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The Reaction of Phenylacetonitriles with Benzaldehydes in Hexamethylphosphoric Triamide Solution Containing the Sodium Salt of α,α-Dimethylbenzyl Hydroperoxide[1,2)]

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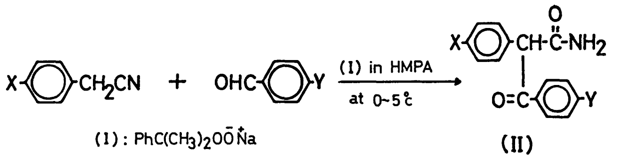
Synopsis. Treatment of phenylacetonitriles with *p*-substituted benzaldehydes in hexamethylphosphoric triamide solution containing the sodium salt of α,α-dimethylbenzyl hydroperoxide gave α-benzoyl-α-phenylacetamides as major products.

The reaction of phenylacetonitriles with *p*-substituted benzaldehydes was carried out in hexamethylphosphoric triamide (HMPA) solutions containing the sodium salt of α,α-dimethylbenzyl hydroperoxide (I). α-Benzoyl-α-phenylacetamide derivatives (II) were obtained as major products (Scheme 1 and Table 1). However, the treatment of diphenylacetonitrile and α-phenylpropionitrile having substituents in the α-position with *p*-anisaldehyde gave oxidation products of the starting materials, but not the corresponding benzoyl-acetamides. I has both strongly basic and oxidative properties. However, no report seems to have been made on the use of these properties of I in reactions. The properties were found to act effectively in an HMPA solution.



Scheme 1.

Results and Discussion

The reactions of phenylacetonitriles with *p*-substituted benzaldehydes were carried out in HMPA solutions in the presence of I, giving benzoyl-acetamides (II) in 40—55% yield (Table 1). The reaction of phenylacetonitrile with *p*-nitrobenzaldehyde, however, gave various products, but no product of type II. In all cases except the case of *p*-nitrobenzaldehyde, the color of the reaction solution was reddish orange. In the case of *p*-nitrobenzaldehyde, it was purple-blue, characteristic of nitrobenzene radical anions.[3)]

The treatment of diphenylacetonitrile with *p*-anisaldehyde gave oxidation products, benzophenone and *p*-anisic acid. The yield of benzophenone was 78%. The expected benzoyl-acetamide was not obtained. Likewise, the treatment of α-phenylpropionitrile with *p*-anisaldehyde gave acetophenone and *p*-anisic acid, but not the corresponding benzoyl-acetamide either.

The mechanism for the formation of the benzoyl-acetamides (II) is assumed as follows. The acidic α-hydrogen of phenylacetonitrile is abstracted by I and the α-cyanophenylmethanide ion thus formed nucleophilically attacks the carbonyl group of benzaldehydes to give III (Eqs. 1 and 2, Scheme 2). Intermediate III is oxidized by the hydroperoxide shown in Eq. 1 or by I to give α-benzoyl-α-phenylacetamide II. The problem is how III is oxidized to give benzoyl-acetamide (II). The reaction of 2-cyano-1,2-diphenylethanol (III′), which is the protonated form of the hypothetical intermediate (III), was assumed to react with I. However, various attempts to synthesize III′ were unsuccessful. It was presumed that the cyano group of α-cyanodeoxybenzoin (V) (Eq. 2) is oxidized by I. However, when α-cyanodeoxybenzoin (V) synthesized[4)] was treated with I, no oxidation of the cyano group took place. When (*E*)-α-phenylcinnamonitrile (IV) obtained as a minor product in *ca.* 10% yield was treated with I, the corresponding benzoyl-acetamide (II) was obtained in 39% yield. The treatment of phenylacetonitrile and benzaldehyde using a base such as sodium hydroxide or sodium ethoxide has been reported to give IV in 87—97% yield.[10)] The low yield of IV in the present work is due to the further conversion of IV into benzoyl-acetamide (II). The formation of the benzoyl-acetamide (II) is accounted for by both the nucleophilic reaction of I to the double bond, and the hydrolysis of the cyano group. The nucleophilic reaction is most likely caused by the complex of ROONa (I) with ROOH produced (Eq. 1), which is more reactive than ROONa itself.[11)] The mechanism (Scheme 2) is further supported by the fact that the reaction with use of diphenylacetonitrile or α-phenylpropionitrile, which cannot form an intermediate such as IV, gave no products corresponding to the compound II.

The mechanism by which the reaction with use of diphenylacetonitrile or α-phenylpropionitrile gave the corresponding ketone is shown in Eqs. 3 and 4 (Scheme 2). The nucleophilic addition of a carbanion to a carbonyl group is thought to be a reversible process.[5)] Since VI cannot undergo a process leading to the formation of α-phenylcinnamonitrile, the oxidation process to give benzophenone or acetophenone would proceed efficiently.

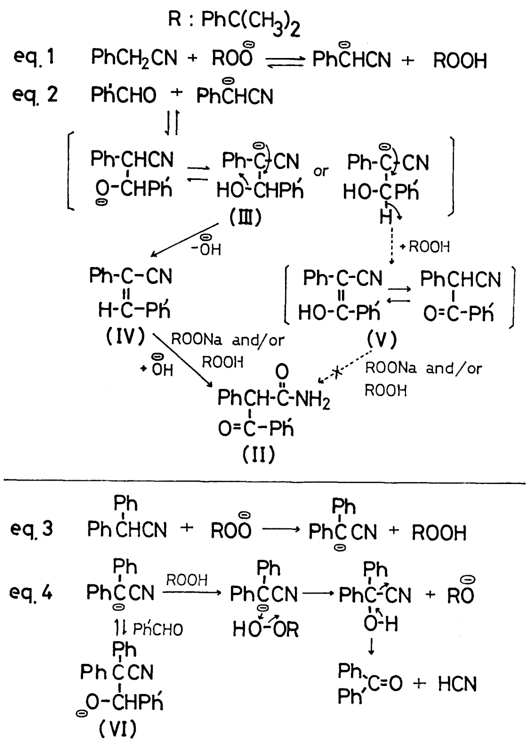
Experimental

All the melting points were uncorrected. The sodium salt of α,α-dimethylbenzyl hydroperoxide (I) was prepared from technical-grade α,α-dimethylbenzyl hydroperoxide according to the procedure of Belyaev and Nemtsov.[6)] The peroxide content of I was estimated to be 65% by iodometric titration. *p*-Tolylacetonitrile and *p*-chlorophenylacetonitrile were synthesized by the reaction of *p*-methylbenzyl and *p*-chlorobenzyl chlorides with sodium cyanide.[7)]

Table 1. Yields and physical data of new compounds (IIa—IIg)[a)]

Compd	Yield %	Mp °C	IR(KBr), cm^{-1}		UV(EtOH)		Mass $M^{+\cdot}$	NMR, δ units (DMSO-d_6)	Calcd(Found)%		
			ν_{NH}	ν_{CO}	λ nm	$\varepsilon \times 10^{-4}$			C	H	N
IIa X=H Y=OCH$_3$	41	181— 181.5	3400 3300 3150	1690 1660	206 235	1.52 1.88	269	7.61(2H, m), 7.5—7.3(7H, m), 6.91(2H, d, J=9 Hz), 4.20(1H, s), 3.79(3H, s)	71.36 (71.47)	5.61 (5.55)	5.20 (5.15)
IIb X=H Y=CH$_3$	55	181— 182	3400 3250 3150	1690 1660	205 236	2.39 2.18	253	7.61(2H, m), 7.5—7.0(9H, m), 4.15(1H, s), 2.30(3H, s)	75.87 (75.82)	5.97 (5.97)	5.53 (5.49)
IIc[b)] X=H Y=H	45	205— 207	3400 3250 3150	1680 1660	206 226	2.00 1.99	239	7.60(2H, b-m), 7.37(10H, s-like), 4.28(1H, s)	75.30 (75.23)	5.48 (5.51)	5.85 (5.82)
IId X=H Y=Cl	43	189.5 —190	3400 3300 3200	1660 (broad)	205 230	2.56 2.35	273	7.65(2H, b-m), 7.5—7.2 (9H, s-like), 4.30(1H, s)	65.82 (65.96)	4.42 (4.35)	5.12 (5.25)
IIf X=CH$_3$ Y=OCH$_3$	37	192— 193	3350 3260 3150	1690 1660	205 236	2.39 2.18	283	7.55(2H, s-like), 7.5—7.1(6H, m), 6.85(2H, d, J=9 Hz), 4.10(1H, s), 3.75(3H, s), 2.30(3H, s)	72.06 (72.35)	6.05 (6.03)	4.94 (4.88)
IIg X=Cl Y=OCH$_3$	40	211— 212	3370 3260 3150	1660 (broad)	211 237	2.10 2.52	304	7.70(2H, m), 7.6—7.2(6H, m), 6.85(2H, d, J=9 Hz), 4.25(1H, s), 3.75(3H, s)	63.27 (63.16)	4.65 (4.46)	4.61 (4.55)

a) The product corresponding to IIe (X=H, Y=NO_2) was not obtained. b) The compound (IIc) is a known compound. However, all its physical data are given since the melting point differs from that (178 °C) reported.[9)]



Scheme 2.

α-Cyanopropionitrile was prepared by the reaction of phenylacetonitrile with methyl bromide.[8)]

Synthesis and Physical Properties of II. Into a 100-ml four-necked flask equipped with a thermometer and inlet and outlet tubes for nitrogen gas was placed 5.36 g (0.02 mol) of I dissolved in 25 ml of HMPA. To the solution maintained at 0—5 °C was added a mixture of 0.585 g (0.005 mol) of phenylacetonitrile and 0.682 g (5.5 mmol) of *p*-anisaldehyde in 5 ml of HMPA under nitrogen atmosphere. The mixture was stirred at 0—5 °C for 4 h and then poured into an aqueous solution of ammonium chloride . The aqueous layer was extracted several times with ether and then with benzene (*ca.* 200 ml each). The combined extracts were washed with water and dried over anhydrous sodium sulfate. After the solvents had been evaporated, compound IIa was separated as white crystals and recrystallized from benzene. Other acetamides (IIa—g) except IIe were prepared in a similar way. Their structures were confirmed by UV and IR spectra, MS and elementary analyses (Table 1).

α-Cyanodeoxybenzoin (V). The benzoin was synthesized by a modification of the procedure of Coan and Becker[4)] and recrystallized from ethanol; mp 93—94.5 °C (lit,[9)] 90 °C), MS: M^+ 221, IR(KBr): νC=O 1690 cm^{-1}, νCN 2250 cm^{-1}, UV: $\lambda_{\max}^{\mathrm{EtOH}}$ 292 nm $\varepsilon = 1.25 \times 10^4$. The benzoin (0.553 g, 2.5 mmol) was treated with (I) (2.68 g, 2.5 mmol) dissolved in 15 ml of HMPA. However, no reaction took place, most of V being recovered.

(E)-*α-Phenylcinnamonitrile (IVc).* The physical properties of IVc (mp 83—84 °C), isolated together with the benzoyl-acetamide (IIc), agreed with those (mp 86 °C) of the known sample synthesized according to the procedure of Wawzonek and Smolin.[10)] The cinnamonitrile (0.683 g, 3.3 mmol) was treated with I (3.57 g, 13 mmol) dissolved in 20 ml of HMPA at 0—5 °C for 4 h. The corresponding benzoyl-acetamide (IIc) was obtained in 39% yield.

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