HETEROCYCLES, Vol. 29, No. 9, 1989

A CONVENIENT ONE POT SYNTHESIS OF 3-THIOSUBSTITUTED COUMARINS

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Abstract - Several 3-thiosubstituted coumarins (5) are prepared by the reaction of thioacetonitriles (2) with o-hydroxybenzaldehydes (3) in ethanol using catalytic amount of sodium hydroxide followed by acidic hydrolysis of intermediate imines (4).

(Benzothiazolylthio)coumarins have been prepared earlier starting from 2-mercaptobenzothiazole following a large number of steps[1,2]. In view of the good antifungal and antibacterial activities of the title compounds[3], it was considered of interest to affect a convenient synthesis of such compounds. In this paper, we describe a convenient one pot synthesis of 3-thiosubstituted coumarins.

As a test case, treatment of 2-[(cyanomethyl)thio]benzothiazole (2a) (obtained by the reaction of 2-mercaptobenzothiazole (1a) with chloroacetonitrile) with salicylaldehyde (3a) in ethanol in the presence of aqueous sodium hydroxide, gave imine (4a) in 90% yield. This compound (4a) was hydrolysed to the corresponding coumarin (5a) by treatment with dilute (1:1) hydrochloric acid. 5a was soluble in hot dilute alkali, but recovered unchanged on acidification. This indicated the presence of a coumarin ring. Ir spectrum of the compound showed the presence of coumarin carbonyl at 1720 cm^{-1} and also 3,4-C=C at 1600 cm^{-1}. In the ^{1}H-nmr spectra ($CDCl_3$ + TFA) of this compound, besides other signals, a singlet at δ 8.65 for 4-H of the coumarin moiety was observed. On this basis, compound (5a) was assigned the structure as 3-(benzothiazol-2'-ylthio)coumarin, identical with the sample obtained earlier[1]. Following the similar procedure, compounds (5b-f) were prepared and structures were assigned on the basis of spectral data and elemental analyses. Coumarins 5a-f could also be obtained in one pot by the

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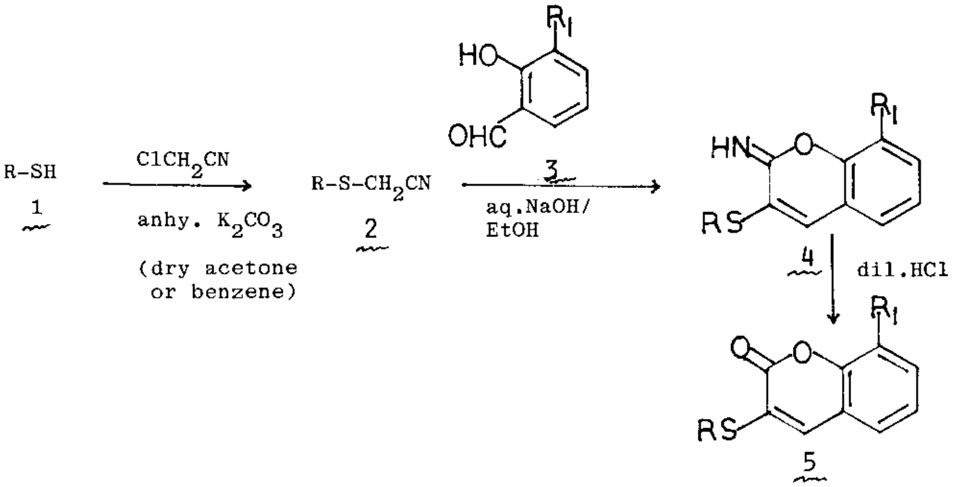
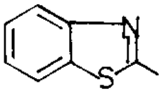
reaction of thioacetonitriles (2a-c) with o-hydroxyaldehydes (3a-b) in ethanolic aqueous sodium hydroxide and subsequent heating of the reaction mixture with dilute hydrochloric acid without isolating the intermediate imines (4a-f).

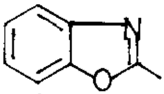


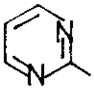
For, 3a, 4a, 4c, 4e and 5a, 5c, 5e, R_1 = H;

3b, 4b, 4d, 4f and 5b, 5d, 5f, R_1 = OCH_3;

For,

1a, 2a, 4a, 4b, 5a, 5b, R = 

1b, 2b, 4c, 4d, 5c, 5d, R = 

1c, 2c, 4e, 4f, 5e, 5f, R = 

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on Perkin Elmer Grating IR spectrophotometer model 621; ^{1}H-nmr spectra were recorded on Perkin Elmer R-32 (90 MHz) instrument using TMS as the internal standard (chemical shifts in δ, ppm).

2-[(Cyanomethyl)thio]benzothiazole (2a) : Typical procedure

A solution of 2-mercaptobenzothiazole (1a, 1.67 g, 0.01 mol) in dry acetone (50 ml) was refluxed for 3 h with chloroacetonitrile (0.755 g, 0.01 mol) in the presence of anhydrous potassium carbonate (5 g). The inorganic salt was filtered out, solvent was distilled off and the residue was treated with crushed ice. The solid thus obtained was crystallised from petroleum ether - chloroform as light brown crystals (1.85 g, yield 90%), mp 65-66°C; ^{1}H-nmr ($CDCl_3$) δ : 4.20 (s, 2H, CH_2), 7.30-8.20 (m, 4H, aromatic protons). Anal. Calcd for $C_9H_6N_2S_2$: C, 52.43; H,2.91; N,13.59. Found : C,52.34; H,2.84; N,13.50.

Similarly, following were prepared :

2b*: Crystallised from petroleum ether-chloroform as light pink crystals (yield 90%), mp 93-94°C; ^{1}H-nmr ($CDCl_3$) δ : 4.00 (s,2H,CH_2), 7.30-7.85 (m,4H,aromatic protons). Anal. Calcd for $C_9H_6N_2OS$: C, 56.84; H,3.16; N,14.74. Found : C,56.73; H,3.27; N,14.64.

2c: Crystallised from petroleum ether-chloroform as cream crystals (yield 92%), mp 106-107°C; ^{1}H-nmr ($CDCl_3$) δ : 3.90 (s,2H,CH_2), 7.00 (t,J=5Hz,1H,5-H), 8.70 (d,J=5Hz, 2H,4-H and 6-H). Anal. : Calcd for $C_6H_5N_3S$: C,47.68; H,3.31; N,27.81. Found : C,47.54; H,3.29; N,27.72.

3-(Benzothiazol-2'-ylthio)coumarin imine (4a) : Typical procedure

Aqueous sodium hydroxide (4%, 1 ml, 0.001 mol) was added to a solution of 2-[(cyanomethyl)thio]benzothiazole (2a, 2.06 g, 0.01 mol) and salicyladehyde (3a, 1.22 g, 0.01 mol) in ethanol (20 ml). The solution was refluxed for 20-25 min, water (100 ml) was added and the precipitate was filtered and dried. It was crystallised from methanol as yellow crystals (2.79 g, yield 90%), mp 113-115°C; ^{1}H-nmr ($CDCl_3$ + TFA) δ : 7.60-8.20 (m, 8H, aromatic protons), 8.80 (s,1H,H-4). Anal. Calcd for $C_{16}H_{10}N_2OS_2$: C, 61.93; H,3.23; N,9.03. Found : C,61.84; H,3.28, N,8.94.

4b: Crystallised from methanol as yellow crystals (yield 90%), mp 79-81°C; ^{1}H-nmr ($CDCl_3$) δ : 4.00 (s, 3H, OCH_3), 7.10-8.00 (m, 7H, aromatic protons), 8.40 (s,1H,H-4). Anal. Calcd for $C_{17}H_{12}N_2O_2S_2$: C,60.00; H,3.53; N,8.24. Found : C,59.84; H,3.43; N,8.14.

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*Benzene was used as solvent for the cyanomethylation of 1b to get 2b.

Compounds 4c, 4d, 4e and 4f could not be isolated in pure form.

3-(Benzothiazol-2'-ylthio)coumarin (5a) : Typical procedure

(i) One pot method

To a solution of 2-[(cyanomethyl)thio]benzothiazole (2a, 2.06 g, 0.01 mol) and salicyladehyde (3a, 1.22 g, 0.01 mol) in ethanol (20 ml) was added aqueous sodium hydroxide (4%, 1 ml, 0.001 mol) and the solution was refluxed for 20 min on a steam bath. 6N hydrochloric acid (10 ml) was added to the cooled reaction mixture and it was refluxed for further 15 min. The reaction mixture was cooled, water (100 ml) was added and it was left at room temperature for 3 h. The yellow precipitate thus obtained was filtered, washed with water and dried. It was crystallised from methanol as yellow needles (2.8 g, yield 90%), mp 170-171°C (Lit.[1] mp 170-171°C).

(ii) Two step method

To the hot ethanolic solution of 4a (0.31 g, 0.001 mol) in 5 ml of ethanol was added 6N hydrochloric acid (1 ml) and the contents were refluxed over a steam bath for 15 min. Cooled reaction mixture was diluted with water when yellow precipitate separated out. It was filtered, dried and crystallised from methanol as yellow needles (0.29 g, yield 94%), mp 170-171°C (Lit.[1] mp 170-171°C).

5b : Crystallised from methanol as light yellow needles (yield 90% in one pot method, 80% in stepwise method), mp 172-173°C (Lit.[1] mp 172-173°C).

5c : Crystallised from methanol as cream crystals (yield 70%), mp 220-221°C; Ir γ_{max}^{Nujol} 1700 cm^{-1} (C=O), 1600 cm^{-1} (C=C); ^{1}H-nmr ($CDCl_3$ + TFA) δ : 7.60-8.10 (m, 8H, aromatic protons), 8.60 (s,1H,H-4). Anal. Calcd for $C_{16}H_9NO_3S$: C, 65.08; H,3.05; N,4.74. Found : C,65.04; H,2.94; N,4.64.

5d : Crystallised from methanol as light yellow crystals (yield 68%), mp 240-241°C; Ir γ_{max}^{Nujol} 1700 cm^{-1} (C=O), 1600 cm^{-1} (C=C); ^{1}H-nmr ($CDCl_3$ + TFA) δ : 4.00 (s,3H,OCH_3), 7.20-7.60 (m,7H,aromatic protons), 8.35 (s,1H,H-4). Anal. Calcd for $C_{17}H_{11}NO_4S$: C, 62.77; H,3.38; N,4.31. Found : C,62.64; H,3.47; N,4.24.

5e : Crystallised from methanol as cream crystals (yield 72%), mp 184-185°C; Ir γ^{Nujol}_{max} 1720 cm^{-1} (C=O), 1600 cm^{-1} (C=C); ^{1}H-nmr (CDCl$_3$ + TFA) δ 7.40 - 8.10 (m, 5H, 5, 6, 7, 8-H and 5'-H), 8.70 (s,1H,H-4), 9.25 (d,J=5Hz, 2H, 4'-H and 6'-H). Anal. Calcd for $C_{13}H_8N_2O_2S$: C, 60.94; H,3.12; N,10.94. Found : C,60.74; H,3.18; N,10.84.

5f : Crystallised from methanol as cream crystals (yield 71%), mp 176-177°C; Ir γ^{Nujol}_{max} 1705 cm^{-1} (C=O), 1600 cm^{-1} (C=C); ^{1}H-nmr (CDCl$_3$ + TFA) δ : 4.00 (s, 3H,OCH$_3$), 7.40-7.80 (m,3H,5, 6 and 7-H), 8.00 (t,J=5Hz,1H,H-5'), 8.80 (s,1H, H-4), 9.30 (d,J=5Hz,2H,H-4' and H-6'), Anal. Calcd for $C_{14}H_{10}N_2O_3S$: C,58.74; H,3.49; N,9.79. Found : C,58.70; H,3.44; N,9.73.

ACKNOWLEDGEMENTS

We are thankful to the DST and UGC (India) for financial help.

REFERENCES

1. V.K. Ahluwalia, H.R. Sharma, and R. Tyagi, *Tetrahedron*, 1987, 43, 1141.
2. V.K. Ahluwalia, R. Tyagi, and V.D. Mehta, *Indian J. Chem*. 1989, 28B, 349.
3. V.K. Ahluwalia et al., unpublished work.

Received, 26th April, 1989