Oximes as Products in the Reactions of 5-Substituted 2-Nitrothiophenes with Arylacetonitriles

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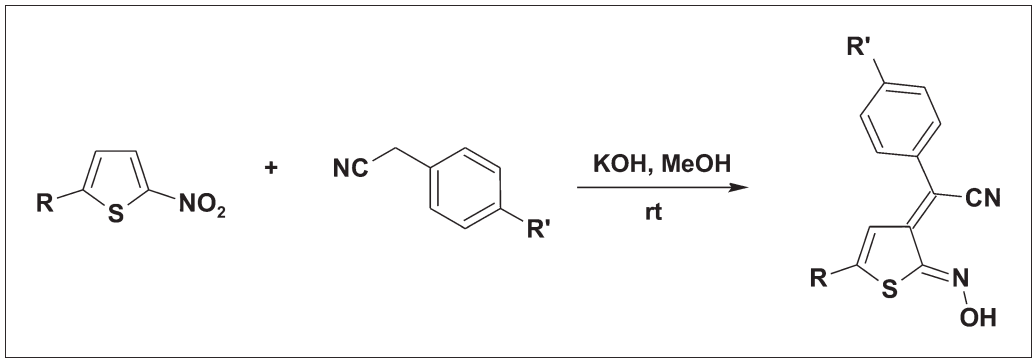

It has been shown that reactions 5-substituted 2-nitrothiophenes with arylacetonitriles in the presence of potassium hydroxide in methanol lead to the formation of the new [2-(hydroxyimino)-5-R-3(2H)-thienylidene](aryl)acetonitriles. Under proposed reaction conditions, the formation of thieno[2,3-*c*]isoxazole was not the case.

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INTRODUCTION

Activated role of nitro group in the nucleophilic substitution is well known. However, reactions with directly participating nitro group where it is reduced to nitroso group under nucleophilic substitution have been mentioned rarely. Davis and coworkers have found that *para*-unsubstituted nitrobenzene with phenylacetonitrile led to produce oxime **1** [1], but *para*-substituted nitrobenzenes give the benzo[*c*]isoxazoles **2** [2] (Fig. 1). Then similar reactions of nitrobenzenes have been carried out [3–10].

Recently, some nitroheteroarenes such as 4-nitroimidazoles and 4-nitropyrazoles have been used in the reactions with nucleophiles in the presence of sodium methoxide–methanol system. So, condensation of phenylacetonitrile with 4-nitro-2-methyl-1-benzylimidazole and 4-nitro-1-phenylpyrazole gave corresponding oxime **3** and methylated oxime **4** [11] (Fig. 2).

Such direction of substitution in nitroheteroarenes is unusual. In spite of neighbor to nitro group carbon is attacked by phenylacetonitrile carbanion, no formation of annulated isoxazole ring resembling benzo[*c*]isoxazole **2** has been observed.

Among the five-membered heteroarenes, thiophene is considered to be closest analogue to benzene. Thus, one would expect that reactions nitrothiophene with arylacetonitriles should proceed in similar way. 2-Nitrothiophene has been already used in such reaction to produce oxime **5** [11] (Fig. 2).

RESULTS AND DISCUSSION

Owing to similarity between nitrobenzene and 2-nitrothiophene, it was decided to investigate the behavior of 5-substituted 2-nitrothiophenes under conditions proposed by Devis [2].

Reactions of 5-iodo-2-nitrothiophene **6** with arylacetonitriles **7 a–d** in the presence of potassium hydroxide in methanol have been carried out. On the basis of the IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra, we conclude that obtained products are oximes **8a–d** (Scheme 1). The formation of thieno[2,3-*c*]isoxazole **9** is not observed.

The ^{1}H-NMR spectrum of compound **8d** consist of singlet at 6.93 ppm for thiophene proton, two doublets at 7.44 and 7.64 ppm for both pairs of 3,5-protons and 2,6-protons of phenyl and singlet at 13.24 ppm for oxime proton. The other oximes **8a–c** have similar spectra.

The attempts to obtain the 5-iodo-2-thienonoximes from (*o*-methyl)- and (*o*-chloro)arylacetonitrile were unsuccessful that to be explained by steric hindrance of *orto*-substituent of arylacetonitriles. The literature [5,6] mentioned that analogous arylacetonitriles react with 4-

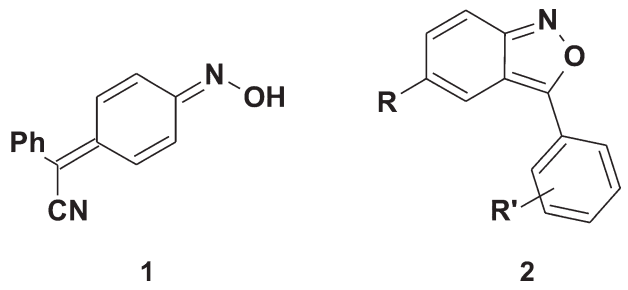


Figure 1. The products formed in the reactions of phenylacetonitrile with *para*-unsubstituted (**1**) and *para*-substituted (**2**) nitrobenzene.

substituted nitrobenzenes to give a complex mixture of products.

5-Iodo-2-nitrothiophene **6** has been used to obtain 5-aryl-2-nitrothiophenes **10a, b** by Suzuki reaction. The latter with arylacetonirtiles in mentioned condition lead to formation of corresponding oximes **11a, b** (Scheme 2).

Probably the reason for arylacetonitriles react with 2-nitrothiophene different from nitrobenzene is difference between dimensional structure of these compounds. The angle between two substituents located in 2 and 3 position of thiophene is larger (72°) than analogical angle between *ortho*-substituents in benzene (60°). The larger distance between neighboring substitutions in thiophene accounts for less stability of thienoisoxazoles system in contrast with benzisoxazoles. Literature review inform that thieno[2,3-*c*]isoxazole has not been synthesized yet, but the methods of obtaining thieno[2,3-*c*]isothiazoles [12,13] and thieno[2,3-*d*]isoxazoles [14] are known.

The results obtained by us and other researchers lead to conclusion that nitro five-membered rings which can be attacked by nucleophile only into *quasi-ortho*-position should react with arylacetonitriles to produce oxime derivatives. However, isoxazole ring may be formed with the use of nitro derivatives of six-membered rings.

The results of X-ray crystallography analysis of compound **11a** have shown the presence of one E-*anty*-isomer in the oxime crystal [15]. Based on ^{1}H-NMR spectra of **8**, **11** and crystallography data of **11a**, it was supposed the formation of one E-isomer for all compounds

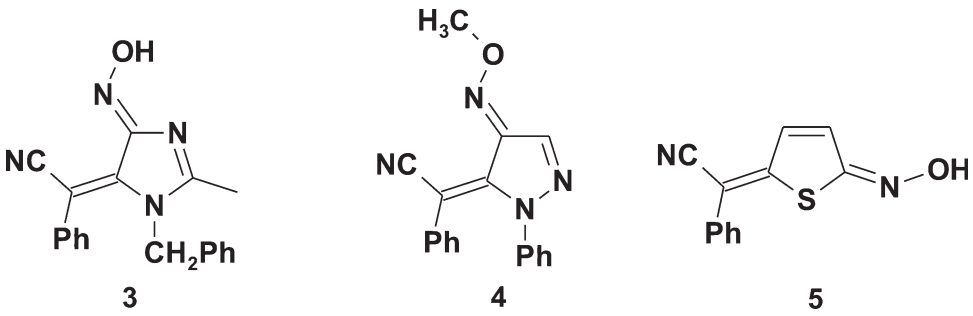
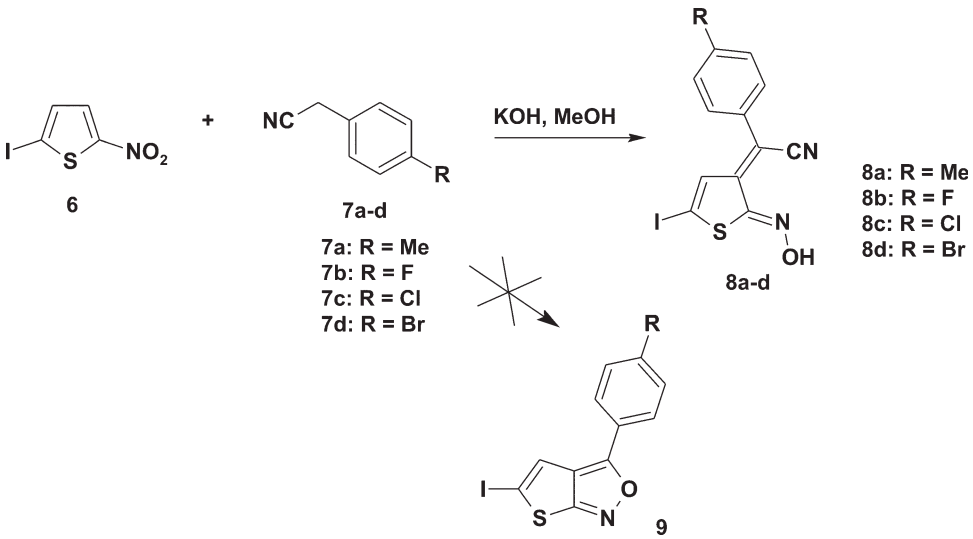
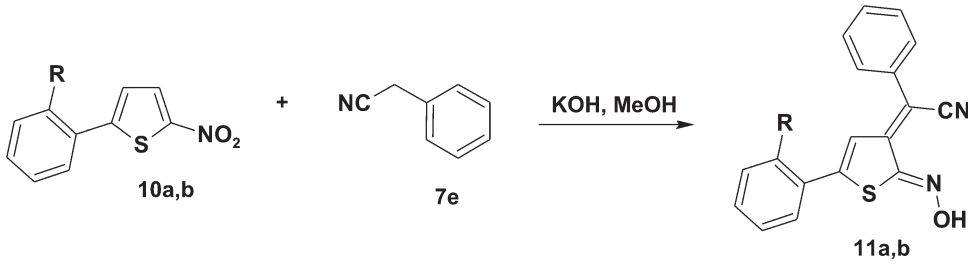


Figure 2. The products formed in the reactions of phenylacetonitrile with five-membered nitroheteroarenes.

Scheme 1



Scheme 2



10a: R = H
10b: R = OEt

11a: R = H
11b: R = OEt

8 and **11** that can have both *syn*- and *anty*-isomers in solution but only one *anty*-isomer in crystal.

The formation of oxime from 2-nitrothiophene is a proof of Davis suggestion [2] that nitro group is reduced to the nitroso group followed by benzisoxazole production.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Mercury 400 instrument (400 MHz for ^{1}H). The ^{1}H chemical shifts were reported in parts per million relative to tetramethylsilane or deuterated solvent as an internal reference. Electron impact (EI) mass spectra were determined on AMD-604 mass spectrometer operating at 70 eV. IR spectra were recorded on Perkin Elmer Spectrum 2000.

General procedure for the reactions of 5-substituted 2-nitrothiophenes 6 or 10a,b with arylacetonitriles 7a–e. Potassium hydroxide (3.36 g, 0.06 mol) was dissolved in methanol (40 mL), and then, arylacetonitrile **7** (0.01 mol) was added. To this solution, a nitrothiophene **6** or **10** (0.01 mol) dissolved in hot methanol was added. The solution was stirred at room temperature. When precipitate has been appeared, the mixture was diluted by water and acidify by acetic acid. The precipitate was isolated by filtration, washed with water and dried. The product was purified by recrystallization from ethanol or ethanol-DMFA mixture. All compounds **8** melting with decomposition.

[2-(Hydroxyimino)-5-iodo-3(2H)-thienylidene](4-methylphenyl)acetonitrile (8a). This compound was obtained in yield 53%. m.p. 187–190°C. ^{1}H-NMR (DMSO-d_6): δ 2.40 (s, 3H, CH_3), 6.92 (s, 1H, 4-H thiophene), 7.28 (d, ^3J = 7.6 Hz, 2H, 3,5-H$_2$ C_6H_4), 7.37 (d, ^3J = 7.6 Hz, 2H, 2,6-H$_2$ C_6H_4), 13.12 (s, 1H, =N—OH). Anal Calcd. for $C_{13}H_9IN_2OS$: C, 42.41; H, 2.46; N, 7.61. Found C, 42.13; H, 2.33; N, 7.82.

[2-(Hydroxyimino)-5-iodo-3(2H)-thienylidene](4-fluorophenyl)acetonitrile (8b). This compound was obtained in yield 67%. m.p. 163–167°C. ^{1}H-NMR (DMSO-d_6): δ 6.90 (s, 1H, 4-H thiophene), 7.23–7.28 (m, 2H, 2,6-H$_2$ C_6H_4), 7.53 (dd, J_{HH} = 8.8 Hz, J_{HF} = 5.8 Hz, 2H, 3,5-H$_2$ C_6H_4), 13.19 (s, 1H, =N—OH). Anal Calcd. for $C_{12}H_6FIN_2OS$: C, 38.73; H, 1.63; N, 7.53. Found C, 38.84; H, 1.58; N, 7.48.

[2-(Hydroxyimino)-5-iodo-3(2H)-thienylidene](4-chlorophenyl)acetonitrile (8c). This compound was obtained in yield 66%. m.p. 198–202°C. ^{1}H-NMR (DMSO-d_6): δ 6.90 (s, 1H, 4-H thiophene), 7.45 (d, ^3J = 8.8 Hz, 2H, 3,5-H$_2$ C_6H_4), 7.48 (d, ^3J = 8.8 Hz, 2H, 2,6-H$_2$ C_6H_4), 13.19 (s, 1H, =N—OH). Anal Calcd. for $C_{12}H_6ClIN_2OS$: C, 37.09; H, 1.56; N, 7.21. Found C, 36.88; H, 1.52; N, 7.44.

[2-(Hydroxyimino)-5-iodo-3(2H)-thienylidene](4-bromophenyl)acetonitrile (8d). This compound was obtained in yield 61%. m.p. 221–222°C. ^{1}H-NMR (DMSO-d_6): δ 6.93 (s, 1H, 4-H thiophene), 7.44 (d, ^3J = 8.8 Hz, 2H, 3,5-H$_2$ C_6H_4), 7.64 (d, ^3J = 8.8 Hz, 2H, 2,6-H$_2$ C_6H_4), 13.24 (s, 1H, =N—OH). Anal Calcd. for $C_{12}H_6BrIN_2OS$: C, 33.28; H, 1.40; N, 6.47. Found C, 33.11; H, 1.49; N, 6.25.

[2-(Hydroxyimino)-5-phenyl-3(2H)-thienylidene](phenyl) acetonitrile (11a). This compound was obtained in yield 55%. m.p. 180–183°C; IR: 3296 OH, 2193 CN, 1652 NO cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.01 (s, 1H, 4-H thiophene), 7.42–7.47 (m, 4H, C_6H_5), 7.50–7.54 (m, 2H, C_6H_5), 7.55–7.60 (m, 4H, C_6H_5), 13.11 (s, 1H, =N—OH); ^{13}C-NMR (Acetone-d_6): 149.23, 146.78, 135.73, 132.32, 131.16, 129.64, 129.42, 126.89, 119.25, 117.93; MS: *m/z* 304 (M^+), 287 (M^+—OH), 227 (M^+-Ph), 121 ($PhCS^+$), 77; Anal Calcd. for $C_{18}H_{12}N_2OS$: C, 71.03; H, 3.97; N, 9.20. Found C, 70.82; H, 3.90; N, 9.33.

[2-(Hydroxyimino)-5-(2-ethoxyphenyl)-3(2H)-thienylidene] (phenyl)acetonitrile (11b). This compound was obtained in yield 49%. m.p. 225–227°C. ^{1}H (DMSO-d_6): δ 1.29 (t, ^3J = 6.8 Hz, 3H, CH_3), 4.07 (q, ^3J = 6.8 Hz, 2H, CH_2), 6.98 (t, ^3J = 7.6 Hz, 1H, 5-H C_6H_4), 7.04 (d, ^3J = 8.3 Hz, 1H, 3-H C_6H_4), 7.36 (d, ^3J = 7.6 Hz, 1H, 6-H C_6H_4), 7.39 (s, 1H, 4-H thiophene), 7.43 (d, ^3J = 7.6 Hz, 2H, 2,6-H$_2$ C_6H_5), 7.47–7.56 (m, 4H, C_6H_5 + C_6H_4), 12.97 (s, 1H, =N—OH); Anal Calcd. for $C_{20}H_{16}N_2O_2S$: C, 68.95; H, 4.63; N, 8.04. Found C, 68.66; H, 4.48; N, 7.92.

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