182. Novel Access to Furan-3-thiols and Derivatives, Impact Meat-Flavor Compounds[1])

by **Ulrich A. Huber*** and **Desirée Bergamin**[2])

Givaudan-Roure Research Ltd, Überlandstr. 138, CH–8600 Dübendorf

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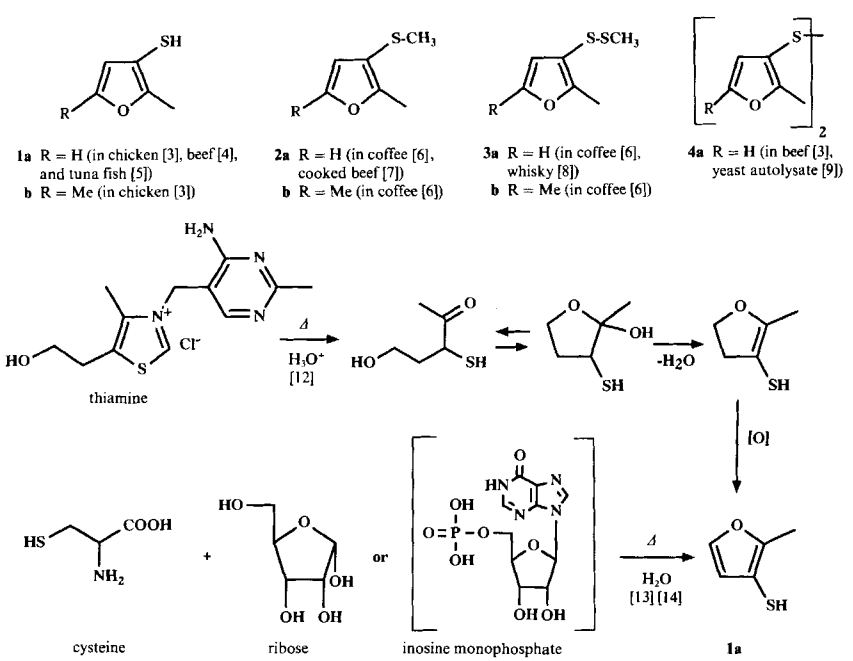
A versatile process for the preparation of a number of 3-thio-substituted furans **1**–**4** is described. These products have very low odor thresholds and are thus potent flavor compounds. Fur-3-yl thiocyanates **10a, b** as well as other S-containing analogues (**2b**, **7a**, **b**, and **8**) were prepared by a *Michael*-type addition of thiocyanic acid, thioacetic acid, alkanethiols, and sodium thiosulfate to alkynones **6** or **15**, followed by cyclization (*Schemes 3* and *4*). The thiocyanates **10a, b** were converted to mixed disulfides **3**, symmetric disulfides **4**, thioethers **2**, and thiols **1**, using 'hard' or 'soft' nucleophiles or reducing agents, respectively (*Scheme 6*).

Introduction. – A number of 3-thio-substituted furan derivatives, including thiols **1**, thioethers **2**, and disulfides **3** and **4** (*Scheme 1*), were identified in food and in model reaction mixtures of the cooking process [1–9]. Most of these compounds are strong

Scheme 1



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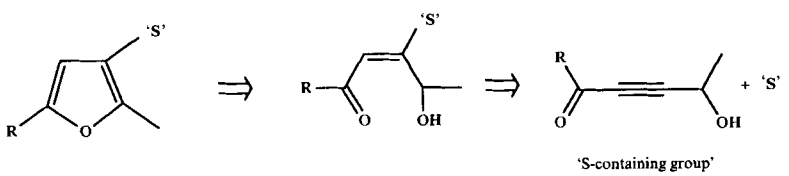
[2]) Current address: Essenpas 6, NL–6685 BJ Haalderen.

odorants and play an important role as naturally occurring flavor materials, their general odor type being known as so-called thiamine odor. *E.g.*, in 1969, in the course of a study of the thermolysis of thiamine (vitamin B_1), *Evers* [10] isolated bis(2-methylfur-3-yl) disulfide (**4a**), whose importance as one of the most active meat-flavor chemicals was only realized, when its threshold was measured in 1984. In addition, *van der Linde et al.* postulated the formation of 2-methylfuran-3-thiol (**1a**) in food by degradation of thiamine [12] (*Scheme 1*). Alternatively, this compound was shown to be generated in the *Maillard* reaction which may also occur during food preparation; accordingly, on heating cystein with sugars or sugar derivatives such as ribose [13] or inosine 5′-monophosphate [14], **1a** was formed in trace amounts.

Some synthetic accesses to **1a** [2] [15–17], **1b** [18] [19], **2b** [19], **3a** [20], **4a** and **4b** [2] have already been reported or disclosed in patents. We now report a versatile process for the preparation of various 3-thio-substituted furans **1–4**.

Results and Discussion. – Our concept is based on the introduction of the S-function before closure of the furan ring (see *Scheme 2*); a related reaction was described by *Obrecht* [21] for the preparation of 3-bromofurans.

Scheme 2



Accordingly, hex-3-yne-2,4-diol (**5**) was oxidized to hydroxy ketone **6** using a known procedure [22] (*Scheme 3*). Subsequent treatment with an alkanethiol RSH (R = Me, Bu) in Et_3N furnished, in a *Michael*-type addition [23], a (*E*/*Z*)-mixture of hydroxy-mercapto-enones. On acidification, (*E*)-isomer **A** afforded, after cyclization and dehydration, the thioether **2b** (R = Me) or **7a** (R = Bu) in good yield (see *Table 1*), the interconversion of the (*E*)- and (*Z*)-enones being rapid under the reaction conditions.

In a similar way, sodium thiosulfate reacted with **6** in aqueous solution at pH 5–6 to give sodium fur-3-yl thiosulfate **8** [24] (*Scheme 3*, *Table 1*). When **8** was then heated with thiourea [25], the symmetrical disulfide **4b** could be directly isolated by distillation. A drawback of this method is the contamination of **4b** with the corresponding trisulfide **9** (see *Exper. Part*).

Analogously, thiocyanic acid [26] or thioacetic acid [27] were employed as nucleophiles. Thus, treatment of **6** with dilute aqueous H_2SO_4 solution containing sodium thiocyanate gave the corresponding fur-3-yl thiocyanate **10b** and 1,3-oxathiolan-2-one **11**. Thiocyanate **10b** was separated by extraction into pentane. This reaction demonstrates the intermediacy of both the (*E*)- and (*Z*)-isomers **B** and **C**, the former giving rise to **10b**, and the latter to **11** *via* intramolecular addition of the OH group to C≡N followed by hydrolysis. The (*Z*)-configuration of **11** was confirmed by NOE experiments (see *Exper. Part*). The *Michael*-type addition of thioacetic acid to **6** yielded **7b** (*Scheme 3*, *Table 1*).

Scheme 3

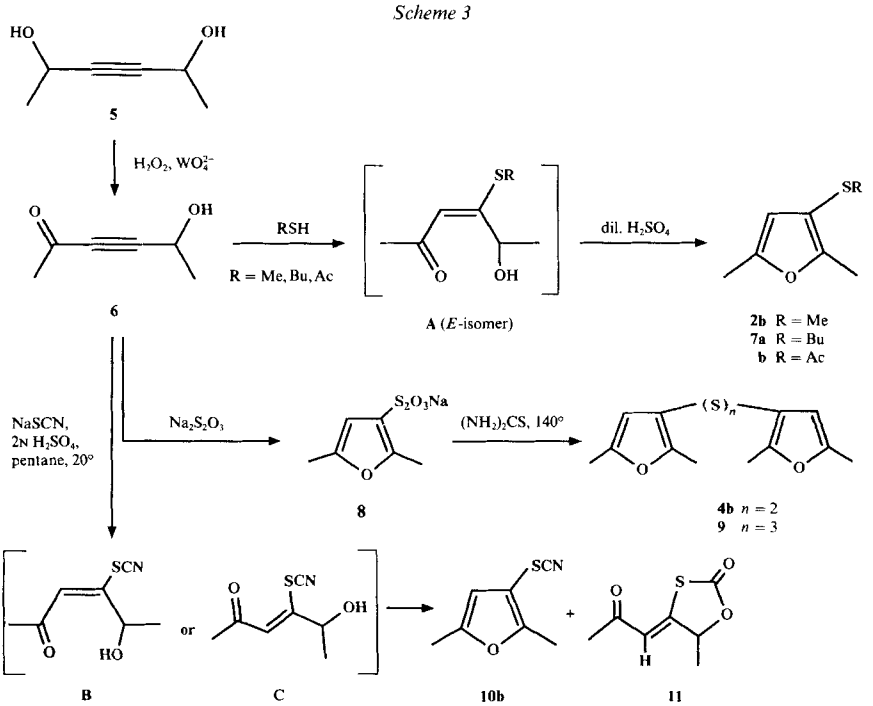
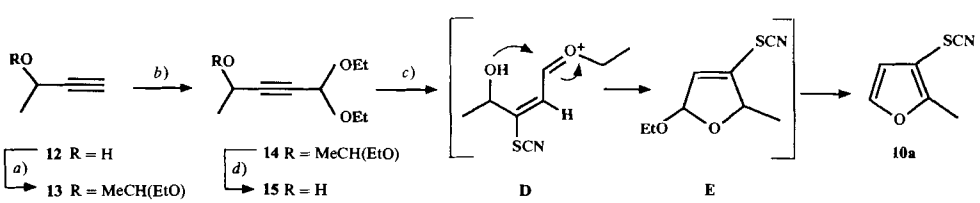


Table 1. Michael-*Like Additions of Different Sulfur Nucleophiles to Hydroxyhexynone* **6**

S-Nucleophile	Product	Reaction conditions	Yield (isolated) [%]
MeSH	**2b**	Et_3N, then 5N H_2SO_4	65
BuSH	**7a**	Et_3N, then 5N H_2SO_4	77
$Na_2S_2O_3$	**8**	H_2O, pH 5–6	42
NaSCN	**10b**	2N H_2SO_4	48
AcSH	**7b**	2N H_2SO_4	48

The monomethylfuryl thiocyanate homologue **10a** was prepared from but-1-yn-3-ol (**12**; *Scheme 4*). After protection (→ **13**), the *Grignard* salt was prepared and treated with diethyl phenyl orthoformate [21], which reacted more readily than trialkyl orthoformate, to give protected acetal **14**. Subsequent addition of thiocyanic acid to the deprotected acetal **15** and ring closure led to **10a** in 75% yield.

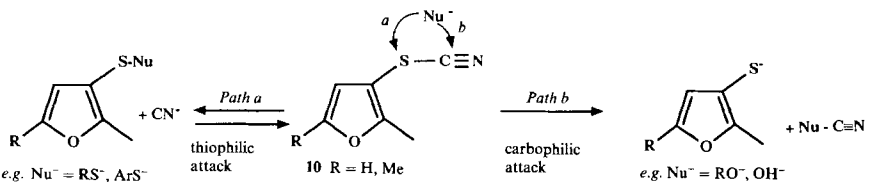
Scheme 4



a) EtOCH=CH_2, HCl; *b*) EtMgBr, then $PhOCH(OEt)_2$; *c*) NaSCN, 2N H_2SO_4, pentane, 20°; *d*) EtOH, conc. H_2SO_4, 20°.

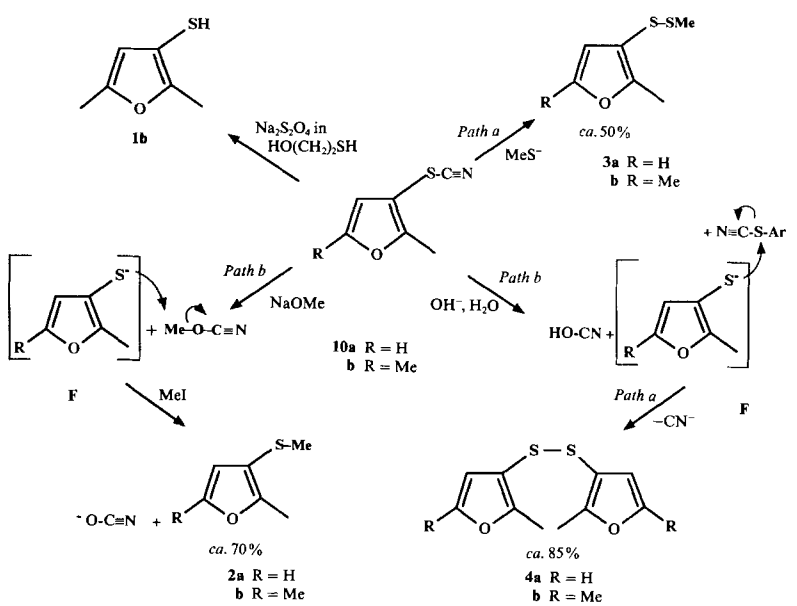
The further transformation of thiocyanates **10** to sulfides **2**, disulfides **3** or **4**, and thiols **1** critically depends on the nucleophiles (Nu^-) chosen, which may attack either at the S-atom (*Path a*) or the C-atom (*Path b*) of the thiocyanate group [28] (*Scheme 5*). The observed pathway may be rationalized according to the HSAB principle of *Pearson* [29]: Hard nucleophiles, such as alcoholates or OH^- ions, attack the C-atom in an irreversible manner to form alkyl cyanates by extrusion of a thiolate anion (*Path b*). Soft nucleophiles such as the thiolate anion attack mainly the S-atom to form disulfides and a cyanide anion (*Path a*).

Scheme 5



Thus, treatment of **10a, b** with sodium methanethiolate in MeOH afforded the mixed disulfides **3a, b** in *ca.* 50% yield, besides the symmetric difuryl disulfides **4a, b**, which could easily be separated by distillation (*Scheme 6*). In contrast, treatment of **10a, b** with aqueous NaOH solution yielded cyanic acid and furanthiolate **F** which reacted further with a second molecule of **10a, b** to give the symmetric disulfides **4a, b** by loss of a cyanide ion in *ca.* 85% yield [30]. Similarly, reaction of **10a, b** with NaOMe generated the methylating agent methyl cyanate and **F** which gave furyl methyl sulfides **2a, b**. This

Scheme 6



methylation was improved by the addition of MeI [31] (see *Exper. Part*). Finally, thiol **1b** was obtained by treating **10b** with the reducing agent sodium hyposulfite in 2-mercaptoethanol [32]. Alternatively, **1b** could be efficiently prepared from the corresponding disulfide **4b** by reduction with a trialkylphosphine [33].

Conclusion. – Substitution of furans in the 3- or 4-position is generally more difficult than substitution in the 2- or 5-position. In the present approach, this difficulty is circumvented by closing the furan ring after the introduction of a substituent to the prospective 3-position. A number of different S-containing substituents were successfully introduced (*Table 1*) and the obtained compounds then transformed to various natural products, such as **1**–**4** which are known to be intense flavor components. Their threshold concentrations in H_2O [2] [7] [11] and in the gas phase [34] [35] were determined by several authors, the latter being summarized in *Table 2*. Notably, *Buttery et al.* [11] determined a threshold concentration of $2 \cdot 10^{-8}$ µg/l of H_2O for **4a**, a value which is probably the lowest ever reported for a flavor chemical. In general, absolute threshold values determined by different authors vary considerably and, therefore, should be compared with the greatest caution. Regarding the thiols **1a** and **1b**, we have not yet succeeded in obtaining reliable threshold values because of their low stability and tendency to produce artifacts in high dilution. The instability of these products was detected by comparing their liquid and the gas-phase compositions during dilution [35] [36].

Table 2. *Olfactory Threshold Concentration in ng/l of Gas*

	Threshold concentration [ng/l] [34]	Threshold concentration [ng/l] [35][a])
1a	0.0025–0.01	
2a	7.6–30.4	200
3a	0.02–0.08	0.8
4a	0.0006–0.0024	0.02–0.057
2b		10.7–24.5
3b		0.57
4b		0.05–0.16

[a]) Determined by methods described in [36].

The significant difference in threshold concentrations for sulfides **2** and the much stronger disulfides **3** and **4** by a factor of *ca.* 1000 (see *Table 2*) leads us to believe that these latter compounds are partially reduced to the corresponding thiols **1** before reaching the olfactory receptor sites. Therefore, **1a** and **1b** exhibit probably the lowest threshold concentrations of flavor compounds[3]), together with, *e.g.* 3-hydroxy-4,5-dimethyl-2(5*H*)-furanone ($2 \cdot 10^{-4}$ ng/l air) [37] and *p*-menth-1-ene-8-thiol (10^{-3} ng/l air) [37].

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[3]) In food, the effective dosage is more relevant than threshold values. A medium dosage for **1a** or **1b** is 10 ppb, which means 10 g of **1** would be sufficient for 1000 t of food material.

Experimental Part

1. *General.* Solvents and reagents: *Fluka* (*puriss.* or *purum*), used without further purification, except for Et_2O and THF which were filtered through alumina *B* (act. I; *ICN Biomedicals GmbH*) for reactions sensitive to moisture. All reactions were carried out under an inert atmosphere (Ar or N_2). TLC: *Merck* precoated plates, silica gel *60* F_{254}, layer thickness 0.25 mm; detection by dipping the plates into a vanillin soln. (8.35 g of vanillin, 7.5 ml of AcOH, 12.5 ml of conc. H_2SO_4, 325 ml of abs. EtOH) followed by drying with hot air. Column chromatography: at *ca.* 1.5 atm; *Merck* silica gel *60* (230–400 mesh). GC: *Carlo-Erba-GI* instrument; glass-packed columns (3 m × 3 mm) containing *Carbowax 20M* (3% on *Chromosorb G AW DMCS*, 80–200 mesh) or *OV-1* (5% on *Gaschrom Q*, 80–100 mesh), He as carrier gas (3.2 atm); isothermal, sample volume 1 µl. M.p.: measured in open capillary tubes; uncorrected. UV Spectra: *Beckman-25* spectrophotometer; λ_{max} (ε) in nm. IR Spectra: *Perkin-Elmer-681* spectrophotometer; in cm^{-1}. ^{1}H-NMR Spectra (200 MHz): *Bruker-AC-200* spectrometer; $CDCl_3$ solns., if not quoted otherwise, with Me_4Si as internal standard; chemical shifts δ in ppm, coupling constants J in Hz. MS: *Varian-MAT-CH-5* instrument; electron energy 70 eV; *m/z* (rel. peak intensities in % of the base peak (= 100%)).

2. *2,5-Dimethyl-3-(methylthio)furan* (**2b**) *from* **6**. To a soln. of 5 g (0.045 mol) of 5-hydroxyhex-3-yn-2-one [22] (**6**) in 45 ml of *t*-BuOMe, 4.5 g (0.045 mol) of Et_3N and *ca.* 3 ml (0.054 mol) of MeSH in 5 ml of *t*-BuOMe were added simultaneously from two dropping funnels under ice cooling. After stirring for 90 min, a new product was observed by TLC. Then, 50 ml of 5N aq. H_2SO_4 were slowly added. Stirring was continued for 1 h. The pink aq. phase was extracted with *t*-BuOMe (2 × 20 ml) and the combined org. phase washed with H_2O, sat. $NaHCO_3$, and sat. NaCl soln., dried ($MgSO_4$), and fractionated by distillation (b.p. 58°/16 Torr): 4.1 g (65%) of clear oil. TLC: R_f (hexane/Et_2O 3:2) 0.51. GC (*Carbowax 20M*, 150° isothermal): t_R 4 min. IR (film): 1610*m*, 1570*s*, 1430*s*, 1220*s*. ^{1}H-NMR: 2.23 (*s*, Me); 2.24 (*s*, MeS); 2.28 (*s*, Me); 5.94 (*s*, H–C(4)). MS: 142 (100, M^+), 127 (54, $[M - Me]^+$), 99 (36).

3. *Sodium 2,5-Dimethylfur-3-yl Thiosulfate* (**8**). To a stirred soln. of 30 g (0.16 mol) of **6** [22] (of 60% purity) in 80 ml of H_2O, 52 g (0.2 mol) of $Na_2S_2O_3 \cdot 5\,H_2O$ in 120 ml of H_2O were slowly added. The rising pH was kept at 5–6 by adding AcOH. After 4 h stirring, the mixture was washed with Et_2O (3 × 200 ml). The Et_2O phase contained, among other compounds, 1.8 g (9%) of **4b** (see below). The aq. phase was concentrated partially *in vacuo* and crystallized at 8°. The crystalline material was sucked off and dried (high vacuum): 15.5 g (42%) of **8**. IR (KBr): 3470*s*, 1610*m*, 1565*m*, 1207*s* (br.), 1036*s*. ^{1}H-NMR (D_2O): 2.26 (*s*, Me); 2.34 (*s*, Me); 6.16 (*s*, H–C(4)).

4. *3,3'-Dithio- and 3,3'-Trithiobis(2,5-dimethylfuran)* (**4b** and **9**, resp.) *from* **8**. A mixture of 0.5 g (0.0022 mol) of **8** and 0.5 g (0.0066 mol) of thiourea was ground with a pistle and heated in a 'Kugelrohr' apparatus to 140°/0.04 Torr. The yellow liquid distillate was dissolved in pentane, the thiourea crystals were removed, and the liquid was evaporated: 0.23 g (82%) of **4b** (see below) containing 25% of **9**. **9**: ^{1}H-NMR: 2.24 (*s*, 2 Me); 2.37 (*s*, 2 Me); 5.99 (*s*, H–C(4), H–C(4')). MS: 286 ($M^{+\cdot}$).

5. *S-(2,5-Dimethylfur-3-yl) Thioacetate* (**7b**, R = Ac). To a stirred mixture of 3.8 g (0.05 mol) of AcSH in 50 ml of CH_2Cl_2 and 50 ml of 2N aq. H_2SO_4 were slowly added 2.8 g (0.025 mol) of **6** [22] in 20 ml of CH_2Cl_2 (GC monitoring). Then further 1.9 g (0.025 mol) of AcSH were added. After refluxing for 2 h, the aq. phase was separated and extracted with CH_2Cl_2 (2 × 150 ml). The combined org. phase was washed with H_2O (2 × 150 ml) and brine (100 ml), dried ($MgSO_4$), and evaporated: 2.9 g of orange oil. Bulb-to-bulb distillation (100°/0.03 Torr) gave 1.96 g (48%) of **7b**. GC (*Carbowax 20M*, 200 isothermal): t_R 2.7 min. IR (film): 1710*s*, 1610*w*, 1580*m*, 1430*m*, 1380*w*, 1350*m*, 1345*w*, 1230*m*. ^{1}H-NMR: 2.21 (*s*, Me); 2.23 (*s*, Me); 2.38 (*s*, Me); 5.90 (*s*, H–C(4)). MS: 170 (20, M^+), 128 (72), 127 (23), 113 (9), 95 (25), 85 (13), 43 (100).

6. *2,5-Dimethylfur-3-yl Thiocyanate* (**10b**) *and (Z)-4-(Acetylmethylidene)-5-methyl-1,3-oxathiolan-2-one* (**11**). To a mixture of 115 g (1.4 mol) of sodium thiocyanate in 1300 ml of 2N aq. H_2SO_4 and 1300 ml of pentane under Ar and vigorous stirring was slowly added 145 g (1.29 mol) of **6** [22] (GC monitoring). After 2 h, the aq. phase was extracted with pentane (2 × 1000 ml) and the combined pentane phase washed with 250 ml of aq. NaCl soln., dried, and evaporated: 115 g (58%) of crude, brown **10b**. Distillation (b.p. 53°/10 Torr) gave 95 g (48%) of yellow liquid. GC (*Carbowax 20M*, 200° isothermal): t_R 3.8 min. IR (film): 2160*s*, 1612*m*, 1580*s*, 1443*m* (br.), 1388*m*, 1340*m*, 1328*s*, 1220*m*. ^{1}H-NMR: 2.26 (*s*, Me); 2.37 (*s*, Me); 6.07 (*s*, 1 H). MS: 153 (61, $M^{+\cdot}$), 126 (100, $[M - HCN]^+$), 110 (8), 84 (19).

The aq. phase was filtered to separate polymeric brown material. After 2 d, white crystals were formed which were filtered off and dried (high vacuum): 9.2 g (4.3%) of **11**. M.p. 84–85°. UV (EtOH): 280 (10686). IR ($CHCl_3$): 2400*w*, 1748*s* (br.), 1680*s*, 1577*s*. ^{1}H-NMR: 1.66 (*d*, *J* = 6.5, Me); 2.34 (*s*, Me); 5.47 (*qd*, *J* = 6.5, 2.5, H–C(5)); 6.46 (*d*, *J* = 2.5, 1 H; NOE: 13% on irrad. at 1.66). MS: 172 (100, $M^{+\cdot}$), 128 (44, $[M - CO_2]^+$), 113 (45), 95 (41), 85 (71), 69 (44).

7. *2-Methylfur-3-yl Thiocyanate* (**10a**). 7.1. *But-1-yn-3-yl 1-Ethoxyethyl Ether* (**13**). To a soln. of 80 g (1.1 mol) of ethyl vinyl ether and 2 drops of conc. HCl soln., 70.6 g (1 mol) of but-3-yn-2-ol (**12**; freshly destilled at 106° over $MgSO_4$) was added during 1 h while cooling in an ice-bath. After 1 additional h, the mixture was washed successively with aq. $NaHCO_3$ soln. (2 × 150 ml) and aq. NaCl soln. (100 ml), dried ($MgSO_4$), and evaporated: 119 g (83%) of **13**. Clear liquid. IR ($CHCl_3$): 3400*s*, (sharp), 1440*m*, 1385*m*, 1370*m*. ^{1}H-NMR (2 diastereoisomers 1:1): 1.21 (*t*, *J* = 7.5, Me); 1.35, 1.36 (2*d*, *J* = 6, Me); 1.45, 1.46 (2*d*, *J* = 6, Me); 2.39, 2.41 (2*d*, *J* = 2, H–C(1)); 3.4–3.84 (*m*, 2 H); 4.35, 4.50 (2*qd*, *J* = 6.2, H–C(3)); 4.86, 4.97 (2*q*, *J* = 6, 1 H).

7.2. *4-(1-Ethoxyethoxy)pent-2-ynal Diethyl Acetal* (**14**). To 18.4 g (0.76 mol) of Mg turnings, a soln. of 88.1 g (0.8 mol) of EtBr in 550 ml of Et_2O was slowly added in a predried reaction flask. After 1 h stirring at 40°, the *Grignard* reagent was treated with a soln. of 97.6 g (0.63 mol) of **13** in 300 ml of Et_2O and stirred for 90 min at 40°. Then a soln. of 123.9 g (0.63 mol) of diethyl phenyl orthoformate [38] in 150 ml of Et_2O was added within 45 min. This mixture was stirred for 18 h at r.t. and added to 600 ml of sat. aq. NH_4Cl soln. The H_2O phase was extracted with Et_2O (2 × 750 ml) and the combined Et_2O phase washed successively with 0.5N NaOH (5 × 350 ml) and sat. NaCl soln. (300 ml), dried ($MgSO_4$), and evaporated: 133 g (86%) of **14**. Yellow liquid. IR ($CHCl_3$): 1440*m*, 1370*m*, 1325*m*, 1250*s* (br.). ^{1}H-NMR (2 diastereoisomers 1:1): 1.15–1.28 (*m*, 3 Me); 1.33, 1.34 (2*d*, *J* = 5, Me); 1.45, 1.46 (2*d*, *J* = 6, Me); 3.4–3.85 (*m*, 6 H); 4.4, 4.56 (2*qd*, *J* = 6, 1.5, H–C(4)); 4.84, 4.94 (2*q*, *J* = 5, 1 H); 5.30 (*s*, H–C(1)). MS: 243 (1, $[M - H]^+$), 229 (3), 199 (5), 171 (4), 155 (85), 127 (28), 99 (67), 81 (74), 73 (100).

7.3. *4-Hydroxypent-2-ynal Diethyl Acetal* (**15**). A soln. of 133 g (0.54 mol) of **14** in 600 ml of EtOH was treated with 10 drops of conc. H_2SO_4 and stirred for 1 h. Then 0.2 g of dry Na_2CO_3 were added, and the mixture was evaporated: 85 g (92%) of crude product. Distillation over a 5-cm *Widmer* column (84°/0.15 Torr) gave 71 g (76%) of pure **15**. TLC (hexane/Et_2O 1:1): R_f 0.31. GC (*Carbowax 20M*, 200° isothermal): t_R 6.2 min. IR ($CHCl_3$): 3600*m*, 3420*m* (br.), 2240*w*, 1440*m*. ^{1}H-NMR: 1.24 (*t*, *J* = 7, 2 Me); 1.47 (*d*, *J* = 6, Me); 2.63 (*d*, *J* = 5, OH); 3.5–3.85 (*m*, 4 H); 4.59 (*qdd*, *J* = 6, 5, 1, H–C(4)); 5.30 (*d*, *J* = 1, H–C(1)). MS: 171 (2, $[M - H]^+$), 155 (3, $[M - OH]^+$), 127 (100), 99 (24), 81 (28), 71 (84).

7.4. *Thiocyanate* **10a**. To a mixture of 80.4 g (0.99 mol) of sodium thiocyanate in 1500 ml of 2N aq. H_2SO_4 and 1500 ml of pentane were slowly added 154 g (0.89 mol) of **15** with vigorous stirring. After 1 h, the aq. phase was extracted with pentane (2 × 1000 ml) and the combined pentane phases washed with 400 ml of sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated: 117 g (94%) of crude product. Distillation (b.p. 47°/0.075 Torr) gave 109 g (78%) of **10a**. GC (*Carbowax 20M*, 200° isothermal): t_R 3.1 min. IR ($CHCl_3$): 2165*s*, 1685*m*, 1590*m*, 1515*m*, 1260*s* (br.). ^{1}H-NMR: 2.44 (*s*, Me); 6.49 (*d*, *J* = 3, H–C(4)); 7.36 (*d*, *J* = 3, H–C(5)). MS: 139 (75, $M^{+\cdot}$), 112 (100), 84 (31), 69 (28).

8. *Methyl 2-Methylfur-3-yl Disulfide* (**3a**). To a stirred soln. of 4.3 g (0.061 mol) of NaSMe in 100 ml of H_2O were added 7.8 g (0.056 mol) of **10a** during 25 min. The turbid soln. was stirred for 90 min (GC monitoring). Then the mixture was extracted with pentane (3 × 150 ml) and the combined org. phase washed with brine (100 ml), dried ($MgSO_4$), and evaporated: 8.6 g of crude product. Distillation (37°/36 Torr) gave 3.4 g (38%) of **3a**. GC (*OV-1*, 170° isothermal): t_R 2.2 min. IR (film): 1690*w*, 1580*s*, 1513*s*, 1430*m* (br.), 1380*s*, 1220*s*. ^{1}H-NMR: 2.40 (*s*, Me); 2.45 (*s*, Me); 6.44 (*d*, *J* = 2, H–C(4)); 7.28 (*d*, *J* = 2, H–C(5)). MS: 160 (100, $M^{+\cdot}$), 113 (70), 112 (48), 85 (14), 81 (8).

The following fraction of the distillation (77°/0.3 Torr) gave 2.4 g (37%) of pure **4a**. GC (above conditions): t_R 6.3 min. Spectra: identical to those described below.

9. *Methyl 2,5-Dimethylfur-3-yl Disulfide* (**3b**). According to *Exper. 8*, 10 g (0.065 mol) of **10b** were treated with NaSMe: 10.7 g of a red liquid. Distillation (54°/0.75 Torr) gave 5.5 g (49%) of pure **3b**. GC (*OV-1*, 170° isothermal): t_R 2.8 min. IR (film): 1610*m*, 1570*s*, 1430*s* (br.) 1380*m*, 1330*m*, 1225*s*. ^{1}H-NMR: 2.24 (*d*, *J* = 0.7, Me–C(5)); 2.34 (*s*, Me–C(2)); 2.44 (*s*, MeS); 6.00 (*q*, *J* = 0.7, H–C(4)). MS: 174 (43, M^+), 127 (44), 126 (23), 43 (100).

The higher fraction of the distillation (90°/0.14 Torr) gave 1.6 g (19%) of **4b**. GC (above conditons). t_R 11.4 min. Spectra: identical to those described below.

10. *3,3'-Dithiobis(2,5-dimethylfuran)* (**4b**). To a stirred soln. of 20.9 g (0.52 mol) of NaOH in 500 ml of H_2O were added at r.t. 40 g (0.26 mol) of **10b**. The mixture was stirred overnight and extracted with Et_2O (3 × 500 ml). The org. phases were washed with brine (100 ml), dried ($MgSO_4$), and evaporated: 29.4 g (89%) of crude product. Distillation (100°/0.1 Torr) gave 27.3 g (83%) of **4b**. Yellow liquid. GC (*OV-1*, 170° isothermal): t_R 13.7 min. IR (film): 3110*w*, 1610*m*, 1570*s*, 1435*m*, 1380*m*, 1335*m*, 1230*s*. ^{1}H-NMR: 2.08 (*s*, 2 Me); 2.24 (*d*, *J* = 0.7, 2 Me); 5.97 (*q*, *J* = 0.7, 2 H). MS: 254 (49, $M^{+\cdot}$), 128 (26), 127 (92), 43 (100).

11. *3,3'-Dithiobis(2-methylfuran)* (**4a**). According to *Exper. 10*, 50 g (0.36 mol) of **10a** gave 37.2 g (91%) of crude product. Distillation (90°/0.15 Torr) yielded 34 g (84%) of **4a**. Yellow liquid. GC (*OV-1*, 150° isothermal): t_R 9.6 min. UV (EtOH): 262 (5183). IR ($CHCl_3$): 3115*w*, 1580*s*, 1510*s*, 1440*m*, 1383*s*, 1210*m* (br.), 1120*s*, 1085*s*.

^{1}H-NMR: 6.27 (*d*, J = 2, H–C(4), H–C(4′)); 7.27 (*d*, J = 2, H–C(5), H–C(5′)). MS: 226 (52, M^+), 155 (4), 114 (17), 113 (100), 85 (17).

12. *2,5-Dimethyl-3-(methylthio)furan* (**2b**) *from* **10b**. To a stirred soln. of 13.7 g (0.34 mol) of NaOH and 35.6 g (0.25 mol) of MeI in 450 ml of MeOH, 35 g (0.23 mol) of **10b** in 50 ml of MeOH were added within 30 min (temp. rise to 35°). Then the mixture was poured on 500 ml of H_2O and extracted with *t*-BuOMe (3 × 700 ml). The combined org. phase was washed with brine (100 ml), dried ($MgSO_4$), and carefully evaporated and the residue distilled (71°/1 Torr): 22.9 g (70%) of **2b**. Faint yellow liquid. Data: identical with those of **2b** prepared according to *Exper. 2*.

13. *2-Methyl-3-(methylthio)furan* (**2a**). According to *Exper. 12*, 6.4 g (0.046 mol) of **10a** yielded 7.6 g of crude product which was distilled (42°/7 Torr): 3.5 g (58%) of **2a**. GC (3 m, 5% *OV-1* on *Gaschrom. Q* glass column, 120° isothermal): t_R 2.2 min. IR (film): 1740*w*, 1665*m*, 1590*m*, 1515*s*, 1430*m* (br.), 1220*s*. ^{1}H-NMR: 2.34 (*s*, Me); 6.36 (*d*, J = 2, H–C(4)); 7.27 (*d*, J = 2, H–C(5)). MS: 128 (100, M^+), 113 (50), 99 (23), 85 (13).

14. *2,5-Dimethylfuran-3-thiol* (**1b**). 14.1. *From Thiocyanate* **10b**. To a stirred soln. of 14.9 g (0.086 mol) of $Na_2S_2O_4$ and 12 g (0.215 mol) of KOH powder in 70 ml of H_2O were successively added 39 g (0.5 mol) of 2-mercaptoethanol and 10 g (0.072 mol) of **10b**. (GC monitoring). After 30 min, 120 ml of 10% aq. H_2SO_4 were added, the mixture was extracted with pentane (3 × 250 ml), the combined pentane phase washed with brine, dried ($MgSO_4$), and concentrated at ambient pressure: 9.8 g of red liquid. Bulb-to-bulb distillation (80–150°/10 Torr) gave 2.3 g (25%) of **1b**, besides 4.4 g of residue, which was a mixture of **4b**, 2′-hydroxyethyl 2,5-dimethylfur-3-yl disulfide, and 2′-mercaptoethyl 2,5-dimethylfur-3-yl sulfide. **1b**: GC (*Carbowax 20M*, 80° for 5 min, then heated to 200°): t_R 6.3 min. IR ($CHCl_3$): 2550*w*, 1615*m*, 1580*s*, 1450*m*, 1430*m*, 1220*s* (br.), 1070*s*. ^{1}H-NMR: 2.21 (*d*, J = 1, Me–C(2)); 2.27 (*s*, Me–C(5)); 2.61 (*q*, J = 1, SH); 5.87 (*s*, H–C(4)). MS: 128 (84, M^+), 127 (32), 113 (16), 95 (21), 85 (41), 43 (100).

14.2. *From Disulfide* **4b**. To a stirred soln. of 20 g (0.079 mol) of **4b** in 300 ml of i-PrOH and 75 ml of H_2O were added 16 g (0.079 mol) of Bu_3P within 10 min. After 30 min, no **4b** was observed by GC. The mixture was added to 1000 ml of H_2O and then extracted with pentane (2 × 700 ml). The combined pentane phase was washed with H_2O (700 ml) and brine (500 ml) and dried ($MgSO_4$) and the solvent carefully removed. Distillation (120°/20 Torr) gave 12.5 g (62%) of **1b**, besides residue of Bu_3PO. Data: identical to those of **1b** obtained in *Exper. 14.1*.

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