

SIMILARITY AND DISSIMILARITY BETWEEN WITTIG AND WITTIG-HORNER SYNTHON REACTIVITY TOWARD CYCLIC AND ACYCLIC *cis*-DISULFIDES

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Abstract: The behavior of different types of α -phosphoryl carbanions such as alkoxycarbonylmethylene, cyanomethylene and viny-phosphonate toward 5-(4-chlorophenyl)-4-cyano-1,2-dithiol-3-thione **1** and tetramethylthiuram disulfide **2** has been investigated. The reactions proceeded in the presence of a base whereby several substituted thiols, dithiols and different types of dimeric products as well as many phosphono substituted *S*-heterocycles were obtained.

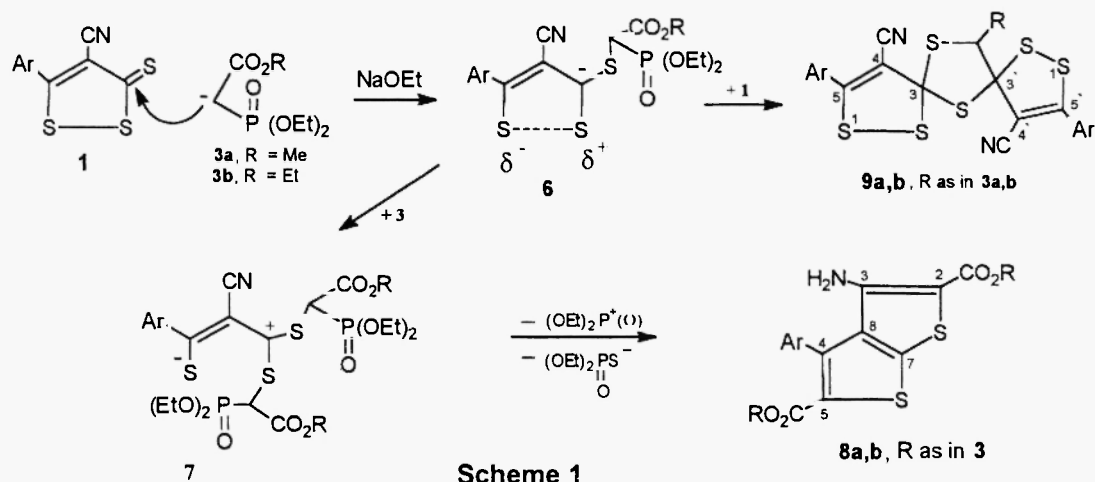
Introduction

In relation to previous reports about alkylidenephosphoranes [1] and α -phosphoryl carbanions [2] as inexpensive and easily accessible synthetic starting materials for a lot of different heterocycles, we reported some time ago the syntheses of a series of sulfur-containing heterocycles from the reactions of phosphorus nucleophiles with cyclic and acyclic *cis*-disulfides [3]. Since these classes of compounds have become remarkably important from a chemical as well as a biological point of view [4], we were interested in the investigation of further transformations based on Wittig-Horner reaction.

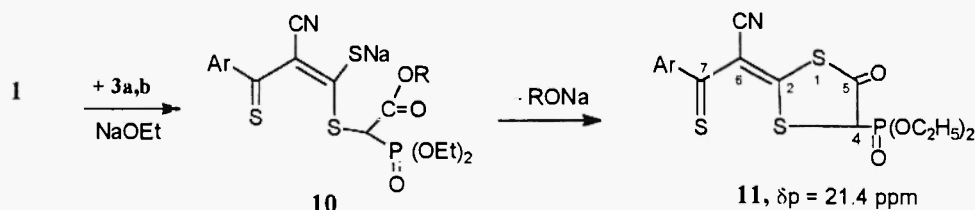
The work detailed here investigated reactivity of α -phosphoryl carbanions (Wittig-Horner (WH) reagents) **3a-c** and **4** toward 5-(4-chlorophenyl)-4-cyano-1,2-dithiol-3-thione **1** and tetramethylthiuram disulfide **2**. A comparative study on the behavior of **1** and **2** to alkylidenephosphorane ($\text{Ph}_3\text{P}=\text{CHR}^1$, R^1 as in **3**) counterparts **5** was also reported.

Results and Discussion

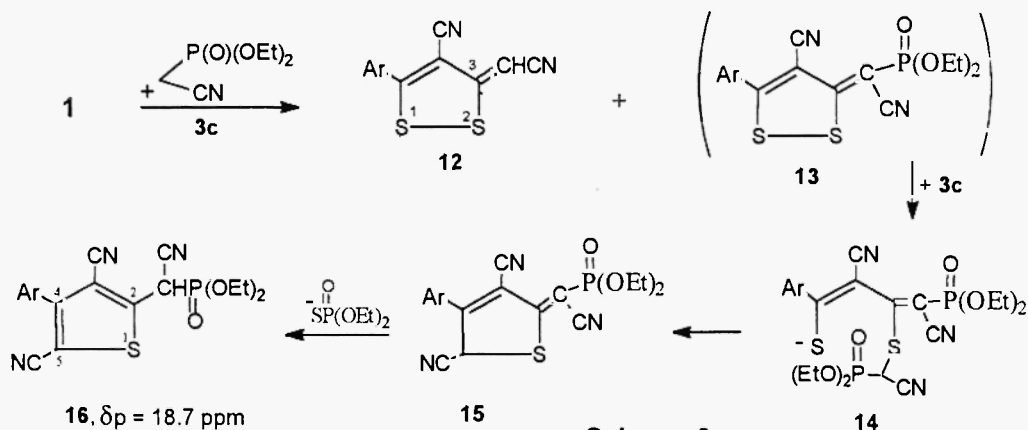
Treatment of the orange dithiol **1** with three molar equivalents diethyl phosphonoacetates **3a** or **3b** in alcoholic NaOEt at room temperature resulted in a greenish coloration of the solution, which later (~ 10 h) became dark brown with formation of a yellow precipitate. The isolated solid was washed with ethyl acetate and assigned the dispiro products **9a** or **9b** (~ 22%). Compounds **9a,b** were assigned *E*-isomers since it is generally accepted [5] that *Z*-alkenes having an electron-withdrawing group (CN) substituent α to the thiocarbonyl group of the substrate, isomerizes to the thermodynamically more stable *E*-isomer. The remaining soluble materials were chromatographed yielding phosphono substituted dithiol **11** (~30%) and 4-(4-chlorophenyl)-thieno-[3,2-*c*]-3-aminothiophene-2,5-dialkylcarboxylate **8a,b** (~15%) according to Schemes 1 and 2. A reasonable mechanistic explanation of these transformations involves an initial thiophilic addition of the carbanion to the thiocarbonyl group activated by an electron-withdrawing substituent (CN group) [6]. This addition leads to a reactive phosphono intermediate **6**, which can undergo two pathways: a) It reacts with a second equivalent of the starting substrate **1** leading to the dispiro product **9** with concomitant elimination of the phosphono moiety (as dialkyl phosphonate). Similar dispiro compound formed from the reaction of substituted 3-thiocyanobutanone and arylazides [7]. b) **6** may react with a second equivalent of the carbanion **3a,b** at the -S-S-linkage in **1** giving the resonance hybrid **7**. Under thermal conditions and in the presence of a base [8] the diphosphonate **7** is presumably formed. The further transformation of **7** afforded **8** via intramolecular WH reaction [3b] and a ring closure with elimination of phosphono and thiophosphoryl moieties (Scheme 1).



On the other hand, **11** resulted from an initial attack by the carbanion center of **3a,b** on the –S–S–bond in **1** affording **10**, which might be expected to be stabilized by ring closure and extrusion of an appropriate alkoxide molecule to give **11** (Scheme 2). **11** exists in the keto form rather than the enol structure as indicated by physical and spectroscopic data (see Table 1).

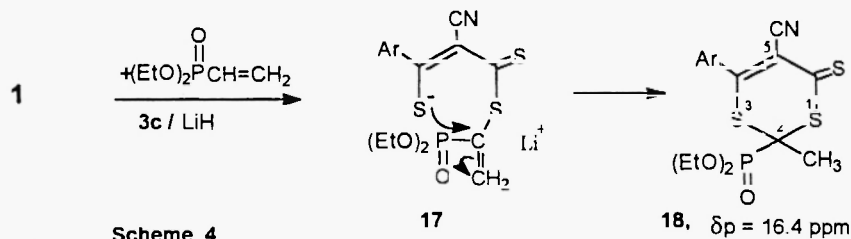


When the dithiol **1** was treated with an excess of diethyl cyanomethylphosphonate **3c**, it produced the Wittig-Horner product **12** (30%) and 4-(4-chlorophenyl)-3,5-dicyanothiophene-2-(cyanomethyldiethylphosphonate) **16** (34%) (Scheme 3).



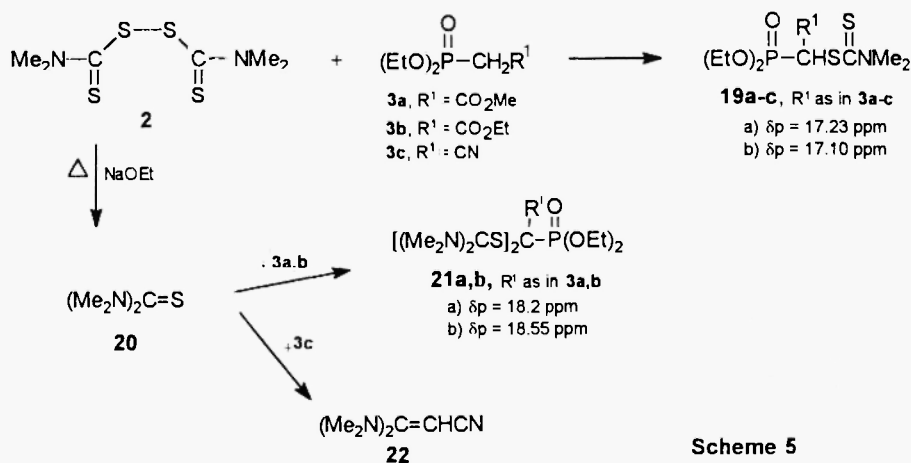
The formation of **16** can be interpreted as occurring through the condensation of the carbanion ion with the thiocarbonyl group and extrusion of H_2S molecule [2e, 9] (Perkin-type condensation) yielding the intermediate **13**. Further reaction of **13** with a second molecule of **3c** gives **14**. Internal WH reaction and hydrogen rearrangement with concomitant elimination of thiophosphoryl moiety would produce the final product **16**.

In contrast, an insertion reaction at the -S-S- linkage had been observed when **1** was treated with diethyl vinylphosphonate in DMF containing LiH yielding 4-(4-chlorophenyl)-5-cyano-2-methyl-6-thioxo-1,3-dithiol-2-yl-diethylphosphonate **18** (48%). This is the only identified product formed regardless of the ratio of the reactants employed. Insertion reaction was previously reported for the reaction of *cis*-disulfides and reactive ylides [8].

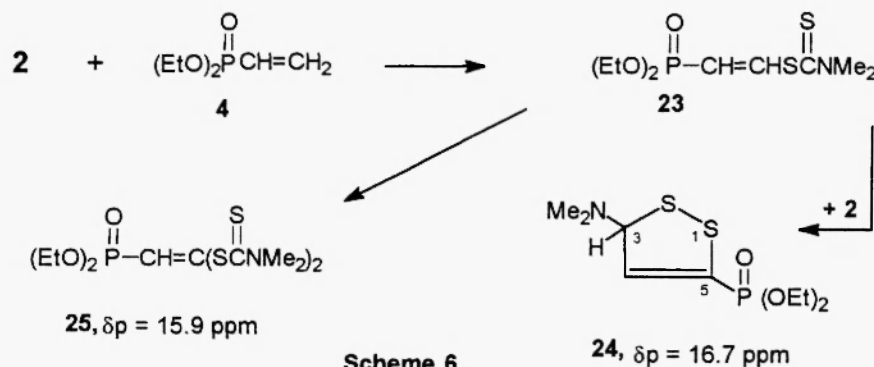


In view of the present results (**1** + **3a-c**), and considering the earlier report [3b], which described the behavior of alkylidenephosphorane counterparts **5a,b** ($\text{Ph}_3\text{P}=\text{CHR}^1$, R^1 as in **3**) (and others) toward the substrate **1**, some interesting observations should be drawn: 1) The reactions of **1** with either **3a,b** or **5a,b** are a two-stage process, initiated by thiophilic addition of the carbanion to the thiocarbonyl group activated by an electron-withdrawing substituent (CN group) [6]. 2) The sequel of the initial step, however, varies markedly according to the type and the α -substituent of the carbanion. 3) The results, however, have shown that the behavior of the nitrile group in **1** with WH reagents is in great disparity with that of the Wittig synthons [3b]. Finally, the findings support the assumption that the basic medium (see **1** + **3**) stimulates the course of the reaction at the S-S bond [8].

Further extension of this study to other acyclic *cis*-disulfide, tetramethylthiuram disulfide **2** was investigated. In a systematic study, the reaction of **2** with **3a,b** proceeded in alcoholic NaOEt solution at the reflux temperature (6 h) affording dimethyldithiocarbonylmethylphosphonnates **19a,b** (~20%) and bis-(dimethyldithiocarbonyl)methylphosphonnates **21a,b** (~40%). However, the reaction of **2** with **3c** in addition to **19c** (24%) gave the known [3f] olefin **22** (38%), according to Scheme 5. It is worth mentioning here that **22** was the reaction product of **2** with **5c** [3f]. The reaction mechanism depicted in Scheme 5 can possibly account for the formation of **19**, **21** and **22**. Compounds **21a,b** are considered to proceed via formation of tetraalkylthiourea **20**. Decomposition of **2** to **20**, carbon disulfide and sulfur is well documented [3f, 10]. Subsequent thiophilic addition [1f, 11] of **3a,b** to **20** affords **21a,b**. Furthermore, the results presented in Scheme 5 show a marked resemblance between **3a-c** and **5a-c** [1f, 8] in their chemical behavior toward the disulfide **2** under investigation.



Finally, treatment of **2** with diethylvinylphosphonate **4** in DMF, in the presence of LiH, yielded [bis-(dimethyldithiocarbamyl)ethylene]diethylphosphonate **24** and dithiocarbamyl **25** in equal yields (28%). The generation of an intermediate like **23** and the products that have been described in Scheme 6 parallel the mechanism, previously reported by Galli for the reaction of **2** with reactive phosphoranes [8].



Elemental analyses, molecular weight measurements (MS), IR and NMR spectroscopy (see the Table) confirm the structure of the new products. The phosphonates **3** and **4** were used in the threefold molar excess based on the corresponding substrates **1** or **2**, otherwise the yields of the resulting products decrease drastically.

In summary, WH reagents are interesting starting materials for the synthesis of heterocyclic compounds.

Table 1 Physical Properties, IR and ^1H NMR Spectral Data for the Products **8**, **9**, **11**, **12**, **16**, **18**, **21**, **24** and **25**

Product/ color	R/R ¹	Mp (°C) ^b (Solvent)	Yield (%)	IR (cm ⁻¹)	^1H NMR ^b (CDCl ₃), δ (ppm); J (Hz)
8a ^c / colorless	Me	159-161 (CH ₂ Cl ₂)	16	3357-3325 (NH ₂), 1725, 1715 (2C=O)	3.7, 3.86 (2s, 6H, 2 x OCH ₃), 5.48 (br, 2H, NH ₂).
8b / colorless	Et	135-137 (CH ₂ Cl ₂)	14	350-3320 (NH ₂), 1717, 1710 (2C=O)	1.05-1.16 (2t (m), 6H, 2 x CH ₃), 3.65, 3.77 (2q, $J_{\text{HH}} = 7$, 4H, OCH ₂), 5.41 (br, 2H, NH ₂).
9a / yellow	Me	226-228 (AcOEt)	20	2218, 2210 (2 CN), 1718 (C=O), 1266 (-S-S-).	3.78 (s, 3H, OCH ₃), 4.82 (s, 1H, CH-R).
9b ^d / yellow	Et	243-245 (AcOEt)	23	2217, 2210 (2CN), 1715 (C=O), 1264 (-S-S-).	0.96 (t, $J = 6.8$, 3H, O.C.CH ₃), 3.88 (q, $J = 6.8$, 2H, OCH ₂), 4.86 (s, 1H, CH-R).
11 ^e / colorless	-	110-112 (cyclohexane)	~ 30	2216 (CN), 1715 (C=O), 1482 (S-S), 1255 (P=O), 1082 (POC).	1.18-1.27 [2t (m), 6H, 2 x CH ₃], 3.98-4.08 [2q (m), 4H, 2 x CH ₂], 4.22 (d, $J_{\text{HP}} = 17.2$, 1H, -CH-P).
12 / colorless	-	155-157 (acetone)	30	2210, 1995 (2CN), 1630 (C=C), 1288 (S-S).	6.82 (s, 1H, =CHCN).
16 / pale yellow	-	166-168 (EtOH)	34	2215-1996 (br, 3CN), 1256 (P=O), 1065 (P-O-C).	1.13-1.25 [2t (m), 6H, 2 x CH ₃], 4.2-4.28 [2q (m), 4H, 2 x CH ₂], 4.31 (d, $J = 15.5$, 1H, -CH-P).
18 ^f / yellow	-	175-177 (EtOH)	48	2220 (CN), 1480 (C=S), 1256 (P=O), 1065 (P-O-C).	1.58 (d, $J_{\text{HP}} = 8.5$, 3H, CH ₃), 1.25-1.34 [2t (m), 6H, 2 x CH ₃], 4.08-4.23 [2q (m), 4H, 2 x OCH ₂].
19a ^g / colorless	R ¹ = CO ₂ Me	185-187 (acetone)	18	1722 (C=O), 1485 (NC=S), 1065 (P-O-C).	1.22, 1.25 (2t, $J_{\text{HH}} = 6.5$, 6H, C.CH ₃), 3.17, 3.25 [2s, 6H, N(CH ₃) ₂], 3.83 (s, 3H, OCH ₃), 4.07-4.22 (2q(m), 4H, OCH ₂), 5.44 (d, $J = 18.2$, CH-P).
19b / colorless	R ¹ = CO ₂ Et	168-170 (acetone)	22	1725 (C=O), 1485 (NC=S), 1055 (P-O-C).	0.94 (t, $J = 6.8$, 3H, CH ₃ , ester), 1.22-1.31 [2t(m), 6H, POCH ₃], 3.27, 3.25 [2s, 6H, N(CH ₃) ₂], 3.68 (q, 2H, OCH ₂ , ester), 4.08-4.19 [2q(m), 4H, OCH ₂], 4.57 (d, $J = 18.2$, CH-P).

19c/ colorless	R ¹ = CN	194-196 (MeCN)	24	2218 (CN), 1488 (NC=S), 1080 (P-O-C).	1.21, 1.25 (2t, <i>J</i> = 7.1, 6H, C-CH ₃), 3.24, 3.27 [2s, 6H, N(CH ₃) ₂], 4.45-4.5 [2q (m), 4H, OCH ₂], 5.15 (d, <i>J</i> = 20.2, HC-P).
21a^b/ light yellow	R ¹ = CO-Me	168-170 (EtOH)	40	1715 (C=O), 1256 (P=O), 1080 (P-O-C).	1.22, 1.24 (2t, <i>J</i> = 7.0, 6H, C-CH ₃), 3.18-3.28 (4s, 24H, NCH ₃), 3.81 (s, 3H, OCH ₃), 4.16-4.25 [2q (m), 4H, OCH ₂].
21b/ light yellow	R ¹ = CO ₂ Et	150-152 (MeCN)	41	1718 (C=O), 1260 (P=O), 1088 (P-O-C).	0.91 (t, <i>J</i> = 6.8, 3H, CH ₃ , ester), 1.21, 1.28 (2t, <i>J</i> = 7.0, 6H, C-CH ₃), 3.08, 3.21 (4s, 24H, NCH ₃), 4.06-4.13 [2q (m), 4H, OCH ₂].
24/ pale yellow	-	126-128 (CH ₂ Cl ₂)	28	1280 (S-S), 1260 (P=O), 1085 (P-O-C).	1.21-1.26 (2t(m), 6H, C-CH ₃), 3.11, 3.18 (2s, 2x3H, NCH ₃), 4.2-4.25 (2q, 4H, OCH ₂), 5.33 (d, <i>J</i> = 5.5, 1H, C-3-H), 6.87 (d, <i>J</i> = 5.5, 1H, C-4-H).
25/ yellow	-	182-184 (CHCl ₃)	28	1618 (C=C), 1487 (C=S), 1258 (P=O), 1080 (P-O-C).	1.2-1.24 (2t (m), 6H, C-CH ₃), 3.12, 3.22 (2s, 2 x 6H, NCH ₃), 4.08-4.13 (2q, 4H, OCH ₂), 6.15 (d, <i>J</i> = 21.6, 1H, CH-P).

a) Satisfactory elemental analyses and molecular weight measurements (MS) are obtained for all new compounds. b) Aromatic hydrogen protons lie in $\delta \sim 7.28$ -8.14 ppm region. c) δ c: 52.8, 55.6 (2 x O-CH₃), 127.5, 128.2 (C-4, C-5), 144.6, 146.2 (C-2, C-5), 159.4, 161.6 (2 x C=O, ester). d) δ c: 14.6, 15.3 (2 x CH₃), 48.8 (C-HR), 62.6 (O-CH₂), 78.2, 84.4 (3'-C, 3-C), 112.4, 112.8 (2 x C-N), 110.5, 111.2 (2 x C-CN). e) δ c: 15.5 (CH₃), 44.8 (d, *J*_{CP} = 85.3, C-H-P), 62.1 (O-CH₂), 110.3 (6-C), 117.6 (CN), 126.7 (2-C), 165.5 (5-C), 189.4 (7-C). f) δ c: 12.6 (d, *J*_{CP} = 12, CH₃), 15.4, 16.1 (2 x C-CH₃), 60.7 (O-CH₂), 73.1 (2-C), 110.3 (5-C), 117.8 (C-N), 189.2 (6-C). g) δ c: 16.2 (CH₃), 31.7, 33.8 [2s, N(CH₃)₂], 41.7 (d, *J* = 135, C-HP), 53.5 (OCH₃), 62.3 (OCH₂), 159.6 (C=O), 183.6 (C=S). h) δ c: 16.2 (C-CH₃), 31.3, 31.38, 31.7, 31.88, 33.2, 33.29, 33.6, 33.8 [4N(CH₃)₂], 48.6 (d, *J* = 137.5, C-HP), 51.3 (C-N), 162.3 (C=O).

Experimental Section

Melting points are uncorrected. Infrared spectra were measured with a Perkin Elmer IR- Spectrometer model 597 using KBr discs. The ¹H and ¹³C NMR spectra were recorded with a Bruker Model WH-300 Hz spectrometer. The ³¹P NMR spectra were run on a Varian CFT-20 relative to external H₃PO₄. Mass spectra were performed at 70 eV on a Shimadzu GCS-QPEX Spectrometer provided with a data system. All reactions were carried out under strictly moisture and oxygen free conditions. Light petroleum refers to the fraction 40-60 °C.

Reaction of 5-(4-Chlorophenyl)-4-cyano-1,2-dithiol-3-thione 1 with α -Phosphonyl Carbanions 3a-c and 4

General Procedure. a) with **3a-c**: A solution of 6 molar amounts of sodium ethoxide (NaOEt) in 25 ml ethyl alcohol was treated with 3 molar amounts of the carbanion **3a-c** and then the dithiol **1** [12] (1.0 g, 3.7 mmol) was added. The resulting reaction mixture was kept stirring for 8 to 10 h (TLC) at room temperature. The product mixture was concentrated and diluted with a small amount of distilled water followed by solvent extraction (CHCl₃), drying and evaporation. Chromatography and crystallization purified the crude product mixture.

- According to this procedure, reaction of **1** with **3a,b** afforded the dispiro products **9a** and **9b**, which were collected from the product mixture. The remaining soluble materials were chromatographed on silica gel by using hexane/AcOEt as the eluents whereupon compounds **11** and **8a** or **11** and **8b** were isolated, respectively.

- With **3c**: the products **12** and **16** were obtained. Data of the new products were summarized in the Table.

b) With **4**: To a stirred solution of 1.8 g (11.1 mmol) vinylphosphonate **4**, 1.0 g (3.7 mmol) **1** and 30 ml DMF 500 mg LiH was added at r.t. After 5 h the reaction mixture was worked up as described in general procedure and chromatographed by hexane/EtOAc (6:4; v/v) to give **18**.

Reaction of Tetramethylthiuram Disulfide 2 with 3a-c and 4:

a) A solution of 12.5 mmol **3a-c**, 1.0 g (4.17 mmol) **2** [13] and 30 ml EtOH was treated with 10 mmol sodium metal. The reaction mixture was refluxed for ~ 8 h (TLC), followed by the above described working up and chromatographed using

hexane-AcOEt as eluents. With **3a,b** the products **21a,b** and **19a,b** were obtained. With **3c**: **19c** and the known **22** were isolated. The olefin **22** was obtained as yellow crystals (220 mg, 38% based on **2**) mp 185-188 °C (CHCl₃) [lit. [3f], mp 186-188 °C].

b) With **4**: From a mixture of **2** and **4** in DMF solution containing LiH, using the same amounts and typical procedure as with dithiol **1**, the products **24** and **25** were obtained. Physical and spectral data of the new products are summarized in the Table.

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