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SYNTHESIS OF SPIROISOXAZOLINE[5.3^1]-CHROMAN-4^1-ONE

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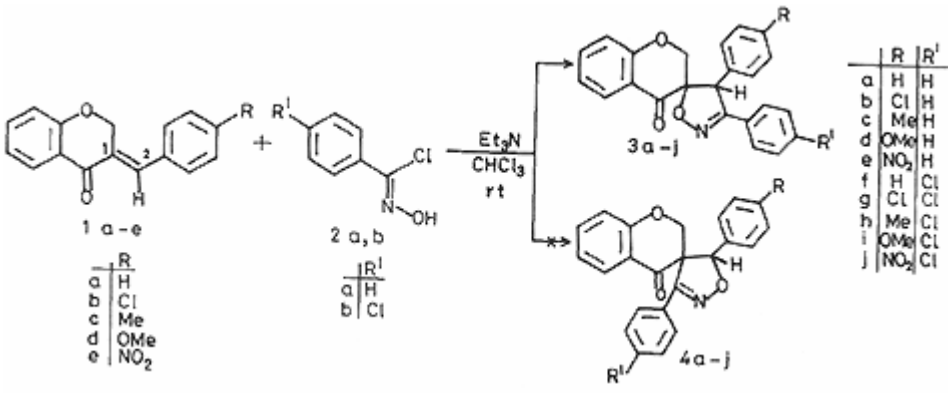
Abstract- Synthesis of a series of spiro[3,4-diaryl-4,5-dihydroisoxazole-5,3^1-chroman-4^1-one] has been accomplished in good yields by regioselective 1,3-dipolar cycloaddition of nitrile oxide to 3-arylidene-4-chromanone. X-Ray crystal structure analysis of one of the products confirms the structure and the regiochemistry of cycloaddition.

1,3-Dipolar cycloaddition reaction of nitrile oxides offers an excellent route for the construction of isoxazoline derivatives.[1] The isoxazoline derivatives have been extended to many natural product syntheses and also proved to be an efficient precursor for many synthetic intermediates including γ-amino alcohols, β-hydroxy ketones etc.[2] Spiroisoxazolines display interesting biological properties such as herbicidal, plant growth regulatory activities and anti-tumor agent.[3] Although a plethora of reports available for the synthesis of isoxazoline derivatives, there appears to be limited number for the spiroisoxazoline derivatives. The high synthetic utility and pharmacological importance have prompted us to synthesis some biologically interesting spiroisoxazoline derivatives. Many 4-chromanone derivatives are used as versatile intermediates for the synthesis of many natural products such as brazillin, hematoxylin, ripariochromene, clausenin, calonlide (A) and inophyllum (B).[4,5] Chromanone heterocycles have also drawn much attention owing to their important pharmacological properties.[4] In continuation of our interest in the area of cycloaddition,[6-9] herein we report the facile synthesis of spiroisoxazoline derivatives.

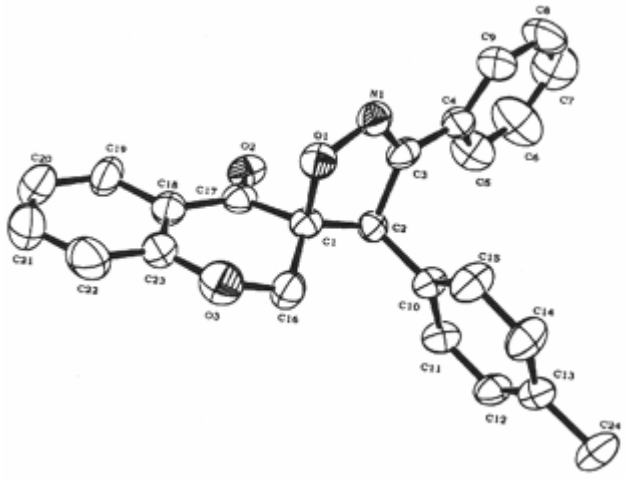
In an attempt to evaluate the effect of the presence of electron-donating and electron-withdrawing groups in direct conjugation with the double bond of the dipolarophile on the regioselectivity in the cycloaddition reactions, the reactions of nitrile oxides with (*E*) 3-arylidene-4-chromanones were studied. Reactions of 3-arylidene-4-chromanones **(1a-e)** with nitrile oxides **(2a-b)** (generated in situ from *N*-benzhydroxyiminoyl chloride in chloroform solution in the presence of triethylamine at rt) led to the formation of 1:1 adducts as a single product in each case, as evidenced by TLC and MS spectral studies (**Scheme**). The reaction has yielded a series of spiro[3,4-diaryl-4,5-dihydroisoxazole-5,3^1-chroman-4^1-one] by the regioselective cycloaddition of the 1,3-dipole across the exocyclic double bond of the 3-arylidene-4-chromanone in each case. The structure of each product **(3a-j)** has been confirmed by spectroscopic data. The NMR spectrum of compound **(3a)** exhibited a singlet δ 5.38 due to the benzylic

proton and the signal at δ 85.09 due to the spiro carbon atom and δ 158.25 due to the C=N-O carbon indicating the presence of 4-substituted spiroisoxazoline derivative. The regiochemistry of the cycloadduct **(3a)** is clearly revealed by the MS spectrum. The absence of (M^+-106) peak corresponding to the loss of benzaldehyde clearly indicates that the C terminal of the 1,3-dipole should be attached to the 4-position of the dihydroisoxazole ring. The structure and the regiochemistry of cycloaddition was further corroborated by X-Ray crystal analysis of the product **(3c)**. (Figure 1)

Scheme



Identical results were obtained with other derivatives of chromanones in the cycloaddition with nitrile oxides, irrespective of the substituent present in the arylidene moiety.

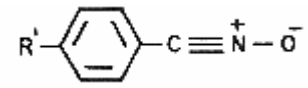


(Figure **1** ORTEP diagram of **3c**)

MOLECULAR ORBITAL CALCULATION

In order to study the electronic effects on the dipolarophile and also to explain the regiochemistry of cycloaddition, frontier molecular orbital method has been used. The computations were performed using the all-valence semiempirical molecular orbital PM3 method[10] included in the GAUSSIAN 94 package (version D.3).[11]

Table 1 Computed data for the 1,3-dipoles **(2a-b)**



Dipole	HOMO Energy (eV)	LUMO Energy (eV)	HOMO Coefficients		LUMO Coefficients	
			C	O	C	O
2a	-9.34	-0.30	-0.35	+0.40	+0.22	+0.23
2b	-9.20	-0.55	-0.28	+0.32	+0.19	+0.22

Table 2 Calculated atomic charge, bond length and bond order

Dipole		Net atomic charge			Bond Length(A°)	Wiberg bond order
		MPA	NPA			
2a	C	+0.30	+0.27	CN	1.170	2.40
	N	+0.06	+0.22	NO	1.208	1.37
	O	-0.57	-0.52			
2b	C	+0.29	+0.26	CN	1.170	2.39
	N	+0.07	+0.23	NO	1.207	1.37
	O	-0.56	-0.51			

From the Table **2**, it is clear that the O position is more electronegative, suggesting that the linear isomer should be favored for the 1,3-dipole.

Table 3 Computed data for the dipolarophiles **(1a-e)**

Substrate	HOMO energy (eV)	LUMO energy (eV)	HOMO coefficients		LUMO coefficients	
			C_1	C_2	C_1	C_2
1a	-9.35	-0.80	+0.21	+0.16	-0.35	+0.42
1b	-9.30	-0.93	+0.29	+0.21	-0.36	+0.41
1c	-9.26	-0.78	+0.31	+0.22	-0.36	+0.42
1d	-9.06	-0.76	+0.31	+0.21	-0.34	+0.42
1e	-9.64	-1.64	+0.09	+0.07	-0.32	+0.27

From Tables **1** and **3**, it is evident that the energy gap between the LUMO of the dipolarophile and the HOMO of the dipole is smaller than that of the LUMO of the dipole and the HOMO of the dipolarophile, irrespective of the substituent in the dipolarophile. Thus, the major interaction involves the LUMO of the dipolarophile and the HOMO of the dipole.

Calculation of the atomic coefficients of the dipolarophiles **(1a-e)** reveals that LUMO coefficients of the olefinic carbons are comparable in magnitude. In the case of the electron-withdrawing substituent present in **(1e)**, it is seen that the atomic coefficient of the olefinic carbon **(C_1)** of the dipolarophile is comparable in value to that of the oxygen terminal of the 1,3-dipole, and the other olefinic carbon **(C_2)** of the dipolarophile is comparable to the carbon terminal of the dipole, resulting in the overlap between these orbitals consistent with the formation of the observed regioisomers **(3e)** and **(3j)**, whereas, in the case of

unsubstituted and electron-releasing substituents **(1a-d)**, the atomic coefficient of the olefinic carbon **(C_1)** of the dipolarophile is comparable in value to that of the carbon terminal of the dipole, and the other olefinic carbon **(C_2)** of the dipolarophile is comparable to that of the oxygen terminal of the dipole, resulting in the overlap between these orbitals, which would lead to the unobserved regioisomers **(4a-d)** and **(4f-i)**.

Thus the molecular orbital overlap concept does not explain the regiochemistry of the observed product **(3a-d)** and **(3f-i).** A plausible explanation for the observed mode of cycloaddition is that a steric effect overweighs the electronic effect.[12,13] In the case of nitrile oxides, the fact that the C atom is more sensitive to steric requirements than the O atom is known in the literature.[12,13] Since there is not much difference in the atomic coefficients of the dipolarophile **(1a-e)** in its LUMO, the carbon terminal of the 1,3-dipole approaches the less substituted carbon of the dipolarophile from the least hindered side to give the observed regioisomer **(3a-j).**

To conclude, efficient synthesis of spiroisoxazoline[5.3^1]-chroman-4^1-one has been demonstrated by the regioselective cycloaddition reaction of 3-arylidene-4-chromanone with nitrile oxide and the regiochemistry of the cycloaddition is independent of the electronic nature of the substituent on the arylidene ring of the dipolarophile.

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EXPERIMENTAL SECTION

GENERAL. All melting points are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR 8300 instrument. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a JEOL FX 90Q at 90 MHz and Bruker DPX200 at 50.3 MHz, respectively. Elemental analyses were carried out on a CEST 1106 instrument. MS spectra were recorded on a Finnigan MAT-8230 GC-Mass spectrometer. Column chromatography was performed on silica gel (100-200 mesh).

The starting materials 3-arylidene-4-chromanone[6] and *N*-benzhydroxyiminoyl chloride[14] were prepared according to the literature procedure.

Reaction of 3-arylidene-4-chromanones with nitrile oxides: General Procedure

To a solution of 3-arylidene-4-chromanone (3 mmol) and corresponding *N*-benzhydroxyiminoyl chloride (3 mmol) in 10 mL of dry chloroform, triethylamine (0.334g,3.3 mmol) was added. The reaction mixture was stirred at rt until the disappearance of the starting materials, as monitored by TLC, was observed. After the reaction was over, the solution was filtered to remove triethylamine hydrochloride, and the solvent was evaporated under a vacuum. The resulting crude product was purified by column chromatography (hexane/ethyl acetate, 9:1) and crystallization from hexane/ether (2:1).

Spiro[3,4-diphenyl-4,5-dihydroisoxazole-5,3^1-chroman-4^1-one] (3a): mp 181-183°C, 88%, IR (KBr): 1689 cm^{-1}; ^{1}H NMR: δ 3.89 (d, J = 13.1 Hz, 1H), 4.32 (d, J = 13.1 Hz, 1H), 5.38 (s, 1H), 6.89 –7.55 (m, 13H), 8.02 (dd, J = 7.7, 1.2 Hz, 1H); ^{13}C NMR: δ 54.67, 70.05, 85.09, 114.82, 117.99, 118.63, 121.96, 123.68, 126.48, 128.24, 128.77, 128.81, 128.88, 130.02, 136.21, 136.67, 158.25, 160.96, 186.58; MS m/z 355(M^+), 193 (M^+-162); Anal. Calcd for $C_{23}H_{17}NO_3$: C 77.81, H 4.81, N 3.94. Found : C 77.72, H 4.91, N 3.74.

Spiro[3-phenyl-4-(4-chlorophenyl)-4,5-dihydroisoxazole-5,3^1-chroman-4^1-one] (3b): mp 123 – 124°C, 90%, IR (KBr) : 1694 cm^{-1}; ^{1}H NMR : δ 3.91 (d, J = 13.2 Hz, 1H), 4.35 (d, J = 13.2 Hz, 1H), 5.37 (s, 1H), 6.92 – 7.64 (m, 12H), 8.00 (dd, J = 7.7, 1.7 Hz, 1H); ^{13}C NMR : δ 54.80, 69.91, 84.86, 117.83, 118.56, 121.99, 127.53, 127.61, 128.20, 128.69, 128.64, 130.26, 130.45, 130.87, 134.73, 136.81, 158.74, 160.86, 186.38; MS m/z : 389(M^+), 227 (M^+-162); Anal. Calcd for $C_{23}H_{16}NO_3Cl$: C 71.01, H 4.14, N 3.59. Found : C 70.59, H 4.26, N 3.41.

Spiro[3-phenyl-4-(4-methylphenyl)-4,5-dihydroisoxazole-5,3^1-chroman-4^1-one] (3c): mp 130 - 132°C, 81%, IR (KBr) : 1689 cm^{-1}; ^{1}H NMR : δ 2.33 (s, 3H), 3.90 (d, J = 12.9 Hz, 1H), 4.24 (d, J = 12.9 Hz, 1H), 5.37 (s, 1H), 6.82 – 7.62 (m, 12H), 8.01 (dd, J = 7.6, 1.6 Hz, 1H); ^{13}C NMR : δ 21.12, 55.18, 70.20, 84.88, 117.89, 121.89, 122.06, 127.63, 127.68, 128.28, 128.56, 128.70, 130.45, 136.63, 136.81, 138.47, 159.12, 160.98, 185.26; MS m/z : 369(M^+), 207 (M^+-162); Anal. Calcd for $C_{24}H_{19}NO_3$: C 78.11, H 5.18, N 3.79. Found : C 77.84, H 4.99, N 3.64.

Spiro[3-phenyl-4-(4-methoxyphenyl)-4,5-dihydroisoxazole-5,3^1-chroman-4^1-one] (3d): mp 135 - 136°C, 79%, IR (KBr) : 1695 cm^{-1}; ^{1}H NMR : δ 3.78 (s, 3H), 3.94 (d, J = 13.1Hz, 1H), 4.22 (d, J = 13.1 Hz, 1H), 5.36 (s, 1H), 6.94 – 7.81 (m, 12H), 8.02 (dd, J = 7.5, 1.6 Hz, 1H); ^{13}C NMR : δ 55.25, 60.36, 70.09, 85.02, 114.82, 117.91, 118.66, 121.94, 123.65, 126.48, 128.13, 128.75, 128.88, 130.03, 136.21, 136.72, 158.23, 159.81, 160.96, 186.55; MS m/z : 385 (M^+), 223 (M^+-162); Anal. Calcd for $C_{24}H_{19}NO_4$: C 74.86, H 4.97, N 3.63. Found : C 74.72, H 4.81, N 3.51.

Spiro[3-phenyl-4-(4-nitrophenyl)-4,5-dihydroisoxazole-5,3^1-chroman-4^1-one] (3e): mp 142 -143°C, 77%, IR (KBr) : 1691 cm^{-1}; ^{1}H NMR : δ 3.98 (d, J = 13.2 Hz, 1H), 4.19 (d, J = 13.2 Hz, 1H), 5.38 (s, 1H), 6.91 – 7.64 (m, 10H), 8.01 (dd, J = 7.8, 1.6 Hz, 1H), 8.31 (d, J = 7.8 Hz, 2H); ^{13}C NMR : δ 54.99, 65.51, 85.48, 117.96, 118.35, 122.36, 124.61, 125.65, 128.37, 128.74, 129.22, 129.94, 136.92, 137.14, 139.51, 148.18, 157.46, 160.77, 185.85. MS m/z : 389 (M^+), 227 (M^+-162); Anal. Calcd for $C_{23}H_{16}N_2O_5$: C 69.05, H 4.03, N 7.00. Found : C 68.75, H 3.97, N 6.94.

Spiro[3-(4-chlorophenyl)-4-phenyl-4,5-dihydroisoxazole-5,3^1-chroman-4^1-one] (3f): mp 162 - 164°C, 80%, IR (KBr) : 1682 cm^{-1} ; ^{1}H NMR : δ 3.95 (d, J = 12.7 Hz, 1H), 4.13 (d, J = 12.7 Hz, 1H), 5.34 (s, 1H), 6.92 – 7.51 (m, 12H), 7.98 (dd, J = 7.5, 1.5 Hz, 1H); ^{13}C NMR : δ 55.26, 70.11, 85.14, 117.88, 117.90, 118.64, 121.96, 126.36, 128.32, 128.80, 128.88, 129.46, 130.15, 131.95, 136.31, 136.81, 158.13, 160.94, 186.34; MS m/z : 389 (M^+), 227 (M^+-162); Anal. Calcd for $C_{23}H_{16}NO_3Cl$: C 71.01, H 4.14, N 3.59. Found : C 70.62, H 4.02, N 3.46.

Spiro[3,4-di(4-chlorophenyl)-4,5-dihydroisoxazole-5,3^1-chroman-4^1-one] (3g): mp 142-144°C, 81%, IR (KBr) : 1693 cm^{-1}; ^{1}H NMR : δ 3.97 (d, J = 12.9 Hz, 1H), 4.22 (d, J = 12.9 Hz, 1H), 5.35 (s, 1H), 6.89 – 7.42 (m, 11H), 7.99 (dd, J = 7.4, 1.6 Hz, 1H); ^{13}C NMR : δ 54.67, 69.82, 85.11, 117.88, 117.98, 118.48, 122.07, 126.03, 128.31, 128.81, 129.02, 130.19, 130.51, 134.94, 136.00, 136.52, 136.91, 157.86, 160.85, 186.20; MS m/z : 423 (M^+), 261 (M^+-162); Anal. Calcd for $C_{23}H_{15}NO_3Cl_2$: C 65.30, H 3.57, N 3.30. Found C 65.09, H 3.45, N 3.20.

Spiro[3-(4-chlorophenyl)-4-(4-methylphenyl)-4,5-dihydroisoxazole-5,3^1-chroman-4^1-one] (3h): mp 136 -137°C, 85%, IR (KBr) 1690 cm^{-1}; ^{1}H NMR : δ 2.32 (s, 3H), 3.97 (d, J = 13.2 Hz, 1H), 4.16 (d, J = 13.2 Hz, 1H), 5.36 (s, 1H), 6.80 –7.57 (m, 11H), 8.02 (dd, J = 7.7, 1.6 Hz, 1H); ^{13}C NMR : δ 21.10, 54.98, 70.12, 85.06, 117.86, 117.97, 118.65, 121.96, 126.45, 128.35, 128.78, 128.88, 130.14, 136.21, 136.76, 138.72, 158.22, 160.96, 186.50; MS m/z : 403 (M^+), 241(M^+-162); Anal. Calcd for $C_{24}H_{18}NO_3Cl$: C 71.52, H 4.50, N 3.47. Found : C 71.83, H 4.41, N 3.41.

Spiro[3-(4-chlorophenyl)-4-(4-methoxyphenyl)-4,5-dihydroisoxazole-5,3^1-chroman-4^1-one] (3i): mp 128 -130°C, 78%, IR (KBr) : 1695 cm^{-1}; ^{1}H NMR : δ 3.77 (s, 3H), 3.94 (d, J = 13.1 Hz, 1H), 4.17 (d, J = 13.1 Hz, 1H), 5.35 (s, 1H), 6.90 – 7.61 (m, 11H), 8.02 (dd, J = 7.7, 1.5 Hz, 1H); ^{13}C NMR : δ 54.69, 55.26, 70.16, 85.03, 114.71, 117.85, 117.98, 118.67, 121.92, 123.04, 123.65, 126.45, 128.88, 129.94, 136.23, 136.75, 158.22, 159.80, 160.96, 186.59. MS m/z : 419 (M^+), 257(M^+-162); Anal. Calcd for $C_{24}H_{18}NO_4Cl$: C 68.79, H 4.32, N 3.34. Found : C 68.98, H 4.26, N, 3.30.

Spiro[3-(4-chlorophenyl)-4-(4-nitrophenyl)-4,5-dihydroisoxazole-5,3^1-chroman-4^1-one] (3j): mp 158-160°C, 80%, IR (KBr) : 1686 cm^{-1}; ^{1}H NMR : δ 3.99 (d, J = 12.9 Hz, 1H), 4.16 (d, J = 12.9 Hz, 1H),

5.39 (s, 1H), 6.91 – 7.57 (m, 9H), 8.00 (dd, J = 7.9, 1.7Hz, 1H), 8.32 (d, J = 7.9Hz, 2H). ^{13}C NMR : δ 54.99, 69.48, 85.47, 117.90, 118.30, 122.34, 124.67, 125.60, 128.22, 128.73, 129.23, 129.94, 136.91, 137.17, 139.50, 148.51, 157.43, 160.75, 185.87. MS m/z : 434 (M^+), 272 (M^+-162); Anal. Calcd for $C_{23}H_{15}N_2O_5Cl$: C 63.60, H 3.48, N 6.45. Found: C 63.78, H 3.39, N, 6.31.

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