Base-promoted Cyclisation of Hydrazonoyl Chlorides Bearing an Alkynylsulphonyl Group

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Treatment of the hydrazonoyl chlorides (**1**) and (**3**) with triethylamine in boiling benzene gives a pyrazolo[5,1-*c*][1,4]benzothiazine *S,S*-dioxide (**12**) arising from intramolecular cycloaddition of a nitrilimine intermediate, as well as 1,4-benzothiazine *S,S*-dioxides (**15**) and (**16**) due to intramolecular Michael-type addition of an aza-anion. The latter pathway is the exclusive one in acetonitrile at room temperature.

Nitrilimines are versatile intermediates undergoing 1,3-dipolar cycloadditions with a wide variety of unsaturated compounds.[1] Intramolecular examples of these reactions are known.[2] In this context, we were interested in the behaviour of the alkynylsulphonyl-substituted nitrilimines (**9**) and (**11**), which were generated *in situ* upon base treatment of the corresponding hydrazonoyl chlorides (**1**) and (**3**) (see Scheme). Actually. a complex pattern of behaviour was observed, some aspects of which lack precedent in the chemistry of the hydrazonoyl halides.

Results and Discussion

Treatment of compound (**1**) with triethylamine in boiling benzene gave, after 72 h, the cyclisation products (**12**), (**15**), and (**19**) in 53, 18, and 6% yield, respectively. However, on monitoring the reaction progress by t.l.c. analysis, other components were observed after short reaction times. When the reaction was stopped after 4 h, chromatographic separation furnished compounds (**12**) (27%), (**4**) (9%), (**2**) (6%), (**15**) (6%), and (**5**) (3%). It was then ascertained that the same product mixture is also formed upon base treatment of each of the hydrazonoyl chlorides (**2**), (**4**), and (**5**). The reaction of compound (**3**) with triethylamine in boiling benzene resulted after 5 h in a very complex mixture containing, in addition to the products already obtained from compound (**1**), the benzothiazine (**16**). After 48 h under reflux, the following products were isolated: (**12**) (45%), (**15**) (13%), (**19**) (4%), and (**16**) (2%). Control experiments showed that compound (**15**) is stable under the conditions of its formation, but can isomerise to (**16**) under acid catalysis.

The reactions of isomers (**1**) and (**3**) with triethylamine were also carried out in acetonitrile. In this solvent, the reactions were much faster than in benzene, being complete within 15 min at room temperature. Moreover, they provided the heterocycles (**15**) and (**16**), respectively, in substantial yields.

The structures of the new compounds were assigned on the basis of analytical and spectral data (see Experimental section). Compound (**19**) was also submitted to *X*-ray diffraction study.[3]

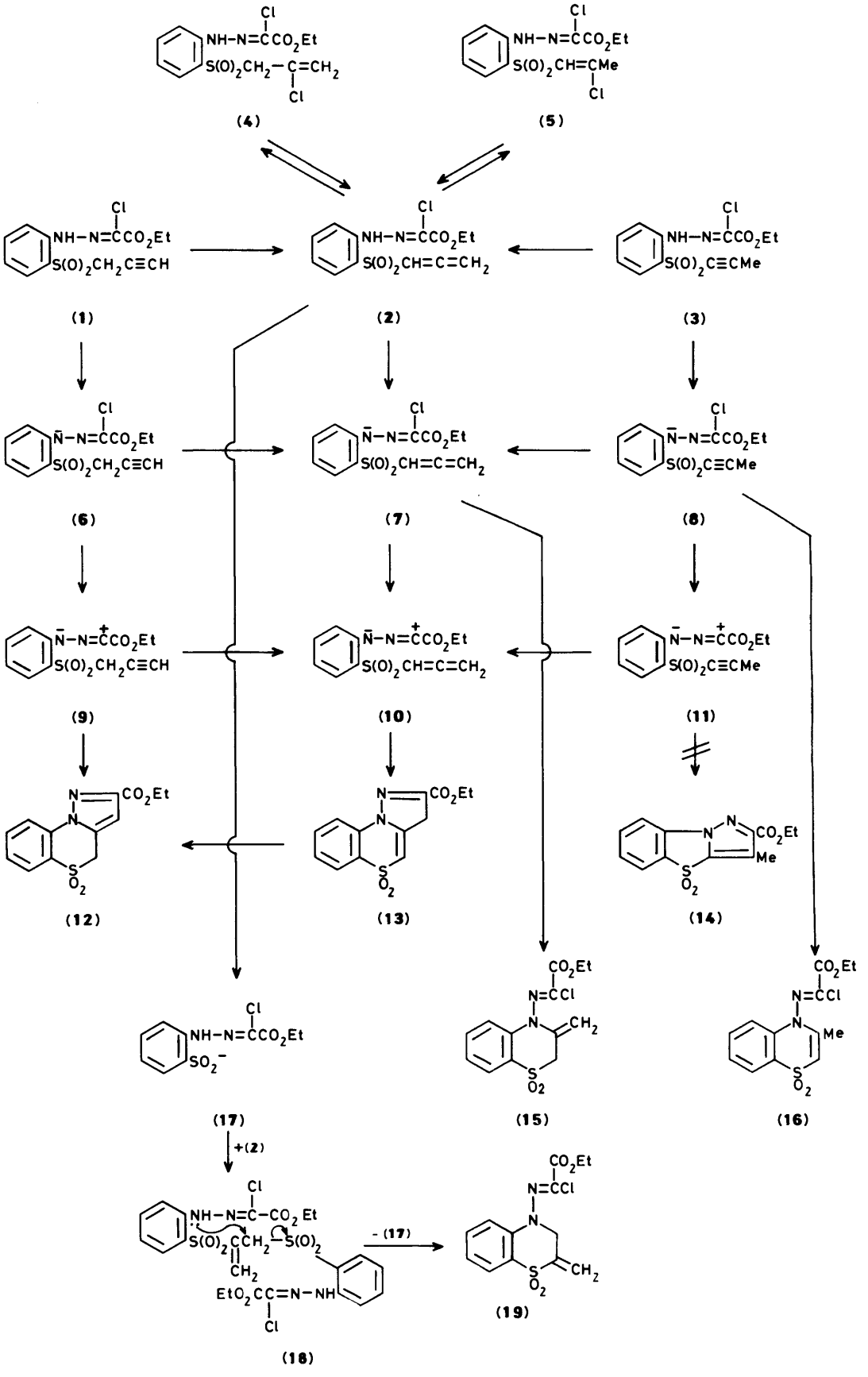
The above results reveal the occurrence of a complex sequence of parallel-consecutive reactions, which are displayed in the Scheme. As expected, compound (**1**) generates the nitrilimine (**9**) which undergoes an intramolecular cycloaddition to the triple bond to afford the pyrazole derivative (**12**). However, compound (**1**) also suffers concomitant base-promoted isomerisation of the alkyne moiety, thus producing the corresponding allene (**2**) which is in turn susceptible to a number of transformations (see Scheme). The reversible conversion of the allene (**2**) into compounds (**4**) and (**5**) closely parallels the reported reaction of phenylsulphonylallene with chloride ion.[4] On the other hand, the benzothiazine (**15**) can be thought of as being derived from allene (**2**) through deprotonation of the NH group and subsequent intramolecular attack of the aza-anion to the central carbon of the allene function. This constitutes a novel mode of reaction in the field of hydrazonoyl halides, since base-promoted reaction of these substrates with carbon–carbon multiple bonds usually results in cycloaddition products *via* nitrilimine intermediates.[1,5] Alternatively, in certain intramolecular cases, only one σ bond is formed between an ethylenic carbon and the *carbon* of the hydrazone moiety.[6,7] In the present case, while steric restraints may disfavour the intramolecular cycloaddition, the strong electron-withdrawing character of the sulphonyl group enhances the electrophilicity of the β-carbon and promotes the Michael-type addition of the aza-anion to this position. The observed solvent effect on the competition between addition and cycloaddition is remarkable, and reflects the different polarity of the corresponding transition states. Similar considerations may explain the behaviour of the hydrazonoyl chloride (**3**): while formation of compounds (**12**) and (**15**) is attributable to the initial allenisation of (**3**), compound (**16**) arises from intramolecular Michael-type addition to the activated triple bond. On the other hand, the lack of formation of the conceivable cycloadduct (**14**) is probably due to both steric restraints and electronic factors. The conversion of the nitrilimine (**11**) into compound (**14**) would have been in contrast with the regiochemical course of the intermolecular cycloaddition between nitrilimines and propynyl sulphones, which has been shown to afford 4-sulphonylpyrazoles.[8]

Finally, the surprising formation of the benzothiazine (**19**) may tentatively be interpreted as proceeding through the intermediacy of species (**17**) and (**18**). Formation of intermediate (**18**) would parallel the reported production of 2,3-bis(phenylsulphonyl)prop-1-ene as a side-product of the reaction between phenylsulphonylallene and hydrazonoyl chlorides in basic medium.[8]

Experimental

M.p.s were determined on a Büchi apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 298 spectrophotometer. N.m.r. spectra were recorded on Varian EM-390 (^{1}H) and Bruker WP80SY (^{13}C) instruments, respectively; chemical shifts are given in p.p.m. from internal $SiMe_4$. Coupling constant for the ethyl group is always 7 Hz. Silica gel used for chromatography was Merck Kieselgel 60 (70—230 mesh ASTM).

Ethyl 2-Chloro-2-[2-(prop-2-ynylsulphonyl)phenylhydrazono]-acetate (**1**).—To a solution of ethyl 2-chloro-2-[2-(prop-2-ynylthio)phenylhydrazono]acetate[9] (6.0 g) in acetic acid (240 ml) was added 30% hydrogen peroxide (57 ml). After being stirred at 55 °C for 4 h, the mixture was poured onto crushed ice (500 g) and neutralised with sodium carbonate. The precipitate



Scheme.

was filtered off and washed with water to afford the *title sulphone* (**1**) (5.5 g, 83%), m.p. 130 °C (from ethanol) (Found: C, 47.7; H, 4.0; N, 8.4. $C_{13}H_{13}ClN_2O_4S$ requires C, 47.5; H, 4.0; N, 8.5%); $\nu_{max.}$(Nujol) 3 275, 2 120, and 1 725 cm^{-1}; $\delta(CDCl_3)$ 1.45 (3 H, t, Me), 2.50 (1 H, t, *J* 3 Hz, C≡CH), 4.12 (2 H, d, *J* 3 Hz, CH_2SO_2), 4.44 (2 H, q, CH_2), 7.1—7.3 (1 H, m, ArH), 7.6—8.0 (3 H, m, ArH), and 10.7 (1 H, br, s, NH); *m/z* 328 (M^+).

Ethyl 2-Chloro-2-[2-(prop-1-ynylsulphonyl)phenylhydrazono]acetate (**3**).—To a solution of ethyl 2-chloro-2-[2-(prop-1-ynylthio)phenylhydrazono]acetate[9] (1.8 g) in acetic acid (80 ml) was added 30% hydrogen peroxide (18 ml). After being stirred at 50 °C for 6 h, the mixture was poured onto crushed ice (300 g) and neutralised with sodium carbonate. The precipitate was filtered off and washed with water to afford the *title sulphone* (**3**) (1.0 g, 50%), m.p. 110 °C (from ethanol) (Found: C, 47.6; H, 3.9; N, 8.4%); $\nu_{max.}$(Nujol) 3 280, 2 200, and 1 715 cm^{-1}; $\delta(CDCl_3)$ 1.40 (3 H, t, CH_2Me), 2.07 (3 H, s, Me), 4.38 (2 H, q, CH_2), 6.95—7.2 (1 H, m, ArH), 7.4—7.9 (3 H, m, ArH), and 10.35 (1 H, br s, NH); *m/z* 328 (M^+).

Reaction of (**1**) *with Triethylamine in Benzene.*—(*A*) A solution of compound (**1**) (1.42 g) and triethylamine (3 ml) in benzene (200 ml) was refluxed for 72 h, then washed successively with 1M-HCl and water. After being dried (Na_2SO_4), the solvent was evaporated off under reduced pressure and the residue was chromatographed on a silica gel column (120 g) with benzene–ethyl acetate (9:1) as eluant to give, first, 4-(α-*chloro*-α-*ethoxycarbonylmethyleneamino*)-2-*methylene*-3,4-*dihydro*-2H-1,4-*benzothiazine* S,S-*dioxide* (**19**) (92 mg, 6%), m.p. 142 °C (from di-isopropyl ether–chloroform) (Found: C, 47.4; H, 3.9; N, 8.6. $C_{13}H_{13}ClN_2O_4S$ requires C, 47.5; H, 4.0; N, 8.5%); $\nu_{max.}$(Nujol) 1 710 cm^{-1}; $\delta(CDCl_3)$ 1.43 (3 H, t, Me), 4.42 (2 H, q, CH_2Me), 5.48 (2 H, s, 3-H_2), 6.01 (1 H, s, =C*H*H), 6.34 (1 H, s, =CH*H*), and 7.0—7.9 (4 H, m, ArH); *m/z* 328 (M^+).

Subsequent fractions contained 4-(α-*chloro*-α-*ethoxycarbonylmethyleneamino*)-3-*methylene*-3,4-*dihydro*-2H-1,4-*benzothiazine* S,S-*dioxide* (**15**) (258 mg, 18%), m.p. 118 °C (from di-isopropyl ether–chloroform) (Found: C, 47.3; H, 4.1; N, 8.5%); $\nu_{max.}$(Nujol) 1 735 cm^{-1}; $\delta(CDCl_3)$ 1.38 (3 H, t, Me), 4.12 (2 H, s, 2-H_2), 4.38 (2 H, q, CH_2 Me), 4.6—4.7 (1 H, m, =C*H*H), 5.0—5.1 (1 H, m, =CH*H*), and 7.0—8.0 (4 H, m, ArH); $\delta_C(CDCl_3)$ 14.1 (q, CH_3), 56.2 (t, CH_2SO_2), 64.2 (t, CH_2Me), 105.4 (t, $=CH_2$), 117.2—139.0 (overlapping, =C–, =C<), and 158.7 (s, CO); *m/z* 328 (M^+).

Further elution gave 2-*ethoxycarbonyl*-4H-*pyrazolo*[5,1-c]-[1,4]*benzothiazine* S,S-*dioxide* (**12**) (675 mg, 53%), m.p. 216 °C (from di-isopropyl ether–chloroform) (Found: C, 53.3; H, 4.1; N, 9.7. $C_{13}H_{12}N_2O_4S$ requires C, 53.4; H, 4.2; N, 9.6%); $\nu_{max.}$(Nujol) 1 720 cm^{-1}; $\delta[(CD_3)_2SO]$ 1.38 (3 H, t, Me), 4.41 (2 H, q, CH_2), 5.35 (2 H, s, CH_2SO_2), 7.08 (1 H, s, 3-H), and 7.5—8.3 (4 H, m, ArH); *m/z* 292 (M^+).

(*B*) A solution of compound (**1**) (2.5 g) and triethylamine (3.5 ml) in benzene (330 ml) was refluxed for 4 h, then washed successively with 1M-HCl and water. After being dried (Na_2SO_4), the solvent was evaporated off under reduced pressure and the residue was chromatographed on a silica gel column (300 g) with benzene–ethyl acetate (9:1) as eluant to give, first, *ethyl 2-chloro-2-[2-(2-chloroprop-1-enylsulphonyl)phenylhydrazono]acetate* (**5**) (80 mg, 3%), m.p. 120 °C (from di-isopropyl ether–chloroform) (Found: C, 42.6; H, 4.0; N, 7.6. $C_{13}H_{14}Cl_2N_2O_4S$ requires C, 42.8; H, 3.9; N, 7.7%); $\nu_{max.}$(Nujol) 3 260 and 1 725 cm^{-1}; $\delta(CDCl_3)$ 1.41 (3 H, t, CH_2Me), 2.67 (3 H, d, *J* 1.2 Hz, Me), 4.43 (2 H, q, CH_2), 6.52 (1 H, q, *J* 1.2 Hz, CH=CCl), 7.0—7.3 (1 H, m, ArH), 7.5—7.9 (3 H, m, ArH), and 10.55 (1 H, br s, NH); *m/z* 364 (M^+).

Subsequent fractions provided a 60:40 mixture (n.m.r. analysis) (0.4 g) of *ethyl 2-chloro-2-[2-(2-chloroprop-2-enylsulphonyl)-phenylhydrazono]acetate* (**4**) (9%) and ethyl 2-chloro-2-[2-(propadienylsulphonyl)phenylhydrazono]acetate (**2**) (6%). The mixture was recrystallised twice from di-isopropyl ether–chloroform to afford the *vinyl chloride* (**4**) (0.2 g), m.p. 125 °C (Found: C, 42.8; H, 3.8; N, 7.7. $C_{13}H_{14}Cl_2N_2O_4S$ requires C, 42.8; H, 3.9; N, 7.7%); $\nu_{max.}$(Nujol) 3 275 and 1 725 cm^{-1}; $\delta(CDCl_3)$ 1.41 (3 H, t, Me), 4.10 (2 H, s, CH_2SO_2), 4.43 (2 H, q, CH_2), 5.3—5.4 (1 H, m, =C*H*H), 5.5—5.6 (1 H, m, =CH*H*), 7.0—7.3 (1 H, m, ArH), 7.5—7.9 (3 H, m, ArH), and 10.65 (1 H, br s, NH); *m/z* 364 (M^+). Evaporation of the mother liquors gave the allene (**2**) (0.15 g) in 70% purity (n.m.r. analysis): $\delta(CDCl_3)$ 1.43 (3 H, t, Me), 4.45 (2 H, q, CH_2Me), 5.51 (2 H, d, *J* 6 Hz, $=CH_2$), 6.19 (1 H, t, *J* 6 Hz, SO_2CH), 7.0—7.3 (1 H, m, ArH), and 7.4—8.0 (3 H, m, ArH).

Further elution gave the heterocyclic sulphones (**15**) (0.15 g, 6%), and (**12**) (0.60 g, 27%).

Reaction of Compounds (**4**), (**5**), *and* (**2**) *with Triethylamine in Benzene.*—A solution of compound (**4**) (0.5 g) and triethylamine (0.8 ml) in benzene (65 ml) was refluxed for 4 h, then washed successively with 1M-HCl and water. After being dried (Na_2SO_4), the solvent was evaporated off under reduced pressure. T.l.c. and n.m.r. analyses showed the residue to be a mixture of compounds (**5**), (**4**), (**2**), (**15**), and (**12**), similar to that obtained from the reaction of compound (**1**) under the same conditions.

The same result was achieved by treatment of compounds (**5**) (0.4 g) and (**2**) (0.5 g).

Reaction of Compound (**1**) *with Triethylamine in Acetonitrile.*—To a solution of compound (**1**) (1.0 g) in acetonitrile (150 ml) was added triethylamine (1.5 ml). After the solution had been stirred for 15 min at room temperature, the solvent was evaporated off under reduced pressure, the residue was taken up with benzene and the solution was washed with water. After being dried (Na_2SO_4), the solvent was evaporated off and the residue was chromatographed on a silica gel column (100 g) with diethyl ether as eluant to give the heterocyclic sulphone (**15**) (0.60 g, 60%).

Reaction of Compound (**3**) *with Triethylamine in Benzene.*—(*A*) A solution of compound (**3**) (1.76 g) and triethylamine (3 ml) in benzene (230 ml) was refluxed for 48 h, then washed successively with 1M-HCl and water. After being dried (Na_2SO_4), the solvent was evaporated off under reduced pressure, and the residue was chromatographed on a silica gel column (180 g) with benzene–ethyl acetate (9:1) as eluant to give, first, compound (**19**) (70 mg, 4%), then its isomer (**15**) (220 mg, 13%), and then the tricyclic ester (**12**) (705 mg, 45%). Subsequent fractions provided 4-(α-chloro-α-ethoxycarbonylmethyleneamino)-3-methyl-4*H*-1,4-benzothiazine *S,S*-dioxide (**16**) (34 mg, 2%) as an undistillable oil; $\nu_{max.}$(film) 1 735 cm^{-1}; $\delta(CDCl_3)$ 1.40 (3 H, t, CH_2Me), 2.27 (3 H, s, Me), 4.52 (2 H, q, CH_2), 5.92 (1 H, s, 2-H), 6.9—7.1 (1 H, m, ArH), 7.2—7.6 (2 H, m, ArH), and 8.0—8.2 (1 H, m, ArH); *m/z* 328 (M^+).

(*B*) A solution of compound (**3**) (2.5 g) and triethylamine (3.5 ml) in benzene (330 ml) was refluxed for 5 h, then washed successively with 1M-HCl and water. After being dried (Na_2SO_4), the solvent was evaporated off under reduced pressure and the residue was chromatographed on a silica gel column (300 g) with benzene–ethyl acetate (9:1) as eluant to give, first, the vinyl chloride (**5**) (55 mg, 2%), then a 60:40 mixture (n.m.r. analysis) (0.35 g) of compounds (**4**) (8%) and (**2**) (5%). Subsequent fractions provided the heterocycles (**15**) (175 mg, 7%), (**12**) (0.55 g, 25%), and finally (**16**) (50 mg, 2%).

Reaction of Compound (**3**) *with Triethylamine in Acetonitrile.*—To a solution of compound (**3**) (0.8 g) in acetonitrile (120 ml)

was added triethylamine (1.2 ml). After the solution had been stirred for 15 min at room temperature, the solvent was evaporated off under reduced pressure, the residue was taken up with benzene, and the solution was washed with water. After being dried (Na_2SO_4), the solvent was evaporated off and the residue was chromatographed on a silica gel column (80 g) with diethyl ether as eluant to give compound (**16**) (0.46 g, 58%).

Isomerisation of Compound (**15**) *into Compound* (**16**).—To a solution of compound (**15**) (50 mg) in chloroform (5 ml) was added a saturated solution of HCl in chloroform (0.2 ml). After the solution had been stirred at room temperature for 24 h, the solvent was evaporated off to give the isomer (**16**) (40 mg, 80%).

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