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Benzylation of *N*-benzyl-2-phenylacetamide

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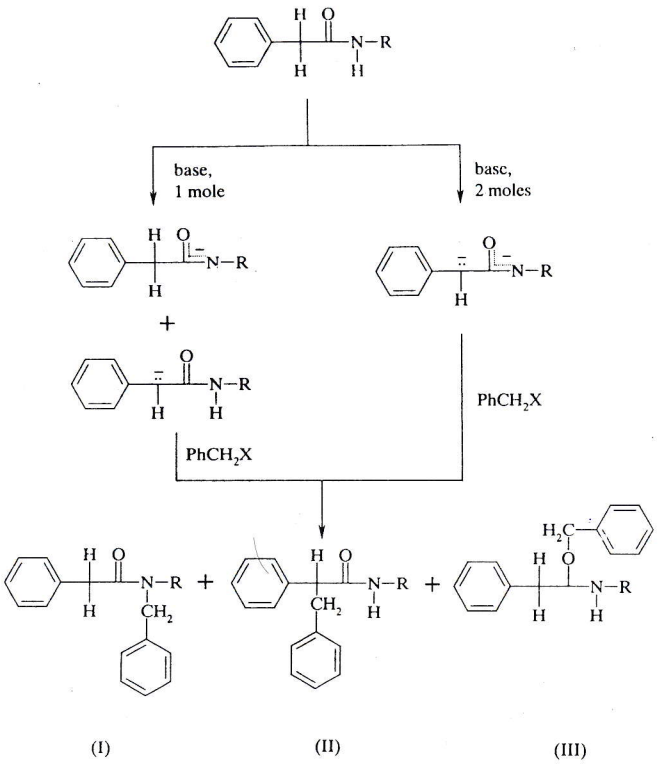
N-Benzyl-2-phenylacetamide was used as a model for the study of the alkylation of *N*-substituted 2-phenylacetamides with benzyl chloride in the presence of powdered KOH. The reactions were carried out in the presence and absence of phase-transfer catalysts, in order to establish any possible difference in the reaction products. Various phase-transfer catalysts, solvents and temperatures were used. A comparative study with the benzylation reaction of other *N*-substituted-2-phenylacetamides is presented. The observed lower reactivity of *N*-benzyl-2-phenylacetamide in comparison with the reactivity of *N*-ethyl-2-phenylacetamide and *N*-phenyl-2-phenylacetamide can be explained in terms of steric and polar effects.

Key words: alkylation, *N*-alkylation, *C*-alkylation, *O*-alkylation, *N*-substituted 2-phenylacetamides, phase-transfer catalysis.

N-Substituted 2-phenylacetamides have been alkylated using various alkylating agents under different conditions.[1-7] Previously *N*-phenyl-2-phenylacetamide (PPA) was also alkylated.[6,7] Work *et al.*[6] showed that when PPA is alkylated with benzyl chloride in the presence of sodium amide, only the *C*-product is formed. Torrossian *et al.*[7] alkylated PPA with benzyl chloride under phase-transfer conditions, and obtained 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.[8] We showed earlier[9] that, when PPA is alkylated with benzyl chloride, the *N*-product was the main product in all reactions and in most reactions the only product.

It is known[6,10] that when a *N*-substituted phenylacetamide is alkylated under basic conditions, an anion or dianion is initially formed (with equal amounts of base and amide) due to the acidity of the nitrogen atom hydrogen and of the $\alpha_{c=o}$-carbon hydrogen. This provides the possibility for the formation of different products of alkylation due to the formed anion or dianion (*N*-(I), *C*-(II), *O*-(III)products) (Scheme 1).

In order to study the alkylation reaction of *N*-benzyl-2-phenylacetamide (BPA) with benzyl chloride under basic conditions with and without phase-transfer catalyst, we alkylated BPA with benzyl chloride using powdered potassium hydrox-



Scheme 1. The reaction products of the alkylation of *N*-substituted 2-phenylacetamides under basic conditions (*N*-product (I), *C*-product (II) and *O*-product (III); R = ethyl, phenyl, benzyl; X=Cl).

ide as the base in different solvents and at various temperatures, with equimolar amounts of base and benzyl chloride, as well as with an excess of each of them. The reactions were also carried out in the presence of different phase-transfer catalysts in the non-polar solvent toluene, at 60 °C.

EXPERIMENTAL

Materials

The starting *N*-benzyl-2-phenylacetamide was obtained by the reaction of phenylacetyl chloride and benzylamine:[1a] ν_{max}(KBr): 3315, 3065, 3015, 2910, 1640, 1450 and 700 cm^{-1}; ^{1}H-NMR-δ_{ppm} (90 MHz; $CDCl_3$; Me_4Si): 3.50 (4H, *s*, 2×CH_2Ar), 4.34 (2H, *m*, N-CH_2), 5.85 (1H, *s*, NH), 7.25 (10H, *s*, 2×ArH); m.p. = 116–119 °C, GC purity = 99.9%. *N,N*-Dibenzyl-2-phenylacetamide was obtained by the same method[1a] from phenylacetyl chloride and *N,N*-dibenzylamine: ν_{max}(KBr): 3060, 3040, 2940, 1650 and 1490 cm^{-1}; ^{1}H-NMR-δ ppm (90 MHz; $CDCl_3$; Me_4Si): 3.78 (2H, *s*, –CH_2–CO–), 4.40–4.60 (4H, *def.d*, 2×N–CH_2), 7.30 (15H, *s*, 3×ArH); m.p. = 22–25 °C, GC purity = 99.8%. *N*-Benzyl-2,3-diphenylpropanamide was similarly obtained[1a] from 2,3-diphenylpropanoyl chloride and benzylamine: ν_{max}(KBr): 3285, 3050, 3025, 2915, 1640, 1450 and 700 cm^{-1}; ^{1}H-NMR-δ_{ppm} (90 MHz; $CDCl_3$; Me_4Si): 3.00 (2H, *m*, –CH_2–CO–), 3.60 (1H, *m*, –CH–), 4.22 (2H,*m*, N–CH_2), 6.12 (1H, *s*, –NH–), 7.20–7.30 (15H, *def.s*, 3×ArH); mp=95–98 °C, GC purity = 91.5%. 2,3-Diphenylpropanoyl

chloride was obtained by the reaction of 2,3-diphenylpropanoic acid and thionyl chloride.[8,11] 2,3-Diphenylpropanoic acid was obtained by the hydrolysis of 2,3-diphenylpropanenitrile, which was obtained by the reaction of phenylacetonitrile and benzyl bromide.[8,12]

The *n*-benzyl ester of PAA was prepared from benzyl chloride and phenylacetic acid, in the presence of 40 % sodium hydroxide and tetrabutylammonium hydrogensulfate.[8]

Tetrabutylammonium iodide and tetraethylammonium bromide were prepared from the corresponding trialkylamines and alkyl halide.[13]

The other materials were obtained commercially.

Methods

N-Benzylation of *N*-benzyl-2-phenylacetamide: Typical procedure.

A mixture of powdered KOH (5 mmol), *N*-benzyl-2-phenylacetamide (5 mmoles), benzyl chloride (5 mmol), PTC catalyst (0.5 mmoles, if used), 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 °C) at 60 °C for 4 h. The reaction was stopped by the addition of water (100 ml), the layers were separated and the water layer extracted with methylene chloride (25 ml). *n*-Hexadecane (0.3 g) was added and sample was analyzed by GC on a DB-1 capillary column (Varian 3400 with a Varian integrator 4270) using *n*-hexadecane as an internal standard.

All given results were obtained from at least two similar experiments (±5% error).

RESULTS AND DISCUSSION

We showed earlier that when *N*-substituted-2-phenylacetamides were alkylated with ethyl, *n*-butyl and benzyl halides,[1c,3-5] different products were obtained. As a sequence to the reactions performed earlier,[5,9] we performed the alkylation of BPA with benzyl chloride in the presence of powdered potassium hydroxide in a solid-liquid system both without and with a phase-transfer catalyst.

In the first part of the experimental work, the alkylations were carried out by varying the quantities of used benzyl chloride (Table I). The reactions were performed at 30 °C and at the reflux temperature in toluene as solvent. One can see from the results that no reaction products were detected when equimolar quantities of reactants were employed at 30 °C while at the reflux temperature the *N*-product was formed as the only product. An increase in the reactivity of BPA was observed both at low and high temperature when an excess of benzyl chloride was used.

When the amount of used potassium hydroxide was varied (in toluene) at 30 °C, no increase in reactivity was detected with an excess of potassium hydroxide, while at 60 °C, both the *N*- and the *O*-product were detected. At reflux temperature, increasing the amount of potassium hydroxide resulted in an increase in the reactivity of the BPA, with only the *N*-product being formed. The formation of the *O*-product versus the *N*-product can be explained in terms of kinetic and thermodynamic products of the reaction.[4,10] Since the reaction temperature was not too high (60 °C) to promote the formation of only the thermodynamic product of the reaction (the *N*-product) the kinetic product was also formed (the *O*-product).

The alkylation reactions of BPA were carried out in different solvents at different temperatures (Table I). One can see from the obtained results that in non-polar solvent,

in almost all cases, only the *N*-product was formed. The obtained results for the reaction in polar solvents are as before.[4,5] In polar basic solvent DMSO, the *C*-product and the *O*-product were formed in addition to the *N*-product, which was the main product. This increase in reactivity can be explained by the basicity of solvent which promote the formation of reactive anions or by the change in the mechanism of the reaction (S_N1 to S_N2).[14] As can be seen, increasing the temprature lowers the reactivity of BPA and the yield of the products, especially the *N*-product, due to the decreased solvation of reacting species. Less basic and less polar solvent dioxane[14] do not promote the reaction neither by increasing number of anions nor by changing the mechanisms of the reaction. Concerning the *N*-product, nonpolar solvents, high temperatures and excess of base and benzyl chloride favor the reaction. At reflux temperature with an equimolar ratio of the reactants the highest yields of the *N*-product were obtained in isooctane and then in toluene, indicating that at high temperatures less polar solvents favor *N*-alkylation. Concerning solvents the order for *N*-alkylation (equimolar ratio of reactants, reflux temperature) is: isooctane > toluene > DMSO.

TABLE I. The influence of the solvent, temperature and ratio of reactants of the BPA alkylation reaction with benzyl chloride in the presence of powdered KOH (10 ml of solvent; reaction time 4 h)

Solvent	KOH (mol)	$PhCH_2Cl$ (mol)	temp. (°C)	BPA (%)	*N*-product (%)	*C*-product (%)	*O*-product (%)	Other products (%)
Hexane	5	5	60	99.24				0.76
Isooctane	5	5	60	99.98				0.02
	5	5	reflux	57.70	41.18			1.04
Toluene	5	5	30	99.14				0.86
	5	10	30	95.80	2.80			1.40
	15	5	30	95.96				4.04
	5	5	60	98.17				1.83
	20	5	60	90.30	2.53		1.76	5.41
	5	5	reflux	82.40	16.66			0.94
	5	10	reflux	69.82	27.92			2.26
	10	10	reflux	54.42	43.37			2.21
Dioxane	5	5	30	99.23				0.77
	5	5	60	99.01				0.99
	5	5	reflux	99.50				0.50
DMSO	5	5	30	69.26	27.63	1.44	0.71	0.96
	5	5	60	56.82	22.54	17.50		3.14
	5	5	reflux	80.99	8.53		1.47	9.01

When BPA was alkylated in the presence of different phase-transfer catalysts, the main product was again found to be the *N*-product, while the *C*-product was found in only three cases (tetrabutylammonium (TBA) bromide and chloride, and triethylbenzylammonium (TEBA) bromide, Table II). All the used phase-transfer

catalysts catalyze the reaction, while at reflux temperature the yield of the *N*-product of alkylation is almost as high as in the non-catalyzed reaction with an excess of base and benzyl chloride. The nature of the counter ion has influence on the yield of the *N*-product, but the more important fact is that more organophilic quats give better results. Triethylbenzylammonium (TEBA) bromide, which is not usually good for solid-liquid phase-transfer systems, gave good result. The order of the reactivity of the phase-transfer catalysts for *N*-alkylation is: TBAI > TBACl, 18-crown-6 ether> TEBABr, TBABr> TEABr > $TBAHSO_4$. On the other hand when tetrabutylammonium (TBA) bromide was used, the highest reactivity of BPA was achieved. The order of the influence of anions is: $I^- > Cl^- > Br^- > HSO_4^-$. The obtained results indicate that the phase-transfer catalyzed reactions proceeds by the extraction mechanism.[15]

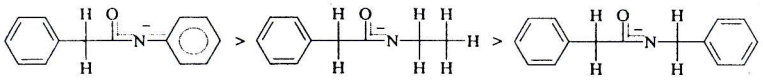
TABLE II. The effect of the catalyst structure on the alkylation of BPA with benzyl chloride in toluene (amount of BPA 5 mmol; amount of benzyl chloride 5 mmol; amount of KOH 5 mmol; amount of catalyst 0.5 mmol; 10 ml of toluene; reaction temperature 60 °C; reaction time 4 h)

quat or catalyst	Counter ion	BPA (%)	*N*-product (%)	*C*-product (%)	*O*-product (%)	Other products (%)
Et_4N^+	Br	63.38	21.49			15.13
Bu_4N^+	Cl	60.13	30.83	4.71		4.33
	Br	50.04	23.87	21.36		4.73
	I	56.19	38.82			4.99
	HSO_4	76.73	17.97			5.30
	HSO_4*	53.30	37.12			9.58
18-crown-6 ether		60.13	30.85			9.02
TEBA	Br	67.74	23.19	5.47		3.60

*reflux

The low reacticity of *N*-benzyl-2-phenylacetamide (BPA), compared to that of *N*-phenyl-2-phenylacetamide (PPA) and *N*-ethyl-2-phenylacetamide (EPA), can be explained in terms of steric and polar effects. The order of reactivity of these three amides is: PPA > EPA > BPA. Since the *N*-product is the main product in most of the performed alkylation reactions,[5,9] the order of reactivity can be explained in terms of the formation of the *N*-product, the formation of which as the main product in all the reactions indicates that the most nucleophilic site in the molecule of *N*-substituted 2-phenylacetamides is the anion formed by the cleavage of the nitrogen hydrogen.[9] As presented in Scheme 2, the nature of the substituent on the nitrogen atom has an important influence on the reactivity of the amide. The formed amide anion is stabilized by resonance with the carbonyl group. If an alkyl group is attached to the nitrogen atom, the positive inductive effect destabilizes the formed anion. An aryl group, if attached to the nitrogen atom, stabilizes the anion by resonance. Thus, *N*-substituted-2-phenylacetamides which have an aryl group as substituent are

more reactive then the corresponding alkyl substituted compounds because their anion is more readily formed having less energy. The steric effect is important when the benzyl group is compared to the ethyl group (Scheme 2). Since the benzyl group has no resonance effect, this group being bulkier hinders the substitution reaction. Thus, EPA is more reactive then BPA, but less reactive then PPA.



(I) (II) (III)

Scheme 2. The order of reactivity – structure of the formed anions of PPA (I), EPA (II) and BPA (III)

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Abbreviations.

EPA	*N*-ethyl-2-phenylacetamide
PPA	*N*-phenyl-2-phenylacetamide
BPA	*N*-benzyl-2-phenylacetamide
$TBHSO_4$	tetrabutylammonium hydrogen sulfate
TEABr	tetraethylammonium bromide
TBABr	tetrabutylammonium bromide
TBACl	tetrabutylammonium chloride
TBAI	tetrabutylammonium iodide
TEBABr	triethylbenzylammonium (TEBA) bromide
DMSO	dimethylsulfoxide

И З В О Д

БЕНЗИЛОВАЊЕ *N*-БЕНЗИЛ-2-ФЕНИЛАЦЕТАМИДА

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N-Бензил-2-фенилацетамид је употребљен као модел за испитивање реакције алкиловања *N*-супституисаних 2-фенилацетамида бензилхлоридом у присуству спрашеног калијум-хидроксида. Испитан је утицај температуре, растварача и почетног односа реактаната на реакцију. Такође су употребљени и међуфазни катализатори. Уочена је мала реактивност испитиваног система и добијени резултати су упоређени са претходно испитиваним системима.

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