Organic Chemistry

3-[Amino(methylthio)methylene]pentane-2,4-dione in the synthesis of functionalized pyridines

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New syntheses of functionalized pyridines from 3-[amino(methylthio)methylene]-2,4-pentanedione *via* its boron chelates were proposed. The products of condensation of dimethylformamide dimethylacetal with the latter chelates were converted into 3-acetyl-2-methylthio-4-hydroxypyridine by refluxing in BuOH and into 1-alkyl-3-cyano-2-methyl-4-pyridones by treatment with primary amines.

Key words: ketene *N,S*-acetal, dimethylformamide dimethylacetal, difluoroboron chelates, diphenylboron chelates, cyclization, intramolecular hydrogen bond, 3-cyano-4-pyridones, 3-acetyl-4-hydroxy-2-methylthiopyridine, primary amines.

Previously we proposed an efficient method for synthesizing *N*-unsubstituted diacetylketene *N,S*-acetals from β-diketones and thiocyanates.[1] Compounds of this type are used for constructing functionalized heterocyclic systems. The reaction of 3-[amino(methylthio)-methylene]-2,4-pentanedione (**1**), the diacetylketene *N,S*-acetal, with isocyanates in the absence of bases is a convenient method for synthesizing derivatives of 1H-pyrimidin-2-one.[2]

It has also been found[1] that acetals *N,S*-ketene of this type are good chelating ligands. In particular, compound **1** readily reacts with Ph_2BOBu to give chelate complex (**2**) with *N,O*-coordination of the B atom. Thus, new possibilities are opened for using ketene *N,S*-acetal **1** in heterocyclic synthesis by applying the "methodology of chelate assisted organic synthesis" based on the change in the reactivity of ligands due to chelate formtion.[3–5]

Recently[6,7] we found that, under mild conditions, acetals of amides react with boron chelates of diacetylketene aminals and enaminones, *e.g.*, 4-amino-5,5,5-trichloro-3-pentene-2-one or its 3-acetyl derivative. The resulting products of condensation at the methyl group directly linked to the boron-containing ring undergo cyclization when alcoholized with boiling butanol to give the corresponding functionalized pyridines.

In the present work we used a similar approach for synthesizing pyridines from boron-containing chelates of ketene *N,S*-acetal **1**. The action of butoxydifluoroborane on compound **1** was found to result in crystalline complex **3**, readily soluble in organic solvents (except petroleum ether). Only one acetyl group of the ligand is involved in the coordination interaction with boron in this compound, similarly to chelate **2**. For example, the signal of the COB moiety in the ^{13}C NMR spectrum of

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3 is strongly shifted upfield (δ 177) relative to the CO signal from the second acetyl group (δ 198) (*cf.* the ^{13}C NMR data in Ref. 1 for chelate **2**). The participation of the enaminone fragment of ketene *N,S*-acetal **1** in the formation of complex **3** is also confirmed by ^1H NMR (nonequivalence of the MeCO groups) and IR spectral data (the presence of a characteristic intense absorption band of NH of the chelate ring in the 3400 cm^{-1} region).

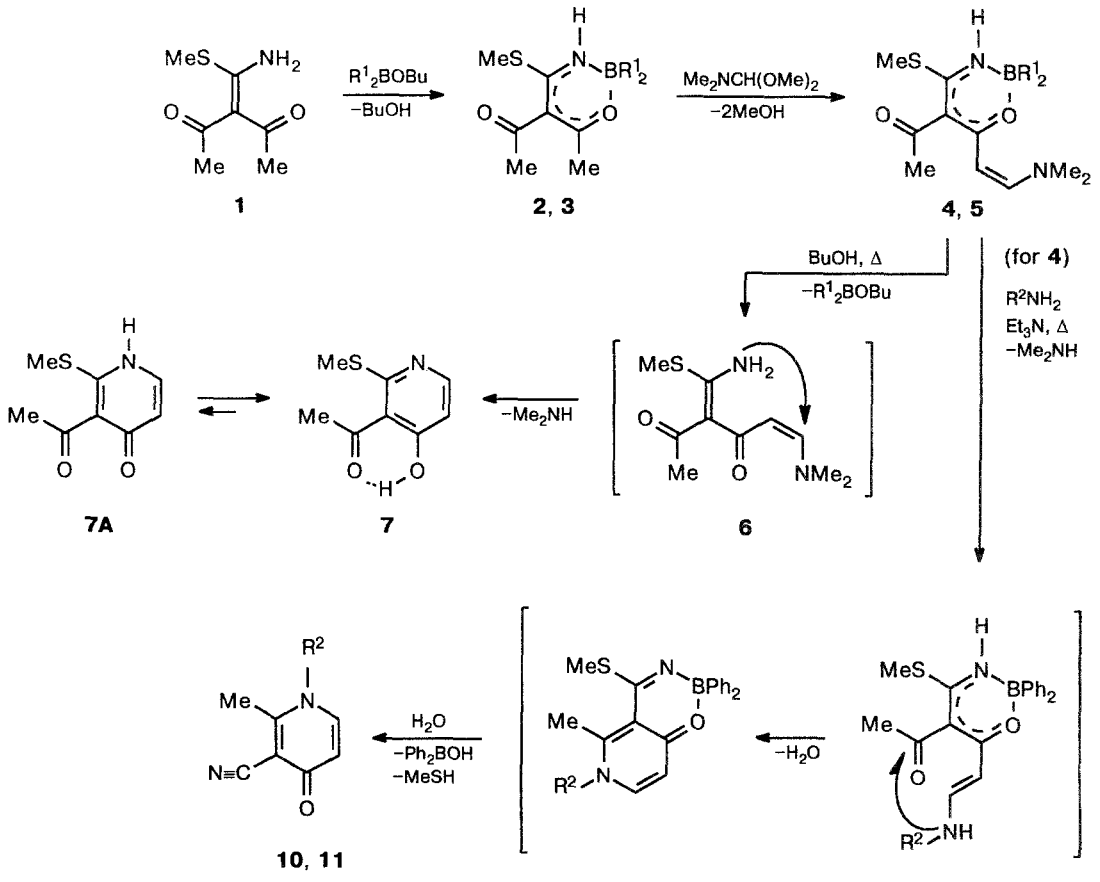
Chelates **2** and **3** react with dimethylformamide dimethylacetal under mild conditions (20 °C, THF) to give yellow crystalline condensation products (**4**, **5**). They also have a chelate structure, which is confirmed by ^1H and ^{13}C NMR spectral (the presence of signals from the dimethylaminovinyl moiety) and mass spectroscopic data (the presence of molecular ions). The ^{13}C NMR spectra contain signals of the carbon atoms of the free acetyl group in chelate complexes **2**—**5** with similar chemical shifts.

Difluoroboron chelate **5** decomposes when refluxed in BuOH. The resulting ligand (**6**) undergoes cyclization with elimination of Me_2NH to give 3-acetyl-4-hydroxy-2-methylthiopyridine (**7**) in 49 % yield (Scheme 1).

Attempts to use diphenylboron chelate **2** in similar transformations gave product **7** in low yields.

Compound **7** is a yellow crystalline substance soluble in the majority of organic solvents but insoluble in hexane. Its mass spectrum contains a molecular ion peak (*m/z* 183). Spectral data (IR, ^1H and ^{13}C NMR) suggest that the equilibrium hydroxypyridine **7** — pyridone **7A** in chloroform is shifted toward the hydroxy form. For example, the chemical shifts of the C(4) (170.7 ppm) and C(6) (150.1 ppm) atoms in the ^{13}C NMR spectrum (in $CDCl_3$) of the compound synthesized are closer to the chemical shifts of the corresponding atoms in 4-methoxypyridine[8] (164.9 and 150.7 ppm) than to those in 1-methyl-4-pyridone[8] (176.6 and 141.4 ppm). The hydroxy form **7** is probably stabilized due to

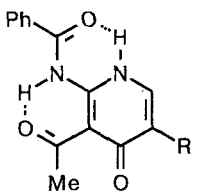
Scheme 1



2, **4**: R^1 = Ph **10**: R^2 = Bu
3, **5**: R^1 = F **11**: R^2 = C_5H_{11}

the formation of an intramolecular hydrogen bond (IHB), O—H···O. In fact, the IR spectrum of this compound in $CHCl_3$ contains a broad absorption band in the 3200—2500 cm^{-1} region (bonded OH), while the highest-frequency band in the 1600—1700 cm^{-1} region is observed at 1622 cm^{-1}. This band should be attributed to the carbonyl group of the acetyl moiety involved in the formation of IHB. A similar picture[9] is observed in the case of ethyl 2-alkylthio-4-hydroxyquinoline-3-carboxylate, which also exists in the hydroxy form when dissolved in inert solvents facilitating the formation of OH···O IHB.

Conversely, the oxo form stabilized by N—H···O intramolecular hydrogen bonds is more typical of functionalized pyridines **8** and **9** obtained previously from diacetylketene aminals[6,10] (see, *e.g.*, the ^{13}C NMR spectral data for compound **8** in Experimental and those for compound **9** in Ref. 10).



8: R = H
9: R = Ph

The treatment of chelate **5** with primary amines in Et_3N results in replacement of the Me_2NH group and cyclization (involving free acetyl group) accompanied by decomposition of the chelate and elimination of MeSH. Using this approach, we synthesized 1-alkyl-3-cyano-2-methyl-4-pyridones (**10** and **11**) (Scheme 1) in 80—90 % yields (see the preliminary communication in Ref. 11). Attempts to synthesize compounds **10** and **11** using difluoroboron chelate **5** instead of complex **4** did not give satisfactory results.

Compounds **10** and **11** are white crystalline substances soluble in the majority of organic solvents but poorly soluble in hexane. Their IR spectra contain a C≡N absorption band at about 2230 cm^{-1} and an intense CO absorption band at 1645 cm^{-1}. The structures of cyanopyridones **10** and **11** were also confirmed by data of ^1H and ^{13}C NMR spectra and mass spectrometry. The chemical shift of the C(4) atom in the ^{13}C NMR spectrum of cyanopyridone **10** in $CDCl_3$ is typical of pyridone systems and equals 175 ppm.

Thus, the choice of intermediate chelate complexes and the conditions of their decomposition, which determine the cyclization behavior and hence the structure of the end products, is important in the "methodology of chelate assisted synthesis ". This was clearly demonstrated in the syntheses of pyridines from ketene *N,S*-acetal **1**.

Experimental

^1H NMR spectra were recorded on a Bruker WM-250 spectrometer. ^{13}C NMR spectra were recorded on a Bruker AM-300. IR spectra were obtained on a UR-20 spectrophotometer. Mass spectra were obtained on a Varian MAT-311A mass spectrometer (EI, 70 eV).

The ^1H and ^{13}C NMR spectra of the compounds synthesized were measured in $CDCl_3$, while the IR spectra were obtained in CH_2Cl_2.

3-[Amino(methylthio)methylene]-2,4-pentanedione (1) and its diphenylboron chelate (2) were obtained using the procedure described previously,[1] and butoxydifluoroborane was obtained by the procedure in Ref. 12.

3-Acetyl-2-benzoylamino-4-pyridone (8) was obtained by a known method.[6] ^{13}C NMR spectrum of compound **8** (DMSO-d_6), δ: 32.8 (Me); 107.8 (C(3)); 118.2 (C(5)); 127.4, 129.2, 132.0, 133.5 (Ph); 134.8 (C(6)); 150.5 (C(2)); 167.3 (NCO); 177.4 (C(4)); 202.8 (COMe).

Difluoroboron chelate of 3-[amino(methylthio)methylene]-2,4-pentanedione (3). A solution of ketene *N,S*-acetal **1** (1.73 g, 10 mmol) and F_2BOBu (1.5 mL, 13.76 mmol) in THF (8 mL) was refluxed for 6 h and left overnight. The crystals of chelate **3** that precipitated were filtered off, washed with ether, and dried. The filtrate was evaporated to dryness, and the residue was recrystallized from THF to give an additional amount of complex **3**. The overall yield of chelate **3** was 1.9 g (86 %), m.p. 130—132 °C. MS, *m/z*: 221 $[M]^+$. IR, ν/cm^{-1}: 3400 (NH), 1640 (CO), 1555. ^1H NMR, δ: 2.37 (s, 3 H, Me); 2.48 (s, 3 H, Me); 2.49 (s, 3 H, Me); 7.50 (br.s, 1 H, NH). ^{13}C NMR, δ: 13.1 (q, MeS, ^1J = 141 Hz); 23.7 (q, MeCOB, ^1J = 130 Hz); 32.3 (q, MeCO, ^1J = 128 Hz); 113.7 (s, OCCCO); 175.9 (br.s, NCS); 177.0 (q, COB, ^2J = 5.5 Hz); 198.3 (q, CO, ^2J = 5.5 Hz).

Diphenylboron chelate of 3-[amino(methylthio)methylene]-5-dimethylamino-5-hexene-2,4-dione (4). A mixture of compound **2** (3.37 g, 10 mmol) and dimethylformamide dimethylacetal (2.65 mL, 20 mmol) in THF (5 mL) was stirred for 24 h at 20 °C. The crystals that precipitated were filtered off to give 3.33 g (85 %) of complex **4**, m.p. 188—189 °C. Found (%): C, 67.09; H, 6.48; N, 7.09; S, 7.75. $C_{22}H_{25}BN_2O_2S$. Calculated (%): C, 67.35; H, 6.43; N, 7.14; S, 8.17. MS, *m/z*: 392 $[M]^{+\cdot}$. IR, ν/cm^{-1}: 3420 (NH), 1630 sh (CO), 1610, 1525. ^1H NMR, δ: 2.28 (s, 3 H, Me); 2.37 (s, 3 H, Me); 2.95 (s, 3 H, NMe); 3.21 (s, 3 H, NMe); 5.26 (d, 1 H, CH); 6.52 (br.s, NH); 7.20—7.40 (m, 10 H, 2 Ph); 7.90 (d, 1 H, NCH). ^{13}C NMR, δ: 13.4 (q, Me, ^1J = 139 Hz); 31.2 (q, MeCO, ^1J = 128 Hz); 37.2 (q, MeN); 45.5 (q, MeN); 92.2 (d, CH, ^1J = 155 Hz); 110.5 (OCCCO); 126.0, 126.9, 127.1, 131.9, 132.1, 149.9 (2 Ph); 153.9 (d, NCH, ^1J = 163 Hz); 171.1 (NCS); 176.8 (COB); 196.2 (CO).

Difluoroboron chelate of 3-[amino(methylthio)methylene]-5-dimethylamino-5-hexene-2,4-dione (5). Chelate **5** was obtained similarly to complex **4**, yield 54 %, m.p. 159—160 °C (THF). MS, *m/z*: 276 $[M]^+$. IR, ν/cm^{-1}: 3422 (NH), 1635 sh (CO), 1612, 1532. ^1H NMR, δ: 2.37 (s, 3 H, Me); 2.45 (s, 3 H, Me); 2.95 (s, 3 H, NMe); 3.25 (s, 3 H, NMe); 5.10 (d, 1 H, CH); 6.41 (br.s, 1 H, NH); 7.90 (d, 1 H, NCH). ^{13}C (DMSO-d_6), δ: 13.5 (q, Me, ^1J = 140 Hz); 31.4 (q, Me, ^1J = 127 Hz); 37.5 (q, NMe, ^1J = 139 Hz); 45.3 (q, NMe, ^1J = 139 Hz); 89.7 (d, CH, ^1J = 160 Hz); 107.5 (d, OCCCO, ^3J = 4 Hz); 154.6 (d, NCH, ^1J = 170 Hz); 171.4 (br.s, NCS); 172.2 (s, COB); 196.5 (q, CO, ^2J = 6 Hz).

3-Acetyl-4-hydroxy-2-methylthiopyridine (7). A. Chelate **5** (1.29 g, 4.67 mmol) and BuOH (4 mL) were refluxed for 4 h.

The solvent was distilled off, and the dry residue was dissolved in $CHCl_3$ and chromatographed on SiO_2 using $CHCl_3$ and $CHCl_3$—EtOH (20 : 1) as eluents to give 0.42 g (49 %) of pyridine **7**, m.p. 162—164 °C (MeCN). Found (%): C, 52.67; H, 4.79; N, 7.51; S, 17.01. $C_8H_9NO_2S$. Calculated (%): C, 52.44; H, 4.95; N, 7.64; S, 17.50. MS, *m/z*: 183 $[M]^+$. IR, ν/cm^{-1}: 3200—2500 br (OH, CH), 1622 (CO), 1570, 1450. ^1H NMR ($CHCl_3$), δ: 2.61 (s, 3 H, SMe); 2.90 (s, 3 H, Me); 6.62 (d, 1 H, CH); 8.21 (d, 1 H, NCH, J = 5.5 Hz); 13.60 (br.s, 1 H, OH). ^{13}C NMR, δ: 14.9 (q, MeS, ^1J = 142 Hz); 33.4 (q, Me, ^1J = 130 Hz); 110.8 (d, C(5), ^1J = 168 Hz, ^2J = 5.5 Hz); 117.9 (C(3)); 150.1 (br.s, C(6), ^1J = 179 Hz); 162.2 (m, C(2)); 170.7 (d, C(4), ^2J = 7 Hz); 204.7 (d, CO, ^2J = 5 Hz).

B. Similarly, chelate **4** was refluxed with BuOH for 11 h to give pyridine **7** in 19 % yield.

1-Butyl-3-cyano-2-methyl-4-pyridone (10). A mixture of chelate **4** (3.33 g, 8.49 mmol) and $BuNH_2$ (3 mL) in Et_3N (4 mL) was refluxed for 4 h, and the solvent was distilled off. The residue was chromatographed on SiO_2 using $CHCl_3$—MeOH (10 : 1) as the eluent to give 1.28 g (79 %) of pyridone **10**, m.p. 103—104 °C (benzene). Found (%): C, 69.57; H, 7.72; N, 15.11. $C_{11}H_{14}N_2O$. Calculated (%): C, 69.44; H, 7.42; N, 14.73. MS, *m/z*: 190 $[M]^+$. IR, ν/cm^{-1}: 2226 (CN), 1645 (CO), 1605. ^1H NMR, δ: 1.00 (t, 3 H, $\underline{Me}CH_2$); 1.40 (m, 2 H, CH_2); 1.75 (m, 2 H, CH_2); 2.61 (s, 3 H, Me); 3.91 (t, 2 H, NCH_2); 6.37 (d, 1 H, CH); 7.35 (d, 1 H, NCH, J = 7.5 Hz). ^{13}C NMR, δ: 13.5 (q, $\underline{Me}CH_2$, ^1J = 126 Hz); 18.56 (t, CH_2, ^1J = 127 Hz); 19.4 (q, Me, ^1J = 131 Hz); 32.2 (t, CH_2, ^1J = 126 Hz); 54.1 (t, NCH_2, ^1J = 140 Hz); 104.9 (C(3)); 115.7 (CN); 118.4 (d, C(5), ^1J = 169 Hz); 141.7 (d, C(6), ^1J = 180 Hz); 155.4 (m, C(2)); 175.5 (d, C(4), ^2J = 8 Hz).

1-Amyl-3-cyano-2-methyl-4-pyridone (11). Pyridone **11** was obtained similarly to compound **10** in 89 % yield, m.p. 87—88 °C (benzene—hexane, 1 : 2). Found (%): C, 70.52; H, 7.34; N, 13.40. $C_{12}H_{16}N_2O$. Calculated (%): C, 70.55; H, 7.90; N, 13.72. MS, *m/z*: 204 $[M]^+$. IR, ν/cm^{-1}: 2260 (CN), 1645 (CO), 1602. ^1H NMR, δ: 0.90—1.81 (m, 9 H, $(CH_2)_3Me$); 2.55 (s, 3 H, Me); 3.61 (m, 1 H, NCH_2); 3.84 (m, 1 H, NCH_2); 6.32 (d, 1 H, CH); 7.30 (d, 1 H, NCH, J = 7.5 Hz).

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References

1. V. A. Dorokhov, M. F. Gordeev, E. M. Shashkova, A. V. Komkov, and V. S. Bogdanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 2600 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 2274 (Engl. Transl.)].
2. V. A. Dorokhov, M. F. Gordeev, A. V. Komkov, and V. S. Bogdanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 2593 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 2267 (Engl. Transl.)].
3. M. F. Gordeev and V. A. Dorokhov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 1690 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1988, **37**, 1505 (Engl. Transl.)].
4. V. A. Dorokhov, M. F. Gordeev, and M. A. Prezent, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 525 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 457 (Engl. Transl.)].
5. V. A. Dorokhov and M. A. Prezent, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1504 [*Russ. Chem. Bull.*, 1993, **42**, 1442 (Engl. Transl.)].
6. V. A. Dorokhov and M. F. Gordeev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 2874 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **39**, 2638 (Engl. Transl.)].
7. L. S. Vasil'ev, O. G. Azarevich, V. S. Bogdanov, B. I. Ugrak, and V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1342 [*Russ. Chem. Bull.*, 1994, **43**, 1282 (Engl. Transl.)].
8. U. Vogeli and W. Philipsborn, *Org. Magn. Res.*, 1973, **5**, 551.
9. I. T. Kay and P. J. Taylor, *J. Chem. Soc.* (C), 1968, 2556.
10. V. L. Gein, S. G. Pitirimova, O. V. Vinokurova, Yu. S. Andreichikov, A. V. Komkov, V. S. Bogdanov, and V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1475 [*Russ. Chem. Bull.*, 1994, **43**, 1398 (Engl. Transl.)].
11. V. A. Dorokhov and M. A. Prezent, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 1455 [*Russ. Chem. Bull.*, 1992, **41**, 1139 (Engl. Transl.)].
12. H. D. Hinton and J. A. Nieuwland, *J. Am. Chem. Soc.*, 1932, **54**, 2017.

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