

Reaction of acetophenone and benzylphenylketone oximes with phenylacetylene: a route to di- and triphenylpyrroles

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This paper is dedicated to Professor Alexander Pozharskii on the occasion of his 70th anniversary

Abstract

The reaction of oximes of aromatic ketones with phenylacetylene in the presence of superbase systems (MOH-DMSO, where M = Li, Na, K) has been extensively studied for the first time. The effects of alkaline metal cation, the ketoximes structure and the reaction conditions (temperature, duration) on the products composition have been evaluated. Acetophenone oxime reacts with phenylacetylene (MOH-DMSO, where M = Li, Na, K, 140 °C, 6 h) to afford 2,5-diphenyl-1*H*-pyrrole in 14-18% isolated yield. The reaction of benzylphenylketoxime with phenylacetylene (LiOH-DMSO, 120 °C, 12 h) delivers 2,3,4-, 2,3,5-triphenyl-1*H*-pyrroles (in 17% total yield) and 2,3,4-triphenyl-1-[(*Z*)-2-phenylethenyl]-1*H*-pyrrole (7% yield).

Keywords: Acetophenone oxime, benzylphenylketoxime, phenylacetylene, 2,5-diphenyl-1*H*-pyrrole, 2,3,4- and 2,3,5-triphenyl-1*H*-pyrroles

Introduction

A number of natural and synthetic pyrroles bearing aryl substituents possess high biological activity.^{1,2} Currently, certain of the di- and triarylpyrroles are extensively employed as pharmaceuticals. For example, the cholesterol reduction drug lipitor (atorvastatin), one of the most commonly used in the United States, contains a 2,3-diphenylpyrrole motif.^{2a,3} A series of 2,3,4-triphenylpyrrole derivatives exert high hypoglycemic action and can be recommended for diabetes treatment.^{2a} Although arylpyrroles are applied for the synthesis of fluorescent azaindacene dyes of BODIPY family⁴ as well as optoelectronic materials,⁵ it is their

pharmacological appeal that seems to be the chief reason for a steady interest in the development of synthetic procedures for these compounds, reported, in particular, in reviews.^{1,2}

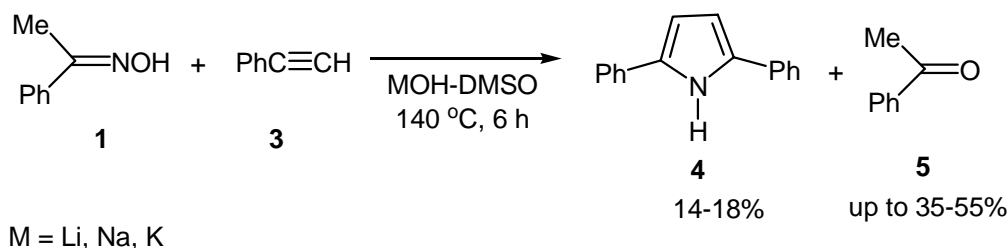
Di- and triphenylpyrroles are normally prepared by condensation of 1,4-diketones with ammonia or ammonium acetate,⁶⁻⁹ as well as by the reaction of 1,3-diketones^{10,11} with different nitrogen-containing compounds (ammonium acetate, aromatic imines, oximes) followed by cyclization of the intermediates formed. Despite the satisfactory yields of the target products, the syntheses reported feature either hard availability of the starting materials¹² or multi-step procedures.¹⁰

The reaction of ketoximes with acetylene (the Trofimov reaction) in the superbase systems MOH-DMSO, where M = Li, Na, K, makes it possible to prepare a wide series of substituted pyrroles in one preparative step.^{1,13} While this reaction is mostly studied with unsubstituted acetylene the applicability of phenylacetylene, an available substituted acetylene, still remains poorly understood.¹⁴ Meanwhile, the reaction of oximes of aromatic ketones with phenylacetylene could open a short-cut to pyrroles with several aromatic substituents.

In this work, using the examples of oximes of acetophenone **1** and benzylphenylketone **2** with phenylacetylene **3**, we have undertaken a more thorough study of the reaction to gain a clearer understanding of the effect of the alkaline metal cation in the catalyzing systems as well as the influence of the ketoxime structure and reaction conditions on the ratio and yields of the reaction products. Apart from extension of the basic knowledge about the scope and limitations of the pyrrole synthesis from ketoximes and acetylenes it was hoped to elaborate one-step preparative protocols for the synthesis of as yet hardly accessible di- and triphenylpyrroles.

Results and Discussion

The experiments have shown that at 140 °C (6 h) in the MOH-DMSO ketoxime **1** gave with phenylacetylene the expected 2,5-diphenyl-1*H*-pyrrole (**4**) in 14-18% isolated yield along with starting acetophenone **5** (yield up to 35-55%) and tar (mostly unidentified products of the base-catalyzed phenylacetylene condensation),^{15,16} the conversion of ketoxime **1** ranging from 69 to 80% (depending on the alkaline metal cation nature) (Scheme 1).



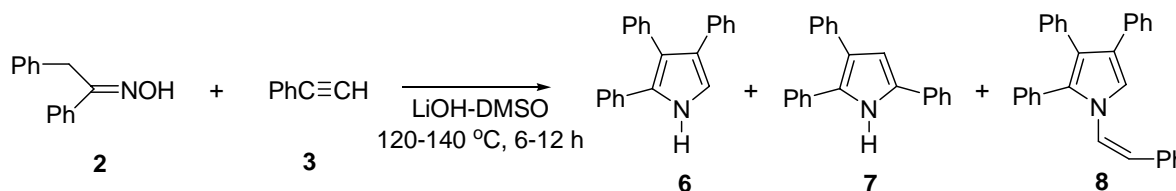
Scheme 1

The highest conversion of **1** (80%) was observed in the case of NaOH whereas those for LiOH and KOH were 77 and 69%, respectively. At the same time the yield of the target pyrrole **4** was not practically affected by the MOH nature, being somewhat higher for KOH (18%). Meanwhile, with LiOH the isolation of pyrrole **4** was found to be easier owing to a lesser amount of persistent side products formed. Therefore, it is LiOH that can be recommended for use in a preparative protocol for synthesis of pyrrole **4** (yield 17%).

The peculiarity of this reaction as compared with those using unsubstituted acetylene is the prevailing of deoxygenation (formation of ketone **5**) over the heterocyclization to pyrrole **4**. In fact, it means that the recovered starting ketone **5** can be returned (recycled) to the same reaction again (*via* ketoxime **1** which can be quantitatively prepared from the ketone and hydroxylamine). Consequently, the yield of pyrrole **4** when calculated on the initial ketone **5** consumed, is about two times higher than isolated one (even not accounting for the incomplete conversion of oxime **1**).

Thus, having in mind availability of the starting materials and the straightforward one-pot synthetic procedure, the reaction of acetophenone oxime with phenylacetylene may be considered as acceptable for the preparation of 2,5-diphenyl-1*H*-pyrrole (**4**) despite the modest yield.

Under analogous conditions (LiOH-DMSO, 140 °C, 6 h), the reaction of benzylphenylketoxime (**2**) with acetylene **3** delivers 2,3,4-triphenyl- (**6**), 2,3,5-triphenyl-1*H*-pyrroles (**7**) and 2,3,4-triphenyl-1-[(*Z*)-2-phenylethenyl]-1*H*-pyrrole (**8**) (their content in the crude product is 37, 24 and 30%, respectively), the conversion of oxime **2** being almost complete (90%) (Scheme 2).



Scheme 2

The pyrrole **8** is a product of further regio- and stereoselective vinylation of pyrrole **6** with phenylacetylene. Noteworthy that other isomeric pyrrole **7** is not vinylated under these conditions, obviously due to the steric hindrance imposed by phenyl substituents in the position 5 of the pyrrole ring. Since the vinylpyrrole **8** can be easily separated from the mixture of pyrroles **6** and **7** (see experimental), there is an opportunity to isolate pure pyrrole **7** by using excess phenylacetylene and carrying out the reaction up to completed vinylation of pyrrole **6**. Another interesting feature of this reaction is that the expected deoxygenation product, phenylbenzylketone was detected in the reaction mixture in negligible quantities (2%) only. At a lower temperature

(120 °C) and dropwise feeding of phenylacetylene, the content of the vinylated pyrrole **8** in the reaction mixture decreased to 9%, and those of 2,3,4-triphenyl- (**6**) and 2,3,5-triphenylpyrroles (**7**) correspondingly dropped (31 and 13%). In this case, the crude product contained 44% of starting oxime **2** (Table 1).

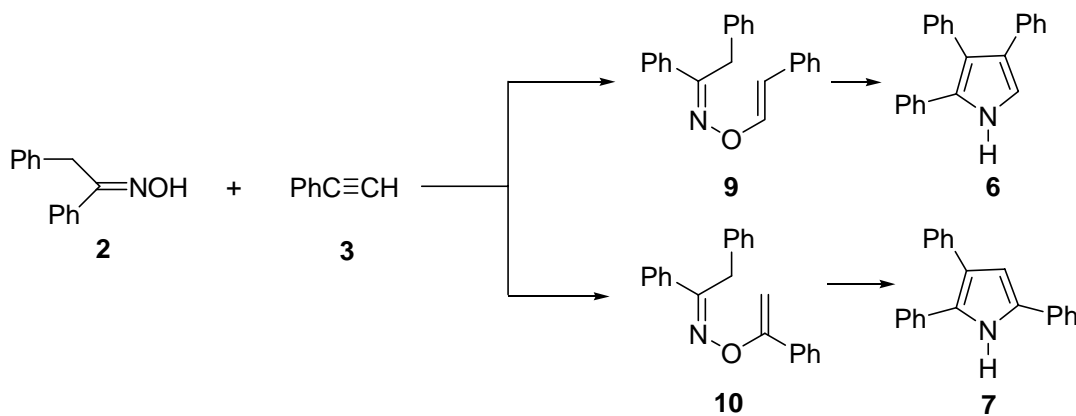
The ¹H NMR monitoring of the reaction of benzylphenylketoxime (**2**) with phenylacetylene (LiOH–DMSO, 120 °C) indicates that the pyrrole **6** is formed first, i.e. at a higher rate than the pyrrole **7** (Table 1).

Table 1. ¹H NMR monitoring of the reaction of benzylphenylketoxime (**2**) with phenylacetylene (LiOH–DMSO, 120 °C)

Time, h	Content of the reaction mixture, % (¹ H NMR)				
	Benzyl-phenylketone	Oxime 2	Pyrrole 6	Pyrrole 7	Pyrrole 8
1	2	92	5	1	0
2	2	83	12	3	0
3	2	74	17	5	2
4	3	62	22	9	4
5	3	50	29	11	7
6	3	44	31	13	9

From the data of Table 1, it may be assumed that the selective preparation of pyrrole **6** is achievable. Indeed, when the reaction was stopped at ~20% conversion of oxime **2**, the ratio of pyrroles **6** and **7** was 4:1.

The formation of two isomeric triphenylpyrroles **6** and **7** may be rationalized by cyclization (via [3,3]-sigmatropic rearrangement) of isomeric *O*-vinylketoximes **9** and **10**, the primary adducts of oxime **2** to acetylene **3** (Scheme 3).



Scheme 3

Such a mechanism was experimentally proved in a number of previous works^{4,13f,17} where the similar intermediate *O*-vinyloximes were isolated and separately rearranged to the corresponding pyrroles.

In summary, the reaction of oximes of aromatic ketones with phenylacetylene in MOH-DMSO systems paves a new path to one-pot preparation of di- and triarylpyrroles – promising precursors of pharmaceutically important compounds and optoelectronic materials.

Experimental Section

General Procedures. IR spectra were recorded from KBr pellets on a Bruker IFS-25 instrument. NMR spectra were run on a Bruker DPX 400 spectrometer [400.13 (¹H) MHz, 100.6 MHz (¹³C)]; CDCl₃ as solvent, HMDS as internal standard. Detailed ¹³C NMR peak assignments were obtained by careful analysis of HSQC and HMBC 2D NMR spectra. GCMS spectrum was run on a MSD5975C (Agilent), microanalyses were obtained in the A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, Russia on an EA FLASH 1112 Series (CHN Analyzer) instrument.

2,5-Diphenyl-1*H*-pyrrole (4). The oxime **1** (20.41 g, 0.151 mol) and LiOH (3.61 g, 0.151 mol) were dissolved under stirring and heating (100-110 °C, 3 h) in DMSO (150 ml). Phenylacetylene (16.85 g, 0.165 mol) was added to the formed lithium oximate solution, temperature of the mixture was raised to 137-140 °C and the reaction mixture was stirred during 6 h. After cooling up to room temperature the reaction mixture was diluted with water and extracted with diethyl ether (50 ml x 5). The ether extracts were washed with water (50 ml x 3) and dried over K₂CO₃. The residue after removal of diethyl ether was distilled in vacuo (2 mm Hg) to remove acetophenone formed (9.94 g, 55%) and then rectified in fine vacuo (6·10⁻² mm Hg) to give 4.70 g of unreacted oxime **1** (77% conversion) and 7.40 g of a fraction containing pyrrole **4** and side products (¹H NMR). Recrystallization of this fraction from heptene afforded 5.59 g (17%) of 2,5-diphenyl-1*H*-pyrrole (**4**), beige crystals, m.p. 141-142 °C [ref.¹⁴ 142 °C]; ¹H NMR δ 8.58 (br s, 1H, NH), 7.45 (m, 4H, H_o), 7.30 (m, 4H, H_m), 7.18 (m, 2H, H_p), 6.57 (d, ⁴J = 2.5 Hz, 2H, H-3, H-4); ¹³C NMR δ 133.2 (C-2, C-5), 132.6 (C_i), 129.0 (C_m), 126.2 (C_p), 123.9 (C_o), 108.0 (C-3, C-4); IR ν 3457, 3058, 3022, 1943, 1868, 1803, 1735, 1605, 1579, 1486, 1459, 1380, 1333, 1314, 1275, 1186, 1156, 1076, 1052, 1028, 903, 783, 753, 691, 665, 510 cm⁻¹. Anal. Calcd. for C₁₆H₁₃N: C, 87.64; H, 5.98; N, 6.38. Found: C, 87.86; H, 5.92; N, 6.20.

Analogously from oxime **1** (20.41 g, 0.151 mol), NaOH (6.04 g, 0.151 mol), phenylacetylene (16.85 g, 0.165 mol) (150 ml DMSO, 137-140 °C, 6 h) was prepared 4.73 g (14%) of pyrrole **4**, the oxime conversion was 80%.

Analogously from oxime **1** (20.41 g, 0.151 mol), KOH (8.47 g, 0.151 mol), phenylacetylene (16.85 g, 0.165 mol) (150 ml DMSO, 137-140 °C, 6 h) was prepared 5.92 g (18%) of pyrrole **4**, the oxime conversion was 69%.

2,3,4-Triphenyl-1H-pyrrole (6), 2,3,5-triphenyl-1H-pyrrole (7) and 2,3,4-triphenyl-1-[(E)-2-phenylethenyl]-1H-pyrrole (8). A mixture of benzylphenylketoxime **2** (5.0 g, 0.024 mol) and LiOH (0.57 g, 0.024 mol) in DMSO (50 ml) was stirred at 95-100 °C for 2 h to give the corresponding oximate. Then a solution of phenylacetylene (2.66 g, 0.026 mol) in DMSO (25 ml) was added to the reaction mixture at 120 °C for 8 h and heated for another 4 h. After cooling to room temperature the reaction mixture was diluted with water, extracted with diethyl ether (30 ml x 5). The extract were washed with water and dried over K₂CO₃. The diethyl ether was removed to afford 6.73 g of mixture containing 39% of 2,3,4-triphenyl-1H-pyrrole (**6**), 30% of the oxime **2**, 15% of 2,3,4-triphenyl-1-[(Z)-2-phenylethenyl]-1H-pyrrole (**8**), 14% of 2,3,5-triphenyl-1H-pyrrole (**7**) and 2% of benzylphenylketone (¹H NMR). The mixture obtained was dissolved in hot ethanol, the latter was cooled and the fine light-yellowish crystals precipitated were filtered off and dried to give 0.69 g (7%) of 2,3,4-triphenyl-1-[(Z)-2-phenylethenyl]-1H-pyrrole (**8**). Ethanol was removed from the filtrate and the residue was separated by preparative TLC (Al₂O₃, eluent – hexane : ethylacetate, 10:1) to obtain 1.21 g (17 %) of 2,3,4-triphenyl- (**6**) and 2,3,5-triphenyl-1H-pyrroles (**7**) mixture (ratio of **6** : **7** was 7 : 3, ¹H NMR), 1.51 g of the starting oxime **2** (70% conversion). The yield of 2,3,4-triphenyl- and 2,3,5-triphenyl-1H-pyrroles mixture was 25% with respect to the benzylphenylketoxime reacted.

2,3,4-Triphenyl-1H-pyrrole (6) and 2,3,5-triphenyl-1H-pyrrole (7). IR ν 3441, 3358, 3060, 3026, 1951, 1883, 1811, 1680, 1600, 1505, 1488, 1450, 1392, 1340, 1317, 1273, 1216, 1177, 1157, 1072, 1028, 957, 912, 903, 758, 698, 668, 623, 507 cm⁻¹. MS m/z ($J_{rel.}$, %): 295 (100) M⁺. Pyrrole **6**. ¹H NMR δ 8.28 (br s, 1H, NH), 7.15-7.30 (m, 15H, Ph), 6.94 (d, ³ $J_{H_2,NH}$ = 3.0 Hz, 1H, H-2); ¹³C NMR δ 135.7, 133.2, 132.5 (C_i), 127.0-130.0 (C_{o,m}), 127.3 (C-2), 125.5-126.5 (C_p), 125.1 (C-4), 123.0 (C-3), 116.7 (C-5).

Pyrrole **7**. ¹H NMR δ 8.41 (br s, 1H, NH), 7.54 (m, 2H, Ph), 7.40 (m, 6H, Ph), 7.34-7.25 (m, 5H, Ph), 7.21 (m, 2H, Ph), 6.73 (d, ⁴ $J_{H_4,NH}$ = 2.80 Hz, 1H, H-3); ¹³C NMR δ 136.5, 133.2 (C_i), 132.3 (C-5), 129.4 (C-2), 128.4-129.1 (C_m), 127.6-128.5 (C_o), 126.0-127.1 (C_p), 124.0 (C-3), 123.9 (C_o), 108.7 (C-4).

2,3,4-Triphenyl-1-[(Z)-2-phenylethenyl]-1H-pyrrole (8). M.p. 146-148 °C; ¹H NMR δ 7.29 (m, 4H, Ph), 7.21 (m, 7H, Ph), 7.10 (m, 5H, Ph), 7.00 (m, 4H, Ph), 6.81 (s, 1H, H-2), 6.49 (d, ³ $J_{H_{\alpha},H_{\beta}}$ = 9.6 Hz, 1H, H _{β}), 6.13 (d, ³ $J_{H_{\alpha},H_{\beta}}$ = 9.6 Hz, 1H, H _{α}); ¹³C NMR δ 135.2, 135.1, 134.5 (C_i, PhC=C), 131.7, 131.5 (C-2), 131.0, 130.8, 128.8 (C_o, PhC=C), 128.5, 128.3, 127.9, 127.8, 127.7 (C_p, PhC=C), 127.2, 125.8, 125.6, 125.5 (C_a), 125.1 (C-4), 122.4 (C-3), 121.4 (C _{β}), 119.6 (C-5); IR (KBr) ν 3064, 3028, 1956, 1886, 1814, 1641, 1600, 1573, 1530, 1494, 1448, 1407, 1391, 1205, 1145, 1070, 1027, 954, 944, 917, 796, 775, 756, 744, 729, 695, 639, 551 cm⁻¹. Anal. Calcd. for C₃₀H₂₃N: C, 90.64; H, 5.83; N, 3.52. Found: C, 90.76; H, 5.62; N, 3.62.

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