Synthesis of Novel Aminothiopyran Dicarboxylates

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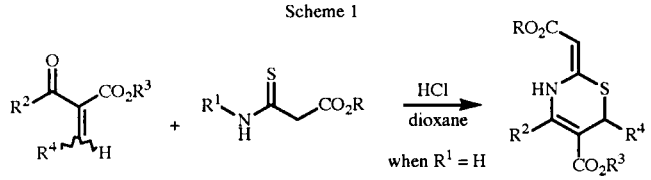
Received November 18, 1999

A one step synthesis of previously unknown aminothiopyran dicarboxylates from readily available starting materials is described. The yields range from 33-74%.

J. Heterocyclic Chem., **37**, 1583 (2000).

During the course of a project aimed at the discovery of novel compounds as crop protection agents, we needed to prepare a series of *N*-substituted 2,3-dihydro-6*H*-1,3-thiazine-5-carboxylates (**1**). We were unaware of any syntheses of compounds of this type, but the synthesis of the corresponding *N*-unsubstituted derivatives of this type from the condensation of α,β-unsaturated ketoesters (**2**) and alkoxycarbonylthioacetamides (**3**) has been described in the literature [1,2].

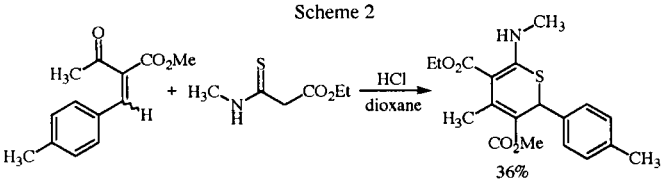
Scheme 1



2 **3** **1**

Condensation of **4** [3] with *N*-substituted alkoxycarbonylthioacetamide **5** [4] using anhydrous hydrogen chloride in dioxane provided a product whose ^{1}H NMR spectrum did not fit the expected dihydrothiazine. Particularly noteworthy was the presence of a broad singlet at δ 9.23, which exchanged with D_2O in the presence of potassium carbonate. These data were consistent with a 2-methylamino-2*H*-thiopyran-3,5-dicarboxylate (**6**). Confirmation of this structural assignment was obtained by single crystal X-ray analysis of an analog (*vide infra*). We could find no trace of the dihydrothiazine in the reaction mixture.

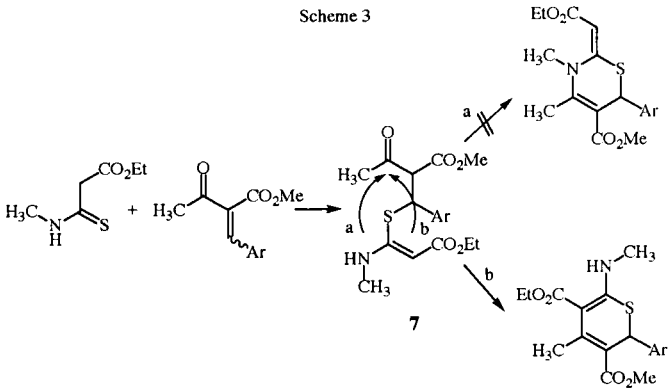
Scheme 2



4 **5** **6**

Examination of the intermediate along the reaction path provides an explanation of this result (Scheme 3). The sulfur atom of the thioamide most likely undergoes a conjugate addition reaction to provide intermediate **7**. This intermediate has two pathways available to it. The nitrogen atom can close on the ketone carbonyl (pathway a) to afford the dihydrothiazine or alternatively the enamine carbon can close yielding the thiopyran (pathway b). *N*-Substitution increases the steric hindrance of pathway a and funnels the reaction to pathway b.

Scheme 3



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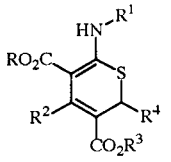
Since these thiopyran-3,5-dicarboxylates appear to be novel substances we decided to explore the scope of the reaction. The results are summarized in Table 1. The reaction appears to be tolerant to structural variation without much effect on the yield. When the substituent on the nitrogen atom was changed to phenyl (entry 2) the thiopyran was obtained in 75% yield. The substituents at the 4 and 6-position could also be modified (entries 3, 4 and 5).

Table 1



Entry	Compound	R	R^1	R^2	R^3	R^4	Yield (%)
1	**6**	Et	Me	Me	Me	*p*-CH_3Ph	36
2	**8**	Me	Ph	Me	Me	*p*-CH_3Ph	74
3	**9**	Me	Ph	Me	Me	Me	45
4	**10**	Me	Ph	CF_3	Et	Ph	41
5	**11**	Me	Ph	Et	Me	Ph	33

An X-ray structure determination was performed on compound **10**. This analysis confirmed the structure as an aminothiopyran dicarboxylate (Figure 1).

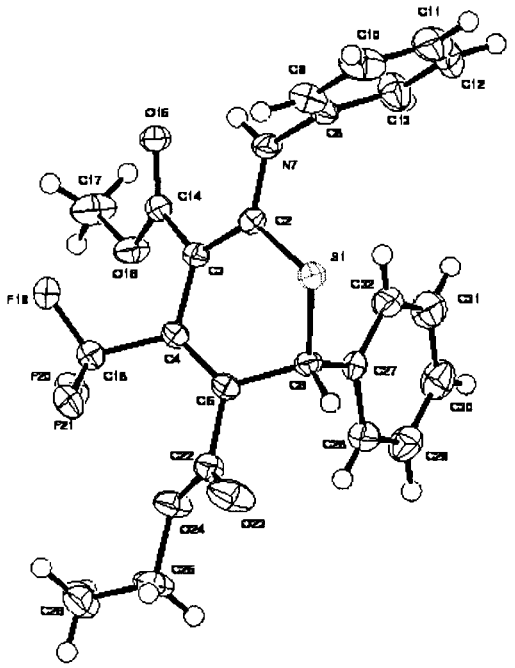
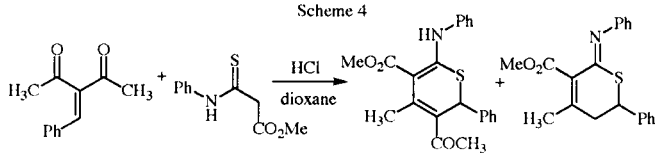


Figure 1. Ortep view of compound **10**.

When an α,β-unsaturated diketone was employed in the reaction, two products were isolated. The major product **12** (22% yield) was the expected ketone. Also isolated was a product lacking the acetyl group (**13**) in 13% yield. This compound most likely arises from a vinylogous retro-Claisen condensation reaction of compound **12**. Compound **13** was also isolated when the *t*-butyl ester was employed.

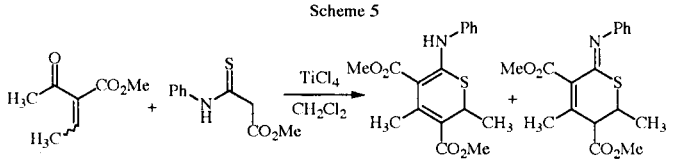
Scheme 4



12 22% **13** 13%

We also briefly examined other catalysts for the reaction. When 1.1 equivalents of titanium tetrachloride in dichloromethane was employed the aminothiopyran dicarboxylate was obtained in 22% yield along with the tautomeric product (**14**) in 29% yield. Zinc chloride was not effective in promoting the reaction.

Scheme 5



9 22% **14** 29%

In conclusion we have developed a flexible route to aminothiopyran dicarboxylates which affords quick access to these previously unattainable molecules.

Table 2. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for Compound **10**

	X	Y	Z	U_{eq}[a]
S(1)	4176(1)	2145(1)	5440(1)	26(1)
F(19)	344(1)	4422(1)	8829(1)	40(1)
F(20)	-261(1)	2523(1)	9698(1)	38(1)
F(21)	1828(1)	3339(1)	9543(1)	37(1)
O(15)	-476(1)	4323(1)	6233(1)	29(1)
O(16)	-1214(1)	2940(1)	7768(1)	33(1)
O(23)	4571(1)	785(2)	8520(1)	49(1)
O(24)	2174(1)	535(1)	9548(1)	35(1)
N(7)	2299(2)	3688(2)	4784(1)	27(1)
C(2)	2441(2)	3025(2)	5707(1)	23(1)
C(3)	1327(2)	2982(2)	6789(1)	23(1)
C(4)	1646(2)	2428(2)	7802(1)	23(1)
C(5)	2737(2)	1456(2)	7690(1)	24(1)
C(6)	3588(2)	820(2)	6502(1)	24(1)
C(8)	3474(2)	3737(2)	3678(1)	25(1)
C(9)	4562(2)	4643(2)	3527(2)	34(1)
C(10)	5681(2)	4712(2)	2458(2)	46(1)
C(11)	5720(2)	3884(3)	1550(2)	50(1)
C(12)	4637(3)	2981(2)	1696(2)	53(1)
C(13)	3496(2)	2899(2)	2766(2)	41(1)
C(14)	-168(2)	3512(2)	6890(1)	24(1)
C(17)	-2737(2)	3404(2)	7942(2)	46(1)
C(18)	874(2)	3160(2)	8972(2)	29(1)
C(22)	3274(2)	921(2)	8633(2)	27(1)
C(25)	2546(2)	-19(2)	10529(2)	43(1)
C(26)	1308(3)	382(2)	11610(2)	48(1)
C(27)	2750(2)	-306(2)	6194(2)	25(1)
C(28)	2526(2)	-1456(2)	6883(2)	32(1)
C(29)	1779(2)	-2527(2)	6664(2)	40(1)
C(30)	1242(2)	-2462(2)	5747(2)	43(1)
C(31)	1458(3)	-1327(2)	5060(2)	46(1)
C(32)	2216(2)	-250(2)	5274(2)	35(1)

[a] U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points (pyrex capillary) are uncorrected. NMR spectra were measured in deuterochloroform solution. Chemical shift values are expressed in ppm downfield from internal chlorotrimethylsilane. ^{19}F NMR spectra are expressed in ppm relative to internal $CFCl_3$. *J* values are in hertz. Medium pressure liquid chromatography (MPLC) was performed using an ISCO CombiFlash™ SG 100 System employing silica gel columns. Mass spectra were measured on a VG Fisons Quattro II spectrometer using atmospheric pressure chemical ionization (APCI +/-).

General Procedure for the Reaction of α,β-Unsaturated Ketoesters (**2**) and Alkoxycarbonylthioacetamides (**3**).

A solution of the α,β-unsaturated ketoester and the alkoxycarbonylthioacetamide in dioxane (one equivalent each, *ca.* 0.3 *M*) was cooled to 0°. Hydrogen chloride gas was bubbled through the solution for 5 minutes. The reaction mixture was allowed to

Table 3. Bond Lengths [Å] and Angles [deg] for Compound **10**

S(1)-C(2)	1.7573(16)	C(2)-C(3)-C(14)	117.95(14)
S(1)-C(6)	1.8089(17)	C(2)-C(3)-C(4)	120.94(14)
F(19)-C(18)	1.347(2)	C(14)-C(3)-C(4)	121.11(14)
F(20)-C(18)	1.335(2)	C(5)-C(4)-C(3)	121.96(15)
F(21)-C(18)	1.346(2)	C(5)-C(4)-C(18)	120.08(15)
O(15)-C(14)	1.224(2)	C(3)-C(4)-C(18)	117.18(14)
O(16)-C(14)	1.342(2)	C(4)-C(5)-C(22)	126.86(15)
O(16)-C(17)	1.449(2)	C(4)-C(5)-C(6)	119.70(15)
O(23)-C(22)	1.203(2)	C(22)-C(5)-C(6)	113.42(13)
O(24)-C(22)	1.322(2)	C(5)-C(6)-C(27)	111.75(13)
O(24)-C(25)	1.459(2)	C(5)-C(6)-S(1)	109.74(11)
N(7)-C(2)	1.344(2)	C(27)-C(6)-S(1)	116.19(12)
N(7)-C(8)	1.436(2)	C(9)-C(8)-C(13)	120.16(17)
C(2)-C(3)	1.389(2)	C(9)-C(8)-N(7)	119.51(16)
C(3)-C(14)	1.461(2)	C(13)-C(8)-N(7)	120.32(16)
C(3)-C(4)	1.470(2)	C(8)-C(9)-C(10)	119.78(19)
C(4)-C(5)	1.347(2)	C(11)-C(10)-C(9)	120.6(2)
C(4)-C(18)	1.525(2)	C(10)-C(11)-C(12)	119.8(2)
C(5)-C(22)	1.497(2)	C(11)-C(12)-C(13)	120.5(2)
C(5)-C(6)	1.516(2)	C(8)-C(13)-C(12)	119.16(19)
C(6)-C(27)	1.525(2)	O(15)-C(14)-O(16)	122.37(14)
C(8)-C(9)	1.376(2)	O(15)-C(14)-C(3)	125.80(15)
C(8)-C(13)	1.381(3)	O(16)-C(14)-C(3)	111.73(14)
C(9)-C(10)	1.383(3)	F(20)-C(18)-F(21)	106.65(14)
C(10)-C(11)	1.366(3)	F(20)-C(18)-F(19)	106.93(14)
C(11)-C(12)	1.370(3)	F(21)-C(18)-F(19)	105.41(14)
C(12)-C(13)	1.394(3)	F(20)-C(18)-C(4)	114.61(14)
C(25)-C(26)	1.478(3)	F(21)-C(18)-C(4)	111.45(14)
C(27)-C(32)	1.386(2)	F(19)-C(18)-C(4)	111.24(14)
C(27)-C(28)	1.389(2)	O(23)-C(22)-O(24)	124.89(16)
C(28)-C(29)	1.383(3)	O(23)-C(22)-C(5)	122.84(16)
C(29)-C(30)	1.385(3)	O(24)-C(22)-C(5)	112.10(14)
C(30)-C(31)	1.377(3)	O(24)-C(25)-C(26)	107.95(17)
C(31)-C(32)	1.392(3)	C(32)-C(27)-C(28)	118.80(16)
C(2)-S(1)-C(6)	98.45(8)	C(32)-C(27)-C(6)	124.01(16)
C(14)-O(16)-C(17)	115.90(13)	C(28)-C(27)-C(6)	117.19(15)
C(22)-O(24)-C(25)	117.75(14)	C(29)-C(28)-C(27)	121.04(18)
C(2)-N(7)-C(8)	123.70(14)	C(28)-C(29)-C(30)	119.89(19)
N(7)-C(2)-C(3)	124.62(15)	C(31)-C(30)-C(29)	119.51(18)
N(7)-C(2)-S(1)	114.46(12)	C(30)-C(31)-C(32)	120.73(19)
C(3)-C(2)-S(1)	120.90(12)	C(27)-C(32)-C(31)	120.03(19)

stand for 24–48 hours. The solvent was removed with a rotary evaporator. The residue was purified by MPLC using an ethyl acetate/hexane mixture as eluent.

5-Ethyl-3-methyl 4-Methyl-6-(methylamino)-2-(4-methylphenyl)-2*H*-thiopyran-3,5-dicarboxylate (**6**).

Mp 81-85°; ^{1}H nmr: δ 1.31 (t, 3H, *J* = 7.1), 2.29 (s, 3H), 2.46 (s, 3H), 2.93 (d, 3H, *J* = 5.1), 3.70 (s, 3H), 4.18 (m, 2H), 5.34 (s, 1H), 7.03 (d, 2H, *J* = 8.0), 7.18 (d, 2H, *J* = 8.0), 9.23 (br, 1H); ^{13}C nmr: δ (CH_3) 14.1, 20.9, 22.5, 31.9, 51.2, (CH_2) 59.4, (CH) 41.7, 127.6, 128.6, (C) 100.5, 111.3, 136.0, 136.7, 163.8, 166.9, 168.7; ir (thin film): 3249, 1704, 1645 cm^{-1}; ms: m/z APCI + 362.

HRMS Calcd. for $C_{19}H_{24}NO_4S$ (M+1): 362.1426. Found: 362.1426.

Dimethyl 4-Methyl-2-(4-methylphenyl)-6-(phenylamino)-2*H*-thiopyran-3,5-dicarboxylate (**8**).

Oil; ^{1}H nmr: δ 2.29 (s, 3H), 2.49 (s, 3H), 3.71 (s, 3H), 3.79 (s, 3H), 5.31 (s, 1H), 7.00 (d, 2H, *J* = 7.8), 7.03 (d, 2H, *J* = 8.4), 7.14 (d, 2H, *J* = 8.4), 7.20 (d, 1H, *J* = 7.2), 7.30 (dd, 2H, *J* = 8.4, 7.2), 10.93 (brs, 1H); ^{13}C nmr: δ (CH_3) 21.0, 22.6, 51.2, 51.5, (CH) 42.5, 114.2, 125.1, 126.0, 127.6, 128.5, 128.7, (C) 102.9, 135.5, 136.9, 139.0, 150.2, 160.4, 166.7, 169.1; ir (KBr): 2946, 1706, 1653 cm^{-1}; ms: m/z APCI+ 410.

Anal. Calcd. for $C_{23}H_{23}NO_4S$: C, 67.46; H, 5.66; N, 3.42. Found: C, 67.41; H, 5.68; N, 3.25.

Dimethyl 2,4-Dimethyl-6-(phenylamino)-2*H*-thiopyran-3,5-dicarboxylate (**9**).

Oil; ^{1}H nmr: δ 1.31 (d, 3H, *J* = 6.9), 2.35 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 4.20 (q, 1H, *J* = 6.9), 7.17 (d, 2H, *J* = 7.5), 7.22 (d, 1H, *J* = 7.3), 7.37 (apparent t, 2H, *J* = 7.4), 11.29 (brs, 1H); ^{13}C nmr: δ (CH_3) 18.7, 22.3, 51.2, 51.4, (CH) 35.5, 125.1, 128.8, 126.1, (C) 100.8, 117.0, 138.9, 147.4, 160.0, 166.6, 169.4; ir (thin film) 2948, 1705, 1649 cm^{-1}; ms: m/z APCI+ 334.

Anal. Calcd. for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.64; H, 5.76; N, 4.06.

3-Ethyl-5-methyl 2-Phenyl-6-(phenylamino)-4-(trifluoromethyl)-2*H*-thiopyran-3,5-dicarboxylate (**10**).

Mp 82-84°; ^{1}H nmr: δ 1.31 (t, 3H, *J* = 7.2), 3.78 (s, 3H), 4.25 (m, 2H), 5.19 (s, 1H), 6.98 (d, 2H, *J* = 7.4), 7.28 (m, 8H), 10.98 (brs, 1H); ^{13}C nmr: δ (CH_3) 13.7, 51.4, (CH_2) 62.2, (CH) 44.6, 95.4, 125.3, 126.5, 127.5, 128.0, 128.5, 128.9, (C) 123.0 ($J_{C,F}$ = 276), 125.4, 134.7 ($J_{C,F}$ = 32), 135.6, 138.8, 159.6, 166.4, 168.1; ^{19}F nmr: δ −56.7; ir (KBr) 3214, 1718, 1664 cm^{-1}; ms: m/z APCI+ 464.

Anal. Calcd. for $C_{23}H_{20}F_3NO_4S$: C, 59.60; H, 4.35; N, 3.02. Found: C, 59.87; H, 4.34; N, 2.80.

Dimethyl 4-Ethyl-2-phenyl-6-(phenylamino)-2*H*-thiopyran-3,5-dicarboxylate (**11**).

Oil; ^{1}H nmr: δ 1.18 (t, 3H, *J* = 9.3), 3.02 (q, 2H, *J* = 9.3), 3.72 (s, 3H), 3.78 (s, 3H), 5.26 (s, 1H), 6.99 (d, 2H, *J* = 7.9), 7.28 (m, 8H), 10.86 (brs, 1H); ir (thin film) 2948, 1705, 1654 cm^{-1}; ms: m/z APCI+ 410.

Anal. Calcd. for $C_{23}H_{23}NO_4S$: C, 67.46; H, 5.66; N, 3.42. Found: C, 67.20; H, 5.41; N, 3.02.

Methyl 3-Acetyl-4-methyl-2-phenyl-6-(phenylamino)-2*H*-thiopyran-5-carboxylate (**12**).

Mp 88-91°; ^{1}H nmr: δ 2.38 (s, 3H), 2.44 (s, 3H), 3.80 (s, 3H), 5.28 (s, 1H), 6.99 (d, 2H, *J* = 7.9), 7.28 (m, 8H), 10.96 (brs, 1H); ^{13}C nmr: δ (CH_3) 22.5, 31.1, 51.2, (CH) 43.0, 125.0, 127.6, 128.0, 126.0, 127.3, 128.7, (C) 102.5, 124.7, 138.0, 138.3, 147.0, 159.4, 168.9, 197.7; ir (KBr) 1659, 1629 cm^{-1}; ms: m/z APCI+ 380.

HRMS Calcd. for $C_{22}H_{21}NO_3S$ (M+1): 380.1320. Found: 380.1320.

Methyl 5,6-Dihydro-4-methyl-6-phenyl-2-(phenylimino)-2*H*-thiopyran-3-carboxylate (**13**).

Mp 98-101°; ^{1}H nmr: δ 2.03 (s, 3H), 2.67 (dd, 1H, *J* = 17.2, 3.2), 3.01 (dd, 1H, *J* = 17.2, 12.5), 3.89 (s, 3H), 4.42 (dd, 1H, *J* = 12.5, 3.2), 6.88 (d, 2H, *J* = 8.3), 7.05 (apparent t, 1H, *J* = 7.3), 7.30 (m, 7H); ^{13}C nmr: δ (CH_3) 23.0, 52.4, (CH_2) 38.8, (CH) 44.7, 121.1, 124.4, 127.6, 128.3, 128.7, 128.8, (C) 131.2, 138.7, 146.0, 149.9, 157.7, 168.4; ir (KBr) 1731, 1579 cm^{-1}; ms: m/z APCI+ 338.

HRMS Calcd. for $C_{20}H_{20}NO_2S$ (M+1): 338.1215. Found: 338.1203.

Dimethyl 5,6-Dihydro-4,6-dimethyl-2-(phenylimino)-2*H*-thiopyran-3,5-dicarboxylate (**14**).

Mp 98-101°; ^{1}H nmr: δ 1.24 (d, 3H, *J* = 7.1), 2.06 (s, 3H), 3.46 (dq, 1H, *J* = 8.3, 2.1), 3.75 (s, 3H), 3.78 (s, 3H), 4.17 (d, 1H, *J* = 2.1), 7.00 (d, 1H, *J* = 7.3), 7.44 (d, 1H, *J* = 7.9), 7.48 (m, 3H); ^{13}C nmr: δ (CH_3) 18.0, 18.6, 51.6, 52.6, (CH) 30.3, 62.3, 126.9, 128.5, 129.3, 129.4, 129.6, (C) 115.4, 141.8, 146.5, 166.9, 171.2, 197.6; ir (KBr): 1729, 1702 cm^{-1}; ms: m/z APCI+ 334.

Anal. Calcd. for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.10; H, 5.74; N, 3.88.

Acknowledgements.

Helpful discussions with Dr. Stephen K. Gee are acknowledged. Mr. John Groce and Mr. Michael Kline are thanked for obtaining the ^{13}C nmr spectra. Dr. Michael Haas, Dr. Bill Herron and Mr. Kent Woudstra are thanked for obtaining the high resolution mass spectra. Mr. Will Marshall is thanked for obtaining the X-ray crystal structure.

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[2] *N*-Unsubstituted 2,3-dihydro-6*H*-1,3-thiazine-5-carboxylates have also been prepared by cycloaddition reactions: F. Reliquet, A. Reliquet and J. C. Meslin, *Phosphorous, Sulfur Relat. Elem.*, **89**, 63, (1994); J. C. Meslin, F. Reliquet, A. Reliquet and F. Sharras, *Sulfur Lett.*, **3**, 139, (1985) and references cited therein.

[3] α,β-Unsaturated ketoesters were prepared according to the method described in reference [1].

[4] Alkoxycarbonylthioacetamides were prepared from alkyl (aryl) isothiocyanates and β-ketoesters according to G. Barnikow, H. Kunzek and D. Richter, *Liebigs Ann. Chem.*, **695**, 49 (1966).