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

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Abstract: Benzylation of *N*-(4-chlorophenyl)-2-phenylacetamide with benzyl chloride in the presence of powdered potassium hydroxide under various reaction conditions was performed in order to establish the possible reaction products. Different temperatures and ratios of reactants and solvents were used. The reactions were also carried out in the presence of different phase-transfer catalysts in toluene as a solvent. The formation of the reaction products was followed using gas chromatography. On the basis of the obtained results, the reactivity and the orientation in the alkylation reaction of the investigated amide is discussed.

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

INTRODUCTION

Alkylation reactions have been widely studied and the results contribute significantly to our understanding of the nucleophilic properties of the amide moiety. N-alkylation of primary and secondary amides has been practiced for decades, both in the presence of stoichiometric amounts of strong bases or under phase-transfer conditions. The transformation is useful in the preparation of various N-substituted amides and amines. C-alkylation of amides has also been employed in the construction of carbon skeletons.[1]

Alkylations of N-monosubstituted 2-phenylacetamides are of interest due to their structural similarity to the lateral chain of benzylpenicillin.[2] Also, different N-substituted and N,N-disubstituted 2-phenylacetamides possess pesticidal and herbicidal activity.[3]

Greater control over the alkylation site can be exercized under alkaline conditions than is possible under neutral or acid conditions. Also, the alkaline reactions are more useful from a synthetic standpoint. It has been shown that when a N-substituted phenylacetamide is alkylated under basic conditions, an anion or dianion is initially formed due to the acidity of the nitrogen atom hydrogen and of the $\alpha_{C=O}$-carbon hydrogen. This provides the possiblity for the formation of different alkylation products (Scheme 1).[1]

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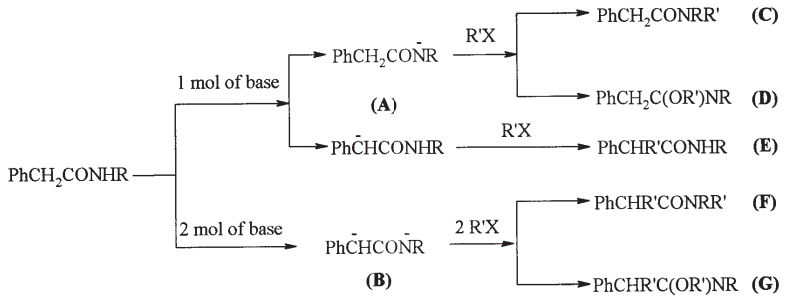


Scheme 1. Alkylation of N-substituted 2-phenylacetamides under basic conditions ((A)-monoanions, (B)-dianion, (C)-N-product, (D)-O-product, (E)-C-product, (F)-C,N-product, (G)-C,O-product).

In our study of the alkylation reaction of 2-phenylacetamides under basic conditions, different systems were used as reaction models. At the beginning, *N*-ethyl-2-phenylacetamide was alkylated under phase-transfer conditions using ethyl bromide,[4] *n*-butyl bromide,[5] allyl bromide[6] and benzyl bromide.[7] When ethyl bromide was used, the N-alkylation product was the only product at 60 ºC after 2.5 h.[4] With *n*-butyl bromide, besides the N-product, the C-product was also detected.[5] Under the same conditions, alkylation of *N*-ethyl-2-phenylacetamide with allyl and benzyl bromide led to the formation of N-, C- and C,N-product of alkylation.[6,7]

N-ethyl, *N*-*n*-butyl, *N*-*i*-butyl, *N*-*t*-butyl, *N*-cyclohexyl and *N*-phenyl-2-phenylacetamides were alkylated under the same conditions (PTC/OH) with ethyl bromide.[8] It was shown that the structure of the starting N-substituted 2-phenylacetamide determines the reactivity and the orientation in N- and O-alkylations.

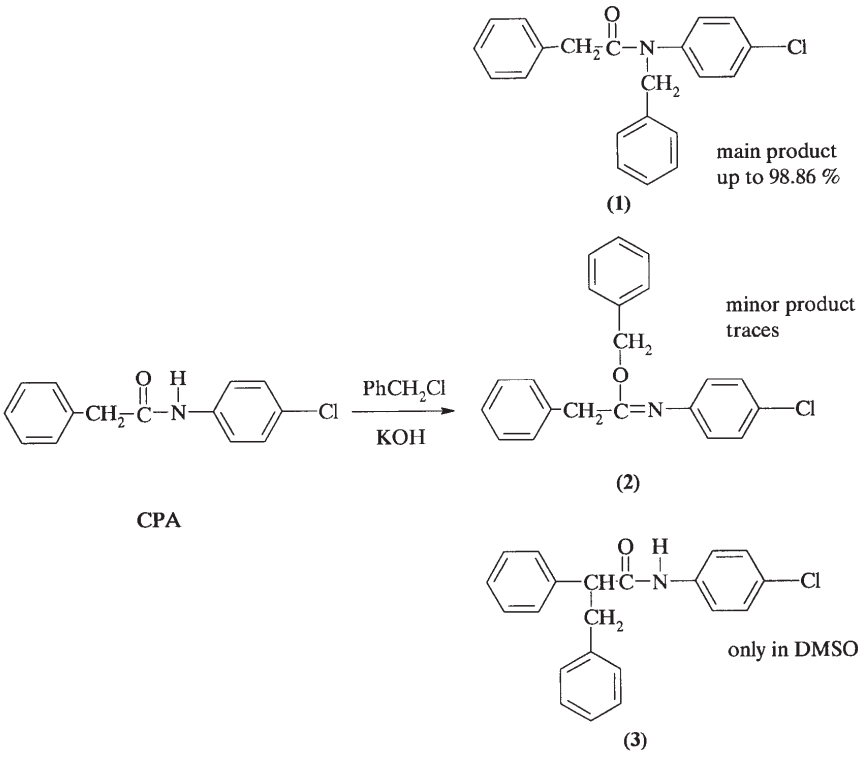
N-ethyl,[7] *N*-phenyl[9] and *N*-benzyl-2-phenylacetamides[10] were alkylated with benzyl chloride under basic conditions, both with and without a phase-transfer catalyst. The reactivity of the starting amides in the alkylation reaction was established to be: *N*-phenyl-2-phenylacetamides > *N*-ethyl-2-phenylacetamides > *N*-benzyl-2-phenylacetamides.

Recently, the benzylation of *N*-(4-nitrophenyl)-2-phenylacetamide[11] under basic condition was reported. It was found that *N*-(4-nitrophenyl)-2-phenylacetamide is, at 60 ºC in toluene, hexane and isooctane, more reactive, but less selective than *N*-phenyl-2-phenylacetamide.

In this paper, a study of the benzylation of *N*-(4-chlorophenyl)-2-phenylacetamide with benzyl chloride in the presence of powdered potassium hydroxide at different temperatures and ratios of reactants and solvents is reported. The reactions were also carried out in the presence of different phase-transfer catalysts in toluene at 60 ºC and at reflux temperature. The alkylation reaction of *N*-(4-chlorophenyl)-2-phenylacetamide was followed using gas chromatography. For the study of the reaction and in order to perform GC analysis, the starting amide as well as the N-, C- and O-products of alkylation were synthesized. On the basis of the obtained results, the reactivity and the orientation of the investigated amide in the alkylation reaction are discussed.

RESULTS AND DISCUSSION

In order to study the alkylation of *N*-(4-chlorophenyl)-2-phenylacetamide (CPA) with benzyl chloride in the presence of powdered potassium hydroxide, it was necessary to synthesize the starting amide as well as the expected products of alkylation. On the basis of expectations, the N- (**1**), O- (**2**) and C-product (**3**) of alkylation, *i.e.*, *N*-benzyl-*N*-(4-chlorophenyl)-2-phenylacetamide (**1**), the benzyl ester of phenylacetic acid, since the O-product (**2**) (iminoether) in contact with water gives an ester, and *N*-(4-chlorophenyl)-2,3-diphenylpropanamide (**3**) were synthesized. The structures of the starting amide and the expected products of alkylation under basic conditions are given in Scheme 2.



Scheme 2. The starting *N*-(4-chlorophenyl)-2-phenylacetamide (CPA) and the products of alkylation ((**1**)-N-product, (**2**)-O-product and (**3**)-C-product); the reaction conditions are given in Table I).

N-(4-Chlorophenyl)-2-phenylacetamide was alkylated with benzyl chloride in the presence of powdered potassium hydroxide in a solid-liquid system. The reactions were performed 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 and isooctane, the reactivity of the starting amide is up to 56.17 %. When toluene, as a slightly polar solvent, was used under the same conditions, the observed reactivity was almost the same (56.91 %). In DMSO, a polar solvent, the reactivity of CPA is increased up to 73.1 %. This in-

crease in reactivity can be explained by the basicity of the solvent, which promotes the formation of reactive anions, organic as well as inorganic. Dioxane, which is more polar and more basic than hydrocarbonic solvents but less polar and less basic than DMSO promotes the reaction to a very small extent (10.68 %) and presents the poorest solvent for the reaction. This observation is in agreement with previous results.[9–11]

TABLE I. The effect of solvents on the alkylation of *N*-(4-chlorophenyl)-2-phenylacetamide with benzyl chloride (amount of *N*-(4-chlorophenyl)-2-phenylacetamide 5 mmol; 10 ml of solvent; reaction time 4 h; reaction temperature 60 ºC)

Solvent	KOH/mmol	$PhCH_2Cl$/mmol	CPA/%	**1**/%	**2**/%	**3**/%	Other products/%
Hexane	5	5	43.83	54.08			2.09
Isooctane	5	5	51.67	46.39			1.94
Toluene	5	5	43.09	56.22			0.69
Toluene*	5	5	10.08	89.04	0.02		0.86
Toluene*	5	10	13.60	85.55	0.09		0.76
Toluene*	10	10	0.04	98.86	0.07		1.03
Dioxane	5	5	89.32	7.33	0.41		2.94
DMSO	5	5	26.90	64.61	0.15	2.05	6.29

* reflux

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

As far as the orientation of the benzylation reaction of CPA is concerned, it can be observed from Table I that under all the studied experimental conditions the N-product was the main product. The N-product was the only product at 60 ºC in hexane, isooctane and toluene. At reflux temperature in toluene, because of the increased reactivity of the starting amide, traces of the O-product were formed.

The highest reactivity in DMSO at 60 ºC led to the highest yield of the N-product in comparison to other solvents. On the other hand, the selectivity is lower in DMSO since besides the N-product, O- and C-products were also formed.

It would be expected that CPA should be more reactive than PPA since the inductive effect resulting because chlorine is an electron-acceptor favours the formation of the corresponding anion which then reacts with benzyl chloride. This is true for the reactions at 60 ºC (Table II). At reflux temperature, the reactivity, especially in the presence of higher initial amounts of potassium hydroxide and benzyl chloride, is almost the same. On the other hand, at 60 ºC NPA is more reactive than PPA but less reactive than CPA. The NPA anion should be formed easier than the CPA anion, but it seems

that the CPA anion reacts faster due to the delocalization of the negative charge in the NPA anion and also the positive resonance effect of the chlorine atom, which both influence the nucleophilicity of the reacting anions.

TABLE II. Comparative alkylation of *N*-(4-substituted phenyl)-2-phenylacetamides (SPA) with benzyl chloride in toluene (amount of SPA 5 mmol; 10 ml of toluene; reaction time 4 h)

SPA	Temperature °C	Mole ratio of SPA:KOH:benzyl chloride	SPA/%	(C)/%	(E)/%	(D)/%
PPA[a]			85.41	11.97		2.12
NPA[b]	60	1:1:1	63.91	30.47		6.17
CPA			43.9	56.22		
PPA[a]			20.65	78.78		2.12
NPA[b]	reflux	1:1:1	28.19	29.96	21.88	17.54
CPA			10.8	89.04		0.02
PPA[a]			0	89.09		
NPA[b]	reflux	1:1:2	33.5	35.33	12.96	16.37
CPA			13.6	85.55		0.09
PPA[a]			0	98.98		
NPA[b]	reflux	1:2:2	0.81	6.71	70.74	6.79
CPA			0.04	98.86		0.07

[a]Ref 9; [b]Ref 11.

When SPA is alkylated under basic conditions, an anion is formed first (equal amount of base and amide) (Scheme 1). The formed anion then participates in the substitution reaction with an alkyl halide. From the obtained results it can be concluded that the reactivities of the investigated SPAs are influenced by the reactivity of the formed anion (rate determining step or slow step) rather than its formation (fast step).

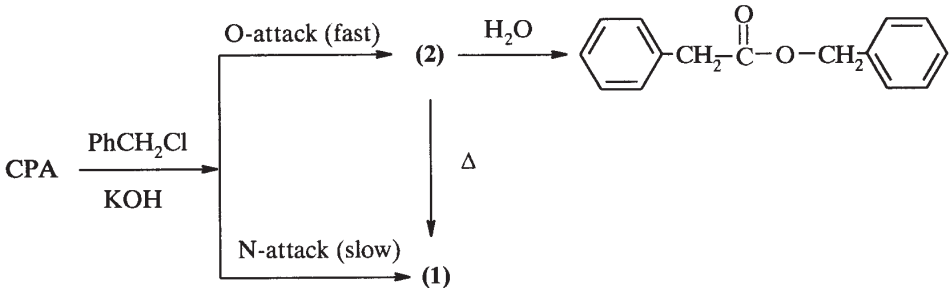
The selectivity of CPA in the reaction of benzylation is higher than that of NPA,[11] and the same as that of PPA.[9] When PPA or CPA react, the most nucleophilic site in the molecule is the nitrogen atom. However, the nitrogen atom in NPA is less nucleophilic due to resonance stabilization and thus other reactive centers, such as the α-carbon and oxygen are favored, which leads to a less selective alkylation.

The used phase-transfer catalysts catalyze the reaction of alkylation in all the investigated systems by increasing the reactivity of the starting CPA. At higher temperatures (reflux temperatures), the reactivity of CPA and the yield of the products of alkylation are almost the same as at 60 ºC. Basides the N-product, the O-product was also formed (Table III). The O-product is the kinetic product while the N-product is the thermodynamic product of alkylation.[12] The O-product is formed to a smaller extent also because it rearranges to the more stable N-product, which is the main product of alkylation (Scheme 3).

TABLE III. The effect of the catalyst structure on the alkylation of *N*-(4-chlorophenyl)-2-phenylacetamide with benzyl chloride in toluene (amount of *N*-(4-chlorophenyl)-2-phenylacetamide 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	CPA/%	(**1**)/%	(**2**)/%	Other products %
TEA	Br	18.65	78.92	0.19	2.24
TBA	Cl	13.99	83.72	0.17	2.12
	Br	15.66	82.98	0.07	1.29
	I	16.15	82.39	0.06	1.40
	HSO_4	19.60	78.70	0.12	1.58
TEBA	Br	13.96	84.69	0.07	1.28
	Br*	14.37	82.94	0.41	2.28

*reflux



Scheme 3. The rearrangement of (**2**) to (**1**) and the hydrolysis of (**2**).

The order of the influence of the counter ions in the TBA series on the reactivity is Cl > Br > I > HSO_4.

It is very hard to discuss the mechanism of the phase-transfer catalysed reaction of alkylation on the basis of the obtained results since according to the rules proposed by Rabinowitz *et al.*[13] TBABr is a slightly better catalyst than TEABr which leads to the conclusion that the reaction proceeds by the extraction mechanism. On the other hand, TEBABr is an even better catalyst than TBABr, and TEBABr is a catalyst which operates well in reactions which proceed by the interfacial mechanism.[13]

Of the studied catalysts, TBACl and TBABr were the best for the investigated reaction.

EXPERIMENTAL

Materials

The starting CPA was obtained by reaction of phenylacetyl chloride and 4-chloroaniline:[9] ν_{max}(KBr): 3280, 3061, 3027, 2916, 2865, 1661; ^{1}H-NMR (δ ppm) ($CDCl_3$) = 3.67 (2H, *s*, CH_2–Ph), 6.98–7.24 (9H, *m*, Ph+disPh); m.p. = 162–164 ºC.

N-Benzyl-*N*-(4-chlorophenyl)-2-phenylacetamide was synthesized by the same method from phenylacetyl chloride and *N*-benzyl-4-chloroaniline:[9] ν_{max}(KBr): 3082, 3028, 2962, 2858, 1645 cm^{-1};

^{1}H-NMR (δ ppm) ($CDCl_3$) = 3.48 (2H, *s*, CH_2–CO), 4.96 (2H, *s*, CH_2–Ph), 6.68–6.88 (2H, *m*, Ph–N), 6.94–7.40 (12H, *m*, 2×Ph+Ph–Cl); m.p. = 69–71 ºC.

N-Benzyl-4-chloroaniline was obtained by alkylation of the corresponding 4-chloroaniline with benzyl chloride in the presence of $NaHCO_3$ and TEBABr using the following procedure: 0.1 mol of 4–chloroaniline, 62.5 mmol of $NaHCO_3$, 5 mmol of TEBABr and 7.5 ml of water were mixed and heated in a boiling water bath. Then 50 mmol of benzyl chloride was added dropwise to the stirred mixture. After 5 h of heating and stirring, the reaction mixture was cooled to room temperature and water was added. The layers were separated and the aqueous layer extracted with diethyl ether. The organic layers were combined, dried over anhydrous sodium sulphate and product isolated by distillation: ν_{max}(neat): 3427, 3062, 3028, 2922, 2852, 1600 cm^{-1}; ^{1}H-NMR (δ ppm) ($CDCl_3$) = 3.80 (1H, *s*, NH), 4.25 (2H, *s*, CH_2–Ph), 6.50 (2H, *d*, Ph–N), 7.10 (2H, *d*, Ph–Cl), 7.33 (5H, *s*, Ph–CH_2); b.p. = 135–142 ºC (0.1 mbar).

N-(4-chlorophenyl)-2,3-diphenylpropanamide was prepared from 2,3-diphenylpropanoyl chloride and 4-chloroaniline:[9] ν_{max}(KBr): 3285, 3061, 3027, 2933, 2858, 1652 cm^{-1}; ^{1}H-NMR (δ ppm) ($CDCl_3$) = 2.90–3.20 (2H, *m*, CH_2), 3.65 (1H, *d*, CH), 7.08–7.42 (14H, *m*, 2×Ph+disPh); m.p. = 168–170 ºC. 2,3-Diphenylpropanoyl chloride was synthesized by the reaction of 2,3-diphenylpropanoic acid and thionyl chloride.[9,14] 2,3-Diphenylpropanoic acid was obtained by the hydrolysis of 2,3-diphenylpropanenitrile, which was obtained by the reaction of phenylacetonitrile and benzyl chloride.[9,15]

The benzyl ester of PAA was prepared from benzyl chloride and phenylacetic acid, in the presence of 40 % sodium hydroxide and tetrabutylammonium hydrogensulfate.[9]

The other materials were obtained commercially.

Methods

Typical procedure for benzylation of CPA. A mixture of powdered KOH (5 mmol), CPA (5 mmol), benzyl chloride (5 mmol), PTC catalyst if used (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 methylene chloride (25 ml). Samples were analysed by GC on an OV-1 packed column (Varian 1440 (FID) with a Varian integrator 4270) using an internal standard.

All given results were obtained from at least two experiments.

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Abbreviations:

PAA	phenylacetic acid
SPA	*N*-(4-substituted phenyl)-2-phenylacetamide
PPA	*N*-phenyl-2-phenylacetamide
NPA	*N*-(4-nitrophenyl)-2-phenylacetamide
CPA	*N*-(4-chlorophenyl)-2-phenylacetamide
$TBHSO_4$	tetrabutylammonium hydrogen sulfate
TEABr	tetraethylammonium bromide
TBABr	tetrabutylammonium bromide
TBACl	tetrabutylammonium chloride
TBAI	tetrabutylammonium iodide
TEBABr	triethylbenzylammonium (TEBA) bromide
DMSO	dimethyl sulfoxide

ИЗВОД

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

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N-(4-хлорфенил)-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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