A second crop of crystals from the mother liquor weighed 0.20 g (7%), mp 127.5–130.5 °C.

Chenodeoxycholic Acid (1). **1a** (2 g) refluxed in 40 mL of 10% methanolic KOH for 12 h was processed by evaporation of the solvent, solution of the residue in water, and acidification (3 N H_2SO_4) of the ice-cooled solution. The precipitated solid was washed with water, dried at 100 °C, and crystallized from ethyl acetate–hexane as fine needles, 1.60 g, mp 119.5-121.0 °C (96%).[12] The latter recrystallized from acetonitrile had mp 167.5–172.5 °C (lit. mp 140–142,[4a] 145–146,[4c] 125–146,[4d] 119, 146,[4e] 138–141,[4f] 168–171 °C[10d]): IR (KBr) 5.92 (C=O), 9.34, 10.25 μm (C—O).[13] TLC: 121 °C crystals, 172 °C crystals and precipitated 1 (dried at 100 °C, without crystallization) all exhibited single spots (R_f 0.80; developing system $CHCl_3$–EtOAc–HOAc, 45:45:10, 2×) and were identical (cospot) with an authentic sample of chenodeoxycholic acid.[11]

Anal. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73,70; H, 10.60.

Acknowledgment. This work was supported by a National Cancer Institute (PHS) grant as part of the National Large Bowel Cancer Project program. Dr. James D. Henderson performed some preliminary experiments. Ms. Susan Brannan contributed able technical assistance.

Registry No. 1, 474-25-9; **1a**, 2616-71-9; **2c**, 28535-81-1; **3**, 76927-60-1.

(12) Calcd for $C_{24}H_4O_4 \cdot 0.2C_6H_{14}$: C, 73.48; H, 10.85. Found: C, 73.61; H, 10.74.

(13) D. H. Small in "The Bile Acids", Vol. I, P. P. Nair and D. Kritchevsky, Eds., Plenum Press, New York, 1971, p 259 (Table I).

Stereochemistry of the Conversion of Sulfoxides into Aminosulfonium Salts

Jozef Drabowicz, Bogdan Bujnicki, and Marian Mikolajczyk*

Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulfur Compounds, 90-362 Lodz, Boczna 5, Poland

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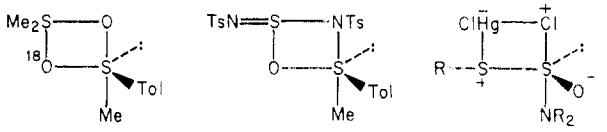
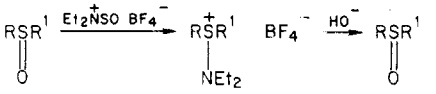
The mechanism of nucleophilic substitution reactions at the tricoordinate sulfur atom has been a subject of considerable interest for the past few years.[1] One of the most important questions is whether such reactions occur synchronously according to a S_N2-S mechanism or stepwise by an addition–elimination (A–E) mechanism involving a tetracoordinate sulfurane intermediate. The second, closely related problem concerns the relationship between the structure of a transition state or intermediate and the stereochemical course of nucleophilic substitution at sulfur. Since the first reported example of inversion at sulfinyl sulfur in the transesterification of chiral sulfinates,[2] numerous instances of nucleophilic substitution reactions have been demonstrated to occur with inversion of configuration at sulfur.[1] However, only in a few cases was the retention mechanism at tricoordinate sulfur observed. Oae et at.[3] found that chiral methyl *p*-tolyl sulfoxide containing ^{18}O exchanged oxygen with dimethyl sulfoxide without racemization, i.e., with retention. The retention of configuration was observed in the conversion of chiral sulfoxides into the corresponding sulfimides using *N*-sulfinyl-*p*-toluenesulfonamide,[4a] bis(*N*-tosylsulfurdiimine),[4b] and *p*-toluenesulfinylnitrene[4c] as reagents. Recently, the reaction of chiral amidothiosulfite with mercury(II) chloride leading to optically active aminosulfinyl chloride was shown to proceed with retention of configuration at the sulfinyl center.[5] It is believed that the formation in these reactions of the trigonal bipyramidal intermediates A, B, and C with the four-membered ring occupying the apical-equatorial position is the main factor responsible for the retention mechanism.[6]



A B C

In this paper we report that the conversion of sulfoxides into aminosulfonium salts by means of *N*-sulfinyldialkyl immonium salts—a reaction described recently by Kresze and Rössert[9]—is accompanied by retention and/or racemization at chiral sulfur, depending on the structure of the starting sulfoxide. We found that optically active sulfoxides (**1a–c**) gave the corresponding optically active aminosulfonium salts (**2a–c**) on treatment with *N*-sulfinyldiethylimmonium tetrafluoroborate (**3**). On the contrary, the reaction of optically active phenyl *p*-tolyl sulfoxide (**1d**) with **3** resulted in the formation of the salt **2d** which exhibited no measurable optical rotation.



1 2 1

a, R = Me, R^1 = *i*-Bu; **b**, R = Me, R^1 = *n*-Bu; **c**, R = Me, R^1 = *p*-Tol; **d**, R = Ph, R^1 = *p*-Tol

In order to establish the stereochemical course as well as the degree of stereospecificity of the **1** → **2** conversion, the base-catalyzed hydrolysis of aminosulfonium salts **2** was carried out. It gave back optically active sulfoxides **1a-c**, however, with the opposite sign of optical rotation to that of the starting **1**. Hydrolysis of **2d** gave completely racemic sulfoxide **1d**. The results of all experiments are collected in Table I.

Since alkaline hydrolysis of aminosulfonium salts has been demonstrated[10] to proceed with inversion of config-

(1) For a review see J. G. Tillet, *Chem. Rev.*, **76**, 747 (1976).

(2) H. Phillips, *J. Chem. Soc.*, 2552 (1925); M. Mikolajczyk, J. Drabowicz, and H. Slebocka-Tilk, *J. Am. Chem. Soc.*, **101**, 1302 (1979).

(3) S. Oae, M. Yokoyama, M. Kise, and N. Furukawa, *Tetrahedron Lett.*, 4131, (1968).

(4) (a) B. W. Christensen and A. Kjaer, *J. Chem. Soc.* D, 934, (1969); F. G. Yamagishi, O. R. Rayner, E. T. Zwicker, and D. J. Cram, *J. Am. Chem. Soc.*, **95**, 1916 (1973); (b) B. W. Christensen, *J. Chem. Soc. D*, 597, (1971); (c) T. J. Maricich and V. L. Hoffman, *Tetrahedron Lett.*, 5309 (1972); *J. Am. Chem. Soc.*, **96**, 7770 (1974).

(5) M. Mikolajczyk and J. Drabowicz, *J. Chem. Soc., Chem. Commun.*, 775 (1974).

(6) In this context, however, it is interesting to note that the alkaline hydrolysis of cyclic *cis*- and *trans*-1-ethoxy-3-methylthietanium salts proceeds with complete inversion at sulfur[7] in spite of the fact that the four-membered ring is present in the molecule. The formation of two intermediates, in which either entering and leaving groups occupy equatorial positions or the ring spans two equatorial positions with the leaving and entering groups axial, may account for inversion. The latter possibility is quite probable in view of the fact that the four-membered ring in the difluorosulfurane derived from thiacyclobutane has been shown by Denney[8] to occupy equatorial positions. Therefore, one can suppose that the four-membered rings containing heteroatoms (O, N, S) with their lone electron pairs show much higher preference for the apical-equatorial arrangement.

(7) R. Tang, and K. Mislow, *J. Am. Chem. Soc.*, **91**, 5644 (1969).

(8) D. B. Denney, D. Z. Denney, and Y. F. Hsu, *J. Am. Chem. Soc.*, **95**, 4064 (1973).

(9) G. Kresze, and M. Rössert, *Angew. Chem.*, **90**, 61 (1978); *Angew. Chem., Int. Ed. Engl.*, **17**, 64 (1978).

(10) O. Bohman, and S. Allenmark, *Chem. Scripta*, **4**, 202 (1973); C. R. Johnson and J. T. Rigau, *J. Org. Chem.*, **33**, 4340 (1968).

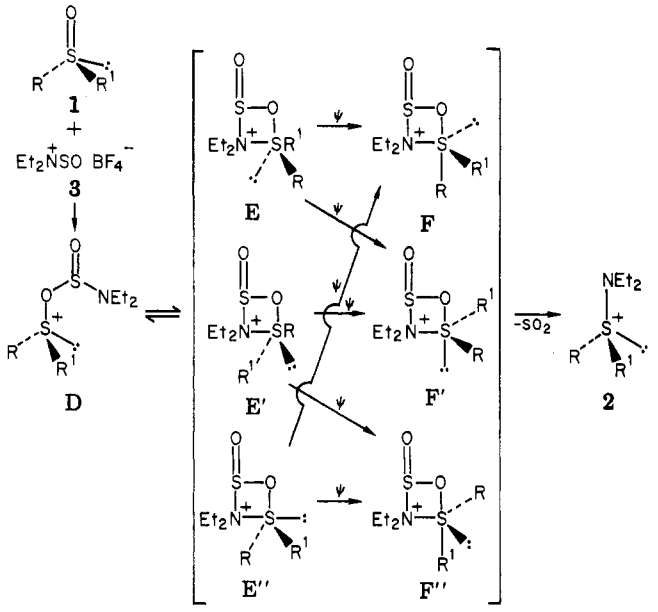
0022-3263/81/1946-2788$01.25/0

Table I. Synthesis and Hydrolysis of Aminosulfonium Salts 2

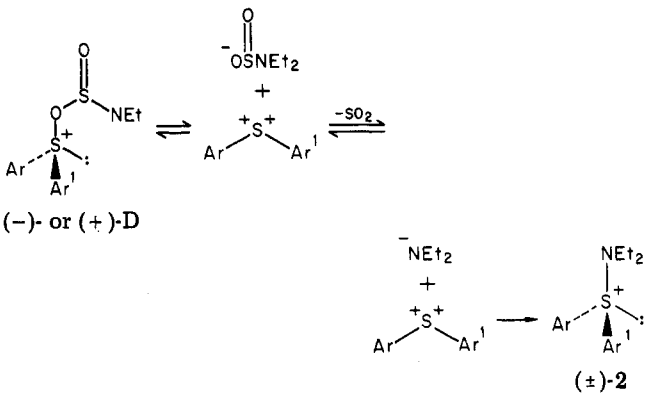
starting sulfoxide 1			aminosulfonium salt 2		sulfoxide 1 from 2			stereospecificity of 1 → 2 → 1 conversion
no.	$[\alpha]_{589}$,[a] deg (ee)	abs config	no.	$[\alpha]_{589}$,[b] deg	$[\alpha]_{589}$,[a] deg (ee)[c]	abs config	% yield[d]	
1a	+64.14 (46.5)	S	2a	+32.5	−53.50 (38.8)	R	90	83.5
1b	−12.25 (11.1)	R	2b	−7.39	+8.70 (7.9)	S	79	71.0
1c	+148.0 (100.0)	R	2c	+10.45	−9.42 (6.4)	S	82	6.4
1d	+27.1 (100.0)	R	2d	0.00	0.00 (0.0)		95	0.0

[a] Optical rotation of sulfoxides 1 was measured in ethanol. [b] Optical rotation of aminosulfonium salts 2 was measured in acetonitrile except for 2a for which the optical rotation value refers to ethanol. [c] Enantiomeric excess values of sulfoxides 1 were calculated based on the following data: $[\alpha]_{589}$ + 138.0° for 1a and $[\alpha]_{589}$ − 109.9° for 1b from M. Mikolajczyk, J. Drabowicz, and B. Bujnicki, unpublished results; $[\alpha]_{589}$ + 148.0° for 1c from B. W. Christensen, *J. Chem. Soc. D* (1971); $[\alpha]_{589}$ + 27.1° for 1d from K. Mislow et al., *J. Am. Chem. Soc.*, 87, 1958 (1965). [d] Yields refer to the full reaction cycle of 1 → 2 → 1.

Scheme I



Scheme II



uration at sulfur as a typical nucleophilic substitution of the S_N2-S type, the conversion of 1 into 2 should occur with retention at the sulfur atom. In regard to the stereospecificity of the reaction sequence 1 → 2 → 1, it is interesting to note that a high stereospecificity was found for dialkyl sulfoxides. Therefore, this reaction cycle involving one reaction with retention and one reaction with inversion may be used to invert the dialkyl sulfoxide configuration, although the method developed by Johnson[11] for inverting the sulfoxide configuration is much better in respect to generality and stereospecificity.

Although the detailed mechanism of the sulfoxide–aminosulfonium salt conversion needs further studies, it is reasonable to expect that the adduct D is formed in the first reaction stage as a result of nucleophilic attack of the sulfinyl oxygen atom of 1 on the sulfur atom of the *N*-sulfinyldiethylimmonium reagent.[9] Then, internal attack of nitrogen on sulfonium sulfur in D may lead to the formation of a short-lived sulfurane intermediate. Theoretically, three different sulfurane species, E, E′, and E″, may be considered to be formed as a consequence of three possible directions of the attack at sulfur (see Scheme I). In all proposed sulfuranes with the four-membered ring in an apical-equatorial position, the S–O bond, which should be broken in the next reaction stage, occupies the equatorial position. Therefore, it is reasonable to assume that they undergo pseudorotations to form new sulfurane intermediates F, F′, and F″ which after SO_2 elimination should give aminosulfonium salts 2 with retention of configuration at sulfur. However, it should be noted that in sulfuranes E″ and F′ the lone electron pair occupies the unfavorable apical position. Therefore, the pathways for the 1 → 2 conversion involving sulfuranes E″ and F′ are less probable. Thus, in our opinion the sequence 1 → D → E → F → 2 best describes the reaction course.

A sharp decrease in the stereospecificity of the reaction under consideration on going from dialkyl to alkyl aryl sulfoxides and its lack in the case of diaryl sulfoxides may be due to the low energy barrier for pyramidal inversion of aminosulfonium salts 2 bearing aromatic substituents or to fragmentation of the intermediate D into the achiral diarylsulfonium dication intermediate (see Scheme II). This point is under current study.

Experimental Section

IR spectra were determined with a Perkin-Elmer 457 infrared spectrophotometer. ^1H NMR spectra were determined at 60 MHz with a R12B Perkin-Elmer spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. Significant ^1H NMR data are tabulated in parentheses in the order number of protons, multiplicity, proton assignments. Elemental analyses of aminosulfonium tetrafluoroborates 2 were not in agreement with the calculated values due to the difficulties of removal of traces of the solvent. Therefore, they were characterized by means of IR and NMR spectroscopy and used for hydrolysis experiments.

***N*-Sulfinyldiethylimmonium Tetrafluoroborate (3).** Ethylsulfinylamine[12] (9.1 g, 0.1 mol) was added to triethyloxonium tetrafluoroborate[13] (14.5 g, 0.077 mol) at 15 °C and the reaction

(11) C. R. Johnson, *J. Am. Chem. Soc.*, 85, 1020 (1963); C. R. Johnson and D. McCants, *ibid.*, 87, 5404 (1965).

(12) A. Dorlares in "Houben-Weyl Methoden der Organischen Chemie", Georg Thieme Verlag, Stuttgart, 1958, Vol. XI/2, p 738.

(13) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, 1967, Vol. 1, p 1210.

mixture was left to stand at this temperature for 10 h. The product **3** formed was washed with methylene chloride and dried in vacuo to give **3** (18.5 g, 90%) as an oil; ^{1}H NMR (CD_3CN) δ 1.50 (6 H, t, CH_3), 4.30 (4 H, q, J = 6.5 Hz, CH_2).

Synthesis of (Diethylamino)isobutylmethylsulfonium Tetrafluoroborate (2a). To a solution of 1.55 g (0.0075 mol) of **3** in 3.75 mL of acetonitrile (2 M solution) at -25 °C was added 0.8 g (0.0075 mol) of sulfoxide (+)-(*S*)-**1a**: $[\alpha]_D$ + 64.14° (46.5% e,e); IR (thin film) 1050, 1070 cm^{-1} (S=O); ^{1}H NMR ($CDCl_3$) δ 1.20 (6 H, d, J = 6 Hz, $(CH_3)_2CH$), 2.30 (1 H, m, $(CH_3)_2CH$), 2.65 (3 H, s, CH_3SO), 2.80 (2H, d,, J = 6 Hz, $CHCH_2$). The reaction mixture was stirred for 1 h and warmed slowly to room temperature and then stirred for an additional 1 h at room temperature. Evaporation of the solvent afforded the crude product which was dissolved in methylene chloride (25 mL). After filtration the solvent was evaporated to give the salt **2a** as a slightly yellow liquid. It was washed with ether and dried in vacuo to afford 1.1 g (94%) of **2a**: $[\alpha]_D$ +32.5°; IR (thin film) 950-1180 cm^{-1} (SN); ^{1}H NMR (CD_3CN) δ 1.23 (6 H, d, J = 6 Hz, $(CH_3)_2CH$), 1.50 (6 H, t, J = 7 Hz, $(CH_3CH_2)_2N$), 2.31 (1 H, m, $(CH_3)_2CH$), 3.35 (3 H, s, CH_3S), 3.50 (4H, q, $(CH_3CH_2)_2N$), 4.55 (2 H, m, C HCH_2); n^{23}_D = 1.4110.

According to the procedure described above other aminosulfonium tetrafluoroborates **2** were prepared. Their optical rotations are given in Table I. The IR and ^{1}H NMR data of **2** are given below.

2b: n^{23}_D 1.4140; IR (thin film) 960-1180 cm^{-1} (SN); ^{1}H NMR (CD_3CN) δ 1.00 (3 H, t, J = 6 Hz, $CH_3CH_2CH_2CH_2$), 1.30 (6 H, t, J = 6 Hz, $(CH_3CH_2)_2N$), 1.35-2.05 (4 H, m, $CH_3CH_2CH_2CH_2$), 2.60 (3 H, s, CH_3S), 2.70 (2 H, m, $CH_3CH_2CH_2CH_2$), 3.65 (4 H, q, J = 6 Hz, $(CH_3CH_2)_2N$).

2c: n^{25}_D 1.4355; IR (thin film) 950-1160 cm^{-1} (SN); ^{1}H NMR (CD_3CN) δ 1.35 (6 H, t, J = 6 Hz, $(CH_3CH_2)_2N$), 2.20 (3 H, s, $CH_3C_6H_4$), 2.65 (3 H, s, CH_3S), 4.00 (4 H, q, J = 6 Hz, $(CH_3CH_2)_2N$), (SN); 7.85-8.20 (4 H, m, aromatic).

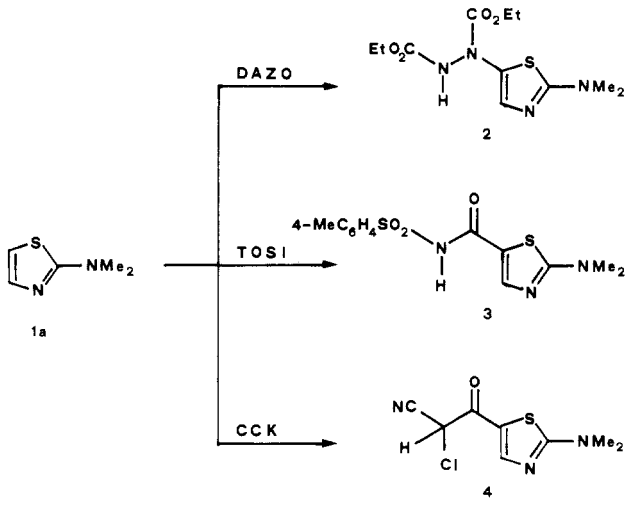
2d: n^{23}_D 1.4850; IR (thin film) 980-1130 cm^{-1} (SN); ^{1}H NMR (CD_3CN) δ 1.30 (6 H, t, J = 6 Hz, $(CH_3CH_2)_2H$), 2.25 (3 H, s, $CH_3C_6H_4$), 3.70 (4 H, q, J = 6 Hz, $(CH_3CH_2)_2N$), 7.90-8.25 (9 H, m, aromatic).

Hydrolysis of 2a. The salt **2a** prepared as above was hydrolyzed with a 0.02 N solution of sodium hydroxide. The aqueous phase was extracted with ether (3 × 20 mL) and chloroform (2 × 20 mL). The combined organic phases were dried over $MgSO_4$. Evaporation yielded 0.72 g (97%) of sulfoxide (-)-(*R*)-**1a**, $[\alpha]_D$ -53.5° (38.8% ee), which had spectral properties indentical with those of the starting sulfoxide (+)-(*S*)-**1a**.

The other salts **2** were hydrolyzed to the corresponding sulfoxides **1** in a similar manner. The optical rotation values and yields of sulfoxides **1** are given in Table I.

Registry No. (*S*)-**1a**, 26451-17-2; (*R*)-**1a**, 62561-56-2; (*R*)-**1b**, 51795-48-3; (*S*)-**1b**, 763-95-1; (*R*)-**1c**, 1519-39-7; (*S*)-**1c**, 5056-07-5; (*R*)-**1d**, 16491-20-6; (±)-**1d**, 77096-69-6; (*S*)-**2a**, 77044-40-7; (*R*)-**2b**, 77060-42-5; (*R*)-**2c**, 77044-42-9; (±)-**2d**, 77044-44-1; **3**, 77044-46-3; ethylsulfinylamine, 77044-47-4; triethyloxonium tetrafluoroborate, 368-39-8.

Scheme I



DAZO = $EtO_2C-N=N-CO_2Et$; TOSI = $4\text{-}MeC_6H_4SO_2-NCO$; CCK = $Cl(CN)C=C=O$

Functionalization of Thiazoles. Selectivity in the Reactions of 2-(Dimethylamino)-1,3-thiazoles with Electrophiles: Formation of Michael-Type Adducts and Thiazolium Salts

Alessandro Medici, Paola Pedrini, Clara Venturoli, and Alessandro Dondoni*

Laboratorio di Chimica Organica, Facoltà di Scienze, Università, Ferrara, Italy

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The functionalization of the thiazole ring[1] is generally a difficult task since, owing to the electron-deficient aromatic character, this heterocycle is very resistant to both electrophilic substitutions and additions[2] as well as cycloadditions across the formal C=C and C=N double bonds.[3] We have described recently two new reactions of thiazoles where proper activation of the reactants overcomes this inertness. One is the reaction of 2-bromothiazole with acetylenic esters activated by aluminum trichloride[4] to give *N*-vinylthiazolines, and the other is the reaction of 2-(dimethylamino)thiazoles with *tert*-butylcyanoketene (TBCK)[5] to give pairs of diastereomeric 2:1 cycloadducts (δ-lactones condensed with the thiazole ring across the C_4-C_5 bond) and an open-chain substitution product (Michael-type adduct at C_5 of the thiazole ring).

In view of the activating and directing effect of the dimethylamino group in position 2 of the thiazole ring toward the strong electron acceptor TBCK,[5] we have now investigated the reactions of 2-(dimethylamino)-1,3-thiazoles (**1**) with compounds containing an electron-poor double or triple bond whose reactivity with electron-rich systems is well documented.[6] The aim of this research was to explore the possibility of obtaining [2 + 2] cycloadducts across the C=C double bond[5] of the thiazole ring whose subsequent opening would provide a cis-stereospecific functionalization at this bond and/or achieve a regiospecific substitution at one center of the heterocyclic system. While efforts directed toward the first objective

(1) For recent reviews on thiazoles, see: (a) Iddon, B.; Lowe, P. A. *Org. Compd. Sulphur, Selenium, Tellurium*, **1979**, *5*. (b) Metzger, J. V., Ed., "Thiazole and Its Derivatives"; Wiley: New York, 1979.

(2) See ref 1b, p 99.

(3) Reinhoudt, D. N. *Adv. Heterocycl. Chem.* **1977**, *21*, 253.

(4) Medici, A.; Pedrini, P.; Fogagnolo, M.; Dondoni, A. *J. Chem. Soc., Chem. Commun.*, **1980**, 1077.

(5) Dondoni, A.; Medici, A.; Venturoli, C.; Forlani, L.; Bertolasi, V. *J. Org. Chem.* **1980**, *45*, 621.

(6) In all cases, the actual choice of reactant was based mainly upon stability toward the basicity of thiazoles **1** (see ref 5 and 12). This prevented the use of unhindered activated ethylenes such as 1,1-dicyanoethylene as well as of highly reactive ketenes such as dichloro- and chloroazidoketene, because of their rapid polymerization in the presence of thiazoles **1**. Nevertheless, in addition to those described in the paper, the compounds which have been tested include various electron-poor olephins (acrylonitrile, diethyl maleoate, fumaronitrile, cinnamoyl azide, maleic anhydride, (phenylsulfonyl)ethylene, 2,4-dihydrothiophene 1,1-dioxide, vinyl isocyanate, tetracyanoquinodimethane), acetylenes (dimethyl acetylenedicarboxylate), and azo esters (4-phenyl-1,2,4-triazoline-3,5-dione). Reactivity was explored in apolar (benzene, ethyl ether, CCl_4) and polar (MeCN, CH_2Cl_2, DMF) solvents at room temperature and/or under reflux of the solvent.

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