitherto been performed.

In our study of the alkylation of *N*-substituted 2-phenylacetamides,[2] in this paper, the alkylation of *N*-phenyl-2-phenylacetamide with benzyl chloride under microwave irradiation is now reported. The reactions were performed in a solvent-free system with and without phase-transfer catalysts.

EXPERIMENTAL

Materials

The starting *N*-phenyl-2-phenylacetamide (**1**) and the expected alkylation products, *i.e.*, the *O*- (**2**), *N*- (**3**) and *C*-product (**4**), were prepared as follows.

The starting amide (**1**) was obtained by the reaction of phenylacetyl chloride and aniline.[9] ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.70 (2H, *s*, Ph–CH_2), 7.0–7.5 (10H, *m*, ArH); m.p. 114–116 °C.

N-Benzylaniline was obtained by the alkylation of aniline with benzyl chloride in the presence of KOH and tetrabutylammonium hydrogensulfate by mixing 0.10 mol aniline, 0.10 mol KOH, 1.25 mmol tetrabutylammonium hydrogensulfate and 11.2 ml of water. Then 0.10 mol benzyl chloride was added dropwise to the mixture heated on a boiling water bath. After 5 h heating and stirring, the reaction mixture was cooled to room temperature and water was added. The layers were separated and the water layer was extracted with diethyl ether. The organic layers were combined and dried over anhydrous sodium sulfate. The product was isolated by distillation. ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.75 (1H, *s*, NH), 4.17 (2H, *s*, CH_2), 6.60 (5H, *q*, Ph–N), 7.23 (5H, *s*, Ph–CH_2); b.p. 112–117 °C (0.40 mbar).

The benzyl ester of PAA (**2**) was prepared from benzyl chloride and phenylacetic acid, in the presence of 40 % sodium hydroxide and tetrabutylammonium hydrogensulfate.[9] ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.62 (2H, *s*, CH_2–Ph), 5.10 (2H, *d*, O–CH_2), 7,27 (10H, *s*, 2×Ph); b.p. 169––171 °C (3.0 mbar).

N-Benzyl-*N*-phenyl-2-phenylacetamide (**3**) was synthesized by the same method as for **1** but from phenylacetyl chloride and *N*-benzylaniline. ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.70 (2H, *s*, CH_2–CO), 4.90 (2H, *s*, N–C**H**$_2$), 6.70–7.30 (15H, *m*, 3×ArH); m.p. 86–88 °C.

N-Phenyl-2,3-diphenylpropanamide (**4**) was prepared from 2,3-diphenylpropanoyl chloride and aniline. ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.10 (2H, *m*, CH_2), 3.60 (1H, *m*, CH), 7.00–7.40 (15H, *m*, 3×ArH); m.p. 168–169 °C.

2,3-Diphenylpropanoyl chloride was synthesized by the reaction of 2,3-diphenylpropanoic acid and thionyl chloride.[10] 2,3-Diphenylpropanoic acid was obtained by the hydrolysis of 2,3-diphenylpropanenitrile, which was obtained by the reaction of phenylacetonitrile and benzyl chloride.[11]

The other materials were obtained commercially.

The ^{1}H-NMR spectra were determined on a Varian EM 390 spectrometer (90 MHz) using TMS as the internal standard.

Methods

In a typical procedure for alkylation under microwave irradiation, a mixture of *N*-phenyl--2-phenylacetamide (2.0 mmol), freshly prepared powdered KOH (2.0 mmol), benzyl chloride (2.0 mmol), PTC catalyst (0.20 mmol, if used) was made in a test tube by mixing the substances for 10 s with a spatula. The reaction mixture was then irradiated in a commercial domestic microwave oven (Samsung M182DN). The reaction temperature was measured using an IR thermometer Ebro TN 4088 LC. The reaction was stopped by the addition of water (2.0 ml), and then dichloromethane (5.0 ml) was added. The water layer was separated and washed with dichloromethane (5.0 ml). The organic layers were combined and analyzed by gas chromatography on a DB-1 capillary column (Varian 3400 with Varian integrator 4270), using *n*-hexadecane as an internal standard.

In addition, alkylation was performed in a microwave synthesizer CEM Discover® BenchMate (initial power 100 W, set temperature 155 °C, run time 30 s, hold time 0.5–5 min, 25 cm^3 flask equipped with a condenser). The subsequent work-up and analysis were same as previously described.

RESULTS AND DISCUSSION

It was shown earlier that when **1** is alkylated under basic conditions different products of alkylation could be obtained.[5] On the basis of these results, **1** was al-

kylated with benzyl chloride in the presence of powdered potassium hydroxide in a solid–liquid system both with and without a phase-transfer catalyst under microwave irradiation. The alkylation of **1** under basic conditions is given in Scheme 1.

The results of the alkylation of **1** with benzyl chloride at 850 W irradiation power for different reaction times are given in Table I. The yield of the *N*-product increased with increasing reaction time. The highest yield was obtained after 5 min of irradiation. The yields of **3** were between 48.56 and 69.78 %.

TABLE I. Alkylation of **1** with benzyl chloride in the presence of KOH at 850 W microwave irradiation (amount of **1**: 2.0 mmol; amount of KOH: 2.0 mmol; amount of benzyl chloride: 2.0 mmol)

Reaction time, min	Yield, %				
	1	**2**	**3**	**4**	Other products
1	50.03	0	48.56	0	1.41
2	31.23	0	59.94	0.32	8.51
3	32.80	0	60.58	0.30	6.32
5	22.93	0	69.78	0	7.29
7	25.49	0	65.82	0	8.69
10	25.51	0	63.80	0	10.69

In addition, the effect of the reactant ratio was investigated. The results of alkylation with excess of benzyl chloride and potassium hydroxide are given in Table II, from which it can be seen that excess benzyl chloride promotes the *N*-alkylation reaction. This was also the case when excess base was used; the maximum yield was achieved with 100 % excess of potassium hydroxide. When excesses of both base and alkylating agent were used, almost all of **1** reacted and the almost highest yield of **2** was achieved. The maximum yield of **3** was about 70 %. In comparison to conventional synthesis (99 % yield of **3**, toluene, reflux, 4 h),[5] the microwave synthesis gave a lower yield of **3** but no solvent was employed and the reaction time was only 1 min. In addition, reaction was performed in a plain test tube. The highest reaction temperature recorded was 151 °C.

Additional experiments were conducted in a microwave synthesizer CEM Discover® BenchMate using an excess of base and alkylating agent, since almost all of **1** reacted in the experiments in a commercial microwave oven. The reaction temperature was set to 155 °C and the initial power was 100 W. In all experiments, the run time was 30 s, while the hold time was varied between 0.5–5 min. The results of alkylation under these conditions are given in Table III. At shorter hold time, the yields of the *O*- and *N*-alkylation products were similar. With increasing hold time, *N*-alkylation prevailed, which is consistent with the fact that the *O*-product is a kinetic product, while the *N*-product is the thermodynamically stable one.[2] According to the obtained results, *N*-phenyl-2-phenylacetamide is less reactive under microwave irradiation than previously[8] investigated amides.

TABLE II. Alkylation of **1** in the presence of various quantities of benzyl chloride at 850 W microwave irradiation (amount of **1**: 2.0 mmol; initial amount of base and alkylating agent: 2.0 mmol; reaction time: 1 min)

KOH:$PhCH_2Cl$	Yield, %				
	1	**2**	**3**	**4**	Other products
1:1	50.03	0	48.56	0	1.41
1:2	50.85	0.58	36.30	0.57	11.70
1:3	31.78	1.72	57.60	0	8.90
2:1	18.54	1.98	71.18	0.74	7.56
3:1	32.10	0	65.85	0	2.05
2:2	1.05	12.50	70.83	0.71	14.91

TABLE III. Alkylation of **1** in a microwave synthesizer CEM Discover® BenchMate (amount of **1**: 2.0 mmol; initial amount of base and alkylating agent: 4.0 mmol; initial power: 100 W; set temperature: 155 °C; run time: 30 s)

Hold time, min	Yield, %				
	1	**2**	**3**	**4**	Other products
0.5	31.33	30.85	34.95	0.61	2.26
1	19.16	8.92	70.20	0.65	1.07
5	8.28	5.57	85.30	0.45	0.40

When **1** was alkylated in the presence of different phase-transfer catalysts under microwave irradiation at 850 W at an equimolar ratio of the reactants, the main product was again found to be the *N*-product, while the *O*-product was a minor product (Table IV). It can also be seen from Table IV that the *C*-product was present in trace amounts only. Although in almost all experiments higher yields were obtained in comparison to the uncatalysed reaction (except when tetrabutylammonium bromide was used), the effects of the phase-transfer catalysts were minor.

Table IV. Alkylation of **1** with benzyl chloride under PTC/OH at 850 W microwave irradiation (amount of **1**: 2.0 mmol; amount of KOH: 2.0 mmol; amount of benzyl chloride: 2.0 mmol; amount of phase-transfer catalyst: 0.20 mmol; reaction time: 1 min)

Quat or catalyst	Counter ion	Yield, %				
		1	**2**	**3**	**4**	Other products
Et_4N^+	Br^-	37.98	0	58.57	0	3.45
Bu_4N^+	Cl^-	41.35	1.08	51.21	0.17	6.19
	Br^-	52.09	0.53	42.27	0	5.11
	I^-	33.35	0.90	59.24	0	6.51
He_4N^+	Br^-	26.88	10.16	57.00	0	5.96
TEBA	Cl^-	37.51	0.56	53.10	0	8.83

CONCLUSIONS

When *N*-phenyl-2-phenylacetamide was alkylated with benzyl chloride in the presence of potassium hydroxide under microwave irradiation, the *N*-product was the main product. Excess of base or alkylating agent increased the yield of

the *N*-product. Phase-transfer catalysts promote the reaction to a minor extent. The highest yield of the *N*-product of alkylation of *N*-phenyl-2-phenylacetamide in a domestic microwave oven was around 70 % after 1 min at 850 W while in the microwave synthesizer, the yield was around 85 % after 5 min at 155 °C. The *O*-product was obtained in higher yields (up to 30 %) when excesses of base and benzyl chloride were used.

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И З В О Д

БЕНЗИЛОВАЊЕ *N*-ФЕНИЛ-2-ФЕНИЛАЦЕТАМИДА ПОМОЋУ МИКРОТАЛАСНОГ ЗРАЧЕЊА

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N-Фенил-2-фенилацетамид је алкилован бензил-хлоридом у присуству спрашеног калијум-хидроксида помоћу микроталасног зрачења. Испитиван је утицај односа реактаната и природе међуфазних катализатора на принос очекиваних производа реакције алкиловања. Настајање производа реакције алкиловања (*N*-, *O*- и *C*-производ) је праћено гасном хроматографијом. Утврђено је да је *N*-производ главни производ реакције алкиловања при микроталасном зрачењу. Кад се за алкиловање употребљава вишак бензил-хлорида и калијум-хидроксида у вишем приносу се добија и *O*-производ.

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