ISSN 1070-3632, Russian Journal of General Chemistry, 2010, Vol. 80, No. 4, pp. 776–780. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © Yu.V. Popov, T.G. Korchagina, V.S. Kamaletdinova, 2010, published in Zhurnal Obshchei Khimii, 2010, Vol. 80, No. 4, pp. 614–618.

Synthesis of Nitriles Containing 3-Phenoxyphenyl Fragment

Yu. V. Popov, T. G. Korchagina, and V. S. Kamaletdinova

Volgograd State Technical University, pr. Lenina 28, Volgograd, 400131 Russia
e-mail: viktori_2008@bk.ru

Received June 16, 2009

Abstract—Reactions of the aldol-crotonic condensation, acylation of acetonitrile, and addition of amine to the activated double bond of acrylonitrile in the series of diphenyl oxide derivatives are studied. Effective procedures for preparing the nitriles containing diphenyl oxide fragment like 3-(3-phenoxyphenyl)-propenonitrile, 3-(3-phenoxyphenyl)-2-butenonitrile, 3-phenoxybenzoylacetonitrile, 3-(3-phenoxyphenyl)-propionitrile, and 3-phenoxybenzylamino)propionitrile are developed.

DOI: 10.1134/S107036321004016X

Diphenyl oxide derivatives containing various functional groups present significant practical interest. These compounds were used for the first time for the introduction of diphenyl oxide fragment in the molecule of cyclopropanecarboxylic acid derivatives to improve photochemical stability of synthetic insecticides (pyrethroids) which are the analogs of natural insecticides, pyrethrins. It occurred however that pyrethroids exhibit also the physiological activity. For example, permethrin, (3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate, a mixture of *cis*- and *trans*-isomers (3:1), and phenothrin, (3-phenoxyphenyl)methyl-2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate, are used as medicines exhibiting antiparasite, antipedicular, insecticide, and ovocide pharmacological activity [1].

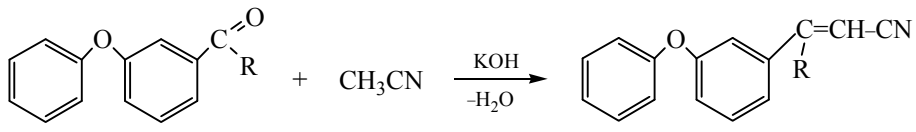
It is known also that phenoxyphenylacetylenes prepared on the basis of 1-(2-methyl-4-phenoxyphenyl)ethanone and 1-(3-phenoxyphenyl)ethanone are used as antithrombic, antiseptic, antipyretic, and analgetic drugs [1].

Great interest in the series of functionalized diphenyl oxide derivatives present the nitriles containing another functional groups in the side chain. These compound exhibit various types of biological activity and may serve also as the starting substances for the synthesis of derivatives possessing medico-biological activity.

Recently synthetic procedure for preparing 3-phenoxybenzonitrile was developed [3], and on its basis the corresponding nitro- and bromoderivatives were prepared [4].

Diphenyl oxide-based nitriles containing the unsaturated bond in the side chain present great interest in the organic synthesis because they may take part in the reactions proceeding by the nitrile group as well as by the double bond.

Such compounds are 3-(3-phenoxyphenyl)-2-acrylonitrile **III** and 3-(3-phenoxyphenyl)-2-butenonitrile **IV** which we prepared by the reaction of 3-phenoxybenzaldehyde **I** or 3-phenoxyphenyl methyl ketone **II** with acetonitrile according to the following scheme.



I, II **III, IV**

R = H, CH_3.

Reaction was carried out in acetonitrile in the presence of potassium hydroxide at 80–82°C at the carbonyl compound, acetonitrile, and potassium hydroxide molar ratio 1:(20–22):1.

The reaction was carried out under a large excess of acetonitrile. Potassium hydroxide was dissolved in it under nitrogen. Under the action of base the acetonitrile was deprotonated to form carbanion which reacts with the carbonyl compound added to the reaction mixture by portions. The cyanhydrine formed eliminates the molecule of water to give the unsaturated nitrile. The formation of ester according to Tishchenko process was not observed because under the above-described reaction conditions the hydride ion transfer did not take place.

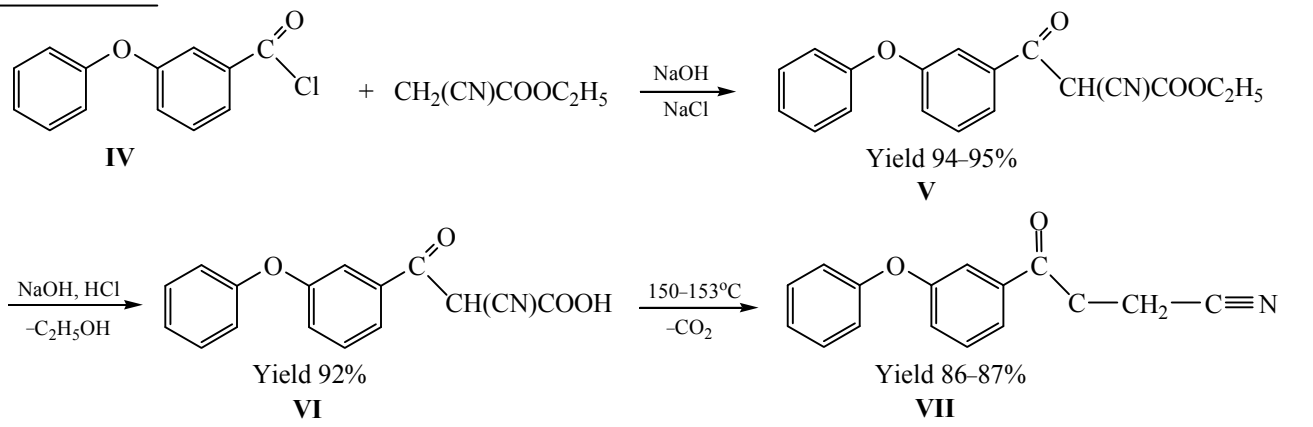
Our studies showed that the optimum and technologically feasible reaction procedure should take 10 min in the case of 3-phenoxybenzaldehyde 3 h in the case of 3-phenoxyphenylmethylketone at the indicated molar ratio of the carbonyl compound, acetonitrile, and potassium hydroxide. Smaller acetonitrile excess leads to some decrease in the yield of unsaturated nitriles (40–42%) due to the incomplete conversion of the carbonyl compound and the formation of a heterophase system because of the incomplete dissolution of potassium hydroxide in acetonitrile. Significant duration of the reaction in the synthesis of 3-(3-phenoxyphenyl)-2-butenonitrile is due to the lower reactivity of 3-phenoxyphenyl methyl ketone as compared to 3-phenoxybenzaldehyde. Further increase in the acetonitrile excess and in the reaction time does not affect the yield of the target products **III**, **IV** and is unnecessary.

3-(3-Phenoxyphenyl)-2-acrylonitrile and 3-(3-phenoxyphenyl)-2-butenonitrile were purified by vacuum distillation with the addition of hydroquinone to avoid polymerization. The nitriles are colorless liquids obtained in 48–51% yield. Moderate yield of the target products is caused by partial polymerization of unsaturated nitriles in the course of vacuum distillation under the action of high temperature.

Structure and composition of the nitriles synthesized were confirmed by the IR and ^{1}H NMR spectroscopy and elemental analysis.

The developed procedure permits the preparation of unsaturated nitriles containing 3-phenoxyphenyl fragment in one stage and in good yields. It is simple, and the target products are easily isolated in a highly pure form.

3-Phenoxybenzoylacetonitrile we prepared through acylation of ethyl cyanoacetate with 3-phenoxybenzoyl chloride. The reaction proceeded according to the following scheme.



IV Yield 94–95% **V**

Yield 92% **VI** Yield 86–87% **VII**

In the first stage of the reaction ethyl 3-phenoxybenzoylcyanoacetate **V** is formed. The acylation was carried out in presence of sodium hydroxide in acetone over 2 h at the temperature not exceeding 20°C. The organic layer was separated and washed with distilled water until neutral reaction. Ethyl 3-phenoxybenzoylcyanoacetate **V** is an oily yellow liquid. It was prepared in 94–95% yield.

The second stage of the reaction was the hydrolysis of ethyl 3-phenoxybenzoylcyanoacetate **V** to the free acid **VI**. No hydrolysis of the nitrile group was observed. It can be probably ascribed to performing the reaction in the alkaline medium at low temperature and to the steric effect of the diphenyl oxide fragment. 3-Phenoxybenzoylcyanoacetic acid is the coarsely dispersed powder, mp 150–152°C. Its structure and

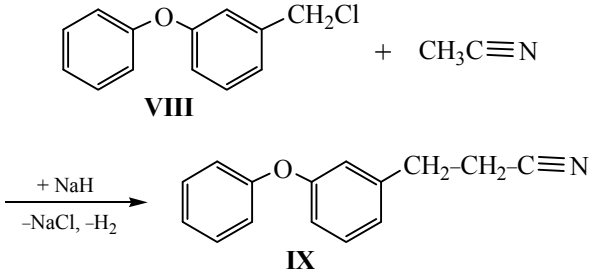
composition were confirmed by the IR and ^{1}H NMR spectroscopy and elemental analysis.

Heating of 3-phenoxybenzoylcyanoacetic acid above its melting point caused decarboxylation to 3-phenoxybenzoylacetonitrile **VII** in 86–87% yield.

3-Phenoxybenzoylacetonitrile is a finely dispersed powder, mp 140–142°C.

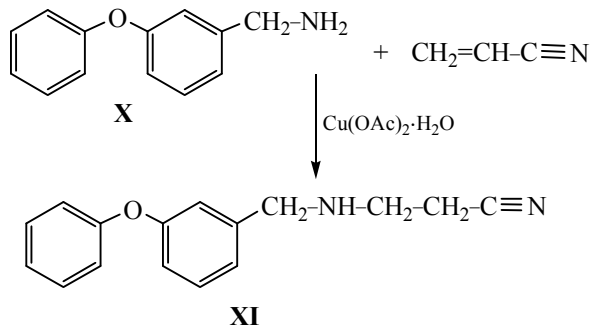
Its structure and composition were confirmed by the IR and ^{1}H NMR spectroscopy and elemental analysis.

The alkylation of acetonitrile with 3-phenoxybenzyl chloride **VIII** lead to the formation of 3-(3-phenoxyphenyl)propionitrile **IX** according to the scheme:



The alkylation was carried out for 2 h under nitrogen in anhydrous benzene at 80–82°C and 1:1.2:1.2 3-phenoxybenzyl chloride : acetonitrile : sodium hydride molar ratio. Lithium amide and sodium hydride were used for metallation of acetonitrile, but in the first case 3-(3-phenoxyphenyl) propionitrile was obtained in 22% yield. Using sodium hydride permitted to achieve 60% yield of the target product. The nitrile obtained is a viscous oily yellow liquid which was purified by vacuum distillation, bp 172–175°C (2 mm Hg). The structure and composition of the product were confirmed by the IR and ^{1}H NMR spectroscopy and elemental analysis.

3-(3-Phenoxybenzylamino)propionitrile **XI** was obtained by cyanoethylation of 3-phenoxybenzylamine **X** with acrylonitrile according to the scheme:



Reaction was carried out in the presence of copper acetate monohydrate, the most effective cyanoethylation catalyst for amines [5], at 95°C over 3 h without a solvent. The nitrile obtained was a viscous yellow liquid which was purified by vacuum distillation, bp 172–175°C (2 mm Hg). Yield of the product after vacuum distillation was 40%. Comparatively low yield of the target product is caused by a partial polymerization of acrylonitrile in the course of the reaction. The structure and composition of the product were confirmed by the IR and ^{1}H NMR spectroscopy and elemental analysis.

EXPERIMENTAL

IR spectra were measured on a Specord M-82 spectrometer in mineral oil, NaCl and KBr prisms were used. ^{1}H NMR spectra were taken on a Varian Mercury 300BB spectrometer in DMSO-d_6 against internal HMDS. GLC was carried out on a Sigma-300 chromatograph equipped with a 2 m column filled with 15% of SKTF-50 on Inerton N–AV, evaporator temperature 270°C, oven temperature 80–240°C, β = 3 mm min^{-1}, programming rate 5°C/min.

3-(3-Phenoxyphenyl)-2-acrylonitrile (III). Potassium hydroxide, 3 g, and 40 ml of acetonitrile were placed in the reactor equipped with a mechanic stirrer, a reflux condenser with a calcium chloride tube, a thermometer, and a dropping funnel. The mixture was heated to boiling and kept under nitrogen until the complete dissolution of potassium hydroxide. After that a solution of 10 g of 3-phenoxybenzaldehyde in 20 ml of acetonitrile was added dropwise in the course of 1–2 min. After the addition was complete the reaction mixture was stirred for 10 min, and the hot solution was poured in 100 g of crashed ice. The two-phase system formed, and the organic layer was separated, the water layer was extracted 2 times with 50 ml of diethyl ether. Combined organic phases were washed with distilled water. 3-(3-Phenoxyphenyl)-2-acrylonitrile was isolated by vacuum distillation with the addition of hydroquinone. Yield 5.3 g (48%), bp 194–196°C (4 mm Hg), purity 98.5% (GLC data). IR spectrum, ν, cm^{-1}: 2218 (C≡N), 1696 (C=C), 3064 (C–H). ^{1}H NMR spectrum, δ, ppm: 6.84–7.2 m (9H, $C_6H_5OC_6H_4$), 7.44–7.46 d (Ar–CH), 5.62–5.67 d (1H, CH–CN). Found.%: C 81.46, 81.42; H 4.98, 5.00; N 6.28, 6.30. $C_{15}H_{11}NO$. Calculated, %: C 81.45; H 4.98, N 6.33.

3-(3-Phenoxyphenyl)-2-butenonitrile (IV). Potassium hydroxide, 3 g, and 40 ml of acetinitrile were

placed in the reactor equipped with a mechanic stirrer, a reflux condenser with calcium chloride tube, a thermometer, and a dropping funnel. Potassium hydroxide must be fresh. The reaction mixture was heated to boiling and refluxed with stirring under nitrogen until the complete dissolution of potassium hydroxide. After that a solution of 10 g of 3-phenoxyphenylmethylketone in 20 ml of acetonitrile was added dropwise in the course of 30–40 min, and the resulting mixture was stirred for 3 h. The hot reaction mixture was then poured on 100 g of crashed ice. After cooling the two-phase mixture was formed. The organic layer was separated, and water phase was extracted with ether. Combined organic phases were washed with distilled water and dried over sodium sulfate. Ether was removed, and the residue was distilled in a vacuum with the addition of hydroquinone to give 6 g (51%) of 3-(3-phenoxyphenyl)-2-butenonitrile, bp 215–218°C (4 mm Hg), purity 97.2% (GLC data).

IR spectrum, ν, cm^{-1}: 2218 (C≡N), 1672 (C=C), 2926–3034 (CH_3). ^1H NMR spectrum, δ, ppm: 6.84–7.2 m (9H, $C_6H_5OC_6H_4$), 1.1–1.3 s (3H, CH_3), 5.34–5.37 s (1H, CH–CN). Found, %: C 81.60, 81.64; H 5.98, 6.00; N 5.49, 6.52. $C_{16}H_{13}NO$ Calculated, %: C 81.70, H 5.96, N 5.53.

3-Phenoxybenzoylacetonitrile (VII). 3-Phenoxybenzoyl chloride, 9.35 g, 5 g of ethyl cyanoacetate, and 40 ml of anhydrous acetonitrile were placed in the three-neck reactor equipped with a mechanic stirrer, a thermometer, and a dropping funnel. The solution obtained was cooled with a mixture of ice and salt, and 40% sodium hydroxide solution was added dropwise until the achievement of constant pH 8–9. The reaction mixture was stirred at 20°C for 2 h and treated with 300 ml of ice water. Ethyl 3-phenoxybenzoylcyanoacetate was precipitated with 10% hydrochloric acid, and then separated. Yield 94–95%.

Ethyl 3-phenoxybenzoylcyanoacetate, 11.8 g, was placed in a three-neck flask equipped with a mechanic stirrer and a reflux condenser, 150 ml of 10% potassium hydroxide solution was added, and the reaction mixture was refluxed with stirring for 1–2 h until the complete dissolution of ethyl 3-phenoxybenzoylcyanoacetate. The mixture obtained was cooled and acidified with 100 ml of 5 N HCl. The crystals of 3-phenoxybenzoylcyanoacetic acid were formed. They were filtered off and washed with distilled water. Yield 92 g, mp 150–152°C. IR spectrum, ν, cm^{-1}: 1790 (C=O). 2198 (C≡N), 2854 (OH). ^1H NMR spectrum, δ, ppm: 3.93 s (H, CH), 6.65–7.4 m (9H, $C_6H_5OC_6H_4$).

Decarboxylation of 3-phenoxybenzoylcyanoacetic acid to 3-phenoxybenzoylacetonitrile was carried out by heating the acid in the ceramic cup above its melting point. After calcinations of 9,8 g of 3-phenoxybenzoylcyanoacetic acid 9,2 g (90%) of 3-phenoxybenzoylacetonitrile was obtained, mp 140–143°C. IR spectrum, ν, cm^{-1}: 1760 (C=O), 2248 (C≡N). ^1H NMR spectrum, δ, ppm: 4.402 s (2H, CH_2), 6.65–7.4 m (9H, $C_6H_5OC_6H_4$). Found, %: C 75.96. 75.99; H 5.96, 6.01; N 4.58, 4.61. $C_{15}H_{10}NO_2$. Calculated, %: C 75.95, H 5.91, N 4.64.

3-(3-Phenoxyphenyl)propionitrile (IX). A mixture of 2.25 g of acetonitrile, 10 g of 3-phenoxybenzyl chloride, and 20 ml of anhydrous benzene was placed in a four-neck reactor equipped with a mechanical stirrer, a reflux condenser, a thermometer, and a dropping funnel, and heated to boiling. Sodium hydride, 60% suspension, 2.2 g, was mixed with 30 ml of anhydrous benzene and added with shaking in small portions to a stirred reaction mixture. After the addition was complete the reaction mixture was refluxed with stirring for 3 h. On cooling it was washed with 100 ml of water. The organic layer was separated, and the water phase was extracted with benzene, 2×100 ml. The combined organic phases were dried over sodium sulfate, and the solvent was removed. The residue was distilled in a vacuum to give 3-(3-phenoxyphenyl) propionitrile, yield 60%, bp 172–165°C (3 mm Hg).

IR spectrum, ν, cm^{-1}: 2250 (C≡N). ^1H NMR spectrum, δ, ppm: 2.2 d (2H, CH_2), 2.7 d (2H, CH_2), 6.8–7.2 m (9H, $C_6H_5OC_6H_4$). Found, %: C 80.64, 80.68; H 6.30, 6.33: N 5.81, 5.83. $C_{15}H_{13}NO$. Calculated, %: C 80.72, H 6.28, N 5.83.

3-(3-Phenoxybenzylamino)propionitrile (XI). A mixture of 10 g of 3-phenoxybenzylamine, 2.65 g of acrylonitrile, and 0.4 g of copper acetate monohydrate (4% to the mass of 3-phenoxybenzylamine) was placed in a three-neck reactor equipped with a mechanic stirrer, a reflux condenser, and a thermometer. The mixture was heated to boiling with stirring and kept for 3 h at 95°C. After that excess acrylonitrile was distilled off and 3-(3-phenoxybenzylamino)propionitrile was purified by vacuum distillation through a high Vigreux column. Yield 40%, bp 230°C (4 mm Hg). IR spectrum, ν, cm^{-1}: 2248 (C≡N), 3304 (N–H).

^{1}H NMR spectrum, δ, ppm: 8.2 br.s (N–H), 3.6 s (2H, Ar–CH_2–N), 2.2 d (2H, CH_2), 2.7 d (2H, CH_2), 6.8–7.2 m ($C_6H_5OC_6H_4$). Found, %: C 76.14, 76.16; H 11.06, 11.09: N 6.37, 6.37. $C_{16}H_{16}N_2O$. Calculated, %: C 76.19, H 11.11, N 6.35.

REFERENCES

1. *Khimicheskaya entsiklopediya* (Chemical Encyclopedia), Knunyants, I.L., Ed., Moscow: Bol'shaya Rossiiskaya Entsiklopedia, 1992, vol. 3, p. 1042.
2. Smirnova, M.V., *Candidate Sci. (Chem.) Dissertation*, Volgograd, 2008.
3. Popov, Yu.V., Korchagina, T.K., and Smirnova, M.V., *Izv. Volgograd. Gos. Tekh. Univ., Ser. Khim. i Tekh. Elementoorg. Monomer. i Polimer. Material*., 2007, vol. 31, no. 5, p. 52.
4. Popov, Yu.V., Korchagina, T.K., Smirnova, M.V., and Kamaletdinova, V.S., *Izv. Volgograd. Gos. Tekh. Univ., Ser. Khim. i Tekh. Elementoorg. Monomer. i Polimer. Material*., 2008, vol. 39, no. 1, p. 87.
5. Heininger, S.A., *Organic Syntheses*, vol. 4, p. 146.