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Alkylation of *N*-substituted 2-phenylacetamides: Benzylation of *N*-(4-nitrophenyl)-2-phenylacetamide

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N-(4-Nitrophenyl)-2-phenylacetamide was alkylated with benzyl chloride in the presence of powdered potassium hydroxide at different temperatures and in various solvents in order to establish the reactivity and orientation in the reaction. The reactions were also carried out in the presence of different phase-transfer catalysts in toluene. Product formation was followed by GC. The obtained results were compared to the results of the benzylation of other *N*-substituted 2-phenylacetamides, especially of *N*-phenyl-2-phenylacetamide.

Keywords: alkylation, benzylation, 2-phenylacetamides, phase-transfer catalysis.

INTRODUCTION

The behaviours of *N*-substituted amides in alkylation reaction have been extensively studied[1] since the amide bond plays a very important role in peptide chemistry, as well as in some other chemistries and industries. The reaction conditions and the structure of the starting *N*-substituted amide have a great influence on the formation of the reaction products. When *N*-substituted 2-phenylacetamides are concerned, alkylation under basic conditions gives several different products. The anion, which is initially formed in the reaction, due to the acidity of the hydrogen on the nitrogen and the hydrogen on the α carbon, attacks the alkyl halide giving the *N*- and *C*-products of alkylation (Scheme 1). Since the anion formed by the cleavage of the N–H bond is a resonance hybrid of two structures, the formation of the *O*-product (imino ether) is also possible.[1]

In our study of the alkylation reaction of 2-phenylacetamides, it was shown earlier[2] that, when *N*-phenyl-2-phenylacetamide (PPA) is alkylated with benzyl chloride, the *N*-product is the main product in all of the reactions and in most of the reactions the only product. In some of the experiments almost quantitative yield was achieved. Torosyan *et al.*[3] also alkylated PPA with benzyl chloride under phase-transfer conditions, and obtained

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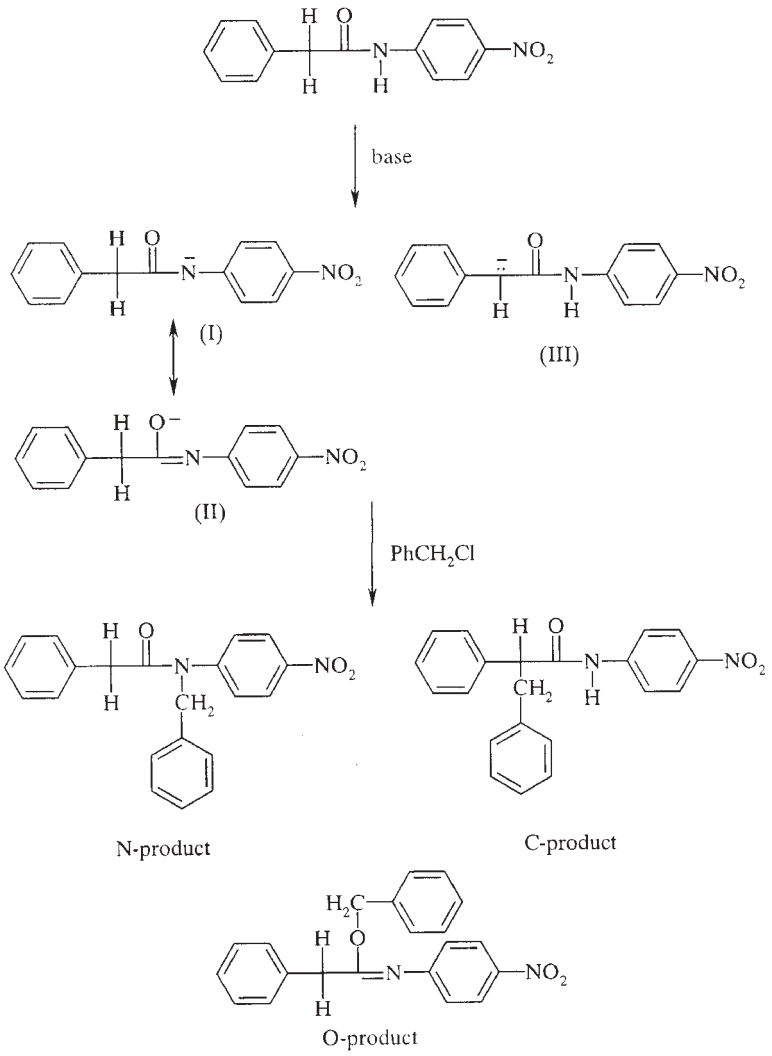


Scheme 1. The reaction products of the benzylation of *N*-(4-nitrophenyl)-2-phenylacetamides under basic conditions.

only the *N*-product in 48 % yield. When PPA was alkylated with ethyl bromide under phase-transfer conditions, besides the *N*-product, the *O*-product was detected.[4,5] Various *N*-substituted 2-phenylacetamides have been alkylated using various alkylating agents under different conditions.[6–10]

In order to study the alkylation reaction of *N*-(4-nitrophenyl)-2-phenylacetamide (NPA) with benzyl chloride, NPA was alkylated with benzyl chloride using powdered potassium hydroxide as the base in different solvents at various temperatures using different ratios of the reactants. The reactions were carried out in the absence and the presence of different phase-transfer catalysts in order to establish the effect of the structure of the phase-transfer catalyst

on the reactivity of the starting NPA and on the orientation of the investigated reaction. To obtain that goal, the starting NPA as well as the expected products of the alkylations (*N*-, *O*- and *C*-product) were synthesized. The alkylation reactions were followed using GC.

EXPERIMENTAL

Materials

The starting NPA was obtained by the reaction of phenylacetyl chloride and 4-nitroaniline:[4] ν_{max} (KBr):3256, 3149, 3086, 2961, 1662, 1508 and 1338 cm^{-1}; ^{1}H-NMR-δ_{ppm}: 3.74 (2H, *s*, Ph–CH_2), 7.32 (5H, *s*, ArH), 7.56 (2H, *d*, N–ArH), 8.10 (2H, *d*, NO_2–ArH); m.p. = 128–130 ºC. *N*-Benzyl-*N*-(4-nitrophenyl)-2-phenylacetamide was synthesized by the same method from phenylacetyl chloride and *N*-benzyl-4-nitroaniline:[4] ν_{max} (KBr): 3064, 3019, 2935, 1652, 1540 and 1282 cm^{-1}; ^{1}H-NMR-δ_{ppm}: 3.48 (2H, *s*, Ph–CH_2–N), 4.37 (2H, *s*, Ph–CH_2–C), 6.48 (2H, *d*, N-ArH), 6.88–7.33 (10H, *m*, 2×ArH), 7.90–8.10 (2H, *m*, NO_2–ArH); m.p. = 106–109 ºC.

N-Benzyl-4-nitroaniline was obtained by the alkylation of 4-nitroaniline with benzyl chloride in the presence of $NaHCO_3$ and TEBABr using the following procedure: 5.5 mol of 4-nitroaniline, 156 mmol of $NaHCO_3$, 12.5 mmol of TEBABr and 12.5 ml of water were mixed and 125 mmol of benzyl chloride was then added dropwise to the mixture heated in a boiling water bath. After 5 h of heating and stirring the reaction mixture was cooled to room temperature and purified by crystallization: ν_{max}(KBr): 3365, 3049, 3019, 2910, 1603, 1540 and 1328 cm^{-1}; ^{1}H-NMR-δ_{ppm}: 4.38 (2H, *s*, Ph–CH_2), 4.86 (1H, *s*, NH), 6.50 (2H, *d*, ArH–N), 7.32 (5H, *s*, ArH), 8.04 (2H, *d*, NO_2–ArH); m.p. = 135–137 ºC.

N-(4-Nitrophenyl)-2,3-diphenylpropanamide was prepared from 2,3-diphenylpropanoyl chloride and 4-nitroaniline:[4] ν_{max} (KBr): 3257, 3088, 3056, 2961, 2935, 1662, 1506 and 1341 cm^{-1}; ^{1}H-NMR-δ_{ppm}: 3.02 (2H, *q*, CH_2), 3.43–3.90 (1H, *m*, CH), 7.15 (5H, *s*, ArH–CH), 7.30 (5H, *s*, ArH–CH_2), 7.50 (2H, *d*, N–ArH), 8.07 (2H, *d*, NO_2–ArH); m.p. = 134–136 ºC. 2,3-Diphenylpropanoyl chloride was synthesized by the reaction of 2,3-diphenylpropanoic acid and thionyl chloride.[4,11] 2,3-Diphenylpropanoic acid was obtained by the hydrolysis of 2,3-diphenylpropanenitrile, which was obtained by the reaction of phenylacetonitrile and benzyl chloride.[4,12]

The *n*-benzyl ester of PAA was prepared from benzyl chloride and phenylacetic acid, in the presence of 40 % sodium hydroxide and tetrabutylammonium hydrogensulfate.[4]

The other materials were obtained commercially.

Methods

Typical procedure for the benzylation of NPA.

A mixture of powdered KOH (5 mmol), NPA (5 mmol), benzyl chloride (5 mmol), PTC catalyst (0.5 mmol), and solvent (10 ml) was stirred at 600 rpm in a three-necked glass reactor equipped with a condenser, magnetic stirrer (Janke-Kunkel, model IKAMAG RET-G) and an ultra thermostat (±0.1 ºC) at 60 ºC for 4 h. The reaction was stopped by the addition of water (25 ml), the layers were separated and the water layer extracted with dichloromethane (25 ml). The samples were analyzed by GC on an OV-17 or OV-1 packed column (Varian 1440 (FID) with a Varian integrator 4270) using an internal standard.

All the reported results were obtained from two experiments.

RESULTS AND DISCUSSION

As a sequence to the PTC/OH reactions of alkylation of *N*-substituted-2-phenylacetamides in solid-liquid systems,[2–9] the starting amide and the expected products of alkylation were prepared in order to investigate the effect of substitutent on the PTC/OH alkylation of *N*-(4-nitrophenyl)-2-phenylacetamide. The formation of *N*-, *O*- and *C*-products were followed using GC. The *O*-product, which is formed as the imino ether, was detected in the form of the ester of PAA.

N-(4-Nitrophenyl)-2-phenylacetamide was alkylated with benzyl chloride in the presence of powdered potassium hydroxide in the solid-liquid system. The reactions were per-

formed at 60 ºC and at reflux temperature in different solvents (Table I). At 60 ºC, with equimolar amounts of reactants, in nonpolar solvents, such as hexane, isooctane or toluene, the reactivity of the starting amide is up to 44 %. In polar solvents, such as DMSO, the reactivity is increased up to 68.7 %. This increase in reactivity can be explained by the basicity of solvent, which promotes the formation of reactive anions, or by a change of the reaction mechanism (S_N2 to S_N1). Less polar and less basic solvents, such as dioxane, promote the reaction to a very small extent and represent the poorest solvents for the reaction.

TABLE I. The effect of the solvent on the alkylation of *N*-(4-nitrophenyl)-2-phenylacetamide with benzyl chloride (amount of SPA 5 mmol; 10 ml of solvent; reaction time 4 h)

Solvents	KOH mmol	$PhCH_2Cl$ mmol	NPA %	*N*-product %	*C*-product %	*O*-product %	Other products %
Hexane[a]	5	5	55.56	40.87	1.79	0.39	1.39
Isooctane[a]	5	5	73.95	21.52	0.53	3.84	0.16
Toluene[a]	5	5	63.98	30.47		6.17	0.08
b	5	5	28.19	29.96	21.88	17.54	2.43
b	5	10	33.50	35.33	12.96	16.37	1.84
b	10	10	0.81	6.71	70.74	6.79	14.95
Dioxane[a]	5	5	93.31	2.80		2.18	1.71
DMSO[a]	5	5	31.32	38.63	13.80	1.57	14.68

[a] 60ºC, [b] reflux

Increasing the reaction temperature increases the reactivity of starting amide if the reaction proceeds with equimolar amounts of the reactants. Increasing the initial amount of benzyl chloride at reflux temperature does not increase the reactivity, but increasing the initial amounts of potassium hydroxide and benzyl chloride increase the reactivity to almost 100 %.

When the orientation of the benzylation reaction of NPA is considered, it can be observed from Table I that the ratio of the products differs and depends on the reaction conditions. At 60 ºC, with equimolar amounts of reactants, the *N*-product is the main product in hexane, isooctane, toluene and DMSO. The same is true in toluene at reflux temperature, with equimolar amounts of reactants and with an excess of benzyl chloride. The *O*-product is detected in every experiment even at reflux temperature. The *O*-product is the kinetic product while the *N*-product is the thermodynamic product of alkylation.[1] The formation of these products over a reaction period of four hours in toluene at 60 ºC with equimolar amounts of reactants is presented in Fig. 1. The *O*-product is formed to a lesser extent and also rearranges to the more stable *N*-product, which is the main alkylation product.

The *C*-product was also detected in almost all experiments except when the reactivity of NPA was low, such as in dioxane and toluene at 60 ºC. At the reflux temperature with the reactants in excess, the *C*-product becomes the main product.

The used phase-transfer catalysts catalyze the alkylation reaction in all the investigated systems by increasing the reactivity of the starting NPA. At higher temperatures (re-

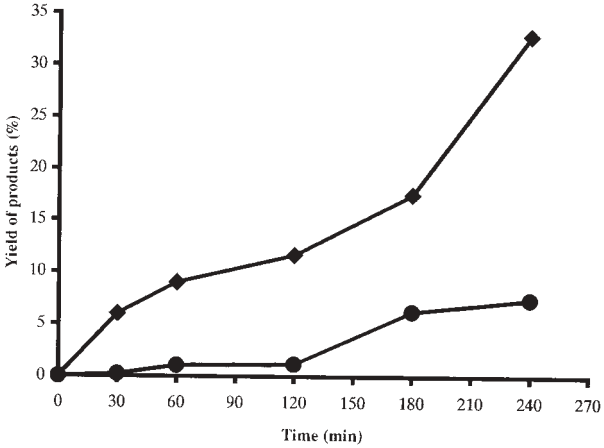


Fig. 1. Formation of *N*- and *O*-products in the alkylation reaction of NPA with benzyl chloride in toluene at 60 ºC (♦ *N*-product, • O-product).

flux temperatures) the reactivity of NPA and the yield of the alkylation products was almost the same as at 60 ºC.

TABLE II. The effect of the catalyst structure on the alkylation of *N*-(4-nitrophenyl)-2-phenylacetamide with benzyl chloride in toluene (amount of SPA 5 mmol; amount of benzyl chloride 5 mmol; amount of KOH 5 mmol; amount of catalyst 0.5 mmol; 10 ml of toluene; reaction temperature 60 ºC; reaction time 4 h)

Catalyst	Counter ion	NPA (%)	*N*-product (%)	*C*-product (%)	*O*-product (%)	Other products (%)
Et_4N^+	Br^-	27.70	61.03	0.61	8.66	2.00
Bu_4N^+	Cl^-	28.03	30.56	5.42	26.37	9.37
	Br^-	24.95	40.69	6.77	20.93	6.66
	I^-	20.22	51.34	1.09	24.98	2.37
	I^{-*}	26.90	35.95	7.50	25.83	3.82
	HSO_4^-	35.01	29.93	7.61	15.07	12.38
TEBA	Br^-	18.55	61.11	0.48	6.57	3.29

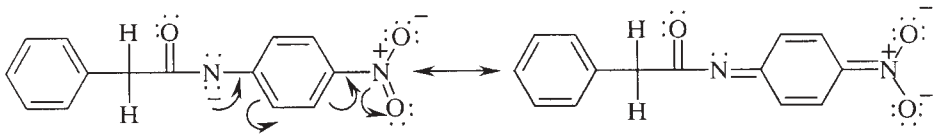
*reflux

When an electron-acceptor group, such as a nitro group, is present, besides the *N*-and *O*-products, the *C*-product was also formed (Table II). The *N*-product was still the main product but the *N*-/*O*-ratio was 1.16–9.30, thus *O*-alkylation is favored in comparison to the other substituents. When the catalyst was TBA as the quaternary salt, the *C*-product was detected up to 7.61 %. The *N*-/*O*-/*C*- ratio varied from 127.31:13.68:1 when TEBABr was used to 3.93:1.98:1 when $TBHSO_4$ was used.

The most selective catalysts (*N*-alkylation) are TEABr and TEBABr and the best phase-transfer catalysts for the benzylation of NPA were TEBABr and TEABr which promote the interfacial mechanism in PTC/OH systems.[13] The order of the influence of the counter ions in the TBA series on the reactivity is I>Br>Cl>HSO_4.

In comparison to *N*-phenyl-2-phenylacetamide, it would be expected that *N*-(4-nitrophenyl)-2-phenylacetamide should be more reactive since the nitro group as an elec-

tron-acceptor group, by inductive and resonance effects, favors the formation of the corresponding anion. That is true for the reactions performed at 60 ºC in toluene, hexane, isooctane, but the reactivity at reflux temperature in toluene or in the presence of phase-transfer catalyst is inversed. This change in reactivity could be explained by a decreasing nucleophilicity of the formed anion through resonance (Scheme 2).



Scheme 2. Resonance in the 4-nitrophenyl-2-phenylacetamide anion.

On the other hand, the selectivity when NPA is considered is lower in comparison to PPA. The reason might be the same. When PPA reacts, the most nucleophilic site in the molecule is nitrogen. However, the nitrogen in NPA is less nucleophilic regarding resonance and thus other reactive centers such as the α-carbon and oxygen are favored, which leads to a less selective alkylation. Under very basic conditions (excess of potassium hydroxide), the α-carbon is the most nucleophilic site, which is consistent with the alkylation of PPA under very basic conditions ($NaNH_2$).[14]

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Abbreviations

PAA – phenylacetic acid
PPA – *N*-phenyl-2-phenylacetamide
NPA – *N*-(4-nitrophenyl)-2-phenylacetamide
$TBHSO_4$ – tetrabutylammonium hydrogen sulfate
TEABr – tetraethylammonium bromide
TBABr – tetrabutylammonium bromide
TBACl – tetrabutylammonium chloride
TBAI – tetrabutylammonium iodide
TEBABr – triethylbenzylammonium (TEBA) bromide

И З В О Д

АЛКИЛОВАЊЕ *N*-СУПСТИТУИСАНИХ 2-ФЕНИЛАЦЕТАМИДА: БЕНЗИЛОВАЊЕ *N*-(4-НИТРОФЕНИЛ)-2-ФЕНИЛАЦЕТАМИДА

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N-(4-Нитрофенил)-2-фенилацетамид је алкилован бензил-хлоридом у различитим растварачима у присуству спрашеног калијум-хидроксида на различитим температурама. Реакције су извођене у присуству различитих међуфазних катализатора као и без катализатора у циљу испитивања утицаја реакционих услова на реактивност и оријентацију реакције алкиловања испитиваног једињења.

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