1,3-DIPOLAR CYCLOADDITION OF 3-ARYLIDENECHROMANONE - 1-THIOCHROMANONE AND -FLAVANONE: REGIO- AND STEREOSELECTIVE FORMATION OF SPIROHETEROCYCLES

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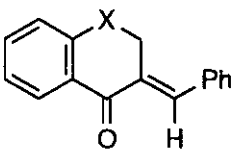
Abstract - The cycloaddition of nitrile oxides, nitrones, and nitrile imines to 3-arylidenechromanone (1), -flavanone (5), -1-thiochromanone (2) and -1-tetralone (3) proceeds regio- and stereoselectively under the formation of spiro-substituted isoxazole and pyrazole derivatives.

The recent observation of strong herbicidal activity, coupled with low toxicity to microorganisms, of spiro lactams,[1] and also that some spiro isoxazolines occur naturally (Araplysillins[2] inhibit ATPase) stimulate our interest in the synthesis of this class of compounds. In a continuation of our effort to utilise heterocyclic compounds as dipolarophiles in 1,3-dipolar cycloaddition reactions,[3-7] we have recently demonstrated that nitrones and nitrile oxides react regio- and stereoselectively with heterocyclic compounds possessing an exocyclic double bond.[3-7] In this paper, we report the regio- and stereoselectivity of nitrone-, nitrile oxide- and nitrile imine-cycloaddition to (*E*)- and (*Z*)-3-benzylidenechromanones and their thio analogues, (*E*)- and (*Z*)-3-benzylideneflavanones, and (*E*)-2-benzylidene -1-tetralone.

The cycloaddition of 4-nitrobenzonitrile oxide to (*E*)-benzylidene derivatives(1-3) possessing an exocyclic double bond proceeds regioselectively under the formation of *trans*- spiroisoxazolines (7-9) with respect to the position of the C=O and phenyl groups, while the *Z*- isomer (4) gives the



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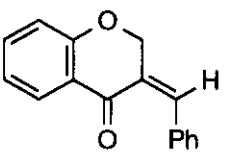
2 X = S

3 X = CH_2



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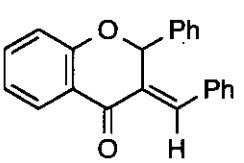

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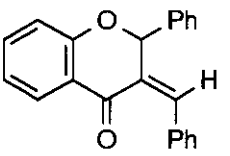

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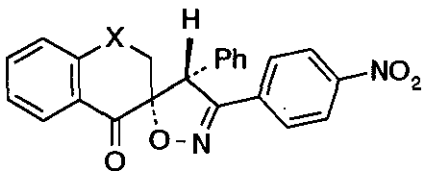
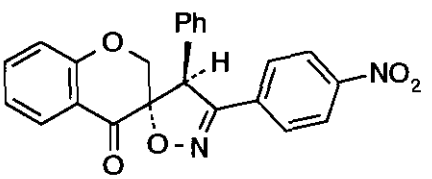
corresponding *cis*-derivative (10). Spiroisoxazolines (7-10) are formed by the attack of the carbon of the nitrile oxide at the CH terminus of the exocyclic double bond. Cycloaddition with acetonitrile oxide proceeded analogously. The structures of spiroisoxazolines (7-10) were unambiguosly elucidated by their ^{1}H and ^{13}C NMR chemical shifts.[8] The corresponding second possible regioisomer has not been detected in the crude reaction mixture by NMR spectroscopy.



7 X = O

8 X = S

9 X = CH_2



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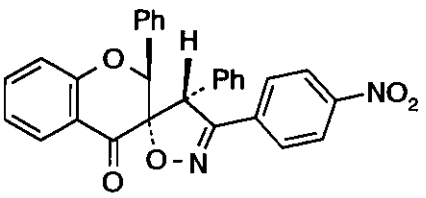
On the other hand, cycloadditions of 4-nitrobenzonitrile oxide and (*E*)- and (*Z*)-3-benzylidene-flavanones (5) and (6) afforded exclusively the spiroisoxazolines (11) and (12), respectively, despite the appearance of a further centre of chirality at C-2. The stereochemical assignment in compounds (11) and (12) was based on nuclear Overhauser effect difference spectroscopy.



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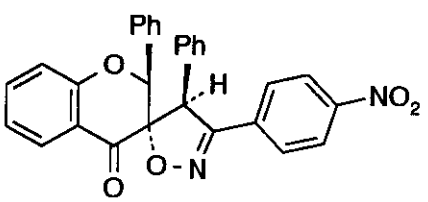

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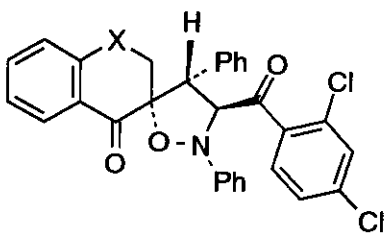
Previously by the cycloaddition of diazomethane to 5 and 6 we have found[9,10] that the conformational behaviour of the starting 3-benzylideneflavanone is a decisive factor in the high stereoselectivity, because the attack of the 1,3-dipole proceeds from the sterically less hindered side, i.e. opposite to the C-2 phenyl group.

C-(2,4-Dichlorobenzoyl)-*N*-phenylnitrone reacts regio- and stereoselectively to the C=C exocyclic double bond of title compounds to give exclusively single spiroisoxazolidines (13-16), which are formed by the attack of the nitrone oxygen atom at the spiro carbon.[8] Conversely, *C*-phenyl-*N*-methylnitrone and *C*,*C*-diphenyl-*N*-methylnitrone were found totally unreactive.



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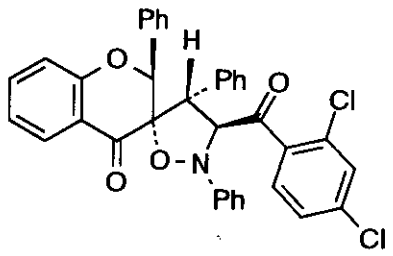
14 X = S

15 X = CH_2



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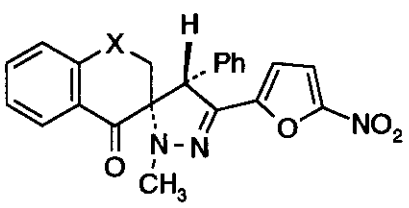
The corresponding *syn*-diastereomers as well as regioisomeric diastereomers have not been detected in the crude reaction mixture by NMR spectroscopy. The stereochemical assignement in 13-16 was based on nuclear Overhauser effect difference spectroscopy.

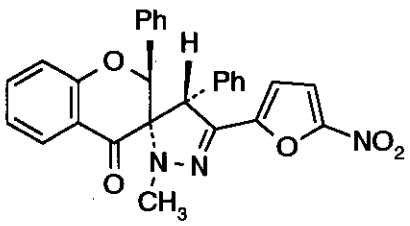
Cycloaddition of the 3-arylidene derivatives by *C*-2-(5-nitrofuryl)-*N*-acetonitrile imines led to spiropyrazolines (17-20) in good yields (63-91%) and complete regio- and diastereoselectivity.



17 X = O

18 X = S

19 X = CH_2



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The cycloadducts (7-20) were formed in lower yields - due to incomplete conversion of starting materials - as compared with those observed in the cycloaddition of nitrile oxides and nitrones to methylenecycloalkanes possessing a 5-membered ring,[3-6] which can be explained by the well known fact that angular strain[11] in a dipolarophile can effect its reactivity. In all case of the 1,3-dipolar cycloaddition to 3-arylideneflavanones, the steric interaction with the axial aryl group directs the attack of the 1,3-dipol to the opposite side.

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8. New compounds were characterised by their NMR spectra and their elemental compositions established by combustion analysis. Selected ^{1}H and ^{13}C NMR data ($CDCl_3$, 300 MHz, TMS as internal standard, δ-values in ppm, J in Hz) for compounds:

7: Yield 50%; mp 225-226 °C. ^{1}H NMR: 4.01 (d, J=13.6 Hz, 1H, H_A-2), 4.20 (d, J=13.6 Hz, 1H, H_B-2), 5.50 (s, 1H, H-4′), 6.96-8.13 (m, 13H, H_{arom}); ^{13}C NMR: 54.84 (d, C-4′), 69.95 (t, C-2), 85.89 (s, C-3), 123.75, 127.03, 128.24, 128.50, 128.68, 128.81, 129.37, 133.52, 134.21, 134.84, 143.54, 148.32 (C_{arom}), 158.44 (s, C-3′), 185.87 (s, C=O).

11: Yield 43%; mp 203-205 °C. ^{1}H NMR: 5.34, 5.42 (s,s, 1H,1H, H-4′, H-2), 6.76-8.34 (m,18H, H_{arom}); ^{13}C NMR: 54.14 (d, C-4′), 82.48 (d, C-2), 88.69 (s, C-3), 118.53, 118.86, 121.71, 123.78, 124.37, 124.54, 127.57, 128.08, 128.53, 128.95, 129.30, 129.45, 129.52, 131.23, 133.98, 134.20, 137.19, 148.51, 158.95, 159.80 (C_{arom} and C-3′), 185.70 (s, C=O).

13: Yield 65%; mp 166-167 °C. ^{1}H NMR: 3.75 (d, J=13.3 Hz, 1H, H_A-2), 4.16 (d, J=13.3 Hz, 1H, H_B-2), 4.91 (d, J= 5.6 Hz, 1H, H-4′), 5.25 (d, J= 5.6 Hz, 1H, H-3′), 6.92-7.97 (m, 17H, H_{arom}); ^{13}C NMR: 55.55 (d, C-4′), 70.23 (t, C-2), 79.54 (d, C-3′), 82.46 (s, C- 3), 114.49, 117.76, 119.49, 121.75, 122.49, 127.16, 128.26, 128.98, 129.02, 129.74, 130.04, 131.45, 134.59, 135.93, 136.65, 137.10, 149.87, 160.97 (C_{arom}), 186.25 (s, C=O), 198.10 (s, C=O).

16: Yield 57%; mp 167-168 °C. ^{1}H NMR: 4.23 (d, J= 3.9 Hz, 1H, H-4′), 5.12 (d, J= 3.9 Hz, 1H, H-3′), 5.29 (s, 1H, H-2), 6.59-8.02 (m, 22H, H_{arom}); ^{13}C NMR: 52.54 (d, C-4′), 82.77 (d, C-3′), 83.26 (d, C-2), (s, C-3), 115.93, 118.01, 119.08, 121.33, 122.82, 127.30, 127.61, 128.11, 128.36, 128.43, 128.76, 129.18, 129.84, 131.42, 131.68, 133.66, 136.52, 136.79, 137.19, 137.89, 149.00, 158.87 (C_{arom}), 189.19 (s, C=O), 196.48 (s, C=O).

18: Yield 68%; mp 204-206 °C. ^{1}H NMR: 2.78 (d, J=14.7 Hz, 1H, H_A-2), 3.23 (s, 3H, CH_3), 3.60 (d, J=14.7 Hz, 1H, H_B-2), 4.65 (s, 1H, H-4′), 6.40 (d, J= 3.9 Hz, 1H, H_{furan}), 7.16 (d, J= 3.9 Hz, 1H, H_{furan}), 7.25-8.24 (m, 9H, H_{arom}).

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