1,3-Dipolar Cycloaddition of Nitrile Oxides to Methyl 3-(*p*-Nitrobenzoyloxy)acrylate: Methyl 3-(*p*-Nitrobenzoyloxy)acrylate as A Methyl Propiolate Equivalent with Reverse Regioselectivity

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3-Aryl-4-methoxycarbonylisoxazoles were prepared from the reaction of a variety of substituted benzonitrile oxides with methyl 3-(*p*-nitrobenzoyloxy)acrylate in moderate to good yields.

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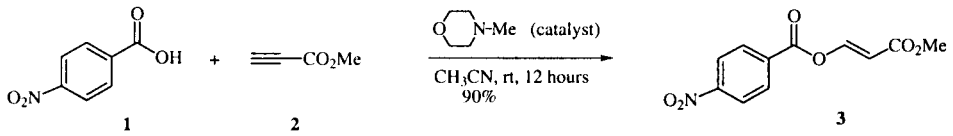
The 1,3-dipolar cycloaddition of nitrile oxides to alkenes or alkynes affords isoxazolines or isoxazoles which have been used as useful intermediates in organic syntheses [1]. For these heterocycles to be of greater value for synthetic purposes, it is very important to control the orientation of cycloaddition. It is well known that the cycloaddition of nitrile oxides to monosubstituted alkenes or alkynes provides 5-substituted cycloadducts predominantly [1]. The cycloaddition of nitrile oxides to methyl propiolate provides 5-methoxycarbonylisoxazoles as a major product with a trace product ratio of the corresponding 4-regioisomers [2]. Recently, Coutouli-Argyropoulou and his coworker reported that the cycloaddition of 2-methoxyvinyl phenyl ketone with nitrile oxides afforded mainly the 4-benzoyl-substituted isoxazoles through cycloaddition followed by the elimination of methanol [3]. In our initial attempts to explore the cycloaddition reactions of nitrile oxides with methyl 3-methoxyacrylate and methyl 3-benyloxyacrylate, we could recover mainly the starting materials with some unidentified materials. However, when we employed methyl 3-(*p*-nitrobenzoyloxy)acrylate, the cycloaddition reactions took place to provide the desired cycloadducts predominantly. Herein, we wish to report a facile synthesis of 3-aryl-4-methoxycarbonyl-substituted isoxzoles from the cycloadditions of a variety of benzonitrile oxides with methyl 3-(*p*-nitrobenzoyloxy)acrylate (**3**) as a methyl propiolate equivalent with reverse regioselectivity.

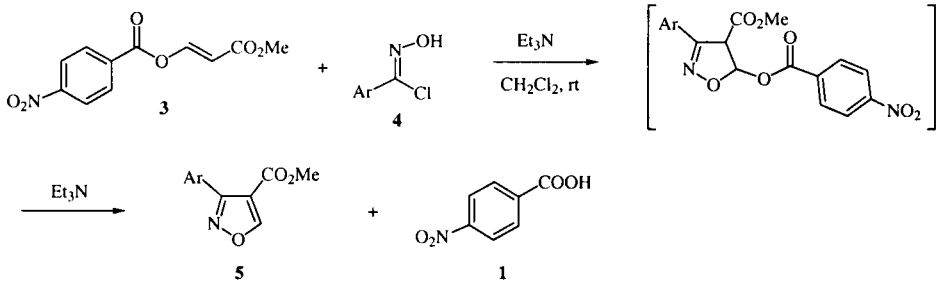
Methyl 3-(*p*-nitrobenzoyloxy)acrylate (**3**) was prepared by treatment of *p*-nitrobenzoic acid (**1**) with methyl propiolate in acetonitrile in the presence of 4-methylmorpholine for 12 hours at room temperature in 90% yield according to the slight modification of the method described in the literature [4]. The 1,3-dipolar cycloadditions of methyl 3-(*p*-nitrobenzoyloxy)acrylate (**3**) to a variety of nitrile oxides afforded the corresponding 3-aryl-4-methoxycarbonyl-substituted isoxazoles **5a-5k** in good yields with excellent regioselectivity. The 1,3-diploar cycloaddition took place in favor of the attack of the oxygen of nitrile oxides generated *in situ* to the carbon atom at the 3-position of the acrylate **3** to give the corresponding isoxazoline intermediate and subsequent elimination of *p*-nitrobenzoic acid afforded the 3-aryl-4-methoxycarbonyl-substituted isoxazoles. The cycloadditions of the nitrile oxides generated *in situ* from 4-methylphenylhydroximoyl chloride (**4b**), 4-nitrophenylhydroximoyl chloride (**4c**), and trifluoromethylphenyl-hydroximoyl chloride (**4d**) to **3** under standard conditions gave only moderate yields of the cycloadducts **5b-5d**, respectively, in repeated experiments. Although the possibility of formation of regioisomers of **5**, 3-aryl-5-methoxycarbonyl isoxazoles, was considered, we

Scheme 1



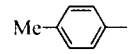
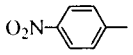
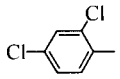
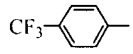
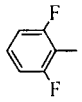
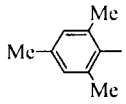
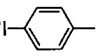
1 2 3

Scheme 2



3 4 5 1

Table
Synthesis of Isoxazoles **5a-5k**.

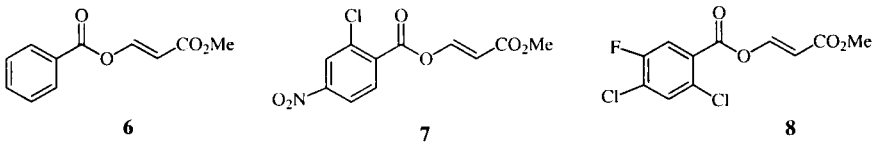
Entry	Hydroximic Acid Chlorides (**4**) Ar	Yields (%) **5**	Entry	Hydroximic Acid Chlorides (**4**) Ar	Yields (%) **5**
a		85	g		75
b		43	h		96
c		68	i		72
d		72	j		80
e		82	k		82
f		90			

could not detect the corresponding regioisomers from the crude products. All spectroscopic data of isoxazoles **5a-5k** gave satisfactory results on ^{1}H nmr, ir, ms, hrms and elemental analysis.

The characteristic ring proton of the isoxaoles obtained from cycloadditions appears at 8.98-9.07 ppm which is in good agreement with the reported data [3,5]. The results for the cycloadditions are summarized in the Table. It is interesting to note that introduction of strong electron-withdrawing substituents such as a nitro group on the aromatic ring of the compound **3** proves to be crucial to increase their dipolarophilicity. In order to determine the substituent-directing effects, methyl 3-benzoyloxyacrylate (**6**), methyl 3-(2-chloro-4-nitrobenzoyloxy)acrylate (**7**), and methyl 3-(2,4-dichloro-5-flurobenzoyloxy)acrylate (**8**) were examined for the cycloaddition reaction to compare their reactivities with nitrile oxides.

As expected, the cycloaddition reaction of the compound **6** with benzonitrile oxide became quite sluggish and gave only low yield of the corresponding cycloadduct (<10%) while the compound **7** readily reacted with benzonitrile oxide to provide the corresponding cycloadduct in good yields (79-83%). The compound **8** appeared to be a less activated dipolarophile than **7** and gave the corresponding cycloadduct in moderate yield (35-40%). These results have suggested to us that the strong electron-withdrawing substituents on the benzoyl group are essential to improve the reactivivity of cycloaddition with regioselectivity, and the nitro substituent at 4-position was found to be of the best choice in our experiments.

In conclusion, 3-aryl-4-methoxycarbonylisoxazoles were synthesized regioselectively by the cycloaddition reaction of methyl 3-(*p*-nitrobenzoyloxy)acrylate to a variety of substituted benzonitrile oxides in moderate to good yields which are otherwise difficult to prepare by the precedent methodology.



6 **7** **8**

Figure

EXPERIMENTAL

Melting points were measured in capillary tubes with a Thomas-Hover capillary melting point apparatus and are uncorrected. The ir (FT) spectra were recorded on a Shimadzu IR-435 spectrophotometer. The ^{1}H nmr spectra were recorded on a Varian GEMINI-200. ^{13}C nmr were recorded on a Bruker DRX-300. All chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane and coupling constants are given in herz (Hz). The mass spectra were recorded on a Shimadzu GCMS-OP 1000 mass spectrometer. Chromatographic separations were carried out on silica gel column (Merck silica gel 230-400).

Methyl 3-(*p*-Nitrobenzoyloxy)acrylate (**3**).

To a solution of *p*-nitrobenzoic acid 10 g (0.060 mole) in dry acetonitrile (100 ml) was added methyl propiolate 5.5 g (0.066 mole) and 4-methylmorpholine 3.0 g (0.03 mole) at room temperature. The reaction mixture was warmed to 40° and stirred for 12 hours. The solvent was removed by rotary evaporater and purified by recrystallization in ether/hexane to afford the product as white crystals (90%), mp 149-150°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 8.51 (d, J = 12.4 Hz, 1H), 8.32-8.25 (m, 4H), 5.98 (d, J = 12.4 Hz), 3.80 (s, 3H); ir (potassium bromide): (cm^{-1}) 3125, 3094, 3008, 2961, 2861, 1746, 1662, 1603, 1522, 1267, 1136; hrms Calcd. for $C_{11}H_9NO_6$: 251.0429. Found: 251.0431.

Anal. Calcd. for $C_{11}H_9NO_6$: C, 52.60; H, 3.61; N, 5.58. Found: C, 52.65; H, 3.62; N, 5.54.

General Procedure for the Preparation of Isoxazoles **5a-5k**.

To a solution of methyl 3-(*p*-nitrobenzoyloxy)acrylate 0.5 g (2.0 mmoles, 1.0 equivalent) and hydroximoyl chloride (2.0 equivalents) in methyl chloride was added triethylamine (3.5 equivalents) at room temperature. The reaction mixture was stirred for 5-6 hours and excess methylene chloride (30 ml) was

added. The organic layer was washed with water twice, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel (hexane/ethyl acetate = 5:1) to give the product as an oil or a solid.

3-Phenyl-4-methoxycarbonylisoxazole (**5a**).

This compound was obtained as a solid (85%), mp 49-51°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 8.98 (s, 1H), 7.80-7.75 (m, 2H), 7.49-7.42 (m, 3H), 3.78 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 164.0, 161.0, 160.9, 130.0, 129.1, 128.8, 128.4, 128.0, 126.9, 112.3, 51.7; ir (neat): (cm^{-1}) 3199, 3102, 2956, 1736, 1566, 1449, 1301, 1137, 1018, 761; hrms Calcd. for $C_{11}H_9NO_3$: 203.0570. Found: 203.0566.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.07; H, 4.42; N, 6.90.

3-(4-Methylphenyl)-4-methoxycarbonylisoxazole (**5b**).

This compound was obtained as an oil (43%); ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.00 (s, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 3.84 (s, 3H), 2.43 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 164.1, 161.3, 161.1, 140.3, 134.5, 129.2, 128.9, 126.8, 124.1, 112.4, 51.9, 21.3; ir (neat): (cm^{-1},) 3103, 3028, 2955, 1738, 1587, 1457, 1302 1137, 774; hrms Calcd. for $C_{12}H_{11}NO_3$: 217.0738. Found: 217.0738.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.37; H, 5.18; N, 6.45.

3-(4-Nitrophenyl)-4-methoxycarbonylisoxazole (**5c**).

This compound was obtained as a white crystals (68%), mp 124-125°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.06 (s, 1H), 8.28 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H), 3.83 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 164.7, 160.9, 159.5, 133.4, 131.0, 130.5, 123.8, 123.7, 123.3, 112.6, 52.2; ir (potassium bromide): (cm^{-1}) 3099, 2962, 1735, 1524, 1460, 1312, 1147, 854; hrms Calcd. for $C_{11}H_8N_2O_5$: 248.0433. Found: 248.0430.

Anal. Calcd. for $C_{11}H_8N_2O_5$: C, 53.23; H, 3.25; N, 11.29. Found: C, 53.35; H, 3.30; N, 10.94.

3-(4-Trifluoromethylphenyl)-4-methoxycarbonylisoxazole (**5d**).

This compound was obtained as an oil (72%); ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.04 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.94 (d, J = 8.1 Hz, 2H), 3.84 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 164.4, 161.0, 160.2, 132.2, 131.8, 130.8, 129.9, 125.6, 125.2, 122.1, 112.6, 52.0; ir (potassium bromide): (cm^{-1}) 3115, 2967, 1736, 1566, 1469, 1319, 1144, 841; hrms Calcd. for $C_{12}H_8NO_3F_3$: 271.0456. Found: 271.0466.

Anal. Calcd. for $C_{12}H_8NO_3F_3$: C, 53.15; H, 2.97; N, 5.16. Found: C, 53.18; H, 3.00; N, 5.19.

3-(3-Bromophenyl)-4-methoxycarbonylisoxazole (**5e**).

This compound was obtained as a light brown solid (82%), mp 61-62°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.02 (s, 1H), 7.97-7.31 (m, 4H), 3.85 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 164.4, 161.0, 159.9, 133.1, 132.2, 129.7, 129.0, 128.0, 122.1, 112.5, 52.0; ir (potassium bromide): (cm^{-1}) 3105, 3003, 2955, 1738, 1558, 1449, 1414, 1303, 1139, 774; hrms Calcd. for $C_{11}H_8NO_3$: 280.9703. Found: 280.9704.

Anal. Calcd. for $C_{11}H_8NO_3Br$: C, 46.84; H, 2.86; N, 4.97. Found: C, 46.87; H, 2.83; N, 4.97.

3-(4-Chlorophenyl)-4-methoxycarbonylisoxazole (**5f**).

This compound was obtained as a solid (90%), mp 90-91°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.02 (s, 1H), 7.78 (d, J = 2.1 Hz, 2H), 7.74 (d, J = 2.1 Hz, 2H), 3.85 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 164.4, 161.2, 160.3, 136.5, 130.8, 129.1, 128.8, 128.6, 125.6, 112.5, 52.1; ir (potassium bromide): (cm^{-1}) 3150, 2963, 1735, 1560, 1460, 1313, 1137, 774; hrms Calcd. for $C_{11}H_8NO_3Cl$ 237.0192. Found: 237.0176.

Anal. Calcd. for $C_{11}H_8NO_3Cl$: C, 55.60; H, 3.39; N, 5.89. Found: C, 55.64; H, 3.45; N, 5.86.

3-(2-Chlorophenyl)-4-methoxycarbonylisoxazole (**5g**).

This compound was obtained as an oil (75%); ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.01 (s, 1 H), 7.51-7.31 (m, 4H), 3.73 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 162.8, 160.7, 159.6, 133.8, 131.0, 130.9, 129.4, 127.0, 126.5, 114.2, 51.8; ir (potassium bromide): (cm^{-1}, neat) 3338, 3112, 2956, 1739, 1587, 1517, 1444, 1309, 1141, 759; hrms Calcd. for $C_{11}H_8NO_3Cl$: 237.0192. Found: 237.0197.

Anal. Calcd. for $C_{11}H_8NO_3Cl$: C, 55.60; H, 3.39; N, 5.89. Found: C, 55.62; H, 3.41; N, 5.85.

3-(3-Chlorophenyl)-4-methoxycarbonylisoxazole (**5h**).

This compound was obtained as a solid (96%), mp 73-74°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 8.99 (s, 1H), 7.80 (m, 1H), 7.67 (m, 1H), 7.47-7.33 (m, 2H) 3.81 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 164.5, 161.1, 160.0, 134.1, 130.3, 129.5, 129.4, 128.9, 127.6, 112.5, 52.1; ir (potassium bromide): (cm^{-1}) 3132, 3104, 2967, 1735, 1562, 1435, 1313, 1141, 766; hrms Calcd. for $C_{11}H_8NO_3Cl$: 237.0192. Found: 237.0190.

Anal. Calcd. for $C_{11}H_8NO_3Cl$: C, 55.60; H, 3.39; N, 5.89. Found: C, 55.67; H, 3.42; N, 5.83.

3-(2,4-Dichlorophenyl)-4-methoxycarbonylisoxazole (**5i**).

This compound was obtained as a solid (72%), mp 58-59°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.01 (s, 1H), 7.51 (m, 1H), 7.35 (m, 2H), 7.35 (m, 2H), 3.75 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 163.0, 160.6, 158.8, 136.6, 134.8, 131.8, 129.5, 127.0, 125.6, 114.2, 52.0; ir (potassium bromide): (cm^{-1}) 3110, 2956, 1739, 1593, 1450, 1308, 1141, 777; hrms Calcd. for $C_{11}H_7NO_3Cl_2$: 270.9802. Found: 270.9785.

Anal. Calcd. for $C_{11}H_7NO_3Cl_2$: C, 48.56; H, 2.59; N, 5.15. Found: C, 48.57; H, 2.57; N, 5.14.

3-(2,6-Difluorophenyl)-4-methoxycarbonylisoxazole (**5j**).

This compound was obtained as an oil (80%); ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.08 (s, 1H), 7.54-7.39 (m, 1H), 7.10-7.00 (m, 2H), 3.77 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 163.2, 162.2, 162.1, 132.2, 132.1, 132.0, 129.2, 123.8, 114.3, 51.9; ir (potassium bromide): (cm^{-1}) 3116, 2959, 1742, 1595, 1472, 1307, 788; hrms Calcd. for $C_{11}H_7NO_3F_2$: 239.0394. Found: 239.0393.

Anal. Calcd. for $C_{11}H_7NO_3F_2$: C, 55.24; H, 2.95; N, 5.86. Found: C, 55.24; H, 2.95; N, 5.89.

3-(2,4,6-Trimethylphenyl)-4-methoxycarbonylisoxazole (**5k**).

This compound was obtained as a pale yellow solid (82%), mp 75-76°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 9.07 (s, 1H), 6.95 (s, 2H), 3.74 (s, 3H), 2.34 (s, 3H), 2.07(s, 6H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 163.2, 160.9, 160.8, 139.0, 136.9, 129.7, 128.6, 128.1, 123.8, 113.8, 51.8, 21.1, 19.9, 18.1; ir (potassium bromide): (cm^{-1}) 3106, 2955, 2925, 1736, 1581,

1389, 1295, 1133; hrms Calcd. for $C_{14}H_{15}NO_3$: 245.1051. Found: 245.1047.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.62; H, 6.19; N, 5.65.

Methyl 3-Benzoyloxyacrylate (**6**).

This compound was obtained as a colorless crystal (95%), mp 53-54°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 8.55 (d, J = 12.8 Hz, 1H), 8.14 (m, 2H), 7.65 (m, 1H), 7.49 (m, 1H), 5.94 (d, J = 12.8 Hz, 1H), 3.78 (s, 3H); ms: (20 eV) m/z (relative intensity) 206 (M^+, 0.5), 175 (1.5), 105 (100), 77 (44.8), 51 (16.3).

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.08; H, 4.89. Found: C, 64.07; H, 4.89.

Methyl 3-(2-Chloro-4-nitrobenzoyloxy)acrylate (**7**).

This compound was obtained as a white solid (90%), mp 109-110°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 8.42 (d, J = 12.6 Hz, 1H), 8.00 (m, 1H), 7.80-7.62 (m, 2H), 5.85(d, J = 12.6 Hz, 1H), 3.79 (s, 3H); ms: (20 eV) m/z (relative intensity) 286 (M^+, 1.5), 254 (0.5), 184 (100), 168 (8.4), 138 (3.6), 110 (9.5), 76 (12.2).

Anal. Calcd. for $C_{11}H_8NO_6Cl$: C, 46.25; H, 2.82; N, 4.90. Found: C, 46.23; H, 2.84; N, 4.91.

Methyl 3-(2,4-Dichloro-5-fluorobenzoyloxy)acrylate (**8**).

This compound was obtained as a white solid (95%), mp 107-108°; ^{1}H nmr (200 MHz, deuteriochloroform): δ 8.46 (d, J = 12.5 Hz, 1H), 7.79 (d, J = 8.9 Hz, 1H), 7.60 (d, J = 6.3 Hz, 1H), 5.72 (d, J = 12.5 Hz, 1H), 3.78 (s, 3H); ms: (20 eV) m/z (relative intensity) 294 [$(M+1)^+$, 0.6], 293 (M^+, 0.3), 292 [$(M-1)^+$, 0.9]), 261 (1.0), 193 (75) 191 (100), 163 (19.2), 128 (9.7), 93 (6.9).

Anal. Calcd. for $C_{11}H_8Cl_2FO_4$: C, 45.08; H, 2.41. Found: C, 45.04; H, 2.45.

Acknowledgment.

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