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Chemistry of Coumarins. – Nucleophilic Substitutions of 4-Chloro-3-nitrocoumarin with Hard and Soft Nucleophiles

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Reactions of 4-chloro-3-nitrocoumarin with a variety of nucleophiles produced a number of novel substituted coumarins. Hard and borderline nucleophiles exclusively substitute chlorine in position 4, while soft nucleophiles substitute the nitro group in position 3 (except for iodide) of the title compound. This result of the nucleophilic substitution of 4-chloro-3-nitrocoumarin is rationalized in terms of the HSAB model.

Chemie der Cumarine. – Nucleophile Substitutionen an 4-Chlor-3-nitrocumarin mit harten und weichen Nucleophilen

Umsetzungen von 4-Chlor-3-nitrocumarin mit verschiedenen Nucleophilen ergaben zahlreiche ncue substituierte Cumarine. Harte Nucleophile und solche im Übergangsbereich zu den weichen substituieren ausschließlich das Chlor in Position 4, während weiche Nucleophile (mit Ausnahme von Iodid) die Nitrogruppe in Position 3 der Titelverbindung ersetzen. Dieses Ergebnis wird mit Hilfe der Theorie von den harten und weichen Säuren/Basen diskutiert.

Compounds containing a coumarin subunit possess a wide range of biological activities and show an interesting chemical reactivity¹⁻⁹⁾. This is the consequence of the rich electronic structure of coumarin which offers abundant possibilities for diversified activity and reactivity of the system. In the course of our studies^{10,11)} on the chemistry of coumarins and related structures we have investigated reactions for the preparation of a number of differently 3,4-substituted coumarins. We found that Pearson's HSAB (hard and soft acids and bases) concept¹²⁻¹⁷⁾ of preferred interactions of hard acids (acceptors) with hard bases (donors) and soft acids (acceptors) with soft bases (donors) may be used in the case of nucleophilic attack on 4-chloro-3-nitrocoumarin (1) as a guiding principle for predicting the effect of substitution. The nucleophilic substitutions of 4-chloro-3-nitrocoumarin with a variety of nucleophiles, classified as hard, soft, and borderline¹⁸⁾, led to a number of novel substituted coumarins.

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Results and Discussion

The HSAB principle, although introduced¹² in 1963 and based on some earlier work^{19,20}, has survived until today^{18,21,22} in spite of several strong criticisms²³⁻²⁵. The wide-ranging applicability of this principle to various branches of chemistry^{12-18,21,22,26-31}) prompted us to report reactions of 4-chloro-3-nitrocoumarin with several hard, soft, and borderline nucleophiles. The main synthetic results are summarized in Scheme 1.



Reactions of 4-chloro-3-nitrocoumarin with several hard monofunctional nucleophiles were carried out by refluxing of 1 with the appropriate nucleophile in different solvents. The compounds thus prepared were 2 (with MeO^{\odot}), 3 (with EtO^{\bigcirc}), 6 (with- β picolylamine), 7 [with bis(2-chloroethyl)amine], and 13 (with hydrazine). The reaction of 1 with an excess of glycinonitrile yielded the unexpected product 4-(hexahydro-2,5dioxo-1-pyrazinyl)-3-nitrocoumarin (5), the formation of which can be rationalized according to Scheme 2.

The first molecule of glycinonitrile displaces chlorine in position 4 of 1, leading to the intermediate \mathbf{a} which is attacked by the second molecule of glycinonitrile giving the intermediate \mathbf{b} which cyclises to yield \mathbf{c} . Hydrolysis of the intermediate \mathbf{c} occurs presumably during work-up procedure, giving rise to the final product 5. The latter gave a correct elemental analysis and was characterized on the basis of its mass



(molecular ion peak at m/e = 279), ¹H NMR (broad NH, $\delta = 8.90$; aromatic protons, $\delta = 7.2 - 8.1$; 2H singlet, CH₂, $\delta = 4.22$; 2H singlet, CH₂, $\delta = 3.40$), and IR spectra [v(NH) = 3305, v(pyrone C=O) = 1700, v(amide C=O) = 1680, v(C=C aromatic) = 1605, v(NO₂) = 1560 and 1325 cm⁻¹].

Treatment of 1 with 2-aminoethanol as an ambident nucleophile caused a fast attack of the amino group at position 4 followed by displacement of chlorine. The resulting product, 4-(2-hydroxyethylamino)-3-nitrocoumarin (4) was converted with POCl₃ in DMF into 4-(2-chloroethylamino)-3-nitrocoumarin (4a).

Reactions of 1 with aromatic amines and azide, classified as a borderline nucleophile, proceeded with substitution of chlorine in position 4. The compounds prepared were 8 (with *p*-toluidine), 9 (with *p*-anisidine), 10 (with *p*-acetylaminoaniline), 11 (with 1-aminonaphthalene), 12 (with *p*-cyanoaniline), and 14 (with azide). However, we were not able to purify 4-azido-3-nitrocoumarin (14) because of its thermal instability. Compound 14 was characterized on the basis of its mass (molecular peak, M^{\oplus} , at m/e = 232 and M - 28 at m/e = 204) and IR spectra [v(N₃) = 2140, v(pyrone C=O) = 1725, v(C=C aromatic) = 1600, and v(NO₂) = 1560 and 1330 cm⁻¹].

Refluxing of 14 for 45 minutes in DMF yielded a new heterocyclic compound (14a, 76% yield, Scheme 3).



We believe that only the [1]benzopyranofuroxan **14a** is formed because no high-field shilding effect was observed on the adjacent ring proton which exerts the *N*-oxide group³²⁻³⁵.

We have studied also the reactions of several soft nucleophiles with 1 which resulted in substitution of the nitro group in position 3. The compounds prepared were 16 (with Na salt of phenylmethanthiol), 17 (with N,N-dimethyldithiocarbamate), 18 (with N, N-diethyldithiocarbamate), 19 (with 1-piperidinedithiocarboxylate), and 20 (with cyanide). The compounds 16 and 17 gave correct elemental analyses, and IR and NMR spectra were in accord with the proposed structure. Compounds 18 and 19 were prepared in good yields (86 and 81%, respectively), but could not be obtained analytically pure because of thermal instability. It is noteworthy that the absence of infrared absorptions at ca. 1550 an 1350 cm^{-1} is a diagnostic for the absence of a nitro group. 4-Chloro-3-coumarincarbonitrile (20), obtained by nucleophilic displacement of the nitro group by the cyano group, showed the same m.p. and spectral data as the authentic sample prepared by an independent method³⁶. However, reaction with iodide as a typical soft nucleophile proceeded with substitution of chlorine in position 4. 4-Iodo-3-nitrocoumarin (15) gave a correct elemental analysis and was characterized on the basis of its mass (molecular ion peak at m/e = 317) and IR spectra $[v(pyrone C = O) = 1740, v(C = C \text{ aromatic}) = 1605, and v(NH_2) = 1535 and 1325 cm^{-1}].$ Substitution of chlorine in position 4 of 1 for iodine is an exception to the general reaction pattern.

The above-mentioned experimental observations may be interpreted in terms of the HSAB concept. Namely, hard and borderline nucleophiles substituted chlorine in position 4, while soft nucleophiles substituted the nitro group in position 3 (with the exception of iodide) 4-chloro-3-nitrocoumarin. The charge densities at these two positions should, therefore, differ considerably. For example, the standard HMO calculations, using heteroatomic parameters recommended by *Purcell* and *Singer* for bio-active molecules³⁷⁾, produced the following charge densities: q(3) = 0.9981 and q(4) = 0.5952 (see Scheme 4).

Scheme 4	POSITION	CHARGE DENSITY
$\begin{array}{c} 4 \\ CI \\ 3 \\ 7 \\ 8 \end{array} \begin{array}{c} 4 \\ 7 \\ 9 \\ 9 \\ 1 \\ 2 \\ 02 \end{array} \begin{array}{c} 2 \\ 3 \\ 7 \\ 2 \\ 02 \end{array} \begin{array}{c} 0 \\ 3 \\ 0 \\ 3 \\ 0 \\ 3 \end{array}$	$ \begin{array}{c} 1\\ 2\\ \Rightarrow 3\\ \Rightarrow 4 \end{array} $	1.8381 0.6832 0.9981 0.5952
	5 6	0.9097 1.0919 0.9045
	7 8 9	0.9045 1.0370 0.8509
	10 2'	1.0245 1.4778
	3' 3" 4'	1.0381 1.8305 1.9625

This result indicates that position 4 of 1 is a hard electrophilic position which attracts hard nucleophiles. Similarly, the calculations indicate position 3 of 1 as a soft electro-

philic position which is the site of attack of soft nucleophiles. Therefore, the outcome of the reactions studied in this work is dependent on the degree of deficiency of the electronic population at the reaction sites and the nucleophilic properties of the approaching nucleophile.

However, in the case of iodide which is an extremely large soft nucleophile, it may happen that the electronic factors are less important than the steric. Thus, the stereochemically more favoured site is position 4.

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Experimental

All melting points are uncorrected. – Microanalyses were performed on a Perkin-Elmer Model 240 elemental analyzer. – Infrared spectra were recorded with a Perkin-Elmer M-337 spectrophotometer (KBr disk), ¹H NMR spectra [δ (TMS) = 0] with a Perkin-Elmer R12A (60 MHz) spectrometer, and mass spectra with a Hitachi Perkin-Elmer RMV-GL spectrometer (at 75 eV).

4-Chloro-3-nitrocoumarin (1) was prepared according to lit.³⁸⁾.

4-Methoxy-3-nitrocoumarin (2): A solution of 1 (1.0 g, 4.4 mmol) and MeONa (4.4 mmol) in MeOH (25 ml) was refluxed for 1 h. The resulting solution was evaporated under reduced pressure (1/3 of volume), and then the resulting mixture was cooled to room temperature. The precipitate was collected and recrystallized from MeOH to give 2: 0.6 g (61%); m.p. 117 to 119 °C. – IR: 2940 (CH), 1720 (C=O, pyrone), 1600 (C=C, aromatic), 1550 and 1330 cm⁻¹ (NO₂). – ¹H NMR ([D₆]DMSO): δ = 7.5–8.01 (m, 4H, aromatic), 4.10 (s, 3H, OCH₃).

C10H7NO5 (221.2) Calc. C 54.30 H 3.18 N 6.33 Found C 54.45 H 3.42 N 6.06

4-Ethoxy-3-nitrocoumarin (3): A solution of 1 (1.0 g, 4.4 mmol) and EtONa (4.4 mmol) in EtOH (50 ml) was refluxed for 1 h. The resulting solution was evaporated under reduced pressure (1/3 of volume), and then the resulting mixture was cooled to room temperature. The precipitate was collected and recrystallized from EtOH to give 3: 0.8 g (77%); m. p. 158–160 °C. – IR: 2950 (CH), 1715 (C=O, pyrone), 1605 (C=C, aromatic), 1530 and 1340 cm⁻¹ (NO₂). – ¹H NMR (CDCl₃): δ = 7.3–8.1 (m, 4H, aromatic), 4.5 (q, 2H, CH₂), 3.55 (t, 3H, CH₃).

C11H9NO5 (235.2) Calc. C 56.18 H 3.86 N 5.95 Found C 55.80 H 4.11 N 5.93

4-(2-Hydroxyethylamino)-3-nitrocoumarin (4): A solution of 1 (1.0 g, 4.4 mmol) and 2-aminoethanol in acetonitrile was stirred at room temperature. After 1 hour the yellow precipitate was collected to yield 0.9 g (82%) of 4 which was recrystallized from ethanol: m.p. 168 – 170 °C. – IR: 3420 (OH), 3270 (NH), 2940 and 2890 (CH), 1710 (C = O, pyrone), 1605 (C = C, aromatic), 1520 and 1330 cm⁻¹ (NO₂). – ¹H NMR ([D₆]DMSO): δ = 8.70 (broad s, 1 H, NH), 7.50 – 8.80 (m, 4H, aromatic), 5.0 (t, 2H, CH₂), 8.75 (t, 3H, CH₂). – MS: *m/e* (relative intensity) = 250 (M[®], 40), 207 (17), 175 (20), 163 (100), 162 (42), 161 (20), 147 (25), 133 (40), 132 (40), 122 (25), 121 (50), 120 (87), 104 (37), 103 (51), 92 (32), 91 (40), 89 (30), 77 (42).

C11H10N2O5 (250.2) Calc. C 52.80 H 4.02 N 11.19 Found C 52.79 H 4.25 N 10.99

4-(2-Chlorethylamino)-3-nitrocoumarin (4a): To a stirred solution of DMF (0.33 ml) and POCl₃ (0.5 ml), cooled in an ice-bath, was added dropwise 1.0 g (4.0 mmol) of 4 in 5 ml of DMF. The resulting solution was stirred at room temperature during the next 3 h, and then the mixture was poured into ice-water. The yellow solid was collected and washed with water and an aqueous

solution of sodium hydrogen carbonate, and recrystallized from ethanol to give 0.76 g (71%) of 4a: m. p. 200 – 202 °C. – IR: 3330 (NH), 2950 (CH), 1760 (C=O, pyrone) 1605 (C=C, aromatic), 1520 and 1325 cm⁻¹ (NO₂). – ¹H NMR ([D₆]DMSO): δ = 8.35 (s, 1 H, NH), 7.35 – 8.25 (m, 4 H, aromatic), 4.45 (t, 2 H, CH₂), 3.60 (t, 2 H, CH₂).

 $C_{11}H_9CIN_2O_4$ (268.7) Calc. C 49.18 H 3.38 N 10.43 Found C 49.01 H 3.61 N 10.21

4-(Hexahydro-2,5-dioxo-1-pyrazinyl)-3-nitrocoumarin (5): To a stirred solution of 1 (1.0 g, 4.4 mmol) in methanol (30 ml) was added dropwise 10 ml of a methanolic solution of glycinonitrile (10 mmol) at room temperature. After 30 min the formed brown precipitate was collected to yield 0.98 g (79%) of 5 which was recrystallized from dioxan-water (1:1): m. p. 244-246 °C. – IR: 3305 (NH), 1700 (C=C, pyrone), 1680 (C=C, amide), 1605 (C=C, aromatic), 1560 and 1325 cm⁻¹ (NO₂). – ¹H NMR ([D₆]DMSO): δ = 8.90 (broad s, 1H, NH), 7.20–8.10 (m, 4H, aromatic), 4.22 (s, 2H, CH₂), 3.4 (s, 2H, CH₂). – MS: *m/e* (relative intensity) = 279 (M[⊕], 3) 345 (3), 227 (3), 211 (5), 199 (5), 184 (5), 174 (19), 172 (8), 146 (16), 120 (15), 119 (83), 104 (20), 103 (11), 102 (10), 92 (15), 91 (71), 90 (10), 76 (18), 64 (25), 63 (23), 54 (100).

C13H9N3O6 (303.2) Calc. C 51.49 H 2.98 N 13.85 Found C 51.81 H 2.69 N 14.00

3-Nitro-4-(3-pyridylmethylamino)coumarin (6): A solution of 1 (1.0 g, 4.4 mmol) 3-aminomethylpyridine (5 mmol) in acetonitrile (50 ml) was stirred at room temperature for 1 h. The yellow precipitate was collected to give 0.93 g (71%) of 6 and recrystallized from ethanol: m.p. 158-160 °C. – IR: 3340 (NH), 1660 (C=C, pyrone), 1605 (C=C, aromatic), 1555 and 1325 cm⁻¹ (NO₂). – ¹H NMR ([D₆]DMSO): δ = 9.08 (broad s, 1H, NH), 7.3–8.3 (m, 8H, aromatic), 4.60 (s, 2H, CH₂).

C15H10N3O4 (296.3) Calc. C 60.81 H 3.40 N 14.18 Found C 60.42 H 3.56 N 13.83

4-Bis(2-chloroethylamino)-3-nitrocoumarin (7): A solution of 1 (4.51 g, 20 mmol), bis(2-chloroethyl)amine, and 3 ml of triethylamine was refluxed in acetonitrile (40 ml) during 24 h. The resulting solution was evaporated under reduced pressure (1/3 of volume), and then the residue was poured into water. Recrystallization from acetonitrile gave 4.64 g (69%) of 7: m.p. 189–191 °C. – IR: 2970 (CH), 1730 (C=O, pyrone), 1600 (C=C, aromatic) 1555 and 1350 cm⁻¹ (NO₂). – ¹H NMR ([D₆]DMSO): δ = 7.35–8.0 (m, 4H, aromatic), 3.3–4.0 (m, 8H, CH₂).

C13H12Cl2N2O4 (331.2) Calc. C 47.14 H 3.65 H 8.46 Found C 46.92 H 3.42 N 8.24

General procedure for the synthesis of compounds 8 - 12: To a hot solution of 4.4 g (20 mmol) of 1 in benzene an equimolar amount of the corresponding aromatic amine and 3 ml of triethylamine, dissolved in benzene were added, and the solution was refluxed for 30 min. The precipitate was collected and washed with an aqueous solution of sodium hydrogen carbonate.

4-(4-Methylphenylamine)-3-nitrocoumarin (8): Yield 95%; recrystallization from ethanol: m. p. 193 – 195 °C. – IR: 3380 (NH), 2930 (CH₃), 1680 (C = O, pyrone), 1605 (C = C, aromatic), 1540, 1370 cm⁻¹ (NO₂). – ¹H NMR ([D₆]DMSO): δ = 10.03 (broad, 1H, NH), 7.1–8.6 (m, 8H, aromatic), 3.32 (s, 3H, CH₃).

C16H12N2O4 (296.3) Calc. C 64.86 H 4.08 N 9.45 Found C 64.72 H 4.01 N 9.17

4-(4-Methoxyphenylamino)-3-nitrocoumarin (9): Yield 94%; recrystallization from DMF: m.p. 200-202°C. – IR: 3300 (NH), 2980, 2930, (CH₃), 1700 (C=C, pyrone), 1610 (C=C, aromatic), 1550, 1370 cm⁻¹ (NO₂). – ¹H NMR ([D₆]DMSO): δ = 10.02 (broad, s, 1H, NH), 6.8-8.5 (m, 8H, aromatic), 3.78 (s, 3H, OCH₃).

C15H12N2O5 (300.3) Calc. C 60.00 H 4.02 N 9.33 Found C 60.12 H 4.26 N 9.38

4-(4-Acetylaminophenylamino)-3-nitrocoumarin (10): Yield 88%; recrystallization from 96% EtOH: m. p. 259–260 °C. – IR: 3360 (NH, amide), 3290 (NH-amine), 2930 (CH), 1720 (C=O, pyrone), 1660 (amide, C=O), 1605 (C=C, aromatic), 1535 and 1370 cm⁻¹ (NO₂). – ¹H NMR ([D₆]DMSO): δ = 10.05 (s, 1H, NH, amine), 9.85 (s, 1H, NH, amide), 7.1–8.4 (m, 8H, aromatic), 2.1 (s, 3H, CH₃).

C17H13N3O5 (339.3) Calc. C 60.10 H 3.86 N 12.38 Found C 60.23 H 3.80 N 12.28

4-(1-Naphthylamino)-3-nitrocoumarin (11): Yield 87%; recrystallization from 96% EtOH: m.p. 210-212 °C. – IR: 3280 (NH), 1685 (C=O, pyrone), 1605 (C=C, aromatic), 1535 and 1370 cm⁻¹ (NO₂).

C19H12N2O4 (332.3) Calc. C 68.67 H 3.64 N 8.43 Found C 68.70 H 3.87 N 8.16

4-(4-Cyanophenylamino)-3-nitrocoumarin (12): Yield 91%; recrystallization from 96% EtOH: m. p. $224 - 226 \,^{\circ}$ C. – IR: 3280 (NH), 2220 (CN), 1640 (pyrone, C=O), 1610 (C=C, aromatic), 1540 and 1365 cm⁻¹ (NO₂).

C16H11N3O4 (309.3) Calc. C 62.13 H 3.59 N 13.59 Found C 62.01 H 3.68 N 13.27

4-Hydrazino-3-nitrocoumarin (13): To a stirred solution of 1 (1.0 g, 4.4 mmol) in acetonitrile (50 ml) was added dropwise 1.4 ml of hydrazine (99%) at room temperature. The reaction was continued for 1 h. The orange precipitate was collected to yield 0.67 g (68%) of 13, and then it was recrystallized from ethanol-water (1:1): m.p. 218-220 °C. – IR: 3425 (NH), 3295 (NH), 1700 (C = O, pyrone), 1605 (C = C, aromatic), 1530 and 1325 cm⁻¹ (NO₂). – MS: *m/e* (relative intensity) = 221 (M^{\oplus}, 100), 207 (7), 205 (50), 204 (5), 176 (13), 175 (76), 103 (30), 102 (24), 101 (22), 91 (56), 90 (22), 89 (65), 77 (36), 76 (27).

C₉H₇N₃O₄ (221.2) Calc. C 48.88 H 3.19 N 19.00 Found C 49.10 H 3.36 N 18.84

4-Azido-3-nitrocoumarin (14): A solution of 1 (1.0 g, 4.4 mmol) in dry DMF (12 ml) containing sodium azide (4.6 mmol) was stirred at room temperature for 30 min, and then the reaction mixture was poured into water. The precipitate was collected and recrystallized from ethanol to give 0.9 g (90%) of 14: m.p. 110-112 °C. - IR: 2140 (N₃), 1725 (C=O, pyrone), 1600 (C=C, aromatic), 1560 and 1330 cm⁻¹ (NO₂). - ¹H-NMR (CDCl₃): δ = 7.25 - 8.05 (m, 4H, aromatic). - MS: *m/e* (relative intensity), 232 (M[⊕], 22), 205 (17), 204 (100), 202 (14), 188 (11), 187 (9), 176 (9), 174 (14), 162 (9), 161 (31), 160 (14).

4*H*-[*1*]*Benzopyrano*[3,4-*c*][1,2,5]*oxadiazole-4-one* 3-*oxide* (14a): The solution of 1.0 g (4.3 mmol) of 14 in 20 ml dry DMF was refluxed for 45 min. The product 14a was obtained on cooling, and the reaction mixture was poured into 150 ml ice-water. The solid was filtered and recrystallized from ethanol to give 0.7 g (76%) of 14a: m.p. 180–181 °C. – IR: 1720 (C=O, pyrone), 1635 (furoxane ring), 1610 (C=C, aromatic), 1220 ($\mathring{N} - \mathring{O}$). – ¹H NMR ([D₆]DMSO): $\delta = 7.36 - 8.25$ (m, 4H, aromatic). – MS: *m/e* (relative intensity) = 204 (M[⊕], 100), 144 (76), 116 (62), 102 (33), 88 (52), 73 (52).

C₉H₄N₂O₄ (204.1) Calc. C 52.94 H 1.98 N 13.72 Found C 52.73 H 2.00 N 13.91

4-Iodo-3-nitrocoumarin (15): The solution of 1 (1.0 g, 4.4 mmol) and sodium iodide (4.4 mmol) was heated under reflux in acetonitrile (30 ml) during 3 h. The reaction mixture was cooled and poured into ice-water. The crude product, a light-yellow solid, was collected by filtration to give 0.82 g (61%) of 15 and recrystallized from ethanol: m.p. $210-212 \,^{\circ}$ C. – IR: 1735 (C=O, pyrone), 1605 (C=C, aromatic), 1535 and 1325 cm⁻¹ (NO₂). – ¹H NMR ([D₆]DMSO): $\delta = 7.2-8.2$ (m, 4H, aromatic). – MS: *m/e* (relative intensity) = 317 (M[⊕], 100), 271 (95), 259 (39.6), 215 (63.4), 190 (3), 144 (19), 127 (6.3), 123 (7.9), 120 (4.7), 116 (41.2), 88 (79.3).

C₉H₄NO₄I (317.0) Calc. C 34.10 H 1.26 N 4.41 Found C 34.03 H 1.51 N 4.50

General procedure for the synthesis of compounds 16-19: To a stirred solution of 1 (1.0 g, 4.4 mml) in acetone (50 ml), cooled at 0-5 °C, an equimolar amount of the corresponding sodium salt of phenylmethanthiol or N,N-dialkyldithiocarbamic acid dissolved in acetone (ca. 50 ml) was added dropwise and at a rate which allowed to maintain the temperature of the reaction mixture below 10 °C. After 4 h at room temperature the reaction mixture was poured into ice-water. The resulting yellow crystalline solid was collected by filtration.

4-Chloro-3-benzylthiocoumarin (16): Yield 0.83 g (62%); recrystallized from acetonitrile: m. p. 138–139°C. – IR: 2900 (CH), 1735 (C = O, pyrone), 1600 (C = C, aromatic), 1530 and 1325 cm⁻¹ (NO₂). – ¹H NMR ([D₆]DMSO): δ = 7.25–8.21 (m, 9H, aromatic), 4.37 (s, 2H, CH₂).

C₁₆H₁₁ClO₂S (302.8) Calc. C 63.47 H 3.66 Found C 63.15 H 3.86

4-Chloro-3-coumarinyl N,N-dimethyldithiocarbamidate (17): Yield 1.12 g (87%); recrystallized from acetic acid: m.p. 213-215 °C. – IR: 2920 (CH), 1760 (C=O, pyrone), 1600 (C=C, aromatic). – ¹H NMR (CDCl₃): δ = 7.1-8.2 (m, 4H, aromatic), 2.9 (s, 6H, CH₃).

C12H10ClNO2S2 (299.8) Calc. C 48.07 H 3.35 N 4.67 Found C 48.31 H 3.27 N 4.47

4-Chloro-3-coumarinyl N,N-diethyldithiocarbamidate (18): Yield, 1.19 g (86%); recrystallized from dioxane: m.p. $162 - 163 \,^{\circ}$ C. – IR: 2980, 2940 and 2880 (CH), 1735 (C = O, pyrone), 1600 (C = C, aromatic). – ¹H NMR ([D₆]DMSO, 95 \,^{\circ}C): δ = 7.2 – 8.06 (m, 4H, aromatic), 3.21 (q, 4H, CH₂), 1.19 (t, CH, CH₃).

C14H14CINO2S2 (327.9) Calc. C 51.29 H 4.30 N 4.27 Found C 50.76 H 4.56 N 4.34

4-Chloro-3-(piperidinothiocarbonylthio)coumarin (19): Yield 1.17 g (81%); recrystallized from acetone m.p. 154 - 155 °C. – IR: 2940 and 2860 (CH), 1735 (C=O, pyrone), 1600 (C=C, aromatic). – ¹H NMR ([D₆]DMSO, 150 °C): δ = 7.2–8.1 (m, 4H, aromatic), 3.2 (m, 4H, CH₂), 1.55 (m, 6H, CH₂).

C15H14CINO2S2 (339.9) Calc. C 53.01 H 4.15 N 4.12 Found C 53.68 H 4.02 N 3.96

4-Chloro-3-coumarincarbonitrile (20): A solution of 1 (1.0 g, 4 mmol) and NaCN (4.4 mmol) was heated (60 °C) in dry DMF (75 ml) during 2.5 h, and then the reaction mixture was poured into ice-water. A light brown solid was filtered of and recrystallized from dioxane-water (1:1) to give 0.3 g (37%) of 20: m.p. 197–199 °C (lit.³⁹⁾ m.p. 198–200 °C). – IR: 2240 (CN), 1725 (pyrone, C=O), 1605 (C=C, aromatic). – ¹H NMR ([D₆]DMSO): $\delta = 7.3-8.0$ (m, 4H, aromatic).

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[98/83]