Reactions of 2-Chlorotetrahydrofuran and 2-Chlorotetrahydrothiophene with Phosphorus, Carbon, and Nitrogen Nucleophiles[1]

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Reaction of 2-chlorotetrahydrofuran (**1a**) and 2-chlorotetrahydrothiophene (**1b**) with phosphorus and carbon nucleophiles has provided a number of synthetically useful THF and THT derivatives. Reaction of **1b** with nitrogen nucleophiles of low basicity likewise afforded the 2-substituted tetrahydrothiophenes. Preparation of N^1-(2-tetrahydrothienyl)uracil derivatives **14a,b** necessitated prior conversion of the uracil substrates into their bis-*O*-(trimethylsilyl) derivatives.

Recently, a number of reactive cyclic α-chloro ethers and thioethers have become readily accessible by reaction of the parent ethers and thioethers with sulfuryl chloride.[2-4] As a result, several new synthetic applications of 2-chlorotetrahydrofuran (**1a**),[2] 2-chlorotetrahydrothiophene

1a **1b**

(**1b**),[3] and 2-chloro-1,3-dithiane[4] have been developed. Among these are the introduction of 2′-tetrahydrofuranyl (THF) and 2′-tetrahydrothienyl (THT) protecting groups for alcohols and thiols, by reaction of **1a** and **1b** (or acetal esters derived thereof)[3] with oxygen and sulfur nucleophiles.[2,3]

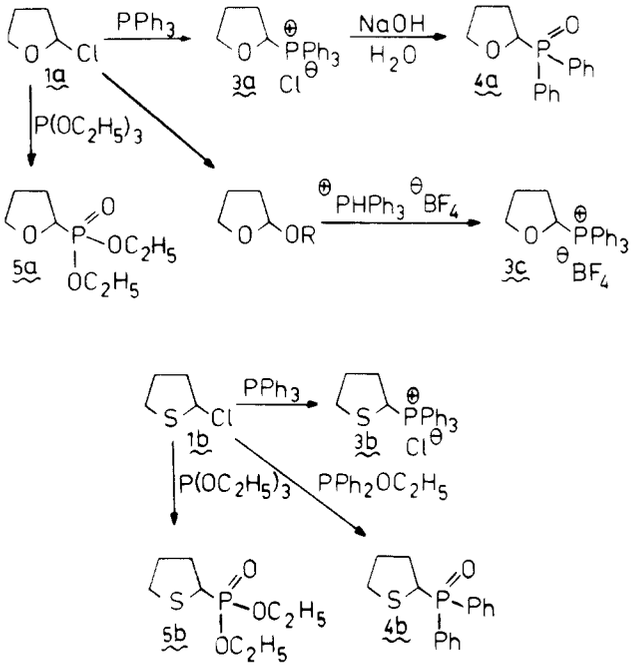
Reaction of **1a** with various nucleophiles resulted in the formation of the corresponding THF derivatives, among which are N^1- and N^3-substituted uracils. The latter are of special interest, because of their carcinostatic and antitumor properties[5] and their structural resemblance to nucleosides. A detailed conformational analysis of these compounds has been carried out in these laboratories.[6]

In this paper some further synthetic applications of **1a** and **1b** are presented. Scope and limitations of the reactions of **1a** and **1b** with phosphorus and carbon nucleophiles and of **1b** with nitrogen nucleophiles are discussed.

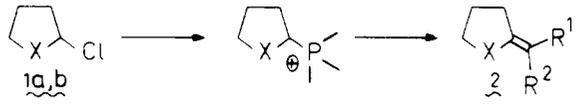
Results and Discussion

Reactions of 1a and 1b with Phosphorus Nucleophiles. The introduction of phosphonium (Ph_3P^+) and phosphinoyl [$(RO)_2PO$ and Ph_2PO] groups at the α-carbon atom of ethers and thioethers has been the subject of considerable recent interest.[7] The resulting compounds can be used as acyl anion equivalents in subsequent

Scheme I



Wittig/Horner reactions. We have studied the possibility of preparing useful intermediates for the synthesis of *cyclic* enol ethers and thioethers of type **2**. The results are



1a,b **2**

visualized in Scheme I.

Triphenylphosphonium chlorides **3a,b** were obtained in fair yields by reaction of **1a,b** with triphenylphosphine. Of these, only **3b** was isolated in a sufficiently pure form for direct application in the Wittig reaction. Following a different route, based on the reaction of an acetal (THF ether) with triphenylphosphonium tetrafluoroborate, THF phosphonium salt **3c** could be prepared in excellent yield (92%).[8,9]

While phosphonium salt **3a**, upon treatment with hydroxide ion,[7d] was quantitatively converted into diphenylphosphine oxide **4a**, the corresponding conversion **3b** → **4b** did not occur. Instead, tetrahydrothiophene and triphenylphosphine oxide were formed, thus illustrating

(1) Part 7 of a series on the synthetic applications of cyclic α-chloro ethers and thioethers. Previous paper: C. G. Kruse, A. Wijsman, and A. van der Gen, *J. Org. Chem.*, **44**, 1847 (1979).
(2) Part 3: C. G. Kruse, F. L. Jonkers, V. Dert, and A. van der Gen, *Recl. Trav. Chim. Pays-Bas*, **98**, 371 (1979).
(3) Part 4: C. G. Kruse, E. K. Poels, F. L. Jonkers, and A. van der Gen, *J. Org. Chem.*, **43**, 3548 (1978).
(4) Part 2: C. G. Kruse, N. L. J. M. Broekhof, A. Wijsman, and A. van der Gen, *Tetrahedron Lett.*, 885 (1977), and ref 1.
(5) See literature cited in ref 6.
(6) Part 5: C. G. Kruse, H. P. M. de Leeuw, and A. van der Gen, *J. Chem. Soc., Perkin Trans. 2*, 827 (1979); C. H. Verdegaal, F. B. Martens, and C. Romers, *ibid.*, 833 (1979).
(7) (a) G. Wittig and M. Schlosser, *Chem. Ber.*, **94**, 1373 (1961); (b) E. J. Corey and J. I. Shulman, *J. Org. Chem.*, **35**, 777 (1970); (c) M. Green, *J. Chem. Soc.*, 1324 (1963); (d) C. Earnshaw, C. J. Wallis, and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 2263 (1977).
(8) D. A. Clark and P. L. Fuchs, *Synthesis*, 628 (1977).
(9) Extension of this method to the preparation of other alkoxy- or thioalkyl-substituted phosphonium salts is currently being investigated.

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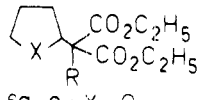
the better leaving group ability of the 2-tetrahydrothienyl substituent.[10]

Arbusov reactions with α-chloro ethers and thioethers often proceed unsatisfactorily.[11] Moreover, reaction of **1a** with triethyl phosphite has been reported to yield only elimination products.[12] As it was anticipated that both **1a** and **1b** would decompose rapidly when exposed to the reaction conditions usually applied (≥100 °C), the reaction of **1a** with triethyl phosphite was carried out at 20 °C in THF solution. Rapid formation of diethyl phosphonate **5a** was observed and the product could be conveniently isolated by distillation. Reactions of **1b** with triethyl phosphite and ethyl diphenylphosphinite are less selective. Phosphinoylated products **5b** and **4b** were only obtained in modest yields after the necessary purification procedures.[13] Wittig/Horner reactions with these reagents are currently being investigated.[14]

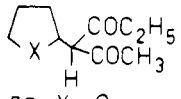
Reactions of 1a,b with Carbon Nucleophiles. The formation of C–C bonds by reaction of α-chloro ethers and thioethers with carbon nucleophiles has been studied extensively.[15] Relatively few examples are known which make use of the *cyclic* α-chloro ether **1a** and thioether **1b**.[16]

If the convenient chlorination procedures described in ref 2 and 3 and the known Grignard coupling reactions[16a,b] are applied, 2-alkyl-, 2-aryl-, and 2-vinyl-substituted tetrahydrofuran and tetrahydrothiophene derivatives can be readily obtained.

Reaction of **1a,b** with the weakly basic malonic ester anions proceeded efficiently to produce THF and THT malonic esters **6a–e** and **6f–h**. The results are presented



6a–e: X = O
6f–h: X = S



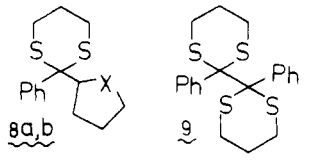
7a: X = O
7b: X = S

in Table I. Stereoselective ring opening of these malonic esters and conversion into the corresponding monoesters are described in the accompanying paper.

Only in the reaction of **1a** with the unsubstituted diethyl malonate anion was the formation of considerable amounts of a side product, tetraethyl 1,1,2,2-ethanetetracarboxylate, observed. The presence of this malonate dimer indicates the occurrence of a competitive process of electron transfer between **1a** and sodium diethyl malonate, leading to the formation of an electrophilic malonate species. Also, it is noteworthy that **7b** could be isolated in good yield (76%) from the reaction of **1b** with the anion of ethyl acetoacetate, whereas it is known that **7a** is only formed in minor amounts (10%).[17] It can be concluded that reactions with relatively soft carbon nucleophiles proceed more efficiently to substitution products in the case of the softer α-chloro *thio*ether **1b**.

With more basic enolates derived from monoesters and aldehydes, the products of C–C bond formation were still obtained, albeit in modest yields because of competing proton abstraction. For example, reaction of **1a** with *tert*-butyl lithioacetate gave the expected *tert*-butyl (2-tetrahydrofuranyl)acetate in only 24% yield; reaction of **1a** with the potassium enolate of 2-ethylhexanal[18] gave 30% C-alkylated and 40% O-alkylated product. With strongly basic carbon nucleophiles such as lithiodimethyl sulfoxide, 2-lithio-1,3-dithiane, and the dianion of ethyl acetoacetate, only proton abstraction occurred. The 2,3-dihydrothiophene formed by β elimination from **1b** reacts with **1b** to form 4-(2′-tetrahydrothienyl)-2,3-dihydrothiophene.[3] In the case of **1a** the 2,3-dihydrofuran formed does not engage in further reactions with the harder α-chloro ether **1a**.

The different modes of reactivity are aptly illustrated by the reaction of **1a** and **1b** with 2-lithio-2-phenyl-1,3-dithiane, where the three processes substitution, proton abstraction, and electron transfer occur side by side.



8a,b **9** **10a,b**

a: X = O **b**: X = S

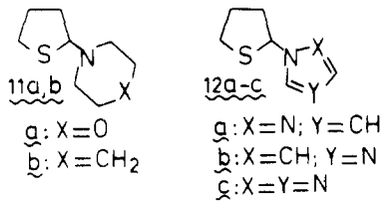
Apart from the products originating from C–C bond formation (**8a**, 50%; **8b**, 10%) and proton abstraction (2-phenyl-1,3-dithiane: with **1a**, 10%; with **1b**, 50%), also products **9** (10% in both cases) and **10a,b** (40% in both cases), both presumably resulting from electron transfer, are present in the reaction mixture.[19]

Summarizing, it can be stated that reactions of cyclic α-chloro ethers and thioethers **1a** and **1b** only result in selective C–C bond formation if carbon nucleophiles of relatively low basicity are used.[20]

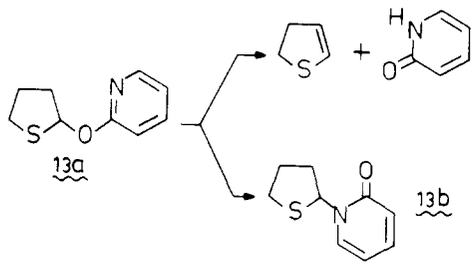
Reactions of 1b with Nitrogen Nucleophiles. Only a few examples of the preparation of aza acetals and thioacetals (R_2NCHXR, X = O, S) by reaction of secondary nitrogen nucleophiles with α-chloro ethers and thioethers have been described.[21,22] Earlier, we reported the application of this method to the synthesis of THF-substituted azoles and amides.[2] As THT derivatives with an amino substituent are virtually unknown,[23] we have studied the reactions of **1b** with a variety of nitrogen nucleophiles.

Conversion of secondary amines and azoles into THT derivatives **11a,b** and **12a,b,c**, respectively, is conveniently accomplished by reaction with **1b** in acetonitrile at 20 °C. Results and spectral properties of the products have been compiled in Table II.

(10) G. Cilento, *Chem. Rev.*, **60**, 147 (1960).
(11) (a) Chloromethyl methyl sulfide, ref 14c. (b) Cyclic α-chloro ethers, H. Gross, G. Engelhardt, J. Freiberg, W. Bürger, and B. Costisella, *Justus Liebigs Ann. Chem.*, **707**, 35 (1967). (c) Acyclic α-chloro ethers, E. Schaumann and F. Grabley, *ibid.*, 88 (1977).
(12) J. Thiem and H. Paulsen, *Phosphorus*, **6**, 51 (1975).
(13) An alternative route to **4b** by reaction of chlorodiphenylphosphine with a THT ether gave no improvement.
(14) Enol thioether **2** (X = S, R_1 = H, R_2 = Ph; 3:2 mixture of *E* and *Z* isomers) was obtained in 70% yield by reaction of the ylide from **3b** with benzaldehyde.
(15) (a) For a review see H. Gross and E. Höft, *Angew. Chem.*, **79**, 358 (1967); (b) P. E. Sum and L. Weiler, *J. Chem. Soc., Chem. Commun.*, 91 (1977).
(16) (a) Grignard reagents with **1a**, ref 21a; (b) Grignard reagents with **1b**, D. L. Tuleen and R. H. Bennett, *J. Heterocycl. Chem.*, **6**, 115 (1969); (c) **1a** with dienes, *Chem. Abstr.*, **69**, 106361h; **75**, 150982j.
(17) J. Huet, *Bull. Soc. Chim. Fr.*, 2677 (1964).
(18) P. Groenewegen, H. Kallenberg, and A. van der Gen, *Tetrahedron Lett.* 491 (1978).
(19) Formation of **9** has also been observed upon reaction of 2-lithio-2-phenyl-1,3-dithiane with halogen-substituted nitrobenzenes: W. H. Baarschers and T. L. Lok, *Tetrahedron Lett.*, 3483 (1971).
(20) This is not unexpected in view of the known preference of "hard" nucleophiles to induce elimination rather than substitution reactions; see, inter alia, I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, London, 1976, p 84.
(21) Examples are: (a) N. A. Ryabinin and I. P. Kolenko, *Khim. Geterosikl. Soedin*, 8 (1968); *Chem. Abstr.*, **70**, 87417k; (b) H. Gross, J. Gloede, and J. Freiberg, *Justus Liebigs Ann. Chem.*, **702**, 68 (1967).
(22) A disadvantage of this method is the occurrence of competing processes as proton abstraction and ring opening. See e.g.: H. Böhme and H. Bentler, *Chem. Ber.*, **89**, 1468 (1956); L. A. Court and N. R. Francis, *J. Chem. Soc.*, 2799 (1964).
(23) Purine substituted derivatives have been described by L. R. Lewis, F. H. Schneider, and R. K. Robins, *J. Org. Chem.*, **26**, 3837 (1961).

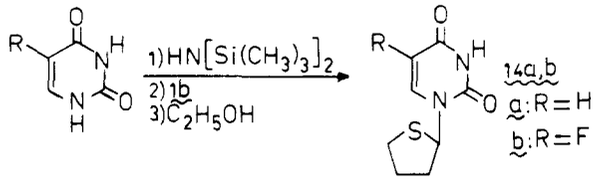


Good yields of substitution products were generally obtained. With relatively strong bases such as piperidine, the competing elimination process became predominant.[22] Reaction of **1b** with pyridone-2 in acetonitrile resulted in quantitative formation of the unstable O-alkylated product **13a**.[24] This product spontaneously converted into a



mixture of pyridone-2 and the N-substituted THT derivative **13b**, either in $CDCl_3$ solution or during chromatography. The thermodynamically favored **13b** was obtained directly when the reaction of pyridone-2 with **1b** was carried out in THF.

In contrast to the results obtained with **1a**,[2] it was not possible to synthesize THT uracil derivatives by direct reaction of uracil with **1b**. It appeared, however, that the THT group could be conveniently introduced at N^1 by reaction of **1b** with the bis(trimethylsilyl) derivatives of uracil and 5-fluorouracil.[25,26] Thus, N^1-(2-tetrahydrothienyl)uracil (**14a**) and N^1-(2-tetrahydrothienyl)-5-fluorouracil (**14b**) were obtained in 20% overall yield.[27]



Experimental Section

General Procedures. NMR spectra were recorded in $CDCl_3$ solution, with Me_4Si as an internal standard; δ is expressed in parts per million and J, in hertz. Elemental analyses from the crystalline products were performed by Mr. W. J. Buys, TNO Laboratory of Organic Chemistry, Utrecht, The Netherlands. Silica gel MN (Mackery Nagel, 70–270 mesh) or Florisil (Fluka) was used for column chromatography. All reactions with **1a,b** were carried out in an atmosphere of dry nitrogen.

Materials. When necessary, solvents and reagents were purified and dried according to standard procedures. Full experimental details about the chlorination of tetrahydrofuran[2] and tetrahydrothiophene[3] have been described elsewhere. Ethyl diphenylphosphinite,[28] triphenylphosphonium tetrafluoroborate,[8] and 2-phenyl-1,3-dithiane[29] were prepared by known procedures. Phenyl- and *p*-methoxyphenylmalonate were synthesized as described in ref 1. *p*-Nitrophenylmalonate was prepared by reaction of *p*-nitrochlorobenzene and sodium diethyl malonate in Me_2SO at 80–90 °C for 15 h (mp 56–57 °C).[30]

(2-Tetrahydrofuranyl)triphenylphosphonium Chloride (3a). A solution of **1a** in THF (from a 24-mmol chlorination)[2] was concentrated in vacuo at 0 °C to a volume of ca. 5 mL. Benzene (40 mL) was added, followed by a solution of triphenylphosphine (5.2 g, 20 mmol) in benzene (20 mL). The reaction mixture was stirred at 20 °C for 80 h. The resulting white precipitate was filtered, yielding 6.34 g (86%) of **3a** as a low-melting solid (mp 74–76 °C). IR and NMR showed the presence of hydroxyl groups and benzene. Crystallization from CH_2Cl_2–THF did not remove the impurities completely. The best sample gave the following: mp 78–80 °C; NMR (Me_2SO-d_6) δ 7.8 (m, 15 H, aromatic), 6.56 (m, 1 H, $\sum J$ = 26, 2-H), 3.89 and 3.41 (m, 1 H, 5-H), 2.7, 2.0, 1.9, 1.45 (m, 1 H, 3- and 4-H).

(2-Tetrahydrothienyl)triphenylphosphonium Chloride (3b). Triphenylphosphine (2.6 g, 10 mmol) was added to a solution of **1b** (from a 10-mmol chlorination) in benzene (20 mL). After the solution was stirred at 20 °C for 16 h, the precipitate was collected by filtration and dried in vacuo at 80 °C, giving 1.6 g (55%, based on 75% yield of **1b**[3]). Crystallization from CH_2Cl_2–THF gave sufficiently pure material to use in subsequent Wittig reactions:[13] mp 226 °C; IR 3050, 3000 (CH); 1590, 1480, 1430, 750, 720, 690 (Ph); 1100 (PPh) cm^{-1}; NMR (Me_2SO-d_6) δ 7.85 (m, 15 H, aromatic), 6.28 (m, 1 H, $\sum J$ = 15, 2-H), 2.88 (m, 2 H, 5-H), 2.3, 2.1, 2.0, 1.6 (m, 1 H, 3- and 4-H).

(2-Tetrahydrofuranyl)triphenylphosphonium Tetrafluoroborate (3c). A solution of equimolar quantities of cyclohexyl (2-tetrahydrofuranyl) ether[2] and triphenylphosphonium tetrafluoroborate (mp 164–166 °C; lit.[7] mp 160–164 °C) in acetonitrile was stirred at 20 °C for 4 h. After evaporation of the solvent, the resulting solid was stirred with benzene, filtered, and crystallized from CH_2Cl_2–Et_2O, yielding **3c** as white needles in 92% yield. The analytical sample gave the following: mp 138–139 °C; IR 1580, 1480, 1440, 725, 685 (Ph); 1050 (COC) cm^{-1}; NMR δ 7.75 (m, 15 H, aromatic), 5.86 (m, 1 H, $\sum J$ = 26, 2-H), 3.94 and 3.55 (m, 1 H, 5-H), 2.82, 2.05, 1.7, 1.2 (m, 1 H, 3- and 4-H). Anal. Calcd for $C_{22}H_{22}OPBF_4$: C, 62.89; H, 5.28; F, 18.09. Found: C, 62.88; H, 5.54; F, 18.03.

(2-Tetrahydrofuranyl)diphenylphosphine Oxide (4a). Phosphonium salt **3a** (1.7 g, 4.5 mmol) was treated with aqueous KOH (20 mL, 1 N) at reflux for 30 min. The salt gradually dissolved and the resulting solution was extracted with $CHCl_3$. After the mixture was dried ($MgSO_4$) and the solvent evaporated, 1.1 g (90%) of **4a** was obtained. The analytical sample (from EtOAc–hexane) gave the following: mp 113–114 °C; IR 3080, 2980, 2880 (CH); 1570, 1480, 1430, 750, 725, 695 (Ph); 1180 (P=O); 1050 (COC) cm^{-1}; NMR δ 7.90 (m, 4 H, ortho aromatic), 7.52 (m, 6 H, aromatic), 4.70 (q, 1 H, J = 8, 2-H), 3.8 and 3.7 (m, 1 H, 5-H), 2.2, 1.8 (m, 2 H, 3- and 4-H). Anal. Calcd for $C_{16}H_{17}O_2P$: C, 70.58; H, 6.29; P, 11.38. Found: C, 70.43; H, 6.53; P, 11.27.

(2-Tetrahydrothienyl)diphenylphosphine Oxide (4b). A solution of **1b** (from a 50-mmol chlorination) and ethyl diphenylphosphinite (25 mmol) in benzene (25 mL) was heated at reflux for 30 min. After cooling, the reaction mixture was washed with K_2CO_3 solution, H_2O, and brine and dried ($MgSO_4$). Evaporation of the volatile components gave a yellow oil, which was treated with EtOAc (2 mL). The resulting precipitate was collected and was shown to contain ca. 60% (NMR) of **4b** (yield 35%). After repeated crystallizations from EtOAc, a sample was obtained: mp 158–160 °C; IR 3050, 2950 (CH); 1480, 1440, 740, 715, 695 (Ph); 1180 (P=O) cm^{-1}; NMR δ 7.9 and 7.5 (m, 10 H, aromatic), 4.08 (m, 1 H, $\sum J$ = 16.5, 2-H), 2.82 (m, 2 H, 5-H), 2.2–1.9 (m, 4 H, 3- and 4-H).

(24) Reactions of **1a** with pyridone-2 in acetonitrile or THF lead to the N-substituted product only, while both *O*- and *N*-THF derivatives were obtained by reaction with 3-methylpyrazone-2.[2]

(25) For reactions of **1a** with bis(trimethylsilyl)uracil, see: (a) D. Snikeris, R. Zugs, E. Stankewicz, G. Duburs, and S. Hillers, *Khim. Generosikl. Soedin*, 170 (1969); *Chem. Abstr.*, **70**, 115105a; (b) U. S. Patent, *ibid.*, 81, P63664n; (c) Japanese Patent, *ibid.*, **83**, P10134z.

(26) Alternatively, **14a** can be obtained in 20% yield by a Hilbert–Johnson reaction of **1b** with 2,4-dimethoxypyrimidine, following the procedure of Noell and Cheng (C. Wayne Noell and C. C. Cheng, *J. Heterocycl. Chem.*, **5**, 25 (1968)).

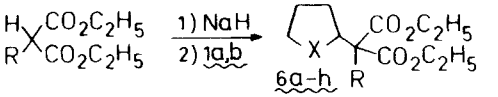
(27) Recently **14b** has been independently synthesized by U. K. Pandit and co-workers via a different route. We thank Professor Pandit for communicating these results to us, prior to publication.

(28) P. F. Cann, D. Howells, and S. Warren, *J. Chem. Soc., Perkin Trans 1*, 304 (1972).

(29) D. Seebach, *Synthesis*, 17 (1969).

(30) J. Bourdais and C. Mahieu, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **263**, 84 (1966); *Chem. Abstr.*, **65**, 10447b.

Table I. Physical Properties of the Reaction Products from 1a,b with Diethyl Malonate Anions



6a-h

X	R	product	yield[a]	mp or bp (mm), °C	^{1}H NMR data: δ(2-H)	δ(3-, 4-, and 5-H) and δ(RH)	δ(OCH_2CH_3)	IR data,[b] cm^{-1}
O	H	**6a**[c]	59 (40)	98 (0.03)	4.44	3.43 (d, ^3J = 9, α-H), 3.85 and 3.75 (m, 5-H), 2.05-1.8 (m, 3- and 4-H)	4.21 and 4.17 (q, 2 H), 1.25 and 1.24 (t, 3 H)	1750 (C=O); 1200-1020 (COC, 5 peaks)
O	CH_3	**6b**[d]	80 (65)	90 (0.03)	4.47	3.85 and 3.75 (m, 5-H), 2.05-1.8 (m, 3- and 4-H), 1.40 (s, α-CH_3)	4.21 and 4.18 (q, 2 H), 1.24 (t, 6 H)	1740 (C=O) 1250, 1110, 1060 (COC)
O	Ph	**6c**[e]	95 (85)	51-52	4.86	7.3 (s, aromatic), 3.66 (t, 5-H), 2.1 and 1.7-1.55 (m, 3- and 4-H)	4.31 and 4.22, 4.29 and 4.20 (dq, 1 H), 1.27 and 1.25 (t, 3 H)	1730 (C=O); 1480, 760, 700 (Ph); 1250-1030 (COC, 5 peaks)
O	*p*-OCH_3Ph	**6d**[f]	80 (68)	68-69	4.81	7.23 and 6.80 (AA'BB', ^3J = 9, aromatic), 3.63 (t, 5-H), 2.1 and 1.7-1.55 (m, 3- and 4-H)	4.29 and 4.19, 4.27 and 4.17 (dq, 1 H), 1.25 and 1.23 (t, 3 H)	1725 (C=O); 1600, 1500, 830 (Ph); 1250, 1180, 1030 (COC)
O	*p*-NO_2Ph	**6e**[g]	60	105-106.5	4.87	8.26 and 7.66 (AA'BB', ^3J = 9.2, aromatic), 3.68 (t, 5-H), 2.1 and 1.6-1.4 (m, 3- and 4-H)	4.33 and 4.31 (q, 2 H), 1.28 and 1.27 (t, 3 H)	1730 (C=O) 1520, 1340 (NO_2); 1250, 1190, 1040 (COC); 855 (Ph)
S	H	**6f**[h]	95 (82)	110 (0.02)	3.92	3.43 (d, ^3J = 10.6, α-H), 2.8 (m, 5-H), 2.1-1.75 (m, 3- and 4-H)	4.22 (q, 4 H), 1.27 (t, 6 H)	1740 (C=O); 1270, 1170, 1020 (COC); 845
S	CH_3	**6g**[i]	95 (82)	100 (0.05)	4.13	2.8 (m, 5-H), 2.1-1.75 (m, 3- and 4-H), 1.47 (s, α-CH_3)	4.19 (q, 4 H), 1.25 (t, 6 H)	1740 (C=O); 1240, 1100, 1020 (COC); 855
S	Ph	**6h**[j]	86 (66)	43-44	4.48	7.3 (m, aromatic), 2.6 and 2.5 (m, 5-H), 1.9-1.65 (m, 3- and 4-H)	4.3-4.2 (m, 4 H), 1.26 and 1.19 (t, 3 H)	1740 (C=O); 1490, 695 (Ph); 1240, 1030 (COC) 850

[a] Calculated (NMR, GC) from crude products; the yield after distillation or crystallization is given in parentheses. [b] 2980, 1440 (CH) cm^{-1}. [c] n^{20}_D = 1.4510. [d] n^{20}_D = 1.4430. [e] Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.73; H, 7.34. [f] Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.31; H, 7.20. [g] Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.15; H, 6.05; N, 3.98. [h] n^{20}_D = 1.4832. [i] n^{20}_D = 1.4849. [j] Anal. Calcd for $C_{17}H_{22}O_4S$: C, 63.33; H, 6.88; S, 9.94. Found: C, 63.55; H, 6.78; S, 9.97.

Table II. Physical Properties of the Reaction Products from 1b with Secondary Amines, Azoles, and Pyridone-2

substrate	yield[a]	product[b]	n^{23}_D	^{1}H NMR data: 2'-H δ/ΣJ	δ(3'-, 4'-, and 5'-H) and δ(R-H)	bp (mm) °C; IR, cm^{-1}
morpholine[c]	70	**11a**	1.5338	4.82/12	3.69 (t, 4 H, OCH_2), 2.54 (m, 4 H, NCH_2), 2.82 (m, 5'-H), 2.1-1.9 (m, 3'- and 4'-H)	91 (0.4); 2940, 2860 (CH); 1100 (COC)
piperidine[c]	40	**11b**	1.5383	4.97/12	2.94 (m, 5'-H), 2.51 (m, 4 H, NCH_2), 2.1-1.9 (m, 3'- and 4'-H), 1.6 (m, 6 H, CH_2)	100 (0.3); 2950, 2880, 1440 (CH)
pyrazole[d]	90	**12a**	1.5617	5.97/9	7.70 (d, 3-H), 7.53 (d, 5-H), 6.23 (t, 4-H) ($^3J_{3,4}$ = 2.0, $^3J_{4,5}$ = 2.0 Hz), 3.2 and 3.0 (m, 5'-H), 2.4-2.2 (m, 3'- and 4'-H)	66 (0.1); 3100, 2950, 2900 (CH); 1510, 740 (pyrazole)
imidazole[e]	77	**12b**	1.5666	5.78/9.5	7.71 (s, 2 H), 7.11 and 7.05 (AB, 5- and 4-H), 3.15 and 2.95 (m, 5' H), 2.3-2.2 (m, 3'- and 4'-H)	3100, 2980 (CH); 1480, 730 (imidazole)
1,2,4-triazole[c]	62	**12c**	1.5542	5.95/8	8.39 (s, 3-H) 7.91 (s, 5-H), 3.2 and 3.0 (m, 5'-H), 2.5 and 2.3-2.1 (m, 3'- and 4'-H)	68 (0.05); 3100, 2950 (CH); 1480, 670 (triazole)
pyridone-2[f]	95	**13a**		6.46/6.4	8.12 (ddd, 6-H), 7.51 (ddd, 4-H), 6.83 (ddd, 5-H), 6.68 (ddd, 3-H) ($^3J_{3,4}$ = 8, $^3J_{4,5}$ = 7, $^4J_{5,6}$ = 5, $^4J_{3,5}$ = 1, $^4J_{4,6}$ = 2, $^5J_{3,6}$ = 1 Hz), 2.8 (m, 5'-H), 2.4-2.1 (m, 3'- and 4'-H)	2950, 2850 (CH); 1590, 1460, 1430, 775, 725, 675 (py); 1260, 940
pyridone-2[g]	50	**13b**	1.5842	6.61/10	7.95 (dd, 6-H), 7.32 (ddd, 4-H), 6.50 (dd, 3-H), 6.24 (ddd, 5-H) ($^3J_{3,4}$ = 9, $^3J_{4,5}$ = 6.5, $^3J_{5,6}$ = 7, $^4J_{3,5}$ = 1.5, $^4J_{4,6}$ = 2 Hz), 3.2 and 3.0 (m, 5'-H), 2.4 and 2.1-1.9 (m, 3'- and 4'-H)	2950, 2850 (CH); 1650 (C=O); 1570, 1520, 795 (py)

[a] Refers to NMR analysis of the crude products; see Experimental Section. [b] Pure samples were obtained by preparative GC (**11a,b**), distillation (**12a,c**) or column chromatography (**12b, 13b**). [c] Partial decomposition upon distillation. [d] 77% yield after distillation. [e] Could not be distilled; purification on Florisil. [f] Chromatography of **13a** yielded **13b** (both on silica and Florisil). [g] Reaction in THF.

Diethyl (2-Tetrahydrofuranyl)phosphonate (5a). Triethyl phosphite (50 mmol) was added to a stirred solution of **1a** (from a 50-mmol chlorination) in THF. After 30 min of stirring at 20 °C, the ensuing mixture was concentrated in vacuo and distilled, yielding **5a** (5 g, 85% pure; yield 50%, based on 85% yield of **1a**[2]); bp 77–80 °C (0.2 mm). A pure sample was obtained by preparative GC: n^{20}_D = 1.4483; IR 3000, 1440 (CH); 1230 (P=O); 1020, 725 (POC) cm^{-1}; NMR δ 4.18 and 4.16 (p, 2 H, J = 7, OCH_2), 4.1 (m, 1 H, 2-H), 3.88 (m, 2 H, 5-H), 2.2–2.0 (m, 4 H, 3- and 4-H), 1.33 (t, 6 H, CH_3).

Diethyl (2-Tetrahydrothienyl)phosphonate (5b). A sample containing ca. 80% of **5b** (NMR) was obtained by reaction of triethyl phosphite with **1b** in CCl_4 at 20 °C for 16 h and workup by washing with aqueous base and H_2O, drying ($MgSO_4$), evaporating the solvent, and distilling the residue; bp 110 °C (0.5 mm). The product decomposed upon attempted purification by preparative GC: IR 1250 (P=O); 1020 (POC) cm^{-1}; NMR δ 4.15 (p, 4 H, OCH_2), 3.43 (m, 1 H, $\sum J$ = 22, 2-H), 2.89 (m, 2 H, 5-H), 2.2–2.0 (m, 4 H, 3- and 4-H), 1.31 (t, 6 H, CH_3).

General Procedure for the Reactions of 1a,b with Diethyl Malonate and Ethyl Acetoacetate Anions. THF solutions of the anions were prepared by addition of the requisite ester to a stirred suspension of NaH (1.0 equiv) at 20 °C (in the case of diethyl phenyl- and *p*-methoxyphenylmalonate at reflux). After addition of **1a,b** (from a 1.5- and 2.0-equiv chlorination, respectively) at 20 °C (in the case of **1a** a yellow color developed), stirring was continued at reflux for 1 h (with **1a**) or 16 h (with **1b**). Products **6a–h** were isolated by standard workup in the yields indicated in Table I. From the reaction mixture of **1a** with sodium diethyl malonate another product was isolated (40% yield) which was identified as tetraethyl 1,1,2,2-ethanetetracarboxylate by NMR and mp 66 °C. (lit.[31] mp 72 °C). Ethyl α-(2-tetrahydrothienyl)acetoacetate **7b** was isolated as a mixture of two diastereoisomers in 76% yield after distillation: bp 108–115 °C (0.02 mm); n_D^{20} = 1.4965; IR 2980, 2900, 1440 (CH); 1750, 1725 (C=O); 1260, 1170, 1020 (COC) cm^{-1}; NMR δ 4.19 (q, 2 H, J = 7.1, OCH_2), 3.92 (m, 1 H, J = 21, 2-H), 3.59 (d, 1 H, J = 11, α-H), 2.25 (s, 3 H, $(C=O)CH_3$), 2.0 (m, 3 H) and 1.6 (m, 1 H, 3- and 4-H), 1.27 (t, 3 H, CH_3).

Reactions of 1a,b with 2-Lithio-2-phenyl-1,3-dithiane. To a stirred solution of 2-lithio-2-phenyl-1,3-dithiane[30] in THF was added dropwise **1a** or **1b** (1.2- and 2.0-equiv chlorination, respectively) at −70 °C. The reaction mixture (50 mL/10 mmol) was warmed to 20 °C in 5 h and subsequently stirred for 16 h and poured into an aqueous $NaHCO_3$–Et_2O mixture. After extraction, drying, and concentration in vacuo, the resulting product was treated with cold Et_2O. White crystals of **9** separated, which were collected by filtration; mp 200 °C (lit.[19] mp 204 °C). The filtrate was subjected to column chromatography on silica (EtOAc/hexane 1:4 and 1:10 in the case of **1a** and **1b**, respectively). The fractions containing mainly 2-(2′-tetrahydrofuranyl- or 2′-tetrahydrothienyl)-2-phenyl-1,3-dithiane (**8a** and **8b**) and 1-benzylthio-3-(2′-tetrahydrofuranyl- or 2′-tetrahydrothienyl)thiopropane (**10a** and **10b**) were concentrated in vacuo. Products **8a,b** contained varying amounts of 2-phenyl-1,3-dithiane; NMR δ 5.16 (s, 2-H). **8a**: IR 1590, 1480, 1440, 730, 700 (Ph); 1060 (COC) cm^{-1}; NMR δ 8.0, 7.4 (m, 5 H, aromatic), 4.20 (t, 1 H, 2′-H), 3.60 (m, 2 H, 5′-H), 2.6 (m, 4 H, 4- and 6-H), 1.9–1.5 (m, 3′-, 4′-, and 5-H). **8b**: NMR δ 3.42 (t, 2′-H). **10a**: IR 1665 (C=O); 1580, 1440, 770, 685 (Ph); 1040 (COC); 905 cm^{-1}; NMR δ 8.0 (dd, 2 H, ortho aromatic), 7.5 (m, 3 H, aromatic), 5.38 (m, 1 H, 2′-H), 3.85 (m, 2 H, 5′-H), 3.17 (t, 2 H, 1-H), 2.7 (tAB, 2 H, 3-H), 2.2–1.8 (m, 6 H, 2-, 3′-, and 4′-H). **10b**: NMR δ 4.48 (m, 2′-H).

(31) K. Weinges and R. Spänig, *Chem. Ber.*, 101, 3010 (1968).

General Procedure for the Reactions of 1b with Secondary Amines, Azoles, and Pyridone-2. A concentrated solution of **1b** in CCl_4 (from a 50-mmol chlorination[3]) was added to a stirred suspension or solution of the substrate (25 mmol) and Et_3N (40 mmol) in CH_3CN (50 mL). Stirring was continued at 20 °C for 2 h, Et_2O was added (50 mL), and the resulting precipitate was filtered after cooling at −16 °C. The filtrate was concentrated in vacuo and either extracted with Et_2O (**11a,b**; **12a,b**) or taken up in EtOAc and extracted with aqueous KOH (**12c**; **13a,b**). The crude products obtained after drying and evaporation of the solvent contained 80–90% of the desired products in the yields given in Table II. In most cases some loss of product was observed upon purification. After the product was allowed to stand overnight at 20 °C, the NMR sample of **13a** was found to contain **13b** (25%), 2,3-dihydrothiophene (δ 6.17 (dt, 5-H), 5.63 (dt, 4-H)), and pyridone-2 (75%).

Synthesis of N^1-(2-Tetrahydrothienyl)uracil Derivatives. A mixture of (5-fluoro)uracil (50 mmol), chlorotrimethylsilane (0.5 mL), and hexamethyldisilazane (25 mL) was heated at 165 °C for 2 h.[25] The volatile components were removed by evaporation in vacuo at 40 °C and the residue was dissolved in CH_2Cl_2 (50 mL). After addition of **1b** (from a 0.1-mol chlorination), the reaction mixture was stirred at 20 °C for 16 h. Then EtOH (10 mL) was added dropwise while cooling and stirring was continued for 1 h. Concentration in vacuo and extraction of the residue with $CHCl_3$ yielded (2-tetrahydrothienyl)uracil derivatives **14a,b**, which were crystallized from EtOAc–hexane.

N^1-(2′-Tetrahydrothienyl)uracil (14a): yield 1.8 g (18%); analytical sample by crystallization from EtOAc; mp 150–152 °C; R_f (acetone–hexane (1:1)) 0.4; IR 3300–2600 (NH); 3000, 1450 (CH); 1700, 1610 (C=O); 1370, 1230, 880, 750 cm^{-1}; NMR δ 10.20 (s, 1 H, NH), 7.81 (d, 1 H, J = 8.2, 6-H), 6.28 (m, 1 H, $\sum J$ = 11, 2′-H), 5.76 (d, 1 H, 5-H), 3.2 and 3.0 (m, 1 H, 5′-H), 2.3 (m, 1 H), 2.0 (m, 3 H, 3′- and 4′-H). Anal. Calcd for $C_8H_{10}N_2O_2S$: C, 48.47; H, 5.08; S, 16.17. Found: C, 48.18; H, 5.04; S, 15.93.

N^1-(2′-Tetrahydrothienyl)-5-fluorouracil (14b): yield 2.1 g (20%); analytical sample from EtOAc; mp 180–181 °C; R_f (acetone–hexane (1:1)) 0.7; IR 3200–2800 (NH); 3000, 2850, 1440 (CH); 1750, 1640 (C=O); 1240 (CF); 870, 780, 740, 690 cm^{-1}; NMR ($CDCl_3$, 5% Me_2SO-d_6) δ 11.45 (s, 1 H, NH), 7.89 (d, 1 H, J = 7, 6 H), 6.24 (m, 1 H, $\sum J$ = 12.5, 2′-H), 3.2 and 3.0 (m, 1 H, 5′-H), 2.3 (m, 1 H), 2.0 (m, 3 H, 3′- and 4′-H). Anal. Calcd for $C_8H_9N_2O_2SF$: C, 44.44; H, 4.20; S, 14.83; F, 8.79. Found: C, 44.43; H, 4.28; S, 14.98; F, 8.80.

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Registry No. **1a**, 13369-70-5; **1b**, 22342-03-6; **3a**, 70398-34-4; **3b**, 70398-35-5; **3c**, 70398-37-7; **4a**, 70398-38-8; **4b**, 70398-39-9; **5a**, 57977-99-8; **5b**, 70398-40-2; **6a**, 70398-41-3; **6b**, 70398-42-4; **6c**, 70398-43-5; **6d**, 70398-44-6; **6e**, 70398-45-7; **6f**, 70398-46-8; **6g**, 70398-47-9; **6h**, 70398-48-0; **7b**, 70398-49-1; **8a**, 70398-50-4; **8b**, 70398-51-5; **9**, 33839-73-5; **10a**, 70398-52-6; **10b**, 70398-53-7; **11a**, 70398-54-8; **11b**, 70398-55-9; **12a**, 70398-56-0; **12b**, 70398-57-1; **12c**, 70398-58-2; **13a**, 70398-59-3; **13b**, 70398-60-6; **14a**, 70398-61-7; **14b**, 68321-44-8; triphenylphosphine, 603-35-0; cyclohexyltetrahydrofuran ether, 1918-61-2; triphenylphosphonium tetrafluoroborate, 12095-42-0; ethyl diphenylphosphinite, 719-80-2; triethyl phosphite, 122-52-1; diethyl malonate, 510-20-3; diethyl methylmalonate, 609-08-5; diethyl phenylmalonate, 83-13-6; diethyl *p*-methoxyphenylmalonate, 23197-67-3; diethyl *p*-nitrophenylmalonate, 10565-13-6; ethyl acetoacetate, 141-97-9; 2-lithio-2-phenyl-1,3-dithiane, 53178-41-9; (5-fluoro)uracil, 51-21-8; morpholine, 110-91-8; piperidine, 110-89-4; pyrazole, 288-13-1; imidazole, 288-32-4; 1,2,4-triazole, 288-88-0; pyridone-2, 142-08-5.