75458-54-7; **8a**, 75458-55-8; **8b**, 75458-56-9; **8c**, 75458-56-9; **9**, 1272-44-2; 2-(1′-*p*-toluoyl-1-ferrocenyl)acetamide, 75458-57-0; 2-(3-*p*-toluoyl-1-ferrocenyl)acetamide, 75458-58-1; ferrocenylacetic acid, 1287-16-7; calcium (1′-*p*-toluoyl-1-ferrocenyl)acetate, 75458-59-2; calcium (3-*p*-toluoyl-1-ferrocenyl)acetate, 75458-60-5; calcium (2-*p*-toluoyl-1-ferrocenyl)acetate, 75458-61-6; 1′-acetyl-1-ferrocenylacetonitrile, 75458-62-7; 3-acetyl-1-ferrocenylacetonitrile, 75458-63-8; ferrocene, 102-54-5.

Reactions of 2-Functionalized 4*H*-Thiopyran-4-ones with Nucleophiles. 2.[1] Reactions with Primary Amines

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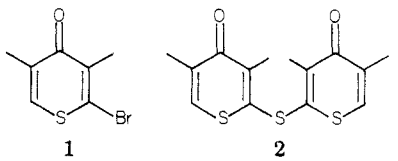
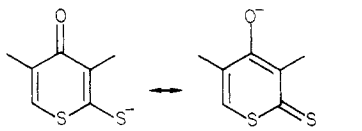
Two thiopyrones (**1**, **2**) substituted with a leaving group at position 2 were reacted with methylamine and benzylamine. The products ranged, according to the amine and reaction conditions, from a 2-(methylamino)-thiopyrone (**4**) to a pyridonyl thiopyronyl sulfide (**10**) and included 2-thiol-4(1*H*)-pyridone derivatives (**5a,b**) and 2-amino-4(1*H*)-pyridone derivatives (**8a,b**). A major product from the cleavage of **2** with the amines is the tautomeric thiopyranthiodione derivative **9** which is also formed from **2** and sodium hydrogen sulfide. The formation of the aminopyridones **8** through open-chain intermediates is discussed.

The introduction of additional functional groups into the thiopyrone and related thiochromone molecules is of interest for various potential applications.[4,5] We have found that a convenient approach to such functionalization could be the substitution of leaving groups at the 2-position of 2-bromo-3,5-dimethyl-4*H*-thiopyran-4-one (**1**) and of



1 **2**

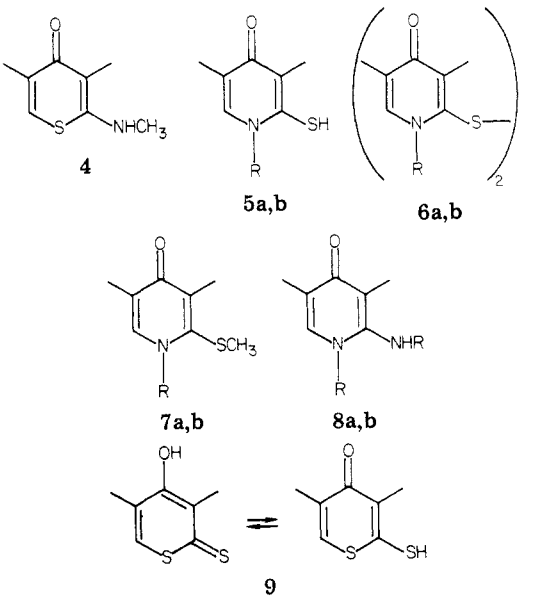


3

bis(3,5-dimethyl-4-oxo-4*H*-thiopyran-2-yl) sulfide (**2**), two substances which had been concomitantly obtained from readily available starting materials.[6] Sulfide **2** may, indeed, be looked upon as a thiopyrone substituted at position 2 by the leaving group **3**. It may, therefore, be expected to undergo substitution reactions of the ring heteroatom or of the 2-group, analogous to those observed with bromide **1**.[1]

The present work is concerned mainly with the reactions of **1** and **2** with methyl- and benzylamine. By analogy to the reactions with the hydroxide ion,[1] reactions with the amines were carried out in the absence or in the presence of water to try to attain selectivity in the formation of either pyridone derivatives or 2-aminothiopyrone derivatives. Such a selectivity has, however, not been realized in the present case.

Chart I[a]



4 **5a,b** **6a,b**

7a,b **8a,b**

9

[a] a, R = CH_3; b, R = $CH_2C_6H_5$.

Treatment of **1** with excess aqueous methylamine/ethanol at room temperature yielded a mixture of the aminothiopyrone **4** and the mercaptopyridone **5a** (with the disulfide **6a** derived from **5a**; see Chart I) in up to 25% and 55% yields, respectively. These were separated by column chromatography and characterized through their analytical and spectral properties. The distinction between **4** and **5a** was made through the ready oxidation of the latter with iodine to **6a** and through its methylation with diazomethane to **7a**. The 2-thiol structure was assigned to **5a** on the basis of the UV spectrum: **5a** has the longest wavelength maximum at 308 nm (320 nm for **7a**) while the tautomeric 2-thione-4-ol structure would be expected to show a maximum at around 350 nm.[7] A similar observation is also made for **4**, which, like its benzo analogues,[5] does not seem to tautomerize to the imino form.

(1) Part I: Greenberg, F. H.; Gaoni, Y. *J. Org. Chem.* **1978**, *43*, 4966-8.
(2) Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel.
(3) To whom correspondence should be addressed.
(4) Chen, C. H.; Reynolds, G. A. *J. Org. Chem.* **1979**, *44*, 3144-7.
(5) Zmurenko, L. A.; Glozman, O. M.; Zagorevskii, V. A. *Chem. Heterocycl. Compd.* **1978**, 182-5; *Chem. Heterocycl. Compd. (Engl. Transl.)* **1978**, 141-4.
(6) Gaoni, Y. *Tetrahedron Lett.* **1976**, 2167-70.
(7) Krowicki, K. *Pol. J. Chem.* **1979**, *53*, 701-7.

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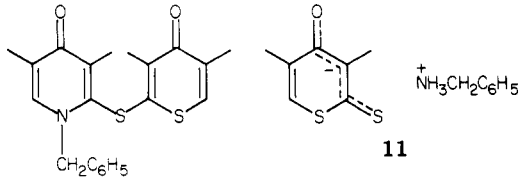
When 1 was reacted with dry methylamine in absolute ethanol, an additional comound, namely, the aminopyridone **8a**, was obtained in up to 33% yield, while the yield of 4 and **5a** totaled 27%. In order to determine the origin of **8a**, we reacted 4 and **5a** further with methylamine under the same reaction conditions, but they were recovered unchanged. An analysis of these results follows the description of the reactions with benzylamine.

Sulfide 2 was reacted with methylamine only under anhydrous conditions because of very low solubility in aqueous amine. A mixture of **5a**, **8a**, and the yellow 4-hydroxydithiopyrone **9** was obtained. The aminopyridone **8a** was separated in 18% yield through acid extraction, while **5a** and **9** were identified through the ^{1}H NMR of the mixture.[8,9] The absence of 4 in the reaction mixture indicates that no attack by the amine has occurred at the more hindered 2-position of 2. A similar observation has been made in the case of the reactions of both 2 and 1 with benzylamine. A 2-aminothiopyrone derivative has thus been obtained only from 1 with methylamine and only to a partial extent.

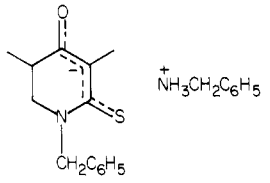
Reactions of 1 and 2 with benzylamine were carried out with excess amine in the presence or in the absence of water in a temperature range of 90–115 °C. By avoidance of an acidic workup, an easier separation of the acidic products **5b** and **9** as their amine salts was made possible.

Bromide 1 yielded a mixture of the mixed sulfide **10** (56–58% yield in the presence of water, 28–37% in the absence of water), the aminopyridone **8b** (18–28%), and the salt **11** (10–20%). Salt **11** was the major product from



10

11

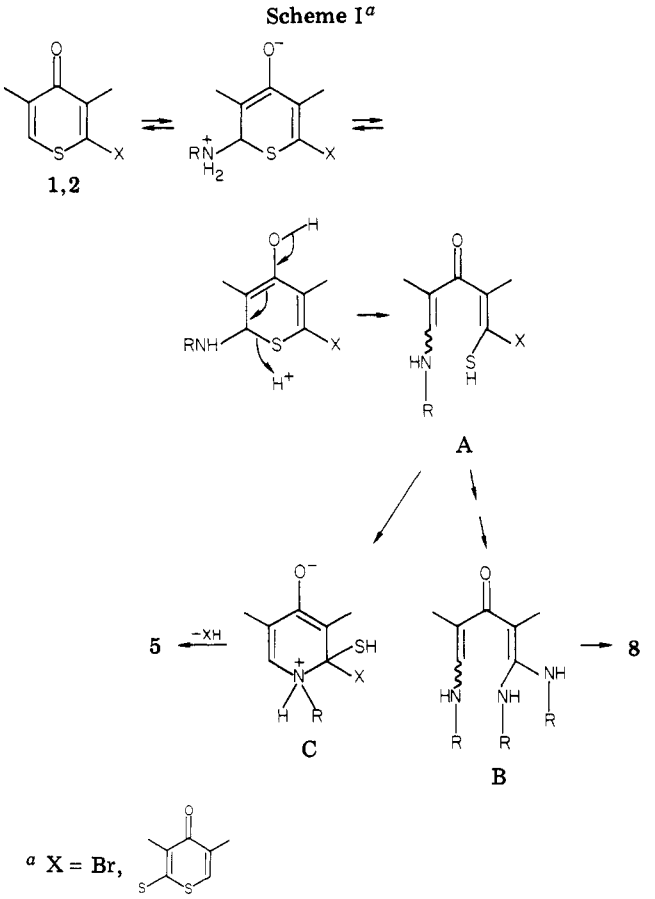


12

the reaction of 2 with benzylamine, either neat or in the presence of water, being accompanied by **8b** and by the salt **12**. Both **11** and **12** may be recognized as the benzylamine salts of the primary reaction products **9** and **5b** resulting from attack at the 6-position of 2. The two salts were formed in a ratio of 7:2, respectively. They were separated through their greatly differing solubility in benzene, while **8b** was recovered from the ethyl acetate mother liquors of the total reaction mixture.

Salt **11** is obtained from 2 in more than the theoretical yield, if it is considered that one molecule of 2 can produce one molecule of **11**. Hence, there is excess formation of **9** over what can be obtained through simple cleavage of 2 by the amine. This excess could result from reaction of 2 with SH^- liberated during formation of **8b**. It was indeed found that 2 was converted into **9** in high yield by reaction

Scheme I[a]



[a] X = Br,

with sodium hydrogen sulfide in aqueous methanol. A similar reaction also occurred with 1,[10] and this could explain the formation of **11** from 1 in the reaction with benzylamine.

The major difference in the reactions of 1 and 2 with benzylamine is the behavior of the primary reaction product **5b**. In the case of 1, **5b** behaves as a nucleophile toward a second molecule of 1, substituting the bromine atom to give **10**, while in the case of 2 it reacts with excess amine to yield the salt **12**.

Since it could be shown that **8b** was, like **8a**, not formed from the primary reaction products under the reaction conditions, it had to be assumed that the exchange for a second molecule of amine, leading to the aminopyridones, had occurred at a stage where the original ring was opened up (Scheme I). Addition of an amine molecule to 2 at position 6, followed by ring opening, produces, in fact, a ketene thioacetal type intermediate (A) in which one or both sulfur groups may be replaced by amino groups,[11] yielding intermediate B, which would then cyclize to **8**.[12] Intermediate A derived from 1 (X = Br) can most probably undergo a similar sequence of additions–eliminations. In both cases the elements of XH and H_2S are eliminated, and this H_2S produces **9** from 2 (or 1) that is still present, as mentioned above. However, a certain fraction of A yields products **5** through intermediate C according to the accepted usual mechanism.[1]

Another way in which the aminopyridone **8b** could have been formed from 1 would be further reaction of the

(8) Chromatographic separation of mixtures involving **9** were rendered difficult by the tautomeric equilibrium of this compound. Pure **9** could, however, be obtained by methods described further on in the text.

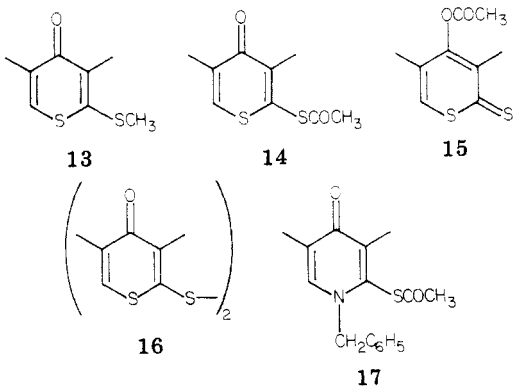
(9) It has been observed that the 6-position vinylic proton of all compounds with sulfur in the ring appeared at lower field and those of the pyridone derivatives at higher field than the chloroform signal.

(10) Compound **9** was accompanied here by a product resulting from the presence of a hydroxide ion in the reaction mixture (see Experimental Section).

(11) Gompper, R.; Töpfl, W. *Chem. Ber.* **1962**, *95*, 2871–80.

(12) Abdulla, R. F.; Fuhr, K. H.; Williams, J. C. *J. Org. Chem.* **1979**, *44*, 1349–50. Abdulla, R. F.; Emmick, T. L.; Taylor, H. M. *Synth. Commun.* **1977**, *7*, 305–12.

Chart II



first-formed **10** with excess amine through attack at position 2 of the pyridone ring. When carried out separately, however, this reaction was found to be relatively very slow and to yield mainly **12** (up to 76% yield), with **8b** being formed in less than 25% yield. It can, indeed, be noticed that a preferred attack at position 6 of the thiopyrone ring of **10** would produce *two* molecules of **5b** (or **12**). Position 2 of the pyridone ring would be, on the other hand, considerably less electrophilic and less accessible than position 6 of the thiopyrone ring, and any **8b** formed is probably obtained by the route shown in Scheme I.

We now turn to the properties of the tautomeric compound **9**, which is readily obtained from **11** by acidification, extraction, and recrystallization. In the solid state this yellow compound probably exists as 4-hydroxy-2-thione, while in solution a tautomeric equilibrium is set up. The UV spectrum of **9** changes considerably from that of the 2-thiol form in isooctane (longest wavelength maximum at 305 nm) to that of the 2-thione form in ethanol [highest maxima at 355 and 418 (sh) nm], probably because of association with the 4-hydroxyl in the latter solvent. Reaction of **9** with diazomethane in ether furnished exclusively the *S*-methyl derivative **13**, while acetylation with acetic anhydride in pyridine yielded the colorless ester **14** and the red ester **15** in a ratio of 5:1, respectively (Chart II).

Like other related thioesters, **14** is a powerful acylating agent toward amines. It reacts instantly at room temperature with two molecules of benzylamine to yield, quantitatively, one molecule of *N*-benzylacetamide and one molecule of **11**. In solution, **9** is slowly oxidized to the disulfide **16**, and this oxidation is very rapid with iodine.

The methylthio group in **13** could not be exchanged with morpholine even after a long reflux in ethanol. A strong electron-attracting group at position 3 is probably needed for this exchange to occur.[13]

Pyridone **5b** is likewise obtained from **12** by treatment with acid and extraction. The tautomeric 2-thione form is not observed in this case (highest maximum in ethanol at 304 nm). Methylation with diazomethane, as well as acetylation, occurs exclusively at sulfur, yielding **7b** and **17**, respectively.

Experimental Section

General Procedures. Melting points were taken on a Büchi 510 apparatus and were uncorrected. Infrared spectra were measured with a Perkin-Elmer 257 grating spectrophotometer in potassium bromide, and absorptions were designed as strong (s), medium (m), or weak (w). Ultraviolet spectra were measured in ethanol with a Shimadzu UV-210A spectrophotometer. Proton NMR spectra were measured in deuteriochloroform with a Varian A-60 spectrometer and are given in δ units downfield from Me_4Si as internal standard; all signals were singlets, unless otherwise specified, except for the highest field methyl signal (C-5 Me), which appeared mostly as a finely split doublet or as a slightly broadened singlet, and the vinylic proton (C-6 H), which appeared as a finely split quartet or as a broadened singlet. Mass spectra were determined with a Varian MAT CH5 spectrometer. TLC was done on Merck Kieselgel 60-F254 precoated aluminum plates. The silica gel for column chromatography was Merk Kieselgel 60 (70–230 mesh). Elemental analyses were performed by Mr. A. Richter of the Microanalytical Laboratory of this Institute.

Reaction of 1 with Aqueous Methylamine in Ethanol. A mixture of **1** (1.97 g), ethanol (20 mL), and 27% aqueous methylamine (50 mL) was warmed for 1 h at 50 °C and then kept at room temperature for 20 h. The resulting solution was evaporated at reduced pressure to a small volume, acidified slightly, and extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated at reduced pressure, yielding 1.56 g of an oily residue. Chromatography on silica gel (90 g), using ethyl acetate and up to 30% methanol in ethyl acetate, gave the following products in the order of elution.

Bromide 1, 0.16 g (8%), unreacted.

3,5-Dimethyl-2-(methylamino)thiopyran-4-one (4): 0.32 g (21%); mp 154–155 °C (benzene); δ 2.13 (Me), 2.36 (Me), 4.04 (NMe), 6.62 (br, NH, exchanged with D_2O), 7.58 (vinylic H); ν_{max} 3200 (br, s), 1640 (s), 1543 (m), 1470 (s), 1395 (s), 1275 (m), 1213 (m), 1180 (s), 1090 (m), 1052 (s), 1032 (m), 1013 (m), 962 (m) cm^{-1}; δ_{max} 240 nm (ϵ 20 800), 249 (sh, 18 600), 275 (7300), 307 (7900); *m/e* 169 (M^+), 136, 124, 108, 98, 78, 77.

Anal. Calcd for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28. Found: C, 56.81; H, 6.59; H, 8.31.

1,3,5-Trimethyl-2-mercapto-4(1*H*)-pyridone (5a): 0.67 g (44%); mp 135–136 °C (benzene); δ 2.08 (Me), 2.20 (Me), 3.45 (NMe), 3.55 (br, SH, exchanged with D_2O); ν_{max} 3070 (w), 3030 (w), 2985 (w), 2935 (w), 2860 (w), 1648 (s), 1585 (s), 1378 (m), 1270 (m), 1026 (m) cm^{-1}; λ_{max} 228 nm (ϵ 19 400), 254 (sh, 5430), 308 (6860); *m/e* 169 (M^+), 140, 136, 126, 108.

Anal. Calcd for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28. Found: C, 56.64; H, 6.75; N, 8.22.

Bis(1,3,5-trimethyl-4(1*H*)-oxopyridin-2-yl) disulfide (6a): 0.23 g (15%); mp 186–187 °C (benzene); δ 2.13 (2 Me), 2.18 (2 Me), 3.45 (2 Me), 7.00 (2 vinylic H); ν_{max} 1643 (s), 1583 (s), 1420 (m), 1371 (m), 1342 (m), 1248 (m), 998 (m), 765 (m) cm^{-1}; λ_{max} 223 nm (ϵ 22 200), 341 (7600).

Anal. Calcd for $C_{16}H_{20}N_2O_2S_2$: C, 57.11; H, 5.99; N, 8.36. Found: C, 56.79; H, 6.19; N, 7.96.

Oxidation of **5a** to **6a** was carried out by addition of an ethanolic solution of iodine to an ethanolic solution of **5a** in the presence of solid K_2CO_3 until the color persisted. Addition of aqueous $Na_2S_2O_3$ and extraction with dichloromethane yielded **6a** quantitatively; mp 186–187 °C.

Reaction of 1 with Anhydrous Methylamine in Methanol. Bromide **1** (2.19 g) was dissolved in absolute methanol (20 mL) containing 9 g of methylamine, and the solution was kept for 42 h at room temperature. Silica gel (5 g) was then added, and the solvent was evaporated to dryness. The residue was introduced on top of a column of 75 g of silica gel, and elution was carried out with ethyl acetate and with up to 30% methanol in ethyl acetate. The following were thus obtained. **4**, 0.16 g (20%). **5a**, 0.37 g (22%). 1,3,5-Trimethyl-2-(methylamino)-4(1*H*)-pyridone (**8a**): 0.13 g (18%); mp 154–155 °C (ethyl acetate); δ 1.90 (Me), 2.03 (Me), 2.92 (Me), 3.35 (Me), 3.60 (br, 1 H, exchanged with D_2O), 6.75 (vinylic H); ν_{max} 3305 (s), 1655 (s), 1580 (s), 1550 (s), 1510 (s), 1345 (s), 1190 (m), 1160 (m), 1050 (m), 1033 (m) cm^{-1}; λ_{max} 226 nm (ϵ 26 000), 276 (8600), 296 (inflexion, 6800); *m/e* 166 (M^+), 151, 149, 137.

Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.97; H, 8.48; N, 16.94.

Very similar results were obtained when the reaction was worked up by acidification and extraction (acid extract, furnishing **4** and **5a**) and then neutralization and saturation of the water layer with potassium carbonate and repeated extraction (basic extract, furnishing **8a**). Small amounts of yellow **9** (see below) appeared, however, in all fractions from the acid extract.

1,3,5-Trimethyl-2-(methylthio)-4(1*H*)-pyridone (7a). A solution of **5a** in ethyl acetate was treated with a slight excess

(13) Augustin, M.; Jahreis, G. *J. Prakt. Chem.* **1979**, *321*, 699–703.

of diazomethane in ether. Evaporation of the solvent and crystallization from hexane provided pure **7a**: mp 71–72 °C; δ 2.15 (Me), 2.22 (Me), 2.33 (SMe), 3.43 (NMe), 6.90 (vinylic H); ν_{max} 3070 (w), 2930 (w), 1645 (s), 1590 (s), 1530 (w), 1420 (m), 1375 (m), 1350 (m), 1316 (w), 1250 (m); λ_{max} 211 nm (ε 19900), 237 (5700), 296 (inflexion, 4700), 320 (5800); *m/e* 183 (M^+), 168, 150, 140, 137, 122.

Anal. Calcd for $C_9H_{13}NOS$: C, 58.98; H, 7.15; N, 7.64. Found: C, 58.96; H, 7.41; N, 7.66.

Reaction of 2 with Anhydrous Methylamine in Ethanol. Sulfide **2** (1.01 g) was added to a solution of methylamine (6 g) in absolute ethanol (30 mL). The mixture was kept for 3 h at 50 °C and then at room temperature for 48 h. Solvent and excess amine were removed under reduced pressure, and the residue was dissolved in a minimum amount of water, acidified with 5 N sulfuric acid, and extracted with ether. The ether extract yielded a yellow oily residue which solidified in tetrachloromethane to give 0.70 g of a mixture of **5a** and **9**, identified through TLC and ^1H NMR. The water layer was neutralized, saturated with K_2CO_3, and then extracted with ethyl acetate, yielding finally 0.10 g (18%) of purified **5a**, mp 153–154 °C.

Reaction of 1 with Benzylamine. Method A. Bromide **1** (1.32 g) and benzylamine (3 mL) were kept under nitrogen at 100–110 °C for 3 h. Excess amine was evaporated at reduced pressure (0.01 torr), and the residue was taken up in ethyl acetate and filtered to remove a salt mixture (1.47 g) consisting of benzylamine hydrobromide and salt **11**. The salt mixture was treated with water, without warming, and filtered. A residue of 0.41 g was then recrystallized from benzene, yielding 0.17 g (20%) of **11**, mp 184–185 °C (see below).

The ethyl acetate solution yielded upon evaporation a product mixture (1.40 g) that was chromatographed on silica gel (100 g), giving the following compounds upon elution with ethyl acetate-hexane (4:1).

(1-Benzyl-3,5-dimethyl-4(1*H*)-oxopyridin-2-yl) (3,5-dimethyl-4-oxo-4*H*-thiopyran-2-yl) sulfide (10): 0.43 g of recrystallized product (37%); mp 158–159 °C (ethanol or benzene–hexane); δ 2.06, 2.13, 2.37, 2.43 (4 Me), 5.20 (CH_2), 7.15 (vinylic H of pyridone), 7.42 (6 H; phenyl and vinylic H of thiopyrone); ν_{max} 1640 (s), 1583 (s), 1463 (m), 1447 (m), 1375 (m), 1365 (m), 1186 (m), 1025 (m), 1000 (m), 972 (m) cm^{-1}; λ_{max} 236 nm (ε 26500), 308 (20200); *m/e* 383 (M^+), 368, 350, 283, 282, 277, 276, 259, 245, 244, 192, 162, 128, 111, 99, 91.

Anal. Calcd for $C_{21}H_{21}NO_2S_2$: C, 65.76; H, 5.52; N, 3.65. Found: C, 65.62; H, 5.48; N, 3.61.

1-Benzyl-2-(benzylamino)-3,5-dimethyl-4(1*H*)-pyridone (8b): 0.52 g (27%); mp 120–121 °C (benzene–hexane); δ 1.93 (Me), 2.16 (Me), 3.83 (1 H, exchanged with D_2O), 4.44 (CH_2), 5.08 (CH_2), 6.87 (vinylic H), 7.33 (10 H, 2 Ph); ν_{max} 3350 (m), 1655 (s), 1580 (s), 1455 (m), 1425 (m), 1342 (m), 1268 (m), 1220 (m), 1155 (m), 982 (m) cm^{-1}; λ_{max} 231 nm (ε 26900), 276 (11200); *m/e* 318 (M^+), 227, 149, 134, 116, 91.

Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 78.99; H, 7.06; N, 8.86.

Method B. Bromide **1** (1.15 g) in benzylamine (2 mL) and water (2 mL) was kept under nitrogen at 90–100 °C for 12 h. The above treatment yielded 1.04 g of a salt mixture of the amine hydrobromide and **11** in a ratio of ca. 9:1 (^1H NMR in Me_2SO-d_6). The ethyl acetate solution furnished a product mixture (1.2 g) that was chromatographed as above (80 g of silica gel) to yield **10** (0.59 g, 58%) and **8b** (0.34 g, 20%).

Reaction of 2 with Benzylamine. Method A. Sulfide **2** (0.76 g) in benzylamine (3 mL) was kept under nitrogen at 115 °C for 1 h. Excess amine was evaporated at reduced pressure, and the residue was taken up in ethyl acetate, which induced crystallization. The solid was collected, treated with warm ethyl acetate, and filtered again, yielding 0.94 g of a crude product. This was recrystallized from benzene–ethanol to yield 0.73 g (theoretical yield 0.68 g) of benzylammonium 3,5-dimethyl-4-oxo-4*H*-thiopyran-2-thiolate (**11**): mp 184–185 °C; δ (Me_2SO-d_6) 1.90 (Me), 2.13 (Me), 4.12 (CH_2), 7.33 (vinylic H), 7.5 (Ph + 3 exchangeable H; 5 H after addition of D_2O); ν_{max} 3440 (br), 2750–3000 (br, s), 1590 (m), 1536, 1523, 1505 (all s), 1378 (m), 1367 (m), 1032 (m), 930 (m) cm^{-1}.

Anal. Calcd for $C_{14}H_{17}NOS_2$: C, 60.10; H, 6.22; N, 5.06. Found: C, 60.30; H, 6.27; N, 5.08.

The combined and concentrated ethyl acetate solutions deposited overnight a second solid which was collected and recrystallized from benzene to yield 85 mg (10%) of benzylammonium 1-benzyl-3,5-dimethyl-4(1*H*)-oxopyridine-2-thiolate (**12**): mp 147–148 °C; δ (Me_2SO-d_6) 2.00 (Me), 2.12 (Me), 3.97 (CH_2), 4.93 (CH_2), 6.67 (br, 3 H, exchanged with D_2O), 7.02 (vinylic H), 7.25 and 7.40 (2 Ph, 10 H); ν_{max} 2700–3000 (br, m), 2630 (m), 1640 (s), 1545 (s), 1526 (m), 1507 (m), 1330 (m), 1040 (m), 1020 (m), 935 (m) cm^{-1}.

Anal. Calcd for $C_{21}H_{24}NOS$: C, 71.56; H, 6.86; N, 7.95. Found: C, 70.98; H, 6.96; N, 7.65.

The residue obtained upon evaporation of the ethyl acetate solution was chromatographed on silica gel (70 g), yielding upon elution with ethyl acetate 0.28 g (36%) of **8b**. (Yields are calculated separately for each product relative to 1 mol of **2**.)

Method B. Sulfide **2** in benzylamine (3 mL) and water (3 mL) was kept under nitrogen at 100 °C for 90 min. The above treatment gave 1.85 g of a mixture of **11** and **12** (^1H NMR, ratio ca. 7:2). Separation was achieved by recrystallization from 150 mL of benzene/ethanol (4:1) which deposited 1.28 g of **11** (theoretical yield, 1.17 g). The solution was concentrated to about one-third of its original volume, cooled, filtered to remove a small additional amount of **11**, and further concentrated to ca. one-tenth of the original solution. When the mixture was cooled, 0.26 g (18%) of **12** could be collected which was recrystallized from benzene.

Chromatography of the ethyl acetate residue as above yielded 0.32 g (24%) of **8b**.

Reaction of 10 with Benzylamine. Mixed sulfide **10** (300 mg) in benzylamine (1 mL) was kept under nitrogen at 100–110 °C for 16 h. Excess amine was evaporated and crystallization was induced by treatment with ethyl acetate. The collected solid (mp 145–147 °C, 150 mg) was identical with **12** (^1H NMR and IR). Chromatography of the residue from the ethyl acetate solution then yielded recovered **10** (90 mg) and **8b** (35 mg).

3,5-Dimethyl-2-mercapto-4*H*-thiopyran-4-one (9) and Disulfide 16. Salt **11** (1.36 g) was dissolved in 5% HCl and extracted with ether, yielding after the usual workup 0.81 g of a yellow solid. Rapid crystallization from benzene–hexane gave 0.59 g (70%) of **9**: mp 115–116 °C; δ 2.15 (Me), 2.28 (Me), 4.20 (1 H, exchanged with D_2O), 7.38 (vinylic H); ν_{max} 3200–3400 (m, br), 3000 (m), 1570, 1510, 1410, 1376, 1335, 1220, 1180, 1030, 987, 960 cm^{-1} (all m to s); λ_{max} 273 nm (ε 30600), 309 (14100), 355 (6300), 418 (inflexion, 4100); λ_{max} (isooctane) 224 nm (ε 12400), 259 (8600), 296 (11000), 305 (10100); *m/e* 172 (M^+), 139, 128, 127, 111, 101, 99.

Anal. Calcd for $C_7H_8OS_2$: C, 48.81; H, 4.68. Found: C, 48.92; H, 4.79.

Salt **11** was quantitatively formed from **9** by treatment with a slight excess of benzylamine, addition of ethyl acetate, and filtration.

Pyrrolidine and morpholine salts were similarly prepared by addition of a slight excess of the base to an ethyl acetate solution of **9** at room temperature, filtration, and recrystallization.

Pyrrolidinium 3,5-dimethyl-4-oxo-4*H*-thiopyran-2-thiolate, mp 131–132 °C (benzene).

Anal. Calcd for $C_{11}H_{17}NOS_2$: C, 54.29; H, 7.04; N, 5.76. Found: C, 54.45; H, 6.96; N, 5.85.

Morpholinium 3,5-dimethyl-4-oxo-4*H*-thiopyran-2-thiolate, mp 135–136 °C (benzene).

Anal. Calcd for $C_{11}H_{17}NO_2S_2$: C, 50.94; H, 6.61; N, 5.40. Found: C, 51.00; H, 6.45; N, 5.39.

Oxidation of **9** with iodine in ethanolic solution was carried out as described above for **6a** to give bis(3,5-dimethyl-4-oxo-4*H*-thiopyran-2-yl) disulfide: mp 190–191 °C (ethanol); δ 2.13 (2 Me), 2.33 (2 Me), 7.53 (2 vinylic H); ν_{max} 1590 (s), 1370 (m), 1275 (m), 1190 (m), 1030 (m), 975 (m) cm^{-1}; λ_{max} 228 nm (ε 21600), 253 (17700), 312 (20900).

Anal. Calcd for $C_{14}H_{14}O_2S_4$: C, 49.09; H, 4.12. Found: C, 48.96; H, 4.17.

Reactions of 1 and 2 with Sodium Hydrogen Sulfide. Bromide **1** (410 mg) in aqueous methanolic NaHS[14] (25 mL, ca. 1 g of salt) was kept at 50–60 °C for 24 h. Most of the methanol

(14) Hodgson, H. H.; Ward, E. R. *J. Chem. Soc.* **1948**, 242.

was evaporated at reduced pressure, and the remaining solution was acidified and extracted with ether. The crude product (0.3 g) was treated in ether solution with diazomethane. Separation on silica gel (20 g; elution with ether–hexane, 3:1) yielded **13** (120 mg, 39%) and 3,5-dimethyl-2-(methylthio)-4*H*-pyran-4-one[1] (60 mg, 22%).

Powdered **2** (310 mg) was stirred at 70 °C in 22 mL of the above NaHS solution for 3.5 h. The crude product was treated in ethyl acetate solution with a slight excess of benzylamine, yielding 440 mg (79%) of **11**, mp 180–183 °C. Acidification, extraction, and methylation of an aliquot from this salt yielded pure **13** (^{1}H NMR).

3,5-Dimethyl-2-(methylthio)-4*H*-thiopyran-4-one (13). Treatment of **9** in ether solution with a slight excess of diazomethane in ether, evaporation of the solvent and recrystallization from hexane yielded **13**: mp 78–79 °C; δ 2.17 (Me), 2.27 (Me), 2.54 (S-Me), 7.50 (vinylic H); ν_{max} 3010 (w), 2920 (w), 1585, 1570, 1555 (all s), 1505 (s), 1435, 1393, 1368, 1278, 1190, 1030, 992, 953 (all m) cm^{-1}; λ_{max} 243 nm (ε 13 600), 262 (7300), 308 (14 000); *m/e* 186 (M$^+$), 171, 153, 143, 140, 99, 71.

Anal. Calcd for $C_8H_{10}OS_2$: C, 51.58; H, 5.41. Found: C, 51.65; H, 5.45.

Acetylation of 9. Compounds 14 and 15. A solution of **9** (0.60 g) in pyridine (3 mL) was treated with acetic anhydride (1 mL) at room temperature for 6 h. The usual workup gave a mixture of two compounds that were separated by chromatography on silica gel (30 g).

4-Acetoxy-3,5-dimethyl-2*H*-thiopyran-2-thione (15): 0.11 g (15%, eluted with dichloromethane); mp 100–101 °C (hexane); δ 2.12 (Me), 2.27 (Me), 2.37 (Me), 7.37 (vinylic H); ν_{max} 1760 (s), 1580 (m), 1500 (m), 1365 (m), 1200 (s), 1190 (s), 1170 (s), 1160 (m), 1030 (m), 1015 (m), 1000 (s), 955 (m), 900 (m), 825 (m) cm^{-1}; λ_{max} 251 nm (ε 12 600), 314 (7800), 437 (5400); *m/e* 214 (M$^+$), 172, 139, 128, 101, 99.

Anal. Calcd for $C_9H_{10}O_2S_2$: C, 50.44; H, 4.70. Found: C, 50.65; H, 4.96.

2-(Acetylthio)-3,5-dimethyl-4*H*-thiopyran-4-one (14): 0.56 g (75%, eluted with dichloromethane–ethyl acetate, 1:1); mp 89–90 °C (hexane); δ 2.17 (Me), 2.25 (Me), 2.47 (Me), 7.60 (vinylic H); ν_{max} 1705 (s), 1580 (s), 1430 (m), 1370 (m), 1255 (m), 1118 (m), 1025 (m), 970 (m), 938 (m), 870 (m) cm^{-1}; λ_{max} 242 nm (ε 8100), 304 (11 400); *m/e* 214 (M$^+$), 197, 181, 162, 139, 128, 101, 99, 71.

Anal. Calcd for $C_9H_{10}O_2S_2$: C, 50.44; H, 4.70. Found: C, 50.63; H, 4.89.

Reaction of 14 with Benzylamine. Benzylamine (183 mg) dissolved in ethyl acetate (1 mL) was added to a solution of **14** (170 mg) in the same solvent (2 mL). Immediate reaction occurred with warming and precipitation of an oil which solidified on scratching. The solid was filtered and identified as **11** (125 mg). The solution was evaporated to dryness to give 220 mg of solid *N*-benzylacetamide, identical with an authentic sample (^{1}H NMR and melting point).

1-Benzyl-3,5-dimethyl-2-mercapto-4(1*H*)-pyridone (5b). Salt **12** (150 mg) was treated with 5% HCl and extracted with ethyl acetate. The crude product was filtered on 10 g of silica gel with ethyl acetate-hexane (7:3), yielding solid **5b** (90 mg). Recrystallization from ether-hexane yielded the pure compound: mp 89–90 °C; δ 2.05 (Me), 2.25 (Me), 3.57 (br, 1 H, exchanged with D_2O), 5.14 (CH_2), 7.02 (vinylic H), 7.37 (Ph); ν_{max} 2520 (m, br), 1640 (s), 1590 (s), 1575 (s), 1500 (m), 1453 (m), 1432 (m), 1363 (m), 1333 (m), 1328 (m), 996 (m), 928 (m), 765 (m), 730 (m) cm^{-1}; δ_{max} 229 nm (ε 20 500), 244 (sh, 8900), 304 (8900); *m/e* 245 (M$^+$), 154, 91.

Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.39; H, 6.16; N, 5.81.

Methylation of **5b** in ether solution, as described above for **13**, yielded 1-benzyl-3,5-dimethyl-2-(methylthio)-4(1*H*)-pyridone (**7b**) as a distillable liquid: bp 160–170 °C (bath temperature; 0.01 torr); δ 2.15 (Me), 2.27 (Me), 2.42 (Me), 5.10 (CH_2), 7.01 (vinylic H), 7.32 (Ph); ν_{max} ($CHCl_3$) 1635 (s), 1578 (s), 1315 (m), 1120 (m), 1000 (m), 980 (m) cm^{-1}; λ_{max} 210 nm (ε 31 300), 238 (sh, 7200), 298 (sh, 5800), 319 (6100); *m/e* 259 (M$^+$), 226, 168, 149, 115, 113, 91.

Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.06; H, 6.63; N, 5.37.

Acetylation of **5b** (0.25 g) with acetic anhydride in pyridine yielded after chromatography (15 g of silica gel; ethyl acetate–dichloromethane, 1:4) 0.18 g (61%) of 2-(acetylthio)-1-benzyl-3,5-dimethyl-4-(1*H*)-pyridone (**17**): mp 99–100 °C (hexane); δ 2.00 (Me), 2.28 (Me), 2.43 (Me), 5.13 (CH_2), 7.05 (vinylic H), 7.33 (Ph); ν_{max} 1702 (s), 1640 (s), 1582 (s), 1527 (m), 1498 (m), 1454 (m), 1437 (m), 1370 (m), 1135 (m), 1118 (m) cm^{-1}; λ_{max} 219 nm (ε 24 400), 329 (6000); *m/e* 287 (M$^+$), 245, 244, 212, 154, 91.

Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 67.13; H, 6.09; N, 5.05.

Registry No. **1**, 61170-10-3; **2**, 61170-12-5; **4**, 75347-29-4; **5a**, 75347-30-7; **5b**, 75347-31-8; **6a**, 75347-32-9; **7a**, 75347-33-0; **7b**, 75347-34-1; **8a**, 75347-35-2; **8b**, 75347-36-3; **9** (isomer 1), 75347-37-4; **9** (isomer 2), 75347-38-5; **10**, 75347-39-6; **11**, 75347-41-0; **11** pyrrolidinium salt, 75347-42-1; **11** morpholinium salt, 75347-43-2; **12**, 75347-45-4; **13**, 75347-46-5; **14**, 75347-47-6; **15**, 75347-48-7; **16**, 75347-49-8; **17**, 75347-50-1; 3,5-dimethyl-2-(methylthio)-4*H*-pyran-4-one, 67844-82-0; methylamine, 74-89-5; benzylamine, 100-46-9.

N-Alkylation of Nitriles Using Chromium Tricarbonyl Complexes of Benzyl Alcohol and Its Derivatives: New Perspectives for the Ritter Reaction

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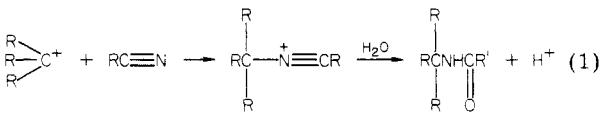
The Ritter reaction, which involves the reaction of nitrile on a carbenium ion, giving rise to an amide, can be considerably improved by using carbenium ion intermediates stabilized by a transition-metal moiety (e.g., $Cr(CO)_3$). However, an excessive stabilization can inhibit the reactivity. In complexed systems the reaction takes place with total stereochemical control.

The conversion of nitriles to amides by reaction with alcohols or alkenes in the presence of sulfuric acid is the Ritter reaction.[1] Acidification of the appropriate alcohol or alkene generates a carbenium ion which reacts with the nitrile as shown in eq 1.



(1)

While the successful course of the reaction certainly depends on the reactivity of the nitrile, a major factor is the stability and reactivity of the carbocationic intermediates. While tertiary alcohols generally give good yields, secondary and primary alcohols give only mediocre results;[2a] this is a reflection of the instability of the primary

(1) L. I. Krimen and D. J. Cota, *Org. React.*, 17, 213 (1969).

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