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.

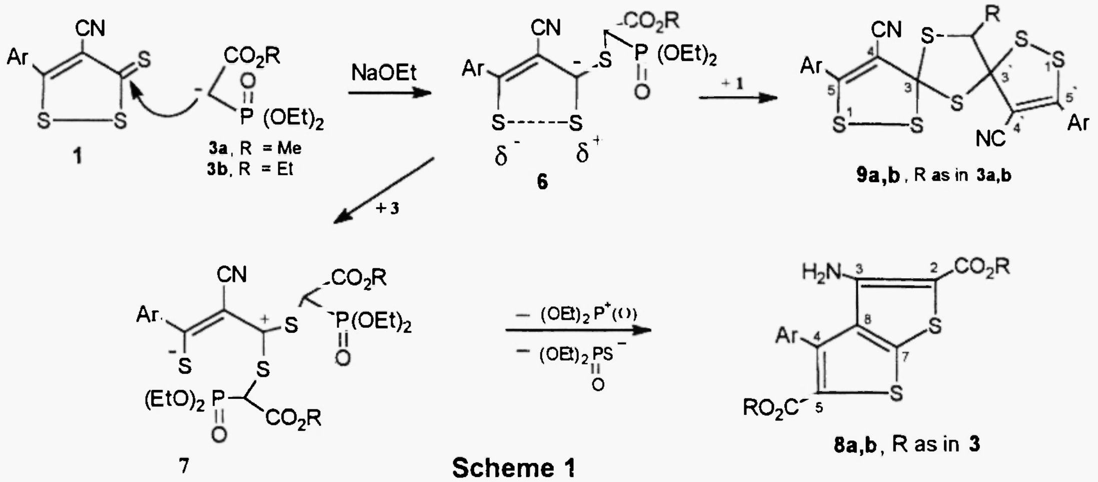
Introduction

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 ($Ph_3P=CHR^1$, R^1 as in **3**) counterparts **5** was also reported.

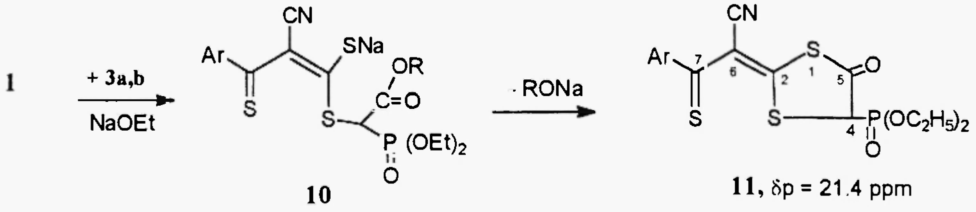
Results and Discussion

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).



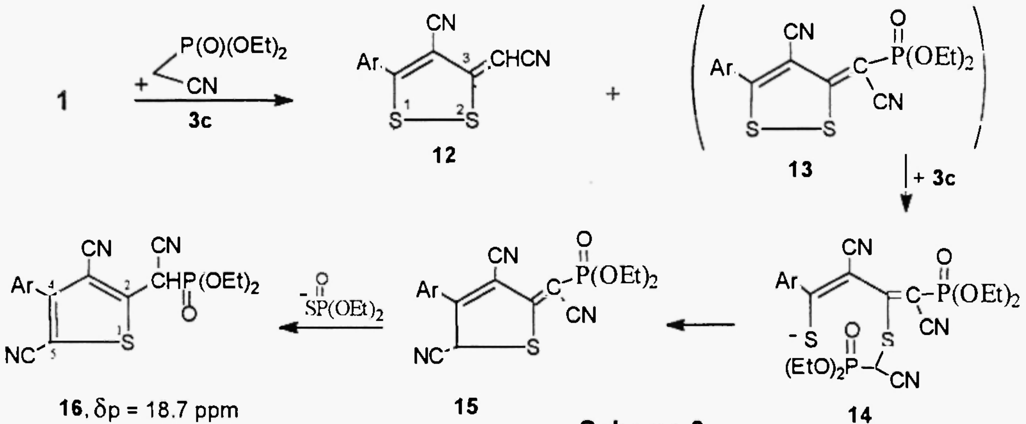
Scheme 1

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).



Scheme 2

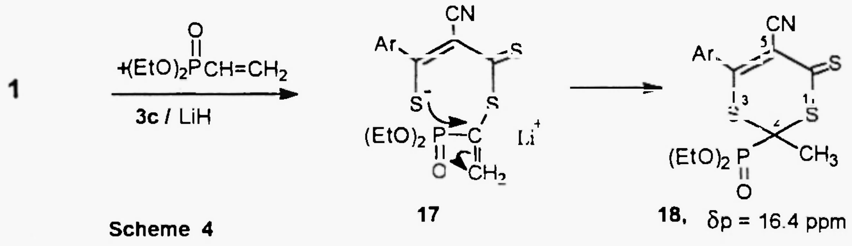
When the dithiol **1** was treated with an excess of diethyl cyanomethylphosphonate **3c**, it produced the Wittig-Horner product **12** (30%) and 4-(4-chlorophenyl)-3,5-dicyanothiophene-2-(cyanomethyldiethylphosphonate) **16** (34%) (Scheme 3).



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**.

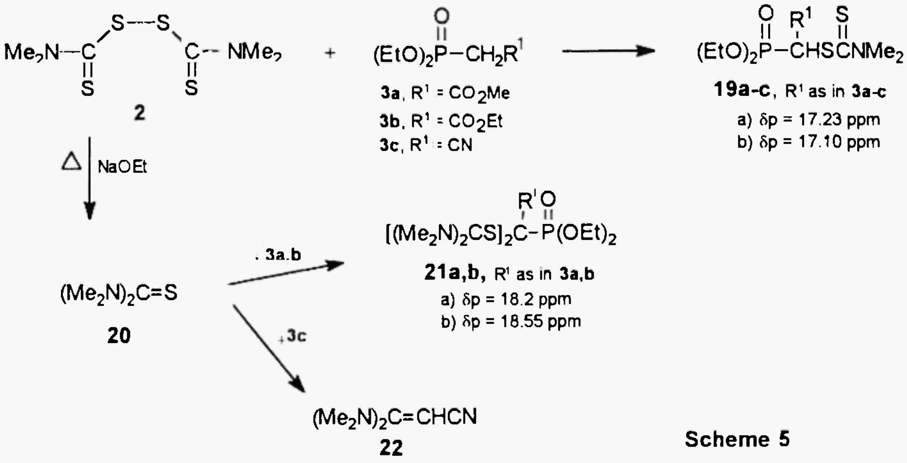
In contrast, an insertion reaction at the -S-S- linkage had been observed when **1** was treated with diethyl vinylphosphonate in DMF containing LiH yielding 4-(4-chlorophenyl)-5-cyano-2-methyl-6-thioxo-1,3-dithiol-2yl-diethylphosphonate **18** (48%). This is the only identified product formed regardless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



Scheme 4

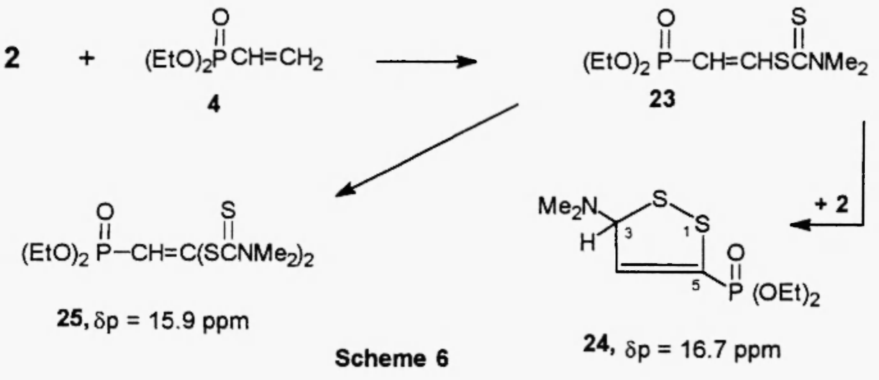
In view of the present results (**1** + **3a-c**), and considering the earlier report [3b], wnich described the behavior of alkylidenephosphorane counterparts **5a,b** ($Ph_3P{=}CHR^1$, R^1 as in **3**) (and others) toward the substrate **1**, some interesting observations should be drawn: 1) The reactions 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 dimethyldithiocarbomylmethylphosphonnates **19a,b** (~ 20%) and bis-(dimethyldithiocarbamyl)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 **2** 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.



Scheme 5

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].



Scheme 6

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

Table 1 Physical Properties, IR and ^{1}H 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})	^{1}H NMR^b ($CDCl_3$), δ (ppm); J (Hz)
8a^c/ *colorless*	Me	159-161 (CH_2Cl_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_2Cl_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_{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 (cyclo-hexane)	~ 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_{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_{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_2Me	185-187 (acetone)	18	1722 (C=O), 1485 (NC=S), 1065 (P-O-C).	1.22, 1.25 (2t, J_{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_2Et	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, *J* = 7.1, 6H, C.C*H*$_3$), 3.24, 3.27 [2s, 6H, N(C*H*$_3$)$_2$], 4.45-4.5 [2q (m), 4H, OC*H*$_2$], 5.15 (d, *J* = 20.2, *H*C-P).
21a[h]/ *light yellow*	R^1 = CO_2Me	168-170 (EtOH)	40	1715 (C=O), 1256 (P=O), 1080 (P-O-C).	1.22, 1.24 (2t, *J* = 7.0, 6H, C.C*H*$_3$), 3.18-3.28 (4s, 24H, NC*H*$_3$), 3.81 (s, 3H, OCH$_3$), 4.16-4.25 [2q (m), 4H, OC*H*$_2$].
21b/ *light yellow*	R^1 = CO_2Et	150-152 (MeCN)	41	1718 (C=O), 1260 (P=O), 1088 (P-O-C).	0.91 (t, *J* = 6.8, 3H, C*H*$_3$, ester), 1.21, 1.28 (2t, *J* = 7.0, 6H, C.C*H*$_3$), 3.08, 3.21 (4s, 24H, NC*H*$_3$), 4.06-4.13 [2q (m), 4H, OC*H*$_2$].
24/ *pale yellow*	-	126-128 (CH_2Cl_2)	28	1280 (S-S), 1260 (P=O), 1085 (P-O-C).	1.21-1.26 (2t(m), 6H, C-C*H*$_3$), 3.11, 3.18 (2s, 2x3H, NC*H*$_3$), 4.2-4.25 (2q, 4H, OC*H*$_2$), 5.33 (d, *J* = 5.5, 1H, C-3-*H*), 6.87 (d, *J* = 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-C*H*$_3$), 3.12,3.22 (2s, 2 x 6H, NC*H*$_3$), 4.08-4.13 (2q, 4H, OC*H*$_2$), 6.15 (d, *J* = 21.6, 1H, C*H*-P).

a) Satisfactory elemental analyses and molecular weight measurements (MS) are obtained for all new compounds. b) Aromatic hydrogen protons lie in δ ~ 7.28-8.14 ppm region. c) δc: 52.8, 55.6 (2 x OCH$_3$), 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) δc: 14.6, 15.3 (2 x CH$_3$), 48.8 (CHR), 62.6 (OCH$_2$), 78.2, 84.4 (3'-C, 3-C), 112.4, 112.8 (2 x CN), 110.5, 111.2 (2 x C.CN). e) δc: 15.5 (CH$_3$), 44.8 (d, J_{CP} = 85.3, CH-P), 62.1 (OCH$_2$), 110.3 (6-C), 117.6 (CN), 126.7 (2-C), 165.5 (5-C), 189.4 (7-C). f) δc: 12.6 (d, $^2J_{CP}$ = 12, CH$_3$), 15.4, 16.1 (2 x C.CH$_3$), 60.7 (OCH$_2$), 73.1 (2-C), 110.3 (5-C), 117.8 (CN), 189.2 (6-C). g) 16.2 (CH$_3$), 31.7, 33.8 [2s, N(CH$_3$)$_2$], 41.7 (d, *J* = 135, CHP), 53.5 (OCH$_3$), 62.3 (OCH$_2$), 159.6 (C=O), 183.6 (C=S). h) δc: 16.2 (C.CH$_3$), 31.3, 31.38, 31.7, 31.88, 33.2, 33.29, 33.6, 33.8 [4N(CH$_3$)$_2$], 48.6 (d, *J* = 137.5, CHP), 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 ^{13}C NMR spectra were recorded with a Bruker Model WH-300 Hz spectrometer. The ^{31}P NMR spectra were run on a Varian CFT-20 relative to external H_3PO_4. Mass spectra were performed at 70 eV on a Schimadzu 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 ($CHCl_3$), 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 Ttetramethylthiuram 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 ($CHCl_3$) [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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