

SOME NOVEL ASPECTS OF REGIOSELECTIVITY IN 1,3 DIPOLAR
CYCLOADDITIONS OF 4H-1-BENZOPYRAN-4-THIONE

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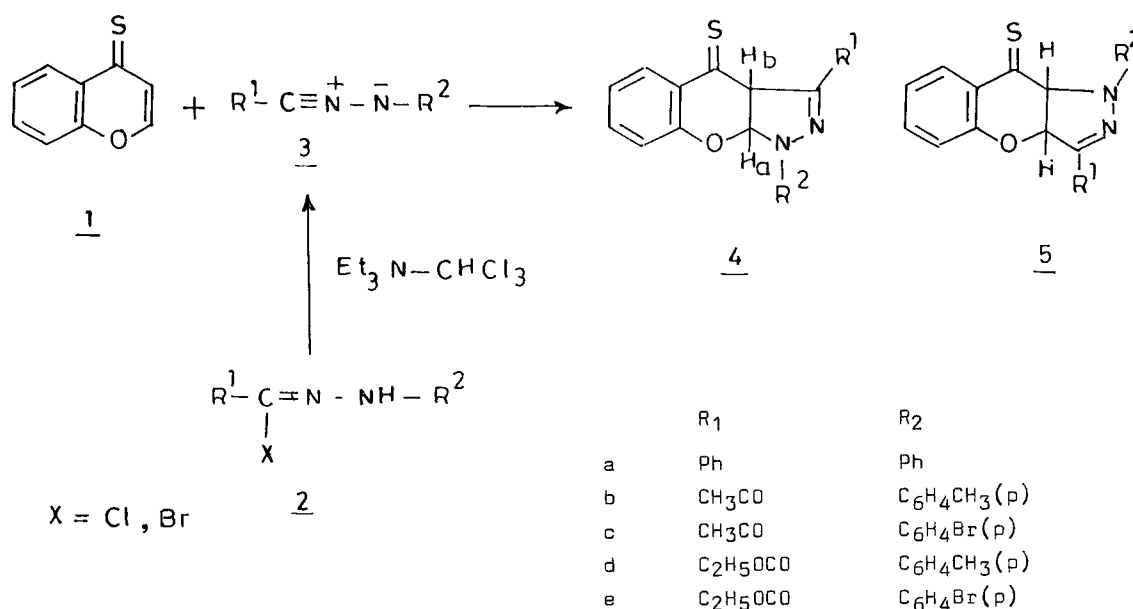
Abstract - 4H-1-Benzopyran-4-thione (1) reacted smoothly with nitrilimines (3a-e) to afford regioselective cycloadducts (4a-e) in good yields. In contrast, benzonitrile oxide (6) and aldonitrones (7a-d) reacted preferentially at the thione function. The unstable cycloadduct (8) or (9) ruptured to give as isolable products chromone (10) and phenyl isothiocyanate (11) and the thioamides (12a-d). This indirectly proves the site of attack of the dipole at the thione group.

Dipolar cycloaddition reactions practically have assumed one of the frontier area of research over the past two decades to be major synthetic strategy for achieving the synthesis of complex natural products¹. The theory and practice in this area still continues to uncover certain fundamental aspects to clear certain basic issues². Some interesting aspects of regioselectivity followed by the dipoles have recently been reported. Diphenyl nitrilimine reacts with tropone at C=C bond leaving C=O bond intact³; in contrast, chromone reacted at the C=O function and C=C bond remained intact⁴. The cycloaddition reactions of thione function are well reported and it readily reacts with a variety of 1,3 dipoles⁵. To our knowledge 1,3 dipolar cycloaddition reactions have not been studied employing conjugated thiocarbonyl compounds⁶. This prompted the authors to investigate 1,3 dipolar cycloaddition reactions of benzopyran-4-thione (1) with selected 1,3 dipoles viz nitrilimines, nitrile oxides and aldonitrones. The system (1) is a bifunctional substrate and dipoles could react either at carbon-carbon double bond or at thione function. It was expectation only that the LUMO of the thiocarbonyl would be quite low in energy and also there would be its more localisation at C=S bond rather than C=C bond. This theoretical prediction could dictate the addition of dipoles at the C=S bond⁷.

The reaction of (1) with diphenyl nitrilimine (3a), generated in situ from the corresponding α -chlorobenzylidene phenylhydrazine (2a) and dry triethylamine in anhydrous chloroform occurred smoothly at 5-10°C to afford the single crystalline cycloadduct (4a) in 60% yield after chromatography (Scheme - 1);

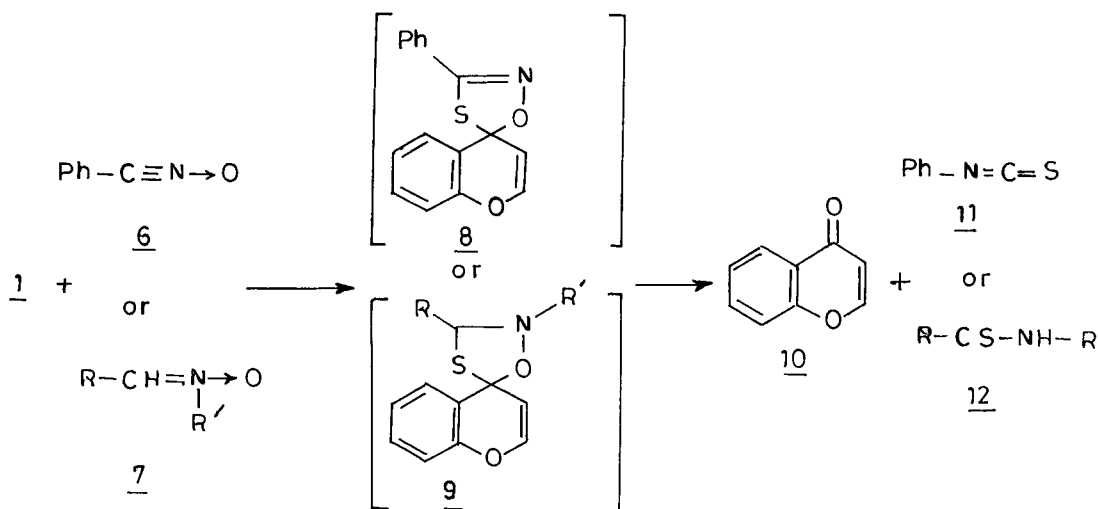
none of the regioisomer (5) or thione dimer could be detected. The formation of (4a) is inferred from the lowfield shift of proton H_a . Interestingly, the dipole here preferred the C=C bond leaving the thiocarbonyl function intact. The cycloadduct was characterised as (4a) and is fully corroborated by elemental and spectral results. The 1H NMR of (4a) δ : 5.35 (1 H_b , d), 6.60 (1 H_a , d), 6.80-7.85 (14H, m, aromatic protons). The mass spectrum showed the molecular ion at m/z (M^+) at 356. The cycloaddition of (1) with other substituted nitrilimines (3b-e) which are more reactive than the diaryl analogue (3a) also occurred at the carbon-carbon double bond only, affording the corresponding cycloadducts (4b-e) in 60-65% yield (Table). The behaviour of this class of dipole is in accordance with theoretical prediction, and it paves the way for the synthesis of novel linear molecules (4).

Then we turned our attention to the reaction of benzonitrile oxide, which is a considerably more reactive dipole. When equimolar quantities of 4H-1-benzopyran-4-thione and benzonitrile oxide (6, generated in situ from benzhydroxamyl chloride using triethylamine in anhydrous chloroform) were reacted at 0°C



Scheme - 1

for 1 h, removal of solvent and usual workup gave chromone (10) m.p. 58 - 59°C in 80% yield, along with phenyl isothiocyanate (11)⁸; there was no evidence for the formation of any cycloadduct of the type (4). Nitrones which are preceded to require more drastic conditions for their cycloadditions, were next investigated. C-Phenyl-N-methylnitron (7a), reacted with (1) in refluxing dry benzene over a period of 36 h, gave (10) and N-methyl thiobenzamide (12a) in good yield. The identity of (11) and (12) was confirmed by analytical data and by comparison with authentic samples⁹. The relatively more reactive C-phenyl-N-methylnitron was our choice here since C-phenyl-N-arylnitrones did not react under a variety of conditions and longer and higher reflux temperatures afforded only



starting materials. It is quite interesting to note here the site selectivity followed by the dipole i.e. cycloaddition occurring only across the thione function followed by the elimination of (10), leaving the chromone double bond intact. This site selectivity seems to be a remarkable contrast in view of the reactivity of chromone double bond with a variety of nitrilimines at this site as described above. Reaction of benzopyran-4-thione (1) with other C-phenyl-N-benzyl- (7b), C-(2-furyl)-N-methyl- (7c) and C-cyclohexane-N-methylnitrone (7d) under similar conditions gave the corresponding thioamides (12b-d) in good yields (Table). The structure of the adducts were unambiguously confirmed by their analytical and spectral data. When the same reaction was carried out with ketonitrone (C-methyl-C-phenyl-N-methylnitrone) in refluxing benzene for (5-6) days, no thioamide was isolated rather only polymeric material separates out. (Scheme -2).

These different site selectivity of these three set of selected dipoles appear to be interesting from theoretical as well as synthetic point of view.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and are uncorrected. The infrared spectra were recorded at potassium bromide discs on a Perkin Elmer 237B IR spectrometer. Mass spectra were determined on AEIMS 30 instrument by electron impact method. The 60 MHz ^1H NMR spectra were recorded at Varian T-60 machine using tetramethyl silane (TMS) as the internal standard. The chemical shifts are recorded in δ unit (parts per million) downfield from TMS. Nitrones (7a-d) were all easily prepared in high yield (ca. 90%) from the corresponding

aldehyde or ketone with N-methyl hydroxylamine hydrochloride in the presence of sodium acetate in ethanol at room temperature. All gave satisfactory physical and spectral data. Petroleum ether refers to that fraction boiling between 40 and 60°C and n-hexane refers to that fraction of petroleum ether boiling between 67 and 70°C.

Preparation of 4H-1-Benzopyran-4-thione (1)

The chromone¹⁰ (2.92 g, 0.02 mol) and Lawesson reagent (4.04 g, 0.01 mol) in 15 ml of anhydrous toluene (dried over sodium) were refluxed (reaction time 2 h, temperature 110°C) until no more starting material could be detected (vide tlc). After cooling the solution was stripped off and the mixture was purified on silica gel using chloroform as the eluent. On distillation of chloroform gave orange red crystals of 4H-1-benzopyran-4-thione (1) in 90% yield, m.p. 94–95°C. ¹H NMR (60 MHz, CDCl₃) δ : 7.00–8.60 (6H, m). MS m/z at 162 (M⁺). Anal. Calc'd for C₉H₆O₂: C, 66.66; H, 3.70; Found: C, 66.81; H, 3.85.

Reaction of 4H-1-Benzopyran-4-thione (1) with Nitrilimines: General Procedure

Dry triethylamine (2.92 g, 0.02 mol) in anhydrous chloroform (25 ml) was added dropwise to a well stirred solution of 4H-1-benzopyran-4-thione (1.62 g, 0.01 mol) and *o*-chlorobenzylidene phenylhydrazine¹¹ (2.30 g, 0.01 mol) in anhydrous chloroform (15 ml) at 0–5°C over a period of 30 minutes. The mixture was further stirred for 1 h. After removal of the solvent, the residue was taken up in benzene (25 ml). The precipitated triethylamine hydrochloride was filtered off and the filtrate was distilled under reduced pressure. The yellow crystalline product (4a) thus obtained was further purified by column chromatography over silica gel and recrystallised from petroleum ether (b.p. 40–60°C). The reaction of (1) with other substituted nitrilimines (3b–e) occurred similarly to afford the corresponding cycloadduct (4b–e) in (60–65%) yield. **4a**: MS m/z 356; IR (KBr) 1080 cm⁻¹; ¹H NMR (60 MHz, CDCl₃) δ : 3.35 (1H_b, d), 6.50 (1H_a, d), 6.85–7.85 (14H, m, aromatic protons). **4b**: MS m/z 336; IR (KBr) 1085, 1680 cm⁻¹; ¹H NMR (CDCl₃) δ : 2.15 (3H, s), 2.45 (3H, s), 5.30 (1H_b, d), 6.65 (1H_a, d), 6.80–7.86 (8H, m, aromatic protons). **4c**: MS m/z 401; IR (KBr) 1080, 1675; ¹H NMR (CDCl₃) δ : 2.50 (3H, s), 5.40 (1H_b, d), 6.65–7.71 (9H, m, 1H_a and aromatic protons). **4d**: MS m/z 366; IR (KBr) 1085, 1710 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.20 (3H, t), 2.15 (3H, s), 4.10 (2H, q), 5.35 (1H_b, d), 6.68–7.76 (9H, m, 1H_a and aromatic protons). **4e**: MS m/z 431; IR (KBr), 1080, 1710 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.25 (3H, t), 4.20 (2H, q), 5.40 (1H_b, d), 6.70–7.72 (9H, m, and aromatic protons).

Reaction of 4H-1-Benzopyran-4-thione (1) with Benzonitrile Oxides (6)

Dry triethylamine (1.01 g, 0.01 mol) in anhydrous chloroform (20 ml) was added to a well stirred solution of benzhydroxamyl chloride¹² (1.41 g, 0.01 mol) and 4H-1-benzopyran-4-thione (1, 1.62 g, 0.01 mol) over a period of 1 h at 0°C. The mixture was further stirred for 2 h. After removal of the solvent the residue was taken up in benzene (20 ml). The precipitated triethylamine hydrochloride was filtered off and the filtrate thus obtained was distilled under vacuum. The products (10) and (11) thus obtained were separated and purified by column chromatography over silica gel. The structure of these products were assigned on the basis of their analysis and by comparison with authentic samples.

Reaction of C-phenyl-N-methylnitrone (7a) with 4H-1-benzopyran-4-thione (1)

A mixture of (7a, 1.34g, 0.01 mol) C-phenyl-N-methylnitrone and 4H-1-benzopyran-4-thione (1, 1.62 g, 0.01 mol) and in 30 ml of dry benzene was heated at reflux under a nitrogen atmosphere for 36 h. The solvent was then remo-

ved under reduced pressure and the crude residue subjected to silica gel chromatography with a 40% ethyl acetate-hexane mixture as eluent. The major fraction isolated was a pale yellow crystalline solid whose structure was assigned as N-methylthiobenzamide (12a) on the basis of the following data, m.p. 78-79°C. (lit¹³ m.p. 79-80°C). IR (KBr): 3300, 1595, 1355, 1230, 1035, 1025, 992, 934, 914 and 765 cm⁻¹; ¹H NMR (60 MHz, CDCl₃) δ: 3.22 (3H, d), 7.15-7.78 (6H, m); MS m/z 151 (M⁺) 136, 121 and 77. Under similar conditions C-phenyl-N-benzyl (7b), C-(2-furyl)-N-methyl (7c) and C-cyclohexane-N-methylnitrone (7d) gave the corresponding thioamides (12b-d) in good yields and their physical and analytical data are as follows: 12b: m.p. 81-82°C (lit¹⁴ m.p. 82-83°C); IR (KBr) 3300, 1615, 1510, 1320, 1280, 1210, 1055, 1025, 916, 900, 760 and 740 cm⁻¹; ¹H NMR (CDCl₃) δ: 7.81-7.03 (11H, m), 4.92 (2H, d). MS m/z 227 (M⁺) 211, 195, 165 and 91. 12c: m.p. 70-71°C (lit⁹ m.p. 71-71.5°C). IR (KBr): 3220, 1580, 1510, 1330, 1275, 1157, 1031, 1010, 955, 865, 825, 745 and 700 cm⁻¹; ¹H NMR (60 MHz, CDCl₃) δ: 3.30 (3H, d), 6.42 (1H, m) and 7.33 (2H, m); MS m/z 141 (M⁺) 124, 111, 100. 12d: IR (KBr) 3300, 1535, 1335, 1290, 1205, 1105, 1020, 975, 884 and 714 cm⁻¹; ¹H NMR (CDCl₃) δ: 7.83 (1H, bs), 3.26 (3H, d), 2.31-1.10 (11H, m). MS m/z 157 (M⁺) 142, 124 and 102.

Table : Physical Characteristics and Micro Analytical Data of (4a-e) & (12a-d)

Compound	Yield (%)	M.p. (°C)	Molecular formula	Analysis		
				Calculated C	H	(Found) N
4a	60	91-93	C ₂₂ H ₁₆ N ₂ O ₅ S	74.16 (74.38)	4.49 4.61	7.87 7.72)
4b	65	161-163	C ₁₉ H ₁₆ N ₂ O ₂ S	67.85 (67.71)	4.76 4.63	8.33 8.21)
4c	60	144-145	C ₁₈ H ₁₃ BrN ₂ O ₂ S	53.86 (53.69)	3.24 3.41	6.98 6.82)
4d	62	145-147	C ₂₀ H ₁₈ N ₂ O ₃ S	65.57 (65.39)	4.91 4.80	7.65 7.78)
4e	60	140-142	C ₁₉ H ₁₅ BrN ₂ O ₃ S	52.90 (52.78)	3.48 3.31	6.49 6.58)
12a	51	78-79	C ₈ H ₉ NS	63.54 (63.38)	6.00 6.20	9.26 9.12)
12b	45	82-83	C ₁₄ H ₁₃ NS	73.97 (73.72)	5.76 5.53	6.16 6.01)
12c	45	70-71	C ₆ H ₇ NOS	51.04 (51.21)	4.99 4.72	9.92 9.79)
12d	40	66-67	C ₈ H ₁₅ NS	61.09 (61.21)	9.61 9.80	8.90 9.02).

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REFERENCES AND NOTES

1. For a recent review see : A. Padwa (Editor), 1,3-Dipolar Cycloaddition Chemistry, Wiley-Intersciences, New York, 1984; Tetrahedron Symposia in Print No. 21; "Synthetic Application of Dipolar Cycloaddition Reactions" Guest Editor, W. Oppolzer, Tetrahedron, 41, 3447-3568 (1985).
2. R. A. Firestone, J. Org. Chem., 2285 (1968); R. Huisgen, J. Org. Chem., 2291 (1968); R. Huisgen, G. Mloston and E. Langhals, J. Am. Chem. Soc., 108, 6401 (1986).
3. K. N. Houk and C. R. Watts, Tetrahedron Lett., 46, 4025 (1970).
4. A. S. Shawali, B. A. Eltauil and H. A. Albar, Tetrahedron Lett., 25, 4139 (1984); A. S. Shawali, B. A. Eltauil and H. A. Albar, Tetrahedron, 41, 1877 (1985).
5. R. Huisgen, Angew Chem., 75, 604, 742 (1963); Angew Chem. Int. Ed. Engl., 2, 565, 633 (1963); For 1,3-dipolar cycloaddition of nitrilimines see : R. Huisgen, R. Grashey, M. Seidel, H. Knupfer and R. Schmidt, Liebigs Ann. Chem., 658, 169 (1962); R. Huisgen, J. Sauer and M. Seidel, Chem. Ber., 94, 2503 (1961); For 1,3-dipolar cycloaddition nitrile oxides and diazomethane see: R. Huisgen and W. Mack, Chem. Ber., 105, 2815 (1972); I. Kalwisch, Li. Xingya, J. Gottstein and R. Huisgen, J. Am. Chem. Soc., 103, 7032 (1981).
6. For a recent review of cycloaddition reactions with conjugated imines which are closely related to aforementioned systems see : J. S. Sandhu and B. Sain, Heterocycles, 26, 777 (1987) and references cited therein.
7. K. N. Houk, Personal Communication.
8. R. Huisgen and W. Mack, Chem. Ber., 105, 2815 (1972).
9. Prepared from N-methylbenzamide by treatment with phosphorus pentasulphide by the method of R. I. Meltzer, A. D. Lewis and J. A. King, J. Am. Chem. Soc., 77, 4062 (1955).
10. S. Fohlisch, Chem. Ber., 104, 348, (1971).
11. J. Prajapati, Ph. D. Thesis, Dibrugarh University, Assam, India, 1985; N. Singh, S. Mohan and J. S. Sandhu, J. Chem. Soc. Chem. Commun., 387 (1969).
12. N. Singh, J. S. Sandhu and S. Mohan, Tetrahedron Lett., 42, 4253 (1968).
13. P. Wolkoff and S. Hammerjm, Acta. Chem. Scand. B., 30, 837 (1976).
14. J. Perregaard, I. Thomsen and S. O. Lawesson, Acta. Chem. Scand. B., 29, 599 (1975).