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1,3-Dipolar cycloaddition of unsaturated ferrocene derivatives with carbonitrile *N*-oxides

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3,5-Disubstituted isoxazolines and isoxazoles have been synthesized using 1,3-dipolar cycloaddition of ferrocene derivatives $FcCH=CH_2$, $FcCOCH=CH_2$ and $FcC\equiv CH$ with aliphatic and aromatic carbonitrile *N*-oxides.

Key words: vinylferrocene, acryloylferrocene, ethynylferrocene; 1,3-dipolar cycloaddition reactions with aliphatic and aromatic carbonitrile oxides.

Many works have been devoted to the 1,3-dipolar cycloaddition of carbonitrile *N*-oxides with various unsaturated compounds. However, unsaturated ferrocene derivatives have not been involved in these reactions so far.

We studied the interaction of ferrocene derivatives containing double or triple bond in the side chain with aliphatic and aromatic carbonitrile *N*-oxides. Vinylferrocene (**1**), acryloylferrocene (**2**) and ethynylferrocene (**3**) were chosen as the unsaturated ferrocene derivatives. Two methods were used for the preparation of nitrile *N*-oxides: dehydration of primary nitrocompounds and dehydrochlorination of hydroximoyl chlorides. The nitrile *N*-oxides formed were introduced *in situ* into the reaction with the unsaturated compounds.

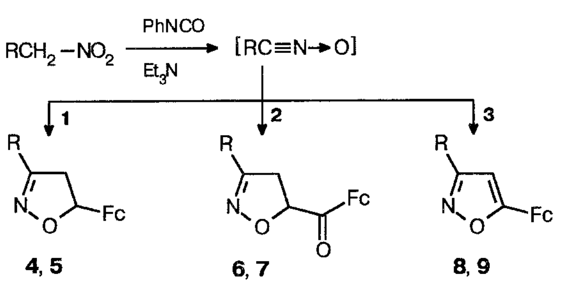
In order to determine the conditions most favorable for the process, the reaction was performed at different temperatures and reagent ratios. The highest yields of the cycloaddition products were obtained at ~20 °C and the ratio dipolarophile : precursor of nitrile oxide (nitroalkane or hydroxamoyl chloride) was equal to 1 : (1.2÷1.5).

N-Oxides of acetonitrile and propionitrile were synthesized by the previously described[1] method of dehydration of nitroethane and 1-nitropropane with phenylisocyanate in the presence of triethylamine, and were introduced *in situ* into the reaction with dipolarophiles **1**—**3** (Scheme 1).

All of the other nitrile *N*-oxides used in the work were obtained by dehydrochlorination of the corresponding hydroximoyl chlorides with triethylamine. The *N*-oxides of nitriles of ethoxycarbonylformic and pyruvic acids thus synthesized from hydroximoyl chlorides **10** and **11** easily react at ~20 °C with dipolarophiles **1**—**3** (Scheme 2) and form the cycloaddition products **12**—**16** with high yields.

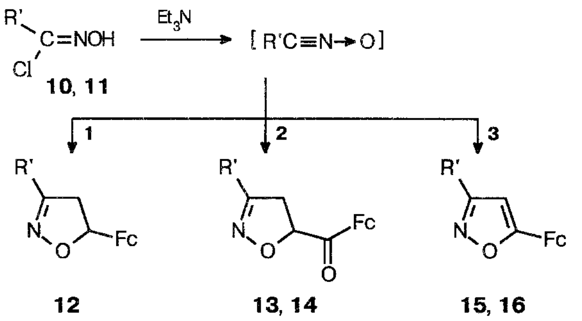
Although *N*-oxides of nitriles of aromatic carboxylic acids under normal conditions are more stable compounds than *N*-oxides of nitriles of aliphatic carboxylic acids, we also reacted them with dipolarophiles *in situ* at ~20 °C. As a result, starting from hydroximoyl chlorides **17**—**19** and dipolarophiles **1**—**3**, we synthesized heterocyclic compounds **20**—**28** according to Scheme 3.

Scheme 1



4, 6, 8: R = Me
5, 7, 9: R = Et

Scheme 2



10, 12, 13, 15: R' = COOEt
11, 14, 16: R' = COMe

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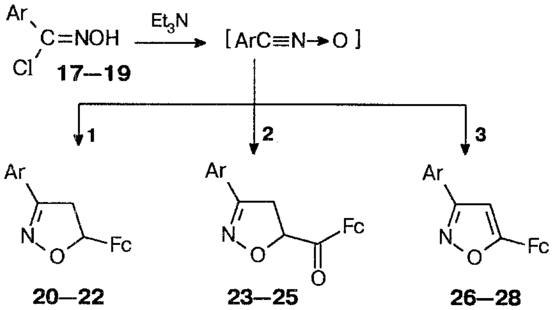
Scheme 3



17, 20, 23, 26: Ar = Ph
18, 21, 24, 27: Ar = m-$O_2NC_6H_4$
19, 22, 25, 28: Ar = p-$O_2NC_6H_4$

Comparing the durations of the interaction of dipolarophiles **1**—**3** with different carbonitrile *N*-oxides, one can conclude that acryloylferrocene **2** is the most reactive. The differences in the relative reactivity of dipolarophiles **1**—**3** in the interaction with carbonitrile *N*-oxides are pronounced when the reactions are performed using the three possible pairs of the dipolarophiles, even despite the fact that one equivalent of each dipolarophile with two equivalents of nitrile oxide EtOC(O)C≡N→O were used in each case. Cycloaddition took place in ether at ~20 °C until the full conversion of one of the dipolarophiles (monitored by TLC).

It turned out that when nitrile oxide interacted with the pair **1** and **3** the full conversion of olefin **1** was obtained in 8 h, resulting in the formation of isoxazoline **12** and isoxazole **15** (yields 86 and 75 %, respectively). In the reaction of nitrile oxide with the pair **1** and **2**, the full conversion of vinylketone **2** was observed in 3 h, and isoxazolines **12** (62 %) and **13** (94 %) were isolated from the reaction products. When nitrile oxide interacted with the pair of dipolarophiles **2** and **3**, the full conversion of vinylketone **2** occurred in 3 h, forming isoxazoline **13** (93 %) and isoxazole **15** (38 %).

Hence, the studied dipolarophiles **1**—**3** can be ranged in the following series with respect to their reactivity in the reaction with nitrile *N*-oxides: acryloylferrocene (**2**) > vinylferrocene (**1**) > ethynylferrocene (**3**).

The results obtained allow one to conclude that of the aliphatic nitrile *N*-oxides studied, those in which the nitrile oxide group is attached to electron acceptor groups (COOEt, COMe) are the most reactive.

Experimental

IR spectra were recorded on a Specord-75 spectrometer in pellets with KBr or in a Vaseline oil. NMR spectra were registered on a Varian device (60 MHz) in CD_2Cl_2, TMS served as the internal standard.

The initial dipolarophiles vinylferrocene,[2] acryloylferrocene[2,3] and ethynylferrocene[4] were obtained by known methods. Hydroximoyl chlorides EtO—CO—C(Cl)=NOH, MeCO—C(Cl)=NOH, ArC(Cl)=NOH (Ar = C_6H_5, *m*- and p-$O_2NC_6H_4$) were synthesized by methods described previously.[5—7]

Preparation of isoxazolines and oxazoles 4—9 (general method)

Triethylamine (0.2—0.3 mL) was added dropwise to a solution of 3—5 mmol of dipolarophile **1**—**3**, 4—7.5 mmol of nitrocompound ($EtNO_2$ or $PrNO_2$), and 9—20 mmol of phenylisocyanate in 20—30 mL of dehydrated benzene. The mixture was stirred at ~20 °C for the time necessary for the completion of the reaction (indicated below for each particular case, monitored by TLC) and filtered. The filtrate was evaporated, and the residue was chromatographed on a column with silica gel, eluting with benzene—ether (10:1) or benzene for the preparation of isoxazolines and isoxazoles, respectively.

5-Ferrocenyl-3-methylisoxazoline (4). The reaction mass was stirred for 20 h, the yield of compound **4** was 53 %, m.p. was 101—102.5 °C (from hexane). Found (%): C, 62.5; H, 5.6; N, 4.8. $C_{14}H_{15}FeNO$. Calculated (%): C, 62.5; H, 5.6; N, 5.2. IR, ν/cm^{-1}: 1100, 1000, 800 (Fc); 1630 (C=C). ^1H NMR, δ: 4.03 (s, 4 H, Fc); 4.01 (s, 5 H, Fc); 3.03 (m, 2 H, CH_2); 5.17 (m, 1 H, CH); 1.92 (s, 3 H, CH_3).

5-Ferrocenoyl-3-methylisoxazoline (6). The reaction mass was stirred for 4 h, the yield of compound **6** was 81 %, m.p. was 93—94 °C (from a benzene—hexane mixture). Found (%): C, 58.6; H, 4.8; N, 5.2. $C_{15}H_{15}FeNO_2$. Calculated (%): C, 58.9; H, 5.3; N, 4.9. IR, ν/cm^{-1}: 1100, 1000, 830 (Fc); 1630—1640 (C=N, cycle); 1660 (C=O). ^1H NMR, δ: 4.55 (m, 2 H, Fc); 4.85 (m, 2 H, Fc); 4.17 (s, 5 H, Fc); 3.2 (m, 2 H, CH_2); 5.27 (m, 1 H, CH); 1.91 (t, 3 H, CH_3).

5-Ferrocenyl-3-methylisoxazole (8). The reaction mass was stirred for 24 h, the yield of compound **8** was 23 %, m.p. was 91—92 °C (from heptane). Found (%): C, 62.9; H, 4.8; N, 5.1. $C_{14}H_{13}FeNO$. Calculated (%): C, 62.9; H, 4.9; N, 5.2. IR, ν/cm^{-1}: 1100, 1000, 800 (Fc); 1615 (C=N, cycle). ^1H NMR, δ: 4.28 (m, 2 H, Fc); 4.59 (m, 2 H, Fc); 4.06 (s, 5 H, Fc); 5.91 (s, 1 H, CH); 2.17 (s, 3 H, CH_3).

3-Ethyl-5-ferrocenylisoxazoline (5). The reaction mass was stirred for 20 h, the yield of compound 5 was 41 %, m.p. was 91—92 °C (from hexane). Found (%): C, 63.6; H, 6.0; N, 4.6. $C_{15}H_{17}FeNO$. Calculated (%): C, 63.6; H, 6.0; N, 4.9. IR, ν/cm^{-1}: 1100, 1000, 815 (Fc); 1630 (C=C, cycle). ^1H NMR, δ: 4.03 (s, 4 H, Fc); 3.99 (s, 5 H, Fc); 3.00 (m, 2 H, CH_2); 5.16 (m, 1 H, CH); 2.37 (q, 2 H, $CH_3C\underline{H}_2$); 1.13 (t, 3 H, $C\underline{H}_3CH_2$).

3-Ethyl-5-ferrocenoylisoxazoline (7). The reaction mass was stirred for 4 h, the yield of compound **7** was 71 %, m.p. was 44—45 °C (from benzene—hexane). Found (%): C, 61.7; H, 5.5; N, 4.5. $C_{16}H_{17}FeNO_2$. Calculated (%): C, 61.7; H, 5.5; N, 4.5. IR, ν/cm^{-1}: 1100, 1000, 830 (Fc); 1600—1630 (C=N, cycle); 1660 (C=O). ^1H NMR, δ: 4.46 (m, 2 H, Fc); 4.77 (m, 2 H, Fc); 4.10 (s, 5 H, Fc); 3.17 (m, 2 H, CH_2); 5.17 (m, 1 H, CH); 2.36 (q, 2 H, $CH_3C\underline{H}_2$); 1.08 (t, 3 H, $C\underline{H}_3CH_2$).

3-Ethyl-5-ferrocenylisoxazole (9). The reaction mass was stirred for 24 h, the yield of compound **9** was 32 %, m.p. was 92—93 °C (from heptane). Found (%): C, 64.0; H, 5.0; N, 4.8. $C_{15}H_{15}FeNO$. Calculated (%): C, 64.1; H, 5.3; N, 5.0. IR, ν/cm^{-1}: 1100, 1000, 820 (Fc); 1610 (C=N, cycle). ^1H NMR, δ: 4.30 (m, 2 H, Fc); 4.63 (m, 2 H, Fc); 4.07 (s, 5 H, Fc); 6.50 (s, 1 H, CH); 2.58 (q, 2 H, $CH_3C\underline{H}_2$); 1.17 (t, 3 H, $C\underline{H}_3CH_2$).

Preparation of isoxazolines 12—16 and isoxazoles 20—28 (general method)

Triethylamine (2—5 mmol) was added dropwise with stirring to a solution of 1.5—4 mmol of dipolarophile **1—3** and 2—5 mmol of the hydrochloride of the corresponding hydroxamic acid (**10**, **11**, **17**, **18**, or **19**) in 15—25 mL of dry ether. The mixture was stirred at ~20 °C for the time necessary for the completion of the reaction (indicated below in each particular case, monitored by TLC). The residue of triethylamine hydrochloride formed was filtered off (when compounds **22**, **25**, and **28** were prepared, the residue on the filter was thoroughly washed with water; the ether filtrate was evaporated, united with the residue washed by water on the filter, and recrystallized). For all other compounds, the residue on the filter was washed with ether, the united ether filtrates were evaporated, and the residues were chromatographed on a column with silica gel eluting with benzene.

3-Ethoxycarbonyl-5-ferrocenylisoxazoline (12). The reaction mass was stirred for 10 h, the yield of compound **12** was 82 %, m.p. was 80—81.5 °C (from hexane). Found (%): C, 58.9; H, 5.3; N, 4.0. $C_{16}H_{17}FeNO_3$. Calculated (%): C, 58.7; H, 5.2; N, 4.3. IR, ν/cm^{-1}: 1100, 1000, 800 (Fc); 1580 (C=C, cycle); 1700, 1730 (C=O, COOEt); 1240 (C—O—C). ^{1}H NMR, δ: 4.17 (s, 4 H, Fc); 4.13 (s, 5 H, Fc); 3.36 (m, 2 H, CH_2); 5.43 (m, 1 H, CH); 4.23 (q, 2 H, $CH_3C\underline{H}_2$); 1.36 (t, 3 H, $C\underline{H}_3CH_2$).

3-Ethoxycarbonyl-5-ferrocenoylisoxazoline (13). The reaction mass was stirred for 3 h, the yield of compound **13** was 91 %, m.p. was 71—72 °C (from benzene—hexane). Found (%): C, 57.6; H, 4.7; N, 3.7. $C_{17}H_{17}FeNO_4$. Calculated (%): C, 57.5; H, 4.8; N, 3.9. IR, ν/cm^{-1}: 1100, 1000, 810 (Fc); 1580 (C=N, cycle); 1660 (C=O); 1730 (C=O, COOEt); 1240 (C—O—C). ^{1}H NMR, δ: 4.53 (m, 2 H, Fc); 4.84 (m, 2 H, Fc); 4.18 (s, 5 H, Fc); 3.50 (m, 2 H, CH_2); 5.43 (m, 1 H, CH); 4.43 (q, 2 H, $CH_3C\underline{H}_2$); 1.35 (t, 3 H, $C\underline{H}_3CH_2$).

3-Ethoxycarbonyl-5-ferrocenylisoxazole (15). The reaction mass was stirred for 15 h, the yield of compound **15** was 78 %, m.p. was 85—87 °C. Found (%): C, 59.5; H, 4.5; N, 4.5. $C_{16}H_{15}FeNO_3$. Calculated (%): C, 59.1; H, 4.6; N, 4.3. IR, ν/cm^{-1}: 1100, 1015, 820 (Fc); 1600 (C=N, cycle); 1570 (C=C, cycle); 1730 (C=O, COOEt); 1240 (C—O—C). ^{1}H NMR, δ: 4.40 (m, 2 H, Fc); 4.66 (m, 2 H, Fc); 4.04 (s, 5 H, Fc); 6.40 (s, 1 H, CH); 4.36 (q, 2 H, $CH_3C\underline{H}_2$); 1.35 (t, 3 H, $C\underline{H}_3CH_2$).

3-Acetyl-5-ferrocenoylisoxazoline (14). The reaction mass was stirred for 3 h, the yield of compound **14** was 71 %, noncrystallizing oil. Found (%): C, 58.9; H, 4.3; N, 4.4. $C_{16}H_{15}FeNO_3$. Calculated (%): C, 59.1; H, 4.6; N, 4.3. IR, ν/cm^{-1}: 1090, 1000, 815 (Fc); 1570 (C=N, cycle); 1650 (C=O); 1680 (C=O, CH_3CO). ^{1}H NMR, δ: 4.60 (m, 2 H, Fc); 4.87 (m, 2 H, Fc); 4.17 (s, 5 H, Fc); 3.37 (m, 2 H, CH_2); 5.43 (s, 1 H, CH); 2.50 (s, 3 H, CH_3).

3-Acetyl-5-ferrocenylisoxazole (16). The reaction mass was stirred for 3 h and allowed to stand overnight. The yield of compound **16** was 68 %, m.p. was 137—138 °C (from hexane). Found (%): C, 60.3; H, 4.3; N, 4.6. $C_{15}H_{13}FeNO_2$. Calculated (%): C, 61.0; H, 4.4; N, 4.7. IR, ν/cm^{-1}: 1100, 1015, 830 (Fc); 1600 (C=N, cycle); 1600 (C=C, cycle); 1730 (C=O, CH_3CO). ^{1}H NMR, δ: 4.43 (m, 2 H, Fc); 4.77 (m, 2 H, Fc); 4.10 (s, 5 H, Fc); 6.43 (s, 1 H, CH); 2.60 (s, 3 H, CH_3).

5-Ferrocenyl-3-phenylisoxazoline (20). The reaction mass was stirred for 8 h, the yield of compound 20 was 52 %, m.p. 142—144 °C (from benzene—hexane). Found (%): C, 68.9; H, 5.0; N, 3.8. $C_{19}H_{17}FeNO$. Calculated (%): C, 68.9; H, 5.1; N, 4.2. IR, ν/cm^{-1}: 1100, 1030, 810 (Fc); 1600 (C=C, cycle); 1410 (C_6H_5). ^{1}H NMR, δ: 4.10 (s, 4 H, Fc); 4.07 (s, 5 H, Fc); 3.43 (m, 2 H, CH_2); 5.47 (m, 1 H, CH); 7.13 and 7.70 (both m, C_6H_5).

5-Ferrocenoyl-3-phenylisoxazoline (23). The reaction mass was stirred for 30 min, the yield of compound **23** was 97 %, m.p. was 111—113 °C (from benzene—hexane). Found (%): C, 67.0; H, 4.6; N, 3.6. $C_{20}H_{17}FeNO_2$. Calculated (%): C, 66.8; H, 4.7; N, 3.9. IR, ν/cm^{-1}: 1100, 1030, 800 (Fc); 1610 (C=N, cycle); 1685 (C=O); 1420 (C_6H_5). ^{1}H NMR, δ: 4.53 (m, 2 H, Fc); 4.83 (m, 2 H, Fc); 4.13 (s, 5 H, Fc); 3.57 (m, 2 H, CH_2); 5.43 (m, 1 H, CH); 7.17 (m, C_6H_5).

5-Ferrocenyl-3-phenylisoxazole (26). The reaction mass was stirred for 10 h, the yield of compound **26** was 70 %, m.p. was 160—162 °C (from benzene—hexane). Found (%): C, 69.6; H, 4.4; N, 3.9. $C_{19}H_{15}FeNO$. Calculated (%): C, 69.3; H, 4.6; N, 4.3. IR, ν/cm^{-1}: 1100, 1000, 820 (Fc); 1615 (C=N, cycle); 1585 (C=C, cycle); 1410 (C_6H_5). ^{1}H NMR, δ: 4.30 (m, 2 H, Fc); 4.66 (m, 2 H, Fc); 4.05 (s, 5 H, Fc); 6.33 (m, 1 H, CH); 7.17 and 7.90 (both m, C_6H_5).

5-Ferrocenyl-3-(*m*-nitrophenyl)isoxazoline (21). The reaction mass was stirred for 30 min, the yield of compound **21** was 80 %, m.p. 124—125 °C (from hexane). Found (%): C, 60.2; H, 4.5; N, 7.8. $C_{19}H_{16}FeN_2O_3$. Calculated (%): C, 60.6; H, 4.3; N, 7.4. IR, ν/cm^{-1}: 1100, 1000, 800 (Fc); 1600 (C=C, cycle); 1500 (C_6H_4); 1530, 1350 (NO_2). ^{1}H NMR, δ: 4.18 (s, 4 H, Fc); 4.15 (s, 5 H, Fc); 3.47 (m, 2 H, CH_2); 5.46 (m, 2 H, CH); 7.13 and 8.33 (both m, C_6H_4).

5-Ferrocenoyl-3-(*m*-nitrophenyl)isoxazoline (24). The reaction mass was stirred for 30 min, the yield of compound **24** was 96 %, m.p. was 152—153 °C (from benzene). Found (%): C, 59.6; H, 3.9; N, 6.8. $C_{20}H_{16}FeN_2O_4$. Calculated (%): C, 59.4; H, 4.0; N, 6.9. IR, ν/cm^{-1}: 1090, 1015, 800 (Fc); 1580 (C=N, cycle); 1660 (C=O); 1500 (C_6H_4); 1530, 1350 (NO_2). ^{1}H NMR, δ: 4.63 (m, 2 H, Fc); 4.94 (m, 2 H, Fc); 4.25 (s, 5 H, Fc); 3.69 (m, 2 H, CH_2); 5.86 (m, 1 H, CH); 8.50 (m, C_6H_4).

5-Ferrocenyl-3-(*m*-nitrophenyl)isoxazole (27). The reaction mass was stirred for 3 h and allowed to stand overnight. The yield of compound **27** was 94 %, m.p. was 161—162 °C (from benzene—hexane). Found (%): C, 61.3; H, 3.9; N, 7.4. $C_{19}H_{14}FeN_2O_3$. Calculated (%): C, 61.0; H, 3.7; N, 7.5. IR, ν/cm^{-1}: 1100, 1000, 820 (Fc); 1610 (C=N, cycle); 1580 (C=C, cycle); 1500 (C_6H_4); 1530, 1350 (NO_2). ^{1}H NMR, δ: 4.40 (m, 2 H, Fc); 4.73 (m, 2 H, Fc); 4.10 (s, 5 H, Fc); 6.43 (m, 1 H, CH); 7.40 and 8.50 (both m, C_6H_4).

5-Ferrocenyl-3-(*p*-nitrophenyl)isoxazoline (22). The reaction mass was stirred for 16 h, the yield of compound **22** was 76 %, m.p. 200—201.5 °C (from benzene). Found (%): C, 60.9; H, 4.4; N, 7.2. $C_{19}H_{16}FeN_2O_3$. Calculated (%): C, 60.6; H, 4.3; N, 7.4. IR, ν/cm^{-1}: 1100, 1030, 800 (Fc); 1600 (C=C, cycle); 1500 (C_6H_4); 1560, 1370 (NO_2). ^{1}H NMR, δ: 4.07 (s, 4 H, Fc); 4.03 (s, 5 H, Fc); 3.46 (m, 2 H, CH_2); 5.50 (m, 1 H, CH); 7.67 and 8.30 (both m, C_6H_4).

5-Ferrocenoyl-3-(*p*-nitrophenyl)isoxazoline (25). The reaction mass was stirred for 30 min, the yield of compound **25** was 70 %, m.p. was 171—173 °C (from benzene). Found (%): C, 59.2; H, 4.0; N, 6.6. $C_{20}H_{16}FeN_2O_4$. Calculated (%): C, 59.4; H, 4.0; N, 6.9. IR, ν/cm^{-1}: 1100, 1030, 820 (Fc); 1590 (C=N, cycle); 1660 (C=O); 1500 (C_6H_4); 1570, 1380 (NO_2). ^{1}H NMR, δ: 4.63 (m, 2 H, Fc); 4.90 (m, 2 H, Fc); 4.13 (s, 5 H, Fc); 3.66 (m, 2 H, CH_2); 5.86 (m, 1 H, CH); 7.95 and 8.23 (both m, C_6H_4).

5-Ferrocenyl-3-(*p*-nitrophenyl)isoxazole (28). The reaction mass was stirred for 10 h, the yield of compound **28** was 80 %, m.p. >250 °C (from alcohol). Found (%): C, 60.5;

H, 3.6; N, 7.1. $C_{19}H_{16}FeN_2O_3$. Calculated (%): C, 61.0; H, 3.7; N, 7.5. IR, ν/cm^{-1}: 1105, 1000, 815 (Fc); 1610 (C=N, cycle); 1600 (C=C, cycle); 1500 (C_6H_4); 1530, 1350 (NO_2). ^{1}H NMR, δ: 4.40 (m, 2 H, Fc); 4.71 (m, 2 H, Fc); 4.00 (s, 5 H, Fc); 6.40 (m, 1 H, CH); 7.48 and 8.43 (both m, C_6H_4).

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