ISSN 1070-3632, Russian Journal of General Chemistry, 2008, Vol. 78, No. 11, pp. 2164–2165. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © Yu.V. Popov, T.K. Korchagina, M.V. Smirnova, V.S. Kamaletdinova, 2008, published in Zhurnal Obshchei Khimii, 2008, Vol. 78, No. 11, pp. 1928–1929.

LETTERS TO THE EDITOR

Synthesis of 3-Phenoxybenzoylacetonitrile

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Received May 15, 2008

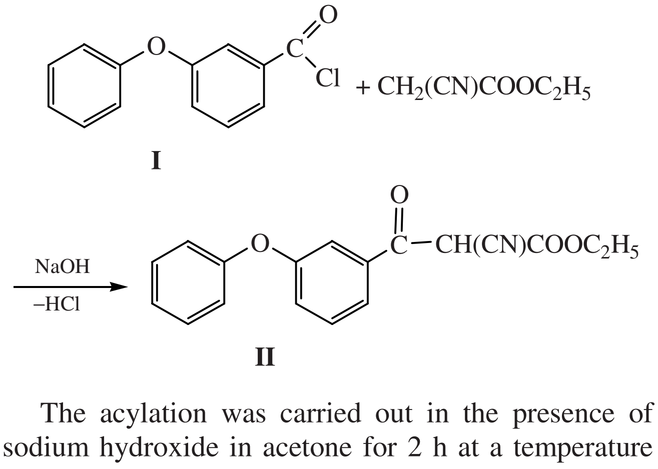
DOI: 10.1134/S1070363208110340

The introduction of 3-phenoxyphenyl fragment into a pharmacophore molecule is promising for the synthesis of the new biologically active substances opening a way to further synthetic modifications. Nitriles with molecules containing in the side chain other functional groups aside from cyano group are of great interest in the diphenyloxide derivatives series.

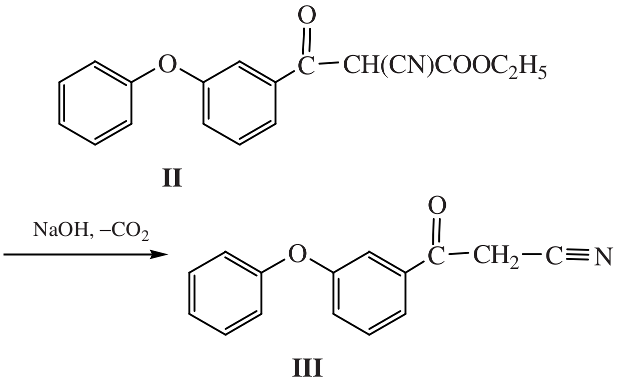
Effective synthetic way to 3-phenoxybenzoylacetonitrile was developed on the basis of 3-phenoxybenzoyl chloride and ethyl cyanoacetate.

It is a common knowledge now that diphenyloxide functional derivatives exhibit pharmacological activity of various kinds [1–4].

We obtained 3-phenoxybenzoylacetonitrile **III** by a two-stage synthesis. In the first stage ethyl 3-phenoxybenzoylcyanoacetate **II** was formed as a result of ethyl cyanoacetate acylation with 3-phenoxybenzoyl chloride **I**.



The acylation was carried out in the presence of sodium hydroxide in acetone for 2 h at a temperature not exheeding 20°C. Yield of ethyl 3-phenoxybenzoylcyanoacetate **II** was up to 94–95%.



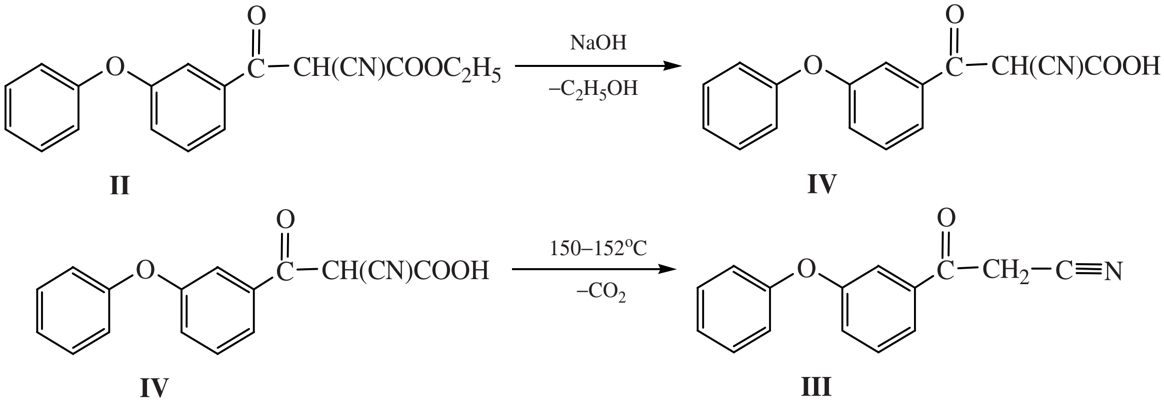
The second stage consists in the alkaline hydrolysis of ethyl 3-phenoxybenzoylcyanoacetate **II** followed by thermal decarboxylation.

The alkaline hydrolysis of the ester obtained and 3-phenoxybenzoylacetonitrile precipitation with carbon dioxide furnished 3-phenoxybenzoylacetonitrile **III** in an yield about 50%.

Better results were achieved using the other way of 3-phenoxybenzoylacetonitrile **III** isolation from ethyl 3-phenoxybenzoylcyanoacetate **II**. This procedure consisted in 3-phenoxybenzoylcyanoacetic acid **IV** isolation followed by its decarboxylation at heating above the melting point.

The structure and composition of the nitrile prepared were proved with IR and ^{1}H NMR spectroscopy.

3-Phenoxybenzoylacetonitrile. To a solution of 9.35 g (0.16 mol) of 3-phenoxybenzoyl chloride in 40 ml of anhydrous acetone was added 5 g (0.176 mol) of ethyl cyanoacetate. To the mixture obtained was added dropwise 40% solution of sodium hydroxide to pH = 8–9 at vigorous stirring and external cooling with



II → IV

IV → III

ice-salt mixture. The reaction mixture was stirred at 20°C for 2 h. Then 300 ml of ice water was added. Ethyl 3-phenoxybenzoylcyanoacetate was isolated by acidification with 10% hydrochloric acid. Yield 94–95%, mp 140–142°C, finely dispersed powder.

Further to ethyl 3-phenoxybenzoylcyanoacetate was added 150 ml of 10% aqueous sodium hydroxide solution. The reaction mixture was refluxed at stirring for 1–2 h to complete dissolution of the ester in alkali. On cooling, the reaction mixture was acidified with 100 ml of 5 N HCl. 3-Phenoxybenzoylcyanoacetic acid precipitated was filtered off and washed with distilled water. mp 150–152°C.

The acid prepared was heated above melting point to form 3-phenoxybenzoylacetonitrile. Yield 90%, mp 140–143°C. IR spectrum, ν, cm^{-1}: 1600–700 (Ar), 1960 (C=O), 2248 (C≡N). ^{1}H NMR spectrum, δ, ppm: 4.402 s (2H, CH_2), 6.65-7.4 m (9H, $C_6H_5OC_6H_4$).

IR spectra were recorded on a Specord M-82 spectrophotometer (mineral oil, NaCl or KBr). ^{1}H NMR spectra were registered on a Varian Mercury 300BB instrument in DMSO-d_6, internal reference HMDS.

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