Tetrahedron Vol. 48, No. 29, pp. 6059-6068, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

SPIROHETEROCYCLES FROM REACTION OF NITRILE OXIDES WITH HETEROCYCLIC *o*-QUINODIMETHANES

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(*Received in UK* 30 *April* 1992)

Key Words: *o*-Quinodimethanes; 1,3-Dipolar Cycloaddition; Pyrazole; Isoxazole; Dispiroisoxazolines

Abstract: *1,3-Dipolar cycloaddition to o-quinodimethanes has been observed for the first time in the reaction of pyrazole and isoxazole o-quinodimethanes* ***4-6*** *with the stable nitrile oxides* ***7*** *and* ***8****. The products, dispiroisoxazolines* ***9-14****, were isolated in moderate yields. In all cases the "anti" addition stereoisomers* ***9a-14a*** *were formed, as was established by X-ray crystallographic analysis on* ***13a*** *and* ***14a****, whereas the "syn" addition stereoisomers were isolated only in the case of* ***11b*** *and* ***13b****. When the bromosubstituted o-quinodimethane* ***16*** *was employed the monospiroisoxazolines* ***17*** *and* ***18*** *were obtained.*

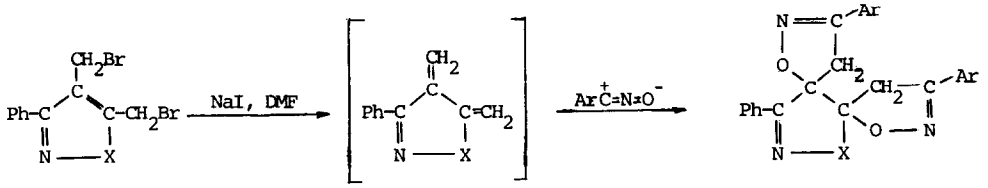
The utilization of *o*-quinodimethane intermediates and their respective derivatives as enophiles for the regio- and stereo-controlled annulation of aromatic systems is of practical importance and has been applied in efficient synthesis of alkaloids, steroids and terpenes.[1] Extension of *o*-quinodimethane/Diels Alder methodology to the synthesis of the heterocyclic analogues is also of major interest from a theoretical point of view and has recently found wide application in synthesis of complex polycyclic compounds.[2]

A survey of the literature reveals that cycloadditions of *o*-quinodimethanes with 1,3-dipoles have not been reported. Such reactions are also of major interest since they can in principle provide a route to new five- and eventually seven-membered heterocyclic systems by competing concerted and stepwise processes. Examples where the stepwise mechanism is discussed are the isolation of oximes in reactions of nitrile oxides with CC double-bonded dipolarophiles[3] and the isolation of [4+3] cycloaddition products from the reaction of 1,1,2,2,3,3-hexamethyl-4,5-bismethylenecyclopentane with nitrones[4]. We speculated that a stepwise mechanism leading to the formation of seven-membered ring compounds could also be favored in the case of 1,3-dipolar cycloadditions of *o*-quinodimethanes because of their high tendency for aromatization.

In continuation with our investigations on heterocyclic *o*-quinodimethanes[5-6] an investigation of the potential of their dipolar additions was undertaken. In this paper we report a study on the cycloadditions of isoxazole and pyrazole *o*-quinodimethanes with the stable nitrile oxides, mesitonitrile oxide and 2,6-dichlorobenzonitrile oxide.

RESULTS AND DISCUSSION

The synthesis of 4,5-bis(bromomethyl)-3-phenyl-isoxazole **1** and 1-benzoyl-4,5-bis-(bromomethyl)-3-phenyl-1*H*-pyrazole **3** required for our purpose has been described[5,6] earlier, whereas 1-acetyl-4,5-bis(bromomethyl)-3-phenyl-1*H*-pyrazole **2** was prepared by analogy of the 1-benzoyl-derivative **3** in two simple steps, namely by acetylation[7] of 4,5(3)-dimethyl-3(5)-phenyl-1*H*-pyrazole followed by subsequent bromination of the isolated 1-acetyl-4,5-dimethyl-3-phenyl-1*H*-pyrazole (see Experimental). The heterocyclic *o*-quinodimethanes **4-6**, generated *in situ* by treatment of the corresponding bisbromides **1-3** with sodium iodide in DMF, were trapped with one molar ratio of the stable nitrile oxides, mesitonitrile oxide **7** and 2,6-dichlorobenzonitrile oxide **8**, to afford moderate yields (25-30%) of the dispiroisoxazolines **9-14** by addition of two molecules of nitrile oxide to the two exomethylenic double bonds respectively (Scheme I). When a two molar



1: X=O
2: X=NCOMe
3: X=NCOPh

4: X=O
5: X=NCOMe
6: X=NCOPh

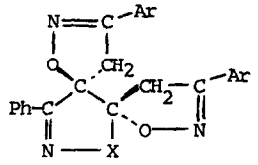
7: Ar=Mes
8: Ar=2,6-$Cl_2C_6H_3$

9: X=O, Ar=Mes
10: X=O, Ar=2,6-$Cl_2C_6H_3$
11: X=NCOMe, Ar=Mes
12: X=NCOMe, Ar=2,6-$Cl_2C_6H_3$
13: X=NCOPh, Ar=Mes
14: X=NCOPh, Ar=2,6-$Cl_2C_6H_3$

Scheme I

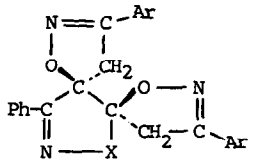
ratio of the nitrile oxide was used the product yield was improved considerably (~40%). A considerable amount of polymeric material was always formed.

In all cases the "anti" dispiroisoxazolines **9a-14a** were isolated. It is of interest to note that from the reaction of the pyrazole *o*-quinodimethanes **5** and **6** with mesito nitrile oxide the "syn" dispiroisoxazolines **11b** and **13b** were also isolated. Searching for the stereoselectivity reasons, one encounters that the "anti" dispiroisoxazolines are sterically favored and that the remarkably high proportion of the "syn" isomers, **11b** and **13b**, could be assigned to the use of polar solvents and high reaction temperatures.[8]



9a - 14a

"anti"



9b - 14b

"syn"

The regioselectivity of the reactions is in accordance with the regioselectivity reported for the additions of nitrile oxides to 1,1-disubstituted alkenes.[9]

The products **9-14** were identified by their spectral data (Table) and elemental analysis, but their configuration was established by X-ray crystallographic analysis. Crystallographic analysis was performed on the dichlorosubstituted dispiroisoxazoline **14a** (Figure 1) and on the faster moving on the tlc isomer of the mesito-dispiroisoxazoline **13**, which proved to be the "anti" addition product **13a** (Figure 2), thus the slower moving isomer being the "syn" addition product **13b**.

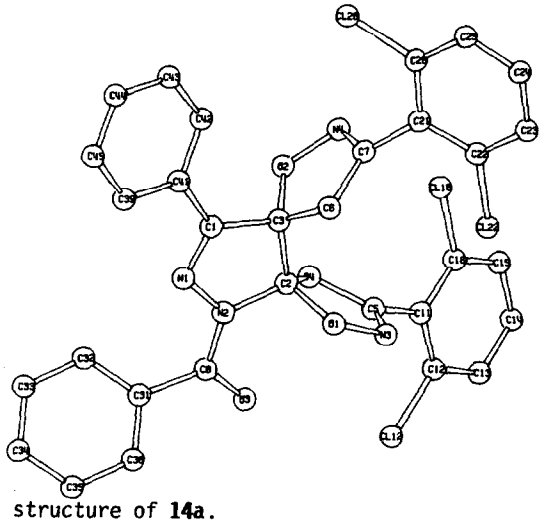


Figure 1. X-ray crystal structure of **14a**.

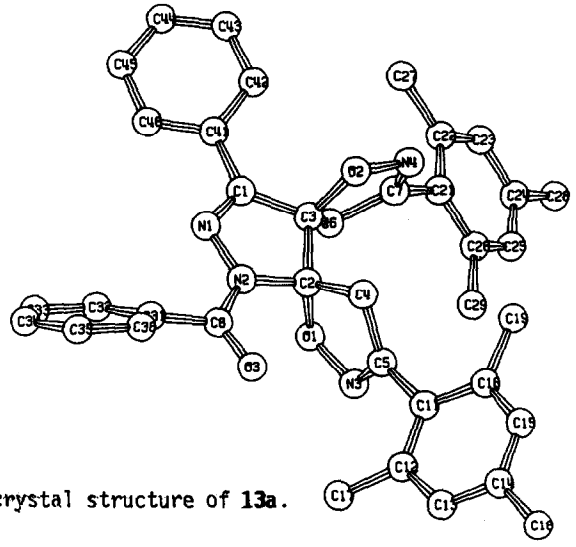
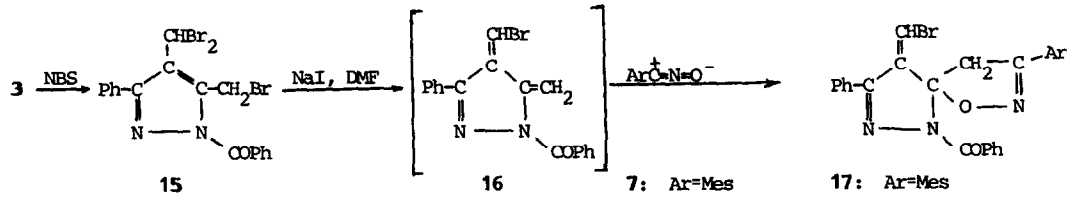


Figure 2. X-ray crystal structure of **13a**.

In the ^{1}H-NMR spectrum all "anti" dispiroisoxazolines **9a-14a** exhibit for the protons of the two isoxazolinic -CH_2-groups two AB systems with *Jgem* 17 Hz with exception of the dichlorosubstituted compounds **12a** and **14a**, where the one -CH_2-group appears as a broad singlet. Concerning the mesito-methyl protons of the "anti" isomers **9a**, **11a** and **13a**, they appear as a 12- and 6-proton singlet, whereas the corresponding protons of the "syn" isomers **11b** and **13b** appear as two 6-proton and two 3-proton singlets. Similarly the mesito-aromatic protons in compounds **9a**, **11a** and **13a** appear as a 4-proton singlet, whereas in compounds **11b** and **13b** as two 2-proton singlets. Analogous differences appear in the ^{13}C-NMR spectra of **9a** and **9b**, where in the case of **9a** three signals and in the case of **9b** five signals are observed for the six mesito-methyl carbons.

In connection with the above results we studied the reactions of the bromosubstituted pyrazole analogue of *o*-quinodimethane **16** with the stable nitrile oxides **7** and **8**. The bromo-quinodimethane **16** was prepared from the tribromosubstituted pyrazole **15** as shown in Scheme 2. The structure of **15** was deduced from its ^{1}H-NMR spectrum, where the -CH_2Br protons resonated at 5.34 δ, in comparison with the ^{1}H-NMR spectrum of the dibromosubstituted pyrazole **3**, where the 4- and 5-CH_2Br protons resonated at 4.49 and 5.05 δ respectively.[10]



Scheme 2

From the reaction of the bromoquinodimethane **16** with the nitrile oxides **7** and **8** only one monospiroisoxazoline, **17** and **18** respectively, was isolated proving that the nitrile oxide does not attack the more hindered and also electronically deactivated vinyl bromide. The IR spectra of the monospiroisoxazolines exhibited a carbonyl absorption at 1670 cm^{-1}, namely at lower frequencies than those associated with aroylsubstituted aromatic pyrazoles.[11] In the ^1H-NMR spectra the isoxazolinic $-CH_2-$ protons appear as a broad singlet at approximately 4.14 δ and the CHBr proton as a singlet at approximately 7.26 δ.

Table. Spectroscopic Characteristics of the Spiroisoxazolines

Compd	IR (cm^{-1}) (Nujol)	^1H-NMR (δ, ppm)
9a	1600	2.20 (s, 6H), 2.27 (s, 12H), 3.42 (d, 1H, *J* = 19 Hz), 3.43 (d, 1H, *J* = 18 Hz), 3.79 (d, 1H, *J* = 18 Hz), 4.04 (d, 1H, *J* = 19 Hz), 6.82 (s, 4H), 7.34-7.56 (m, 3H), 7.58-7.85 (m, 2H)
10a	1580	3.66 (d, 1H, *J* = 18 Hz), 3.67 (d, 1H, *J* = 19 Hz), 3.89 (d, 1H, *J* = 18 Hz), 4.13 (d, 1H, *J* = 19 Hz), 7.30-7.60 (m, 9H), 7.69-7.88 (m, 2H)
11a	1690	2.21 (s, 12H), 2.39 (s, 6H), 2.42 (s, 3H), 3.30 (d, 1H, *J* = 19 Hz), 3.65 (d, 1H, *J* = 18 Hz), 4.20 (d, 1H, *J* = 18 Hz), 4.28 (d, 1H, *J* = 19 Hz), 6.82 (s, 4H), 7.26-7.56 (m, 3H), 7.78-8.02 (m, 2H)
11b	1690	2.04 (s, 6H), 2.22 (s, 3H), 2.25 (s, 3H), 2.38 (s, 6H), 2.44 (s, 3H), 3.27 (d, 1H, *J* = 19 Hz), 3.44 (d, 1H, *J* = 19 Hz), 3.61 (d, 1H, *J* = 19 Hz), 4.39 (d, 1H, *J* = 19 Hz), 6.80 (s, 2H), 6.84 (s, 2H), 7.29-7.51 (m, 3H), 7.73-8.04 (m, 2H)
12a	1690	2.44 (s, 3H), 3.58 (d, 1H, *J* = 23 Hz), 4.18 (s, 2H), 4.19 (d, 1H, *J* = 23 Hz), 7.18-7.56 (m, 9H), 7.71-7.97 (m, 2H)
13a	1665	2.26 (s, 12H), 2.46 (s, 6H), 3.39 (d, 1H, *J* = 18 Hz), 3.86 (d, 1H, *J* = 19 Hz), 4.31 (d, 1H, *J* = 19 Hz), 4.37 (d, 1H, *J* = 18 Hz), 6.89 (s, 4H), 7.33-7.57 (m, 6H), 7.76-8.00 (m, 4H)
13b	1670	2.10 (s, 6H), 2.24 (s, 3H), 2.29 (s, 3H), 2.48 (s, 6H), 3.32 (d, 1H, *J* = 18 Hz), 3.45 (d, 1H, *J* = 18 Hz), 3.68 (d, 1H, *J* = 18 Hz), 4.40 (d, 1H, *J* = 18 Hz), 6.84 (s, 2H), 6.92 (s, 2H), 7.36-7.98 (m, 6H), 7.82-8.09 (m, 4H)
14a	1665	3.73 (d, 1H, *J* = 19 Hz), 4.26 (s, 2H), 4.27 (d, 1H, *J* = 19 Hz), 7.26-7.54 (m, 12H), 7.71-8.03 (m, 4H)
17	1670	2.28 (s, 3H), 2.60 (s, 6H), 4.03 (s, 2H), 6.92 (s, 2H), 7.26 (s, 1H), 7.31-7.70 (m, 8H), 7.79-8.00 (m, 2H)
18	1665	4.27 (s, 2H), 7.29-7.70 (m, 12H), 7.81-8.02 (m, 2H)

CONCLUSION

It is well known that *o*-quinodimethanes exist only as transient intermediates in solution and that their reactions with external reagents must always compete with dimerization or polymerization.[1,2] However, many dienes are sufficiently reactive to compete effectively and to form Diels-Alder adducts in good yields. Concerning the stable nitrile oxides **7** and **8**, although they are comparatively less reactive and short lived in high temperatures, it is remarkable that they reacted with the isoxazole and pyrazole *o*-quinodimethane in accordance with the orbital symmetry rules with formation of five-membered ring compounds in moderate yields.

Evidence for the formation of seven membered ring compounds by a stepwise mechanism has not been found despite the tendency of aromatization of the heterocyclic ring.

A synthetic useful application of these reactions is the formation of otherwise inaccessible pyrazole and isoxazole dispiroisoxazolines.

EXPERIMENTAL SECTION

All melting points are uncorrected. NMR spectra were obtained in deuteriochloroform, unless otherwise indicated, on a Bruker AW 80 or on a Jeol JNM-GX 270 spectrometer. Chemical shifts are given in parts per million from Me_4Si. Mass spectra were recorded at 70 eV on a Hitachi-Perkin Elmer RMU-6L spectrometer. Infrared spectra were obtained on a Perkin-Elmer Model 297 spectrometer. Analyses were performed with a Perkin-Elmer Model 240B CHN Analyzer.

Literature procedures were followed for the preparation of mesitonitrile oxide **7** and 2,6-dichlorobenzonitrile oxide **8**.[11]

Preparation of 4,5-bis(bromomethyl)-3-phenylisoxazole 1.-To an ice-cooled and stirred solution of 4,5-dimethyl 3-phenyl isoxazole dicarboxylate[12] (1.3 g, 5 mmol) in dry ethanol (60 ml) sodium borohydride (0.8 g, 20 mmol) was added portionwise and the solution was stirred for 16 h at 25 °C. Concentrated hydrochloric acid was added to make the reaction mixture acidic. The mixture was immediately neutralized with solid sodium bicarbonate, dried, filtered, and the solvent was evaporated to give 4,5-hydroxymethyl-3-phenylisoxazole (0.65 g, 64 %), which was crystallized from hot chloroform to give a white solid: mp 104-106 °C; IR (Nujol) 3310-3340 (OH) cm^{-1}; ^{1}H-NMR (acetone-d_6) δ 3.82 (s, 2H), 4.09 (d, J = 5 Hz, 2H), 4.62 (br s, 2H), 7.31-7.49 (m, 3H), 7.62-7.83 (m, 2H); MS *m/e* 207 (M^++2); Anal. Calcd for $C_{11}H_{11}NO_3$ (205.21): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.28; H, 5.57; N, 6.86.

Phosphorous tribromide (1.3 g, 5 mmol) in dry dichloromethane (10 ml) was added dropwise with stirring to an ice-cooled solution of 4,5-hydroxymethyl-3-phenylisoxazole (1 g, 5 mmol) and dry pyridine (0.2 ml) in dry dichloromethane (30 ml) The mixture was stirred for 24 h, and then poured into water (50 ml). The organic layer was separated, dried and evaporated. Column chromatography of the reaction mixture (silica gel, 10:1 *n*-hexane/ethyl acetate) gave 4,5-bis(bromomethyl)-3-phenylisoxazole **1** (0.5 g, 31%): oil; IR (neat) 1600 (C=N) cm^{-1}; ^{1}H-NMR δ 4.39 (s, 2H), 4.54 (s, 2H), 7.39-7.63 (m, 3H), 7.63-7.89

(m, 2H); MS *m/e* 329,331,333 (M^+); Anal. Calcd for $C_{11}H_9Br_2NO$ (331.02): C, 39.91; H, 2.74; N, 4.23. Found C, 40.18; H, 2.81; N, 4.34.

Preparation of 1-acetyl-4,5-bis(bromomethyl)-3-phenyl-1H-pyrazole 2.- To a mixture of 4,5(3)-dimethyl-3(5)-phenyl-1*H*-pyrazole (2.6 g, 15 mmol) and pyridine (1.7 ml) in dry dichloromethane (100 ml) acetylchloride (1.3 g, 16 mmol) was added dropwise. The mixture was stirred 1 h and then poured into water (50 ml). The organic layer was washed with 10% sodium hydrogen carbonate solution, dilute hydrochloric acid and then with water, dried and evaporated. Column chromatography of the reaction mixture (silica gel, 10:1 *n*-hexane/ ethyl acetate) gave 1-acetyl-4,5-dimethyl-3-phenyl-1*H*-pyrazole (2.3 g, 71%): mp 56-58 °C (from ether); IR (Nujol) 1720 (C=O) cm^{-1}; ^{1}H-NMR δ 2.04 (s, 3H), 2.52 (s, 3H), 2.68 (s, 3H), 7.26-7.55 (m, 3H), 7.57-7.76 (m, 2H); MS *m/e* 214 (M^+); Anal. Calcd for $C_{13}H_{14}N_2O$ (214.26): C, 72.87; H, 6.58; N, 13.07. Found C, 72.85; H, 6.38 N, 13.16.

A solution of 1-acetyl-4,5-dimethyl-3-phenyl-1*H*-pyrazole (1.07 g, 5 mmol), N-bromosuccinimide (1.78 g, 10 mmol) and benzoyl peroxide (0.4 g) in carbon tetrachloride (50 ml) was refluxed for 2 h. The suspension was filtered, and the filtrate was washed with water, dried and evaporated. Recrystallization from ether gave 1-acetyl-4,5-bis(bromomethyl)-3-phenyl-1*H*-pyrazole (1.1 g, 59%): mp 104-107 °C; IR (Nujol) 1730 (C=O) cm^{-1}; ^{1}H-NMR δ 2.76 (s, 3H), 4.46 (s, 2H), 4.98 (s, 2H), 7.39-7.54 (m, 3H), 7.60-7.86 (m, 2H); MS *m/e* 370,372,374 (M^+); Anal. Calcd for $C_{13}H_{12}Br_2N_2O$ (372.07): C, 41.97; H, 3.25; N, 7.53. Found C, 42.08; H, 3.11; N, 7.39.

Preparation of 1-benzoyl-4,5-bis(bromomethyl)-3-phenyl-1H-pyrazole 3.- To a mixture of 4,5(3)-dimethyl-3(5)-phenyl-1*H*-pyrazole (1.72 g, 10 mmol) and pyridine (1.7 ml) in dry dichloromethane (100 ml) benzoylchloride (1.5 g, 11 mmol) was added dropwise. The mixture was stirred for a further hour, and then worked-up as described above. Column chromatography of the reaction mixture (silica gel, 20:1 *n*-hexane/ethyl acetate) gave 1-benzoyl-4,5-dimethyl-3-phenyl-1*H*-pyrazole (2.2 g, 79%): mp 138-140 °C (from ether); IR (Nujol) 1690 (C=O) cm^{-1}; ^{1}H-NMR δ 2.16 (s, 3H), 2.64 (s, 3H), 7.28-7.76 (m, 8H), 7.96-8.16 (m, 2H); MS *m/e* 276 (M^+); Anal. Calcd for $C_{18}H_{16}N_2O$ (276.32): C, 78.24; H, 5.83; N, 10.14. Found C, 78.32; H, 6.08 N, 10.31.

A solution of 1-benzoyl-4,5-dimethyl-3-phenyl-1*H*-pyrazole (1.6 g, 5 mmol), N-bromosuccinimide (1.5 g, 10 mmol) and benzoyl peroxide (0.46 g) in carbon tetrachloride (50 ml) was refluxed for 2 h. The suspension was filtered, and the filtrate was washed with water, dried and evaporated. Recrystallization from ether gave 1-benzoyl-4,5-bis(bromomethyl)-3-phenyl-1*H*-pyrazole (1.7 g, 78%): mp 96-98 °C; IR (Nujol) 1710 (C=O) cm^{-1} ^{1}H-NMR δ 4.49 (s, 2H), 5.05 (s, 2H), 7.23-7.86 (m, 8H), 7.94-8.19 (m, 2H); MS *m/e* 436,434,432 (M^+); Anal. Calcd for $C_{18}H_{14}Br_2N_2O$ (434.14): C, 49.80; H, 3.25; N, 6.45. Found C, 50.01; H, 3.31; N, 6.55.

Preparation of 1-benzoyl-4-dibromomethyl-5-bromomethyl-3-phenyl-1H-pyrazole 15.- Bromination of 1-benzoyl-4,5-bis-(bromomethyl)-3-phenyl-1*H*-pyrazole 3 (868 mg, 2 mmol) with N-bromosuccinimide (712 mg, 4 mmol) and benzoyl peroxide (0.1 g) for 10 h gave,

after work-up as described above the tri-bromopyrazole **15** (480 mg, 47%): mp 111-114 °C; IR (Nujol) 1685 (C=O) cm^{-1}; ^{1}H-NMR δ 5.34 (s, 2H), 6.68 (s, 1H), 7.28-7.78 (m, 8H), 7.92-8.19 (m, 2H); MS *m/e* 510,512,514,516 (M^+); Anal. Calcd for $C_{18}H_{13}Br_3N_2O$ (513.05): C, 42.14; H, 2.55 N, 5.46. Found C, 42.39; H, 2.51; N, 5.68.

General Procedure for Adduct Formation between o-Quinodimethanes 4-6, 16 and the stable Nitrile Oxides, Mesitonitrile Oxide 7 and 2,6-Dichlorobenzonitrile Oxide 8.-Sodium iodide (2 mmol) was added in one portion to a stirred solution of the bromide (1 mmol) and nitrile oxide (1-2 mmol) in DMF (30 ml). The mixture was stirred at 120-130 °C for 2 h, the solvent was evaporated under reduced pressure, and the residue was extracted into dichloromethane. The suspension was washed with saturated aqueous sodium hydrogen sulfite and then with water. The products were isolated either by column chromato-graphy (silica gel, 10:1 *n*-hexane/ethyl acetate) or by crystallization.

3,3''-Bis(2,4,6-trimethylphenyl)-3'-phenyl-isoxazole-5-(4H)-spiro-5'-isoxazole-4'-spiro-5''(4''H)-isoxazole **9a**: The reaction was carried out using one molar ratio of nitrile oxide and the product **9a** was isolated by column chromatography (99 mg, 20%), mp 105-106 °C (from ether/*n*-hexane); MS *m/e* 493(M^+); Anal. Calcd for $C_{31}H_{31}N_3O_3$ (493.58): C, 75.43; H, 6.33; N, 8.51. Found C, 75.70; H, 6.11; N, 8.46. When a two molar ratio of nitrile oxide was used the product yield was increased to 31%.

3,3''-Bis(2,6-dichlorophenyl)-3'-phenyl-isoxazole-5(4H)-spiro-5'-isoxazole-4'-spiro 5''(4''H)-isoxazole **10a**: The reaction was carried out using a two molar ratio of nitrile oxide and the product **10a** was isolated by crystallization from methylene chloride/*n*-hexane (235 mg, 43%), mp 136-138°C; Anal. Calcd for $C_{25}H_{15}Cl_4N_3O_3$ (547.27): C, 54.87; H, 2.76; N, 7.68. Found C, 54.91; H, 2.58, N, 7.88.

2'-Acetyl-3,3''-bis(2,4,6-trimethylphenyl)-5'-phenyl-isoxazole-5(4H)-spiro-3'(2'H)-pyrazole-4'-spiro-5''(4''H)-isoxazole **11**: The reaction was carried out with one molar ratio of nitrile oxide and the mixture was chromatographed. The "anti" addition isomer **11a** was eluted first (64 mg, 12%), mp 180-181 °C (from ether); MS *m/e* 534 (M^+); Anal. Calcd for $C_{33}H_{34}N_4O_3$ (534.63): C, 74.13; H, 6.41; N, 10.48. Found C, 74.00; H, 6.28; N, 10.30. The "syn" addition isomer **11b** was eluted second (43 mg, 8%), mp 106-109 °C (from methylene chloride/*n*-hexane). Despite several attempts it was not possible to obtain a sample of this compound suitable for elemental analysis.When a two molar ratio of nitrile oxide was used, **11a** and **11b** were isolated in 19% and 15% yield respectively.

2'-Acetyl-3,3''-bis(2,6-dichlorophenyl)-5'-phenyl-isoxazole-5(4H)-spiro-3'(2'H)-pyrazole-4'-spiro-5''(4''H)isoxazole **12a**: The reaction was carried out with one molar ratio of nitrile oxide and the product was isolated by crystallization from ether (147 mg, 25%), mp 183-185 °C; MS *m/e* 586,588,590,592,594 (M^+); Anal. Calcd for $C_{27}H_{18}Cl_4N_4O_3$ (588.27): C, 55.13 H, 3.08; N, 9.52. Found C, 55.34; H, 3.18; N, 9.43. When a two molar ratio of nitrile oxide was used the product yield was increased to 37%.

2'-Benzoyl-3,3''-bis(2,4,6-trimethylphenyl)-5'-phenyl-isoxazole-5(4H)-spiro-3'(2'H)-pyrazole-4'-spiro-5''(4''H)-isoxazole **13**: The reaction was carried out with one molar

ratio of nitrile oxide and the mixture was chromatographed. The "anti" addition isomer **13a** was eluted first (83 mg, 14%), mp 103-105 °C (from ethanol); Anal. Calcd for $C_{38}H_{36}N_4O_3$ (596.70) C, 76.48; H, 6.08; N, 9.39. Found C, 76.36; H, 6.00; N, 9.61. The "syn" addition isomer **13b** was eluted second (71 mg, 12%), mp 215-217 °C (from ether); Anal. Calcd for $C_{38}H_{36}N_4O_3$ (596.70): C, 76.48; H, 6.08; N, 9.39. Found C, 76.50; H, 5.98; N, 9.28. When a two molar ratio of nitrile oxide was used, **13a** and **13b** were isolated in 21% and 19% yield respectively.

2'-Benzoyl-3,3''-bis(2,6-dichlorophenyl)-5'-phenyl-isoxazole-5(4H)-spiro-3'(2'H)-pyrazole-4'-spiro-5''(4''H)-isoxazole **14a**: The reaction was carried out with one molar ratio of nitrile oxide and the product **14a** was isolated by column chromatography (201 mg, 31%), mp 212-214 °C (from methylene chloride/*n*-hexane); Anal. Calcd for $C_{32}H_{20}Cl_4N_4O_3$ (650.34): C, 59.10; H, 3.10; N, 8.61. Found C, 59.21; H, 3.10; N, 8.81. When a two molar ratio of nitrile oxide was used, the product yield was increased to 46%.

2'-Benzoyl-4'-bromomethylene-3-(2,4,6-trimethylphenyl)-5'-phenyl-4'H-pyrazole-3'-(2'H)-spiro-5(4H)-isoxazole **17**: The reaction was carried out with one molar ratio of nitrile oxide and the product **17** was isolated by column chromatography (41 mg, 16%), mp 113-115 °C (from ether/*n*-hexane); Anal. Calcd for $C_{28}H_{24}BrN_3O_2$ (514.08): C, 65.37; H, 4.70; N, 8.17. Found C, 65.12; H, 4.75; N, 7.98.

2'-Benzoyl-4'-bromomethylene-3-(2,6-dichlorophenyl)-5'-phenyl-4'H-pyrazole-3'(2'H)-spiro-5(4H)-isoxazole **18**: The reaction was carried out with one molar ratio of nitrile oxide and the product was isolated by column chromatography (51 mg, 19%), mp 138-139 °C (from ether/*n*-hexane); MS *m/e* 541 (M^+); Anal. Calcd for $C_{25}H_{16}BrCl_2N_3O_2$ (541.47): C, 58.25; H, 2.79; N, 7.28. Found C, 58.36; H, 2.59; N, 7.17.

X-Ray Crystallographic Analysis of **13a**. The compound $C_{38}H_{36}N_4O_3$, M_r=596.73, crystallizes as monoclinic crystals in space group Cc, a=21.9368(8), b=19.3071(7) and c=9.1979(3) Å, β=80.503(1)°, V=3842.25(7) Å^3, Z=4, D_m=1.02 g cm^{-3}, D_c=1.031 g cm^{-3}, F(000)=1264, μ=4.60 cm^{-1}. Data were collected on a Nicolet P2$_1$ diffractometer upgrated by CRYSTAL LOGIC, θ-2θ mode, Cu K$\bar{\alpha}$, Ni-filtered radiation (λ=1.5418), with scan width 1.6° (2θ) plus α_1-α_2 divergence, $2\theta_{max}$=130°. Out of 5529 measured reflections 3425 unique were considered observed. Lorentz and polarization corrections were applied. The structure was solved by direct methods using SHELX86[13] and refined by full matrix least squares using SHELX76[14] with all non-H atoms refined anisotropically. Although most hydrogens were located from differences Fourier maps, all except four were placed in calculated positions at 0.96 Å from their respective C-atoms. Final R/R_w=0.0516/0.0710 with unit weights. $\Delta\rho_{max}/\Delta\rho_{min}$=0.020/-0.194 eÅ^{-3} $|\Delta/\sigma|$=0.262.

X-Ray Crystallographic Analysis of **14a**. The compound $C_{32}H_{20}Cl_4N_4O_3$, M_r=650.35, crystallizes as triclinic crystals in space group P1, a=9.522(1), b=12.923(1) and c=12.973(1) Å, α=72.837(3), β=74.175(3) and γ=82.863(3)° V=1465.8(2) Å^3, Z=2 D_m=1.46 g cm^{-3}, D_c=1.473 g cm^{-3}, F(000)=664, μ=38.68 cm^{-1}. Data were collected on a Nicolet P2$_1$ diffractometer upgrated by CRYSTAL LOGIC, θ-2θ mode, Cu K$\bar{\alpha}$, Ni-filtered radiation (λ=

1.5418), with scan width 1.6° (2θ) plus α_1-α_2 divergence, $2\theta_{max}$=130°. Out of 5277 measured reflections 4945 were considered observed with $|Fo| \geq 3\sigma(|Fo|)$. Lorentz, polarization and absorption corrections were applied. The structure was solved by direct methods and refined by full matrix least squares using SHELX76[14] with all non-H atoms refined anisotropically. The H-atoms were located from difference Fourier maps. Final R/R_w=0.0497/0.0726 for observed data using a weighting scheme $w=1/(\sigma^2(Fo)+0.00007Fo^2)$. $\Delta\rho_{max}/\Delta\rho_{min}$=0.403/-0.428 e A^3. $|\Delta/\sigma|$= 0.013.

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