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**LETTERS TO THE EDITOR**

# Synthesis of 3-Phenoxyphenyl-Containing 1,3-Diketones

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Diphenyl oxide derivatives containing various functional groups have been used as drugs showing a wide range of physiological activity.

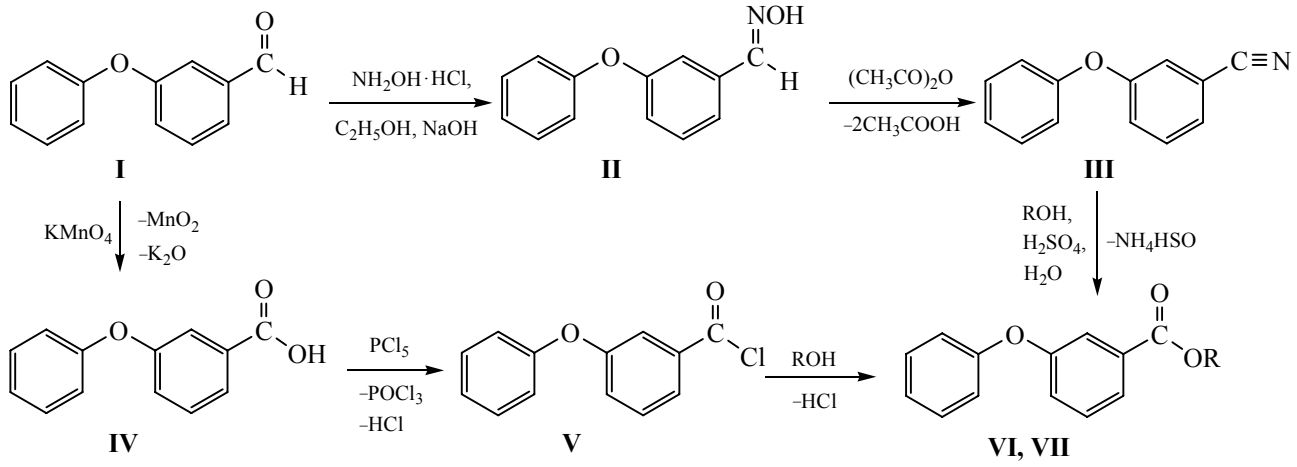
A promising direction in the chemistry of diphenyl oxide compounds is synthesis of dicarbonyl compounds, namely, 1,3-diketones. This class of diphenyl oxide derivatives has been scarcely studied so far. Aromatic β-diketones have attracted increased attention because of the valuable pharmacological properties. For instance, some of them are active blood anticoagulants and are used to treat thrombosis and myocardial infarction. They also possess pronounced antiviral activity against herpes simplex virus types 1 and 2 as well as DNA and RNA viruses [1, 2].

In this work we developed a convenient and efficient method of 3-phenoxyphenyl-containing 1,3-diketones synthesis. Esters of 3-phenoxybenzoic acid and ketones containing α-hydrogen atom were used as starting compounds.

Synthesis of alkyl 3-phenoxybenzoates **VI** and **VII** was performed via two pathways starting from 3-phenoxybenzaldehyde **I**. In the first scheme, 3-phenoxybenzaldehyde **I** reacted sequentially with hydroxylamine and acetic anhydride to give 3-phenoxybenzonitrile **III** [3], its interaction with alcohols in the presence of catalytic amounts of concentrated sulfuric acid at heating leading to formation of the corresponding alkyl 3-phenoxybenzoates **VI** and **VII** [4] with yields of 52–55% (Scheme 1).

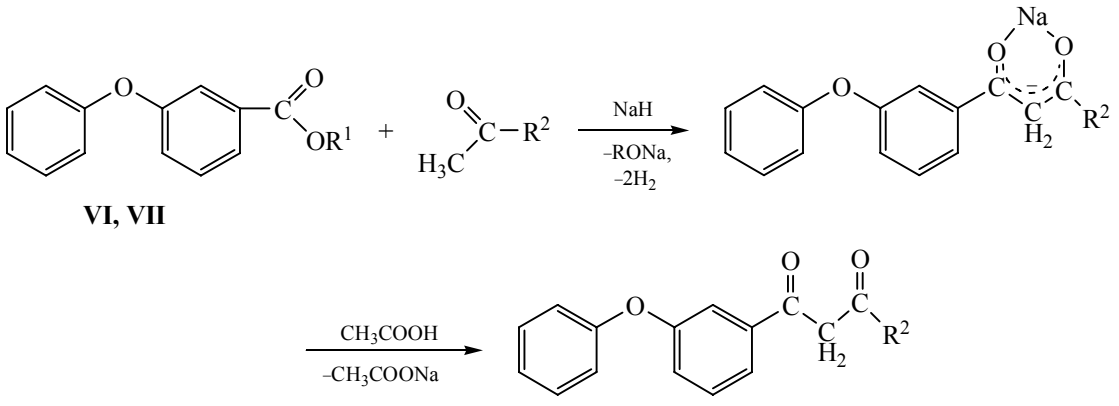
The second approach involved acylation of alcohols with a corresponding acid chloride. Acid chloride **V** was prepared by reacting 3-phenoxybenzoic acid **IV**

**Scheme 1.**




R = $CH_3$ (**VI**), $C_2H_5$ (**VII**).

**Scheme 2.**

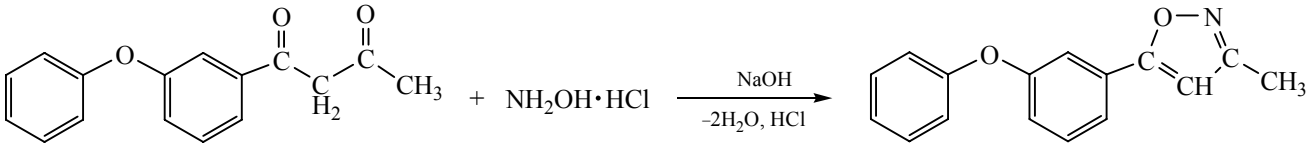



**VI, VII**

**VIII–X**

$R^1 = CH_3$ (**VI**), $C_2H_5$ (**VII**); $R^2 = CH_3$ (**VIII**), $C_2H_5$ (**IX**), $C_6H_5$ (**X**).

**Scheme 3.**




**VIII** **XI**

with phosphorus(V) chloride. The method enabled to improve the yield of 3-alkyl phenoxybenzoates **VI** and **VII** to reach 94% (Scheme 2).

Synthesis of 3-phenoxyphenyl-substituted 1,3-diketones **VIII**–**X** was performed via the Claisen reaction between alkyl 3-phenoxybenzoates and ketones (acetone, butan-2-one, or acetophenone) at the molar ratio of 2.0:1 in anhydrous cyclohexane in the presence of catalytic amounts of sodium hydride under reflux during 2.5–3 h. Yields of 3-phenoxyphenyl derived 1,3-diketones were as high as 50–74% (Scheme 3).

1,3-Diketones comprising diphenyloxide moiety could undergo the cyclocondensation reaction. In particular, 1-(3-phenoxyphenyl)butane-1,3-dione reacted with hydroxylamine to form 5-methyl-3-(3-phenoxyphenyl)isoxazole **XI** with yield of 62%.

Structures of the prepared compounds were established from IR and NMR spectroscopy data.

**Ethyl 3-phenoxybenzoate (VII).** A mixture of 10 g (50.0 mmol) of 3-phenoxybenzonitrile, 9.8 g (212.0 mmol) of anhydrous ethanol, and 11.7 g (119.5 mmol) of conc. sulfuric acid was refluxed during 8 h. The reaction mixture was cooled and poured into 50 mL of distilled water. The organic layer was separated, diluted with 20–30 mL of diethyl ether, washed with saturated aqueous sodium bicarbonate solution until carbon dioxide evolution ceased, then washed with water until neutral reaction, and dried with anhydrous sodium sulfate. After removal of the solvent, the residue was distilled under vacuum. Yield 6.6 g (55%), bp 195–197°C (4 mmHg), $n_D^{20}$ 1.5578. IR spectrum, ν, $cm^{-1}$: 1745, 1696 (C=O), 2975–3545 (C–H), 1294 (C–C, $CH_2$). $^1H$ NMR spectrum, δ, ppm: 1.80–2.25 m (3H, $CH_3$), 4.2 m (2H, $CH_2$), 6.0 s (H, =CH), 6.94–7.76 m (9H, $C_6H_5OC_6H_4$).

**Methyl 3-phenoxybenzoate (VI)** was prepared similarly. Yield 74%, bp 187–189°C (4 mmHg). IR spectrum, ν, $cm^{-1}$: 1750 (C=O), 1250 (C–O). $^1H$ NMR spectrum, δ, ppm: 1.7 s (3H, $CH_3$), 6.32–7.46 m (9H, $C_6H_5OC_6H_4$).

**1-(3-Phenoxyphenyl)butane-1,3-dione (VIII).** A suspension of 0.2 g (7.07 mmol) of sodium hydride in 50 mL of anhydrous cyclohexane was added upon stirring and cooling to a solution of 3 g (12.3 mmol) of ethyl 3-phenoxybenzoate **VII** in 10 mL of cyclohexane. Then a mixture of 0.3567 g (6.15 mmol) of anhydrous acetone and 10 mL of anhydrous cyclohexane

was slowly added. The reaction started spontaneously at room temperature and was accompanied by hydrogen evolution and slight heating of the reaction mixture. When the gas evolution ceased (2.5 h), the mixture was cooled to room temperature and incubated overnight. The reaction mixture was acidified with 10% acetic acid and diluted with 50 mL of icy water. The precipitate was filtered off, washed with cyclohexane and dried. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2Ч50 mL). The combined organic extracts were washed with 200 mL of distilled water until neutral reaction, dried over anhydrous sodium sulfate, and evaporated. The resulting crystals were filtered off, washed with cyclohexane, dried in air, and recrystallized from methanol. Yield 1.16 g (74%), mp 125–130°C. IR spectrum, ν, $cm^{-1}$: 2740–2890 (OH), 2900–3300 (C–H), 1780, 1696 (C=O), 1546 (C=C), 1294 ($CH_3$). $^1H$ NMR spectrum, δ, ppm: 0.80–2.25 m (3H, $CH_3$), 16.0 s (H, OH), 4.2 m (2H,$CH_2$), 6.03 s (H, =CH), 6.94–7.76 m (9H, $C_6H_5OC_6H_4$).

**1-(3-Phenoxyphenyl)pentane-1,3-dione (IX)** was prepared similarly. Yield 1.34 g (69%), mp 142–145°C. IR spectrum, ν, $cm^{-1}$: 2758–2890 (OH), 2920–3300 (C–H), 1786, 1654 (C=O), 1546 (C=C). $^1H$ NMR spectrum, δ, ppm: 1.047–1.3 m (3H, $CH_3$), 8.780 s (H, OH), 2.98 m (H, =CH), 4.2 s (2H, $CH_2$), 6.94–7.76 m (9H, $C_6H_5OC_6H_4$).

**1-(3-Phenoxyphenyl)-3-phenylpropane-1,3-dione (X)** was prepared similarly. Yield 1.15 g (52%), mp 152–157°C. IR spectrum, ν, $cm^{-1}$: 2740–2896 (OH), 2900–3300 (C–H), 1786, 1654 (C=O), 1546 (C=C). $^1H$ NMR spectrum, δ, ppm: 7.978 s (H, OH), 3.81 s (2H, $CH_2$), 6.07 s (H, =CH), 6.92–7.73 m (14H, $C_6H_5OC_6H_4$, $C_6H_5$).

**5-Methyl-3-(3-phenoxyphenyl)isoxazole (XI).** A solution of 1.6 g (23.6 mmol) of hydroxylammonium hydrochloride in 4 mL of water containing a drop of 40% aqueous sodium hydroxide solution was added to a solution of 3 g (11.8 mmol) of 1-(3-phenoxyphenyl)-butane-1,3-dione **VIII** in 30 mL of ethanol. The mixture was refluxed during 8 h. After cooling to room temperature, the resulting crystals were filtered off and recrystallized from ethanol. Yield 1.84 g (62%), mp 245°C. $^1H$ NMR spectrum, δ, ppm: 2.24 s (3H, $CH_3$), 6.02 s (=CH), 6.82–7.45 m (9H, $C_6H_5OC_6H_4$). Mass spectrum, $m/z$ ($I_{rel}$): 251 (100), 252 (17.8), 253 (2).

IR spectra were recorded with a SPECORD-M-82 (Perkin-Elmer) spectrometer at 400–5000 $cm^{-1}$. The spectra of liquid samples were registered in thin film, and the solid samples were examined in the form of suspension in paraffin oil. $^1H$ NMR spectra of the solutions in $CDCl_3$ were registered with a Varian Mercury 300BB instrument relative to HMDS. Mass spectra were obtained using a Variant MAT-11 spectrometer with ionizing voltage of 70 eV.

## ACKNOWLEDGMENTS

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## REFERENCES

1. Diana, G.D., Carabateas, Ph.M., and Johnson, R.E., *J. Med. Chem*., 1977, vol. 20, no. 6, p. 757. DOI: 10.1021/jm00216a004.
2. Diana, G.D., Salvador, U.J., and Zalay, E.S., *J. Med. Chem*., 1978, vol. 21, no. 9, p. 889. DOI: 10.1021/jm00207a010.
3. Smirnova, M.V., *Cand. Sci. (Chem.) Dissertation*, Volgograd, 2008,.
4. Furniss, B.S., Hannaford, A.J., Smith, P.W.G., and Tatchell, A.R., *Vogel's Text-Book of Practical Organic Chemistry*, London: Longman, 1989, p. 1514.