Adduct Formation between Pyridine-2-thiones and Acetylenic Carbonyl Derivatives

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1 : 1 Adducts are formed between pyridine-2-thiones and acetylenic amides, esters, and ketones. The reaction rate increases with increase in activation of the triple bond by the carbonyl group and is affected by the pyridine 6-substituent, which also may influence the stereochemical course. The product isomer ratios corresponding to kinetic control were obtained in chloroform; the amides yielded mainly the *cis*-isomers, the ketones the *trans*-isomers, and the esters a slight preponderance of the *cis*-isomers.

THE stereochemical course of the formation of 1 : 1 adducts between thiols and acetylenes has been the subject of several investigations.[1–5] The product of kinetic control, however, may isomerise under the reaction conditions.[4,6] Rapid equilibrations have also been observed with the related adducts of amines with acetylenes.[7–9] The product configuration depends on the nature of the solvent and the reactants.[4,5,8,10]

Michael 1 : 1 adducts may also be formed between thiolactams and acetylenecarboxylic acids.[11] We report here further studies on the reactions between acetylenic carbonyl derivatives and pyridine-2-thiones in which the pyridine 6-substituent is H, Me, or Pr^n. Differential electronic activation of the acetylene was effected by the use of propiolic acid derivatives such as the ethyl ester and various amides, and ethynyl methyl ketone. Different steric requirements are inherent in the carbonyl substituents. The steric influence on the course of the reaction was further investigated in the case of the amides by change of the amide *N*-substituents. Chloroform was a good solvent for both reactants and products and the reaction rates for the amides were suitable for kinetic work. The kinetic studies were for these reasons limited to n.m.r. analysis of reactions in deuteriochloroform at 0 °C; the preparative reactions were carried out in chloroform at room temperature. No side-reactions were observed and the 1 : 1 adducts were formed in high yields.

The propiolamides were first synthesised by aminolysis of propiolates;[12] the amides, however, tended to be contaminated by the products of Michael addition across the triple bond. In our hands propiolic anhydride in cold ethereal solution gave the amides without any adduct formation. Propiolic anhydride has been prepared by treatment of sodium propiolate with thionyl chloride;[13] we found oxalyl chloride to be a better reagent for this purpose. The thiolactams were prepared by thiation of the corresponding lactams with phosphorus pentasulphide[14] as described for compound (8).

Rate constants and stereoisomer ratios in adduct formation between pyridine-2-thiones and acetylenic compounds in deuteriochloroform at 0 °C (n.m.r.)

Compd.	HOAc equiv.	10^5k_2/l mol^{-1} s^{-1}	*cis* : *trans*	Compd.	HOAc equiv.	Rel. rate const.[a]	*cis* : *trans*
(10)	0	4.3	1 : 0	(22)[b]	0	1	2 : 1
(11)	0	2.9	1 : 0	(23)[b]	0	1	2 : 1
(11)	1	7.7	1 : 0	(24)[b]	0	0.3	3 : 1
(12)	0	1.9	1 : 0				
(13)	0	1.5	*c*	(25)	0	1	4 : 5
(14)	0	0.9	8 : 1	(25)	1		4 : 5
(15)	0	0.4	1 : 0	(26)	0	0.1	0 : 1
(16)	0	2.3	5 : 1	(26)	1		2 : 3
(17)	0	1.5	6 : 1	(27)	0	0.06	0 : 1
(17)	1	4.1	7 : 1				
(17)	3	4.1	7 : 1				
(18)	0	1.0	1 : 0				

[a] Determined in competitive experiments with pyridine-2-thione (6). [b] Reactions run at 20 °C. [c] Spectrum not resolved.

N.m.r. spectroscopy was used in the structural assignments of the crude and the purified products. The vinyl proton signals as well as characteristic signals from the reactants were usually well separated or resolved. The vicinal vinyl proton couplings in the *cis*-isomers were about 10 Hz and in the *trans*-isomers 14—16 Hz; these agree well with the values reported for related vinyl sulphides.[15] The vinylic proton β to the carbonyl group in both stereoisomers resonated in the region τ 1.5—1.7. In acidic solutions (CF_3·CO_2H or MeOD·DCl) diamagnetic shifts were observed of about 0.4 and 1.0 p.p.m. for the β-proton in the *trans*- and the *cis*-isomers, respectively. These observations are rationalised in

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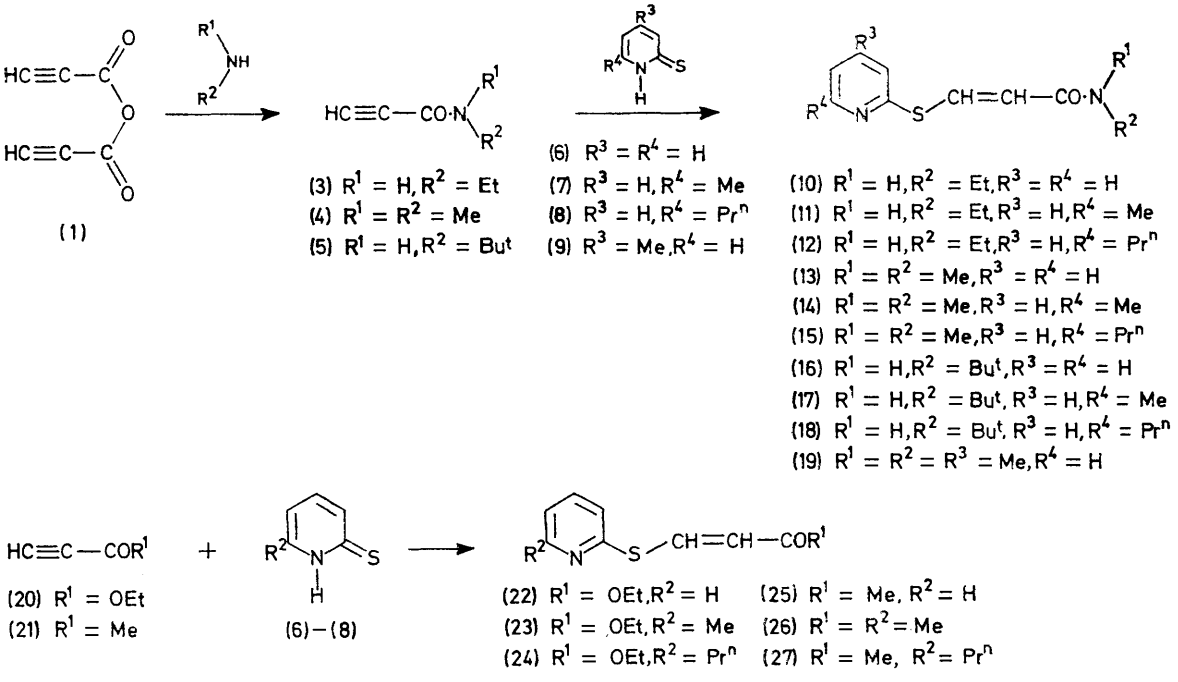
terms of a dominating deshielding effect of the pyridine ring in deuteriochloroform solution; the deshielding effect is lost on protonation of the pyridine. The lower field signal for the β-proton in the *trans*-isomer is attributed to an anisotropic effect from the carbonyl group which is *cis* with respect to the β-proton.

The Table shows that the *cis*-adduct constituted 80—100% of the acrylamide formed. N.m.r. spectra recorded during the reactions did not show any variation in the *cis–trans* ratio of the products. Nor was this ratio affected by an excess of either reagent or by warming the products in chloroform. These results indicated no equilibration of the isomer initially formed unless this was very rapid. In order to check this possibility the simplest amide (10) was heated in acetic acid; after 12 h is more efficient in this respect than *N*-t-butyl substitution presumably because the effective bulk in the di-*N*-methylamide is closer to the reaction centre; the higher inductive effect in the dimethylamide may also in part be responsible for the rate differences.

The ester (20) and the ketone (21) reacted too fast for kinetic studies by direct n.m.r. measurements. The relative rate constants for the reactions of the thiolactams with the ester (20) and with the ketone (21) were therefore established in competitive reactions (Table). Correlation of the relative rate constants between the two series, however, was not possible since all the ketone had reacted with the thiolactam before any ester adduct was detected in competitive experiments. The observed differences in the reaction rates for the ketone, the ester, and



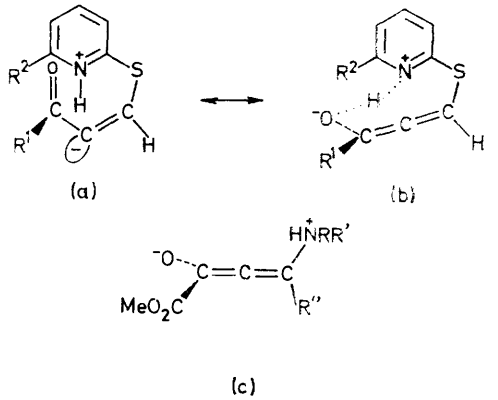
SCHEME 1

only about 12% of the *trans*-isomer had been formed. The isomerisation was more efficiently carried out by u.v. irradiation of a solution in deuteriochloroform in an n.m.r. tube; after 3 h the solution contained 30% *trans*-isomer and after 6 h *ca.* 60%. Further irradiation did not change the isomer ratio. Other compounds behaved similarly, but the equilibrium positions varied. When the *cis–trans* product mixtures thus obtained were left or heated in chloroform solution no significant equilibration was detected. We therefore conclude that the product ratios obtained represent kinetic control of the addition.

The reactions of the amides obey second-order kinetics. The rate constants decrease with increase in the size of the pyridine 6-substituent. The same steric effect from a 6-substituent can be deduced from the relative rate constants for the ester and the ketone. The rate constants for the amides further decrease with increasing size of the amide *N*-substituents. Di-*N*-methyl substitution the amide series follow the expected direction for differential activation of the multiple bond. The predominant product configuration in the ketone series, however, is *trans* as opposed to the dominating *cis*-configuration in the amide series; in the ester series the product contains 60—80% of the *cis*-isomer (Table). The pyridine 6-substituent markedly affects the product isomer composition in the ketone series, which changes from nearly 100% *cis* for (25) to almost 100% *trans* for (26) and (27). In the presence of acetic acid the yield of the *trans*-isomer (26) was reduced to about 60% while the isomer ratio for (25) was hardly affected. In the amide series the presence of acetic acid has only a weak effect on the isomer ratios but increases the reaction rate.

It appears most likely that the acrylic adducts are formed through a zwitterionic intermediate (Scheme 2). Dipolar or electrostatic attraction between the proton-bearing pyridine nitrogen atom and the polarised un-

saturated reagent will favour the orientation indicated in Scheme 2. The preference for this orientation allows the effect of the pyridine 6-substituents on the reaction to be rationalised and is supported by the relative rates for the reactions between 4-methylpyridine-2-thione (9) and the 6-methyl isomer (7) with the di-*N*-methylamide (4), determined as 1.1 and 0.6, respectively, from competitive reactions with the parent thiolactam (6); both (7) and (9) have the methyl group in a *meta*-position with respect to the sulphur group. A related zwitterionic intermediate has been proposed for the addition of amines to propiolic ester.[8,10] The latter differs, however, in that it is the added amino-group which carries the positive charge [(c), Scheme 2].



SCHEME 2

In contrast to the discussed thiolactams, thiols react slowly with propiolic ester; studies of thiol additions are normally carried out on thiolates or on thiols in the presence of catalytic amounts of bases.[4,5] Predominant *trans*-addition to propiolic ester is observed for both amines and thiolates in protic media whereas *cis*-addition is favoured in aprotic media. The thiolactams, however, undergo preferential *trans*-addition to the propiolamides in chloroform solution. The rate enhancement observed on addition of acetic acid may be due to better solvolysis of the ionic intermediate. It seems reasonable that the carbanionic charge is more developed in the ketone than in the amide intermediates owing to better resonance stabilisation of the anionic charge. The stabilisation of the ketone intermediates allows for *cis*-protonation and the non-bonded interaction between the pyridine 6-substituent and the carbonyl substituent affects the geometry of the intermediates in such a way that predominant *cis*-protonation occurs. The protonation may be intramolecular as postulated in *cis*-addition of amines [8] and of thiols in the presence of basic catalysts [5] to propiolic esters in aprotic solvents. The acetic-acid-promoted *trans*-addition in the case of the 6-methyl ketone (26) may in part be due to competitive external protonation. The less stabilised amide intermediates undergo protonation *trans* to the added nucleophile but the available evidence does not clearly differentiate between inter- or intra-molecular protonation. Intermediate ratios of the isomer adducts were obtained with ester carbonyl group activation.

EXPERIMENTAL

N.m.r. spectra were recorded with a Varian A-60A instrument.

Kinetic Measurements.—Rate studies of adduct formation between the pyridine-2-thiones (6)—(8) and the propiolamides (3)—(5) were carried out on M-solutions in deuteriochloroform at 0 °C in n.m.r. tubes. N.m.r. spectra were recorded at intervals. The reactions required 2—3 days for completion. Second-order kinetics were observed.

The relative rate studies were run at 0 °C for the ketone (21) and at 20 °C for the ester (20). The competitive reactions between pyridine-2-thione (6) and its 6-methyl (7) and 4-methyl (9) homologues with *NN*-dimethylpropiolamide (4) were also run at 20 °C. A simplified procedure was used. M-Solutions of pyridine-2-thione, its homologue, and the acetylene in deuteriochloroform were left until the reaction was complete and the product ratios were determined by n.m.r. The relative rate constants were calculated according to the expression (i), which is applicable for equimolar concentrations of the reactants.

$$k_{rel} = k_1/k_2 = [x_1(\alpha - x_2)]/[x_2(\alpha - x_1)] \simeq x_1^2/x_2^2 \quad \text{(completion)} \quad \text{(i)}$$

Propiolic Anhydride (1).—Sodium propiolate (4.6 g, 0.05 mol) was suspended by vigorous stirring in anhydrous ether (50 ml), and oxalyl chloride (3.1 g, 0.025 mol) was added in one portion at 0 °C. The ice-bath was then removed until gas evolution (*ca.* 10 °C) had started, and the mixture was then again placed in the ice-bath. Gas evolution had ceased after about 15 min. The insoluble material was filtered off and washed with a little anhydrous ether. The combined filtrate and washings contained 95—100% of the theoretical amount of the anhydride and were used as such for subsequent reactions. Evaporation of a sample and distillation of the residue led to extensive losses, but the product had physical properties as described.[13]

N-*Ethylpropiolamide* (3).—A solution of ethylamine (2.3 g, 0.05 mol) in absolute ether (20 ml) was added dropwise to a solution of the propiolic anhydride (0.03 mol) in absolute ether (50 ml) at 0 °C with stirring. A white solid was immediately precipitated. After a total of 15 min at 0 °C the solid was filtered off and the filtrate evaporated at reduced pressure. The residual oil crystallised at 0 °C; it melted on reaching room temperature and was further purified by washing with light petroleum; yield 2.2 g (97%), m.p. *ca.* 20 °C (slow decomp.). The product was characterised by its spectroscopic properties.[12]

NN-Dimethylpropiolamide (4), prepared as above from dimethylamine in 85% yield, had m.p. 74—76 °C (from ether–light petroleum) (lit.,[12] 75—76 °C). N-*t-Butylpropiolamide* (5), prepared as above from t-butylamine in 77% yield, had m.p. 99—100 °C (from ether–light petroleum) (Found: C, 67.2; H, 8.8; N, 11.2. $C_7H_{11}N$ requires C, 67.15; H, 8.85; N, 11.2%).

3-(2-*Pyridylthio*)*acrylamides* (10—19).—The propiolamide (0.005 mol) and the pyridine-2-thione (0.005 mol) were dissolved in chloroform (50 ml) at room temperature. The solution was left for 12—16 h, then evaporated at reduced pressure, and the residual oily material was crystallised from benzene–light petroleum. The white crystalline products were as follows: N-*ethyl-* (10), (87%) m.p. 152—154 °C (Found: C, 57.65; H, 5.8; N, 13.3. $C_{10}H_{12}N_2OS$ requires C, 57.65; H, 5.8; N, 13.45); τ ($CDCl_3$) 6.6 and 8.8 (NEt), 1.5 (H-6′), 3.9 (H_α, d, *J* 10 Hz), and 1.7 (H_β, d); N-*ethyl*-6′-*methyl-* (11) (90%), m.p. 124—126 °C (Found: C, 59.4;

H, 6.25; N, 12.7. $C_{11}H_{14}N_2OS$ requires C, 59.45; H, 6.35; N, 12.6%); N-*ethyl-6'-n-propyl-* (12) (82%), m.p. 111—113 °C (Found: C, 62.5; H, 7.25; N, 11.3. $C_{13}H_{18}N_2OS$ requires C, 62.35; H, 7.25; N, 11.2%); NN-*dimethyl* (13) (77%), m.p. 116—118 °C (Found: C, 57.6; H, 5.8; N, 13.4. $C_{10}H_{12}N_2OS$ requires C, 57.65; H, 5.8; N, 13.45%); NN-*dimethyl-6'-methyl-* (14) (70%), m.p. 92—95 °C (Found: C, 59.6; H, 6.35; N, 12.5. $C_{11}H_{14}N_2OS$ requires C, 59.45; H, 6.35; N, 12.6%); NN-*dimethyl-6'-n-propyl-* (15) (87%), m.p. 72—74 °C (Found: C, 62.3; H, 7.1; N, 11.25. $C_{13}H_{18}N_2OS$ requires C, 62.4; H, 7.25; N, 11.2%); N-*t-butyl-* (16) (83%), m.p. 145—147 °C (Found: C, 60.95; H, 6.7; N, 11.75. $C_{12}H_{16}N_2OS$ requires C, 60.95; H, 6.8; N, 11.85%); N-*t-butyl-6'-methyl-* (17) (75%), m.p. 141—142 °C (Found: C, 62.55; H, 7.4; N, 11.2. $C_{13}H_{18}N_2OS$ requires C, 62.4; H, 7.25; N, 11.2%); N-*t-butyl-6'-n-propyl-* (18) (81%), m.p. 133—134 °C (Found: C, 64.4; H, 8.0; N, 10.15. $C_{15}H_{22}N_2OS$ requires C, 64.7; H, 7.95; N, 10.1%); NN-*dimethyl-4'-methyl-* (19) (66%), m.p. 162 °C (Found: C, 59.6; H, 6.15; N, 12.45. $C_{11}H_{14}N_2OS$ requires C, 59.45; H, 6.35; N, 12.6%).

Addition of Pyridine-2-thiones to Ethyl Propiolate.— A solution of ethyl propiolate [16] (0.49 g, 0.005 mol) in chloroform (25 ml) was added dropwise to a solution of the pyridine-2-thione (0.005 mol) in chloroform (25 ml) at 20 °C. The solution was kept at 20 °C for 1 h and then evaporated. The residual pale yellow oily product contained 20—40% of the *trans*-adduct. The crude adduct was dissolved in ethanol (30 ml) and water added gradually at 40—50 °C until precipitation was initiated. When the solution was left in the cold the *cis*-isomer was precipitated and was collected after 2 days. The *cis–trans* mixture remaining in the filtrate was not further worked up. *Ethyl* cis-3-(2-*pyridylthio)acrylate* (22) (60%), had m.p. 65—67 °C (Found: C, 57.5; H, 5.25; N, 6.9. $C_{10}H_{11}NO_2S$ requires C, 57.4; H, 5.3; N, 6.7%); τ ($CDCl_3$) 5.8 and 8.7 (OEt), 1.5 (H-6'), 3.9 (H_α, d, *J* 10 Hz), and 1.5 (H_β, d). The *6'-methyl derivative* (23) (58%) had m.p. 57—59 °C (Found: C, 59.1; H, 5.8; N, 6.2. $C_{11}H_{13}NO_2S$ requires C, 59.2; H, 5.85; N, 6.25%). The *6'-n-propyl derivative* (24) (75%) had m.p. 55—56 °C (Found: C, 61.95; H, 7.0; N, 5.65. $C_{13}H_{17}NO_2S$ requires C, 62.1; H, 6.8; N, 5.55%).

4-(2-*Pyridylthio)but-3-en-2-one* (25) (cis–trans-*Mixture*).— A solution of ethynyl methyl ketone [17,18] (0.34 g, 0.005 mol) in chloroform (25 ml) was added dropwise to an ice-cold solution of pyridine-2-thione (0.49 g, 0.0045 mol) in chloroform (25 ml). The reaction was rapid and the yellow colour of the pyridine was discharged when all the ketone had been added. The solution was then evaporated and the *residue* crystallised from light petroleum at −20 °C; yield 0.70 g (90%); m.p. 31—32 °C (Found: C, 60.3; H, 5.05; N, 7.75. C_9H_9NOS requires C, 60.3; H, 5.05; N, 7.8%); τ ($CDCl_3$) 7.7 (MeCO), 1.5 (H-6'), 3.5 (H_α, d, *J* 10 Hz; *cis*), 3.6 (H_α, d, *J* 16 Hz; *trans*), 1.5 (H_β, d; *cis*), and 1.4 (H_β, d; *trans*).

trans-4-(6-*Methyl-2-pyridylthio)but-3-en-2-one* (26) was similarly prepared from 6-methylpyridine-2-thione. The residual oil could not be made to crystallise and underwent extensive decomposition on attempted distillation. When a slight excess of ketone was used, however, the crude product was sufficiently pure for elemental analysis after drying *in vacuo* (Found: C, 62.0; H, 5.85; N, 7.2. $C_{10}H_{11}NOS$ requires C, 62.15; H, 5.75; N, 7.25%); τ ($CDCl_3$) 7.7 (MeCO), 7.5 (6'-Me), 3.6 (H_α, d, *J* 16 Hz), and 1.4 (H_β, d). The *6'-n-propyl analogue* (27) was similarly prepared from 6-n-propylpyridine-2-thione. The crude oily material was subjected to elemental analysis (Found: C, 65.1; H, 7.0; N, 6.2. $C_{12}H_{15}NOS$ requires C, 65.1; H, 6.85; N, 6.3%).

6-n-Propylpyridine-2-thione (8).— 6-n-Propylpyridin-2-one [19] (2.9 g, 0.02 mol) was ground together with phosphorus pentasulphide (4.4 g, 0.02 mol) and the mixture heated at 160 °C for 5 h with protection from atmospheric moisture. The cold, solid melt was broken up and hydrolysed with aqueous sodium hydrogen carbonate and a little acetone. The aqueous solution was extracted with chloroform (4 × 100 ml) at pH 7.5 and the extracts were dried and evaporated. The solid *residue* was recrystallised from ethyl acetate–light petroleum (charcoal); yield 2.2 g (70%), m.p. 112—114 °C (Found: C, 62.9; H, 7.2; N, 9.15. $C_8H_{11}NS$ requires C, 62.7; H, 7.25; N, 9.15%).

4-*Methylpyridine-2-thione* (9) was prepared as above from 4-methylpyridin-2-one [20] in 60% yield, m.p. 178—180 °C (from ethyl acetate) (Found: C, 57.7; H, 5.5; N, 11.1. C_6H_7NS requires C, 57.6; H, 5.6; N, 11.2).

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