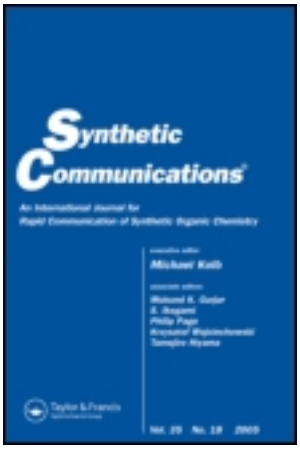

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Convenient Synthesis of 2,4-Disubstituted Tetrahydrothiophenes from Mannich's Adducts

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Convenient Synthesis of 2,4-Disubstituted Tetrahydrothiophenes from Mannich's Adducts

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Abstract: Ammonium salts of β-functionalized allylic amines **1** were successfully employed as electrophilic agents with functional thiols. The obtained intermediate **2** underwent intramolecular cyclization in the presence of potassium *tert*-butoxide to afford 2,4-disubstituted tetrahydrothiophenes **3**.

Keywords: Mannich's adduct, mercaptoacetonitrile, methyl mercaptoacetate, tetrahydrothiophene

INTRODUCTION

We have recently reported[1,2] that the ammonium salts derived from Mannich's adducts constitute interesting precursors for allylphosphonates functionalized at the beta position. The latter were obtained by nucleophilic displacement of the ammonium moiety by the phosphonate group.

In the present work, we intend to examine the extension of the reactivity of these substrates to functionalized thiols. The nucleophilic substitution of the ammonium group leads to the formation of a new series of methylprop-2-enylthioacetonitrile and methyl prop-2-enylthioacetate **2**. These intermediates are easily converted, under basic conditions, into substituted tetrahydrothiophene **3** (Scheme 1).

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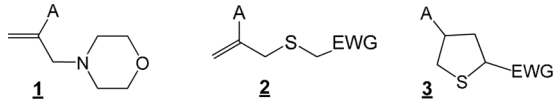


Scheme 1. Allylamines **1**, precursors of thioallyls **2** and thiophens **3**.

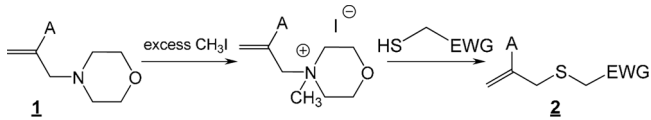
Such heterocyclic compounds exhibit a wide spectrum of biological activities,[3,4] are useful building blocks in the synthesis of a variety of natural products,[5] and are widely used as ligands in asymmetric catalysis.[6,7]

RESULTS AND DISCUSSION

Alkyl mercaptoacetates and mercaptoacetonitrile are extensively used in heterocyclic synthesis. These reactants possess dual reactive properties. The thiol's end represents the nucleophilic site, and the nitrile and or ester constitute the electrophilic center. Reactions involving these species are believed to start by a nucleophilic attack of the thiol followed by a rather unexpected attack of the carbon α to the nitrile or ester group. The latter seems to lose reactivity in favor of the α-carbon particularly under basic conditions.[8–10]

Synthesis of Prop-2-enylthioacetonitriles and Methyl Prop-2-enylthioacetates 2

Mannich's ammonium salt adducts **1** react with methyl mercaptoacetate or mercaptoacetonitrile to form the corresponding intermediate **2** (Scheme 2) in fair to excellent yields (Table 1). Considering the steric bulk involved, the mechanism by which the substitution proceeds is believed to be S_N2'.



Scheme 2. Functionalized thioallyls obtained from allylamines **1**.

Table 1. *Cis–trans* ratio and yields obtained with the starting products **1a–d**

Substrate **1**	A	Product **2**	EWG	Yield[a]	Product **3**	Yield[a,b]	*Cis–trans*
1a	CN	**2a$_1$**	CN	78	**3a$_1$**	62	31:69
		2a$_2$	CO_2Me	91	**3a$_2$**	75	30:70
1b	CO_2Et	**2b$_1$**	CN	55	**3b$_1$**	56	30:70
		2b$_2$	CO_2Me	65	**3b$_2$**	66	32:68
1c	$PO(OEt)_2$	**2c$_1$**	CN	79	**3c$_1$**	53	34:66
		2c$_2$	CO_2Me	82	**3c$_2$**	62	35:65
1d	*p*.NO_2Ph	**2d$_1$**	CN	71	**3d$_1$**	44	29:71
		2d$_2$	CO_2Me	75	**3d$_2$**	59	27:73

[a]Yields obtained after column chromatography.
[b]Yields obtained with respect to products **2**.

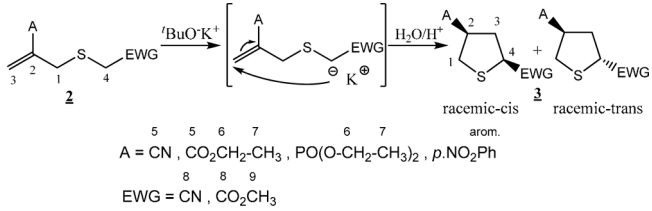
The structures of compounds **2** were determined by analytical means. Indeed, ^{1}H NMR reveals the absence of the morpholinylic hydrogens and the appearance of the methylenic protons α to the electron-withdrawing groups (CN, CO_2Me).

Synthesis of Tetrahydrothiophenes 3

Presenting highly activated methylenic hydrogens, compounds **2** are easily converted into reactive carbanionic species when subjected to potassium *tert*-butoxide.

We anticipated that the carbanion would autocondense on the nitrile or the ester group respectively in **2a** and **2b** to form the corresponding aromatic five-membered ring thiophene derivatives.

However, the analysis of infrared (IR) and NMR data suggested that an intramolecular Michael addition has occurred instead to lead to the formation of tetrahydrothiophene **3**. The latter are obtained in a mixture of *cis* and *trans* diastereomers (Scheme 3).



Scheme 3. Cyclization of functionalized thioallyls to thiophens diastereoisomers **3**.

The *cis*/*trans* ratio (Table 1) is apparently dictated by the steric interactions between the EWG on one side and the A group on the other.

The obtaining of this *cis*/*trans* ratio could be explained by the more favorable carbanion attack of the vinylic less-hindered side leading to the major *trans* isomer.

To the best of our knowledge, with the exception of compound **3b$_2$**, the rest of the series has not been described in the literature.[11] The *cis*/*trans* ratios were determined after isolating the individual compounds (**3a$_1$**, **3a$_2$**, and **3b$_1$**) or by ^{1}H and ^{31}P NMR for the rest of the tetrahydrothiophenes. The attribution of the isomers was based on the few examples reported in the literature. In general observation, the protons of the *trans* isomer appear at higher chemical shift than their corresponding *cis* counterparts.[12]

CONCLUSION

A convenient route to 2,4-disubstituted tetrahydrothiophenes has been described. This synthesis constitutes a cornerstone in the access to multifunctionalized tetrahydrothiophenes, highly desired building blocks in the synthesis of natural products. A more comprehensive study is being developed 1) to investigate the regioselectivity outcome of the intramolecular condensation and 2) to examine a kinetic versus thermodynamic control of the reaction as well as a possible interconversion between the diastereomers.

EXPERIMENTAL

Reactions were monitored by thin-layer chromatography (TLC) using ether–petroleum ether 60/40 (v/v) as eluent system.

Substrates **1** and their corresponding salts were prepared as described in Ref. 13 and 1, respectively.

IR spectra were recorded in chloroform solution on a Perkin-Elmer Paragon 1000 PC spectrometer with a standard error of 4 cm^{-1}.

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded in $CDCl_3$ on a 300-MHz Bruker instrument. Tetramethylsilane (TMS) was used as an internal reference for ^{1}H and ^{13}C. Phosphoric acid solution (80%) was used as external reference for ^{31}P spectra. Chemical shifts are reported in parts per million (ppm), and the following abbreviations were used for ^{1}H NMR attributions: s: singlet, d: doublet, dd: doublet of doublet, t: triplet, q: quartet, m: multiplet, and ABd: doublet of AB system.

Mass spectra were obtained by the electronic impact technique and recorded on an Agilent 5975B spectrometer (70 eV). The analyses were

performed at the National Institute of Research in Physical and Chemical Analyses, Tunis, Tunisia.

Melting points were determined by capillary tube on a Buchi instrument.

Synthesis of Compounds 2

Methyl mercaptoacetate or mercaptoacetonitrile (10 mmol) was added dropwise to an ethanol solution (50 mL) of ammonium salt of substrate **1** (12 mmol). The mixture is allowed to stir for 24 h at room temperature. The residual insoluble salt was filtered, and the filtrate was concentrated in vacuuo. The obtained residue is diluted in 20 mL of water and then extracted with $CHCl_3$ (3×30 mL). The organic extracts were combined and dried over $MgSO_4$. The chloroform was removed, and then residue was chromatographed on silica gel (ether-pet. ether: 60/40 v/v).

Data

Compound **2a$_1$**: 2-Cyanoprop-2-enylthioacetonitrile

Oil. IR ($CHCl_3$): $\nu_{CN} = 2110$ and $2220\,cm^{-1}$. ^1H NMR ($CDCl_3$): 6.01 (s, 1H); 5.91 (s, 1H); 3.46 (s, 2H, –$\underline{CH_2}$-S); 3.24 (s, 2H, –$\underline{CH_2}$N). ^{13}C NMR ($CDCl_3$): (C1), 35.23; (C2), 118.20; (C3), 134.36; (C4), 18.06; (C5), 115.77; (C8), 117.01. EIMS m/z (relative intensity): 138 ($M^{+\cdot}$, 53); 85 (100); 52 (22); 54 (44); 45 (37). HRMS calcd. for $C_6H_6N_2S$ m/z 138.0252; found m/z 138.0245.

Compound **2a$_2$**: Methyl 2-Cyanoprop-2-enylthioacetate

Oil. IR ($CHCl_3$): $\nu_{CN} = 2227\,cm^{-1}$; $\nu_{C=O} = 1736\,cm^{-1}$. ^1H NMR ($CDCl_3$); 6.02 (s, 1H); 5.92 (s, 1H); 3.74 (s, 3H, –O–$\underline{CH_3}$); 3.45 (s, 2H, –$\underline{CH_2}$–S); 3.20 (s, 2H, –$\underline{CH_2}$–CO_2Me). ^{13}C NMR ($CDCl_3$): (C1), 35.04; (C2), 118.81; (C3), 132.55; (C4), 31.33; (C5), 117.38; (C8), 169.98; (C9), 52.40.

Compound **2b$_1$**: 2-Ethoxycarbonylprop-2-enylthioacetonitrile

Oil. IR ($CHCl_3$); $\nu_{CN} = 2285\,cm^{-1}$; $\nu_{C=O} = 1716\,cm^{-1}$. ^1H NMR ($CDCl_3$): 6.30 (s, 1H); 5.75 (s, 1H); 4.28–4.21(q, 2H,–O–$\underline{CH_2}$–CH_3, $J = 6.00$ Hz); 3.60 (s, 2H, –$\underline{CH_2}$–S); 3.30 (s, 2H, –$\underline{CH_2}$–CN); 1.34–1.30 (t, 3H, O-CH_2-$\underline{CH_3}$, $J = 6.00$ Hz) . ^{13}C NMR ($CDCl_3$): (C1), 32.62; (C2), 127.53; (C3), 135.28; (C4), 16.30; (C5), 165.34; (C6), 60.77; (C7), 14.24; (C8), 116.32.

Compound **2b$_2$**: Methyl 2-Ethoxycarbonylprop-2-enylthioacetate

Oil. IR ($CHCl_3$): $\nu_{C=O} = 1716$ and 1627 cm^{-1}. ^1H NMR ($CDCl_3$); 6.24 (s, 1H); 5.70 (s, 1H); 4.28–4.20 (q, 2H, -O-$\underline{CH_2}$-CH_3, $J = 6.00$ Hz); 3.73 (s, 3H, –O-$\underline{CH_3}$); 3.51 (s, 2H, –$\underline{CH_2}$-S); 3.17 (s, 2H, –$\underline{CH_2}$-CO_2Me); 1.34-1.28 (t, 3H, O-CH_2-$\underline{CH_3}$, $J = 6.00$ Hz). ^{13}C NMR ($\underline{CDCl_3}$): (C1), 34.09; (C2), 127.37; (C3), 135.89; (C4), 33.24; (C5), 166.05; (C6), 60.49; (C7), 14.22; (C8), 170.55; (C9), 52.65. EIMS m/z (relative intensity): 218 ($M^{+\cdot}$, 19); 186 (34); 172 (38); 159 (26); 145 (98); 99 (100); 85 (23); 74 (27); 59 (51); 45 (48); 39 (22). HRMS calcd. for $C_9H_{14}O_4S$ m/z 218.0613; found m/z 218.0622.

Compound **2c$_1$**: 2-Diethoxyphosphorylprop-2-enylthioacetonitrile

Oil. IR ($CHCl_3$): $\nu_{CN} = 2246$ cm^{-1}. ^{31}P NMR ($CDCl_3$): 16.95. ^1H NMR ($CDCl_3$): 6.24–6.10 (d, 1H, $^3J_{PH} = 21.00$ Hz); 6.12–5.97 (d, 1H, $^3J_{PH} = 45.01$ Hz); 4.15–4.11 (m, 4H, 2xO-$\underline{CH_2}$-CH_3), 3.61–3.56 (d, 2H, –CH_2-S-, $^3J_{PH} = 15.00$ Hz); 3.33 (d, 2H, –$\underline{CH_2}$-N); 1.88–1.33 (m, 6H, 2xO-CH_2-$\underline{CH_3}$). ^{13}C NMR ($CDCl_3$); (C1: d, $^2J_{PC} = 13.58$ Hz), 33.64; (C2: d, $^1J_{PC} = 178.87$ Hz), 134.46; (C3: d, $^2J_{PC} = 14.34$ Hz), 132.49; (C4), 33.23; (C6: d, $^2J_{PC} = 6.23$), 62.34; (C7), 16.23; (C8), 116.14.

Compound **2c$_2$**: Methyl 2-Diethoxyphosphorylprop-2-enylthioacetate

Oil. IR ($CHCl_3$); $\nu_{C=O} = 1733$ cm^{-1}. ^{31}P NMR ($CDCl_3$): 17.49. ^1H NMR ($CDCl_3$); 6.21–6.14 (d, 1H, $^3J_{PH} = 21.00$ Hz); 6.12–5.96 (d, 1H, $^3J_{PH} = 48.02$ Hz); 4.13–4.09 (m, 4H, 2xO-$\underline{CH_2}$-CH_3); 3.73 (s, 3H, –O-CH_3); 3.51–3.47 (d, 2H, -CH_2-S-, $^3J_{PH} = 12.00$ Hz); 3.21 (s, 2H, –CH_2-CO_2Me); 1.37–1.32 (m, 6H, 2xO-CH_2-$\underline{CH_3}$). ^{13}C NMR ($CDCl_3$); (C1: d, $^2J_{PC} = 75.47$ Hz): 33.27; (C2: d, $^1J_{PC} = 175.85$ Hz): 134.69; (C3: d, $^2J_{PC} = 12.07$ Hz), 131.56; (C4), 33.18; (C6: d, $^2J_{PC} = 5.28$), 61.75; (C7), 16.03; (C8), 170.12; (C9), 51.85.

Compound **2d$_1$**: 2-(*p*-Nitrophenyl)prop-2-enylthioacetonitrile

Solid. Mp = 78–79°C. IR ($CHCl_3$): $\nu_{CN} = 2360$ cm^{-1}. ^1H NMR ($CDCl_3$): 8.23–7.61 (m, 4H, -Ph-NO_2); 5.71 (s, 1H); 5.53 (s, 1H); 3.85 (s, 2H, –$\underline{CH_2}$-S); 3.24 (s, 2H, –$\underline{CH_2}$-CN). ^{13}C NMR ($CDCl_3$): (C_{arom}), 147.72–123; (C1), 36.50; (C2), 144.66; (C3), 119.93; (C4), 16.30; (C8), 116.06.

Compound **2d$_2$**: Methyl 2-(*p*-Nitrophenyl)prop-2-enylthioacetate

Solid. Mp = 80–81°C. IR ($CHCl_3$): $\nu_{C=O} = 1742\,cm^{-1}$. ^1H NMR ($CDCl_3$); 8.20-7.62 (m, 4H, -Ph-NO_2); 5.64 (s, 1H); 5.46 (s, 1H); 3.76 (s, 3H, –O-$\underline{CH_3}$); 3.74 (s, 2H, –$\underline{CH_2}$-S); 3.19 (s, 2H, -$\underline{CH_2}$-CO_2Me). ^{13}C NMR ($CD\underline{Cl_3}$): (C_{arom}), 145.42–123; (C1), 36.55; ($\underline{C2}$), 147.25; (C3), 119.26; (C4), 33.35; (C8), 170.40; (C9), 52.26.

Synthesis of Compounds 3

Substrate **2** (5 mmol in 5 mL of THF) was added, dropwise and with stirring, to a cooled THF solution of potassium *tert*-butoxide (8 mmol, in 10 mL THF) at −78°C under nitrogen. When all substrate **2** has been added, the reaction mixture was allowed to reach room temperature. The reaction was allowed to stir for an additional 4 h, after which it was hydrolyzed with 0.5 N HCl, and the stirring was continued for 20 min. The mixture was then extracted with diethyl ether (3 × 10 mL).

The organic extracts were combined and dried over $MgSO_4$. After removal of the solvents, the crude material was subjected to chromatography. Two consecutive columns were performed to separate the diastereomers **3**. The first column was eluted with an isocratic mixture of diethylether–petroleum ether mixture (60: 40 v/v), whereas the second was subjected to a gradient of polarity 40/60 to 60/40 of diethyleteher–petroleum ether mixture.

Data

Compound **3a$_1$**: *cis*-Tetrahydrothiophene-2,4-dicarbonitrile

Oil. IR ($CHCl_3$): $\nu_{CN} = 2346$ and $2399\,cm^{-1}$. ^1H NMR ($CDCl_3$): 4.24–4.19 (dd, 1H, CN-$\underline{CH}$-S-, $J = 3.00$ Hz); 3.52-3.40 (m, 1H, –CH_2-$\underline{CH}$-CH_2-, 1H, –S-$\underline{CH_2}$-CH-); 3.24–3.15 (m, 1H, -S-$\underline{CH_2}$-CH-); 2.75–2.65 (m, 1H, –CH-$\underline{CH_2}$-CH–); 2.63–2.48 (m, 1H, CH-$\underline{CH_2}$-CH–). ^{13}C NMR ($CDCl_3$): (C1), 31.12; (C2), 35.78; (C3), 32.08; (C4), 39.95; (C5), 117.92; (C8), 118.85.

Compound **3a$_1$**: *trans*-Tetrahydrothiophene-2,4-dicarbonitrile

Oil. IR ($CHCl_3$); $\nu_{CN} = 2346$ and $2399\,cm^{-1}$. ^1H NMR ($CDCl_3$): 4.21–4.17 (dd, 1H, CN-$\underline{CH}$-S-, $J = 3.00$ Hz); 3.49-3.39 (m, 1H, –CH_2-$\underline{CH}$-CH_2–, 1H, –S-$\underline{CH_2}$-CH-); 3.25–3.17 (m, 1H, –S-$\underline{CH_2}$-CH-); 2.74–2.66 (m, 1H, -CH-$\underline{CH_2}$-CH-); 2.60–2.50 (m, 1H, CH-$\underline{CH_2}$-CH-). ^{13}C NMR

($CDCl_3$): (C1), 30.35; (C2), 35.09; (C3), 32.26; (C4), 39.36; (C5), 118.17; (C8), 119.02.

Compound **3a$_2$**: *cis*-Methyl 4-Cyanotetrahydrothiophene-2-carboxylate

Oil. IR ($CHCl_3$): $\nu_{CN} = 2399\,cm^{-1}$; $\nu_{C=O} = 1735\,cm^{-1}$. ^1H NMR ($CDCl_3$): 4.09–4.03 (dd, 1H, -CH-CO_2Me, $J = 3.02$ Hz); 3.39 (s, 3H, -CO_2Me); 3.60–3.46 (m, 1H, -CH-CN); 3.30–3.06 (ABd, 2H, -S-CH_2-CH-, $J = 9.02$ Hz); 2.77–2.71 (m, 1H, -CH-CH_2-CH-); 2.18–2.14 (m, 1H, CH-CH_2-CH-). ^{13}C NMR ($CDCl_3$): (C1), 35.24; (C2), 32.74; (C3), 36.61; (C4), 53.05; (C5), 118.91; (C8), 171.83; (C9), 46.08.

Compound **3a$_2$**: *trans*-Methyl 4-Cyanotetrahydrothiophene-2-carboxylate

Oil. IR ($CHCl_3$): $\nu_{CN} = 2399\,cm^{-1}$; $\nu_{C=O} = 1735\,cm^{-1}$. ^1H NMR ($CDCl_3$): 4.07–4.04 (dd, 1H, -CH-CO_2Me, $J = 3.00$ Hz); 3.37 (s, 3H, -CO_2Me); 3.54–3.44 (m, 1H, -CH-CN); 3.29–3.07 (ABd, 2H, -S-CH_2-CH-, $J = 9.00$ Hz); 2.76–2.69 (m, 1H, -CH-CH_2-CH-); 2.21–2.13 (m, 1H, CH-CH_2-CH-). ^{13}C NMR ($CDCl_3$): (C1), 34.26; (C2), 32.29; (C3), 36.92; (C4), 52.80; (C5), 118.98; (C8), 172.68; (C9), 45.40. EIMS m/z (relative intensity): 171 ($M^{+\cdot}$, 24); 112 (100); 85 (31); 45 (14). HRMS calcd. for $C_7H_9NO_2S$ m/z 171.0354, found m/z 171.0349.

Compound **3b$_1$**: *cis*-Ethyl 5-Cyanotetrahydrothiophene-3-carboxylate

Oil. IR ($CHCl_3$): $\nu_{CN} = 2399\,cm^{-1}$; $\nu_{C=O} = 1731\,cm^{-1}$. ^1H NMR ($CDCl_3$): 4.25–4.18 (q, 2H, O-CH_2-CH_3, $J = 6.00$ Hz); 4.07–4.02 (dd, 1H, CN-CH-S-, $J = 3.00$ Hz); 3.41–3.38 (m, 1H, -CH_2-CH-CH_2-, 1H, -S-CH_2-CH-); 3.19–3.15 (m, 1H, -S-CH_2-CH-); 2.65–2.58 (m, 2H, -CH-CH_2-CH-); 1.32–1.27 (t, 3H, O-CH_2-CH3, $J = 6.00$ Hz). ^{13}C NMR ($CDCl_3$): (C1), 31.91; (C2), 48.68; (C3), 38.28; (C4), 34.65; (C5), 170.92; (C6), 61.77; (C7), 14.14; (C8), 119.67.

Compound **3b$_1$**: *trans*-Ethyl 5-Cyanotetrahydrothiophene-3-carboxylate

Oil. IR ($CHCl_3$); $\nu_{CN} = 2399\,cm^{-1}$; $\nu_{C=O} = 1731\,cm^{-1}$. ^1H NMR ($CDCl_3$): 4.23–4.16 (q, 2H, O-CH_2-CH_3, $J = 6.00$ Hz); 4.11–4.08 (dd, 1H, CN-CH-S-, $J = 3.00$ Hz); 3.39–3.30 (m, 1H, -CH_2-CH-CH_2-, 1H, -S-CH_2-CH-); 3.25–3.21 (m, 1H, -S-CH_2-CH-); 2.57–2.52

(m, 2H, -CH-$\underline{CH_2}$-CH-); 1.31–1.26 (t, 3H, O-CH_2-CH_3, $J = 6.00$ Hz). ^{13}C NMR ($CDCl_3$): (C1), 32.18; (C2), 47.58; (C3), 38.34; (C4), 34.35; (C5), 171.32; (C6), 61.55; (C7), 14.33; (C8), 120.16.

Compound **3b$_2$**: Ethyl Methyl Tetrahydrothiophene-2,4-dicarboxylate

Oil. IR ($CHCl_3$); $\nu_{C=O} = 1718\ cm^{-1}$ wide. ^{1}H NMR ($CDCl_3$): 4.46–4.33 (m, 2H, 2x-CH-CO_2Me); 4.23–4.17 (m, 4H, 2x-O-$\underline{CH_2}$-CH_3); 3.37 (s, 3H, -CO_2Me); 3.36 (s, 3H, -CO_2Me); 3.33–3.30 (m, 2H, 2x-S-$\underline{CH_2}$-CH-); 2.95–2.92 (m, 2H, 2x-S-$\underline{CH_2}$-CH-); 2.46–2.44 (m, 4H, 2x-CH-$\underline{CH_2}$-CH-); 2.34–2.30 (m, 2H, 2x-CH_2-CH-CH_2-). ^{13}C NMR ($CDCl_3$): (C1), 34.15, 34.08; (C2), 35.55, 35.12; (C3), 36.76, 36.17 (C4), 55.39, 55.17; (C5), 172.93, 172.23; (C6), 60.88, 60.62; (C7), 14.18, 14.16; (C8), 170.22, 169.92; (C9), 52.78, 52.24.

Compound **3c$_1$**: 4-Diethoxyphosphoryltetrahydrothiophene-2-carbonitrile

Oil. IR ($CHCl_3$): $\nu_{CN} = 2239\ cm^{-1}$. ^{31}P NMR ($CDCl_3$): 25.14 ; 25.06. ^{1}H NMR ($CDCl_3$): 4.18–4.13 [m, 2H, 2x-CH-CN, 8H, 2x(-O-$\underline{CH_2}$-CH_3)$_2$]; 3.27–3.13 (m, 2H, 2x-S-CH_2-CH-, 2H, 2x-S-$\underline{CH_2}$-CH); 2.79–2.54 (m, 2H, 2x-S-$\underline{CH_2}$-CH, 2H, 2x-CH_2-CH-CH_2-); 2.30–2.23 (m, 2H, 2x-CH-$\underline{CH_2}$-CH-); 1.37–1.33 (m, 12H, 2x-O-CH_2-$\underline{CH_3}$). ^{13}C NMR ($CDCl_3$): (C1: 2xd, $^2J_{PC} = 36.98$ Hz), 33.99; (C2: 2xd, $^1J_{PC} = 140.38$ Hz), 39.95; (C3: 2xd, $^2J_{PC} = 21.88$ Hz): 37.81; (C4), 33.48, 32.59; (C6: 2xd, $^2J_{PC} = 6.79$ Hz), 62.62; (C7), 16.62, 16.61; (C8), 120.41, 119.41. EIMS m/z (relative intensity): 249 ($M^{+\cdot}$, 39); 193 (12); 138 (56); 111 (100); 82 (26); 45 (14). HRMS calcd. for $C_9H_{16}NO_3PS$ m/z 249.0589; found m/z 249.0595.

Compound **3c$_2$**: Methyl 4-Diethoxyphosphoryltetrahydrothiophene-2-carboxylate

Oil. IR ($CHCl_3$): $\nu_{C=O} = 1725\ cm^{-1}$. ^{31}P NMR ($CDCl_3$): 28.94; 28.35. ^{1}H NMR ($CDCl_3$): 4.19–3.79 [m, 2H, 2x-CH-CO_2Me, 8H, 2x(-O-$\underline{CH_2}$-CH_3)$_2$]; 3.74 (s, 3H, -OCH_3); 3.73 (s, 3H, -OCH_3); 3.11–3.04 (m, 2H, 2x-S-CH_2-CH-, 2H, 2x-S-$\underline{CH_2}$-CH); 2.69–2.64 (m, 2H, 2x-S-$\underline{CH_2}$-CH, 2H, 2x-CH_2-CH-CH_2-); 2.08–2.04 (m, 2H, 2x-CH-$\underline{CH_2}$-CH-); 1.36–1.31 (m, 12H, 2x-O-CH_2-CH_3). ^{13}C NMR ($CDCl_3$): (C1: 2xd, $^2J_{PC} = 40.00$ Hz), 32.46; (C2: 2xd, $^1J_{PC} = 144.91$ Hz), 41.65; (C3: 2xd, $^2J_{PC} = 18.11$ Hz), 34.54; (C4), 48.92, 47.71; (C6: 2xd, $^2J_{PC} = 6.81$ Hz), 62.52; (C7), 16.59, 16.57; (C8), 174.79, 173.86; (C9), 42.55, 31.63.

Compound **3d$_1$**: 4-(*p*-Nitrophenyl)tetrahydrothiophene-2-carbonitrile

Solid. Mp = 96–97°C. IR ($CHCl_3$): $\nu_{CN} = 2399\,cm^{-1}$. ^1H NMR ($CDCl_3$): 8.23–7.46 (m, 4H); 4.20–4.15 (m, 2H, 2xCN-CH-S-); 3.55–3.51 (m, 2H, 2x-CH_2-CH-CH_2-); 3.29–3.24 (m, 4H, 2x-S-CH_2-CH-); 2.90–2.85 (m, 2H, 2x-CH-CH_2-CH-); 2.43–2.35 (m, 2H, 2x-CH-CH_2-CH-). ^{13}C NMR ($CDCl_3$): (C_{arom}), 147.34–123.86; (C1), 33.79, 33.53; (C2), 49.62, 49.32; (C3), 41.67, 40.89; (C4), 31.62, 31.22; (C8), 119.32, 118.97.

Compound **3d$_2$**: Methyl 4-(*p*-Nitrophenyl)tetrahydrothiophene-2-carboxylate

Solid. Mp = 90–91°C. IR ($CHCl_3$): $\nu_{C=O} = 1733\,cm^{-1}$. ^1H NMR ($CDCl_3$): 8.20–7.46 (m, 4H); 4.18–4.12 (dd, 1H, CN-CH-S-, $J = 6{,}00$ Hz); 4.06–4.03 (dd, 1H, CN-CH-S-, $J = 3.00$ Hz); 3.77 (s, 3H, -OCH_3); 3.76 (s, 3H, -OCH_3); 3.56–3.50 (m, 1H, -CH_2-CH-CH_2-); 3.31–3.25 (m, H, -CH_2-CH-CH_2-); 3.19–3.10 (m, 2H, -S-CH_2-CH-); 3.06–2.95 (m, 2H, -CH-CH_2-CH-); 2.78–2.72 (m, H, -CH-CH_2-CH-); 2.67–2.59 (m, H, -CH-CH_2-CH-); 2.51–2.39 (m, H, -CH-CH_2-CH-); 2.19–2.08 (m, H, -CH-CH_2-CH-). ^{13}C NMR ($CDCl_3$): (C_{arom}), 149.06–123.87; (C1), 38.99, 38.39; (C2), 47.17, 46.71; (C3), 39.83, 39.64; (C4), 53.07, 52.64; (C8), 173.90, 173.29; (C9), 50.69, 50.38.

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