Synthesis of functionalized dithiocarbamates via *N*-(1-benzotriazolylalkyl)dithiocarbamates

Alan R. Katritzky,* Shailendra Singh, Prabhu P. Mohapatra, Nicole Clemens, and Kostyantyn Kirichenko

Center for Heterocyclic Compounds, University of Florida, Department of Chemistry, Gainesville, Florida 32611-7200, USA
E-mail: Katritzky@chem.ufl.edu

Submitted in honor of the 70th anniversary of Jose Elguero and the 60th anniversary of Pedro Molina

(received 05 Nov 04; accepted 23 Jan 05; published on the web 01 Feb 05)

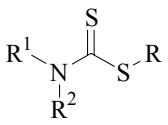
Abstract

Reactions of 1-(1-hydroxyalkyl)benzotriazoles **19a–d** with thiazolidine-2-thione **13**, 1,3-thiazinane-2-thione **25**, and alkyl *N*-alkyldithiocarbamates **29a–c** give intermediate *N*-[1-(benzotriazol-1-yl)alkyl] dithiocarbamates **20a–d**, **26a–c**, and **30a–e** respectively, which gave *N*-(1-sulfanylalkyl) dithiocarbamates **23a–l**, **27a–c** and **31a–e** or *N*-[1-(dialkylphosphono)alkyl] dithiocarbamates **24a–e**, **28a,b** and **32a–d** on treatment with thiols or trialkyl phosphates, respectively, in the presence of zinc bromide.

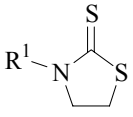
Keywords: Dithiocarbamates, benzotriazole, functionalization

Introduction

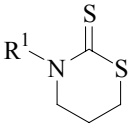
Dithiocarbamates of general structure **1** including cyclic derivatives **2–4** show antibacterial,[1–4] anthelmintic,[5,6] fungicidal,[1,2,4,7–10] herbicidal,[7,11] antifouling,[12] growth depressant,[13] and algicidal activity.[14] They are also effective catalysts for photopolymerization[15] and vulcanization.[16,17]



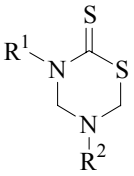
1



2



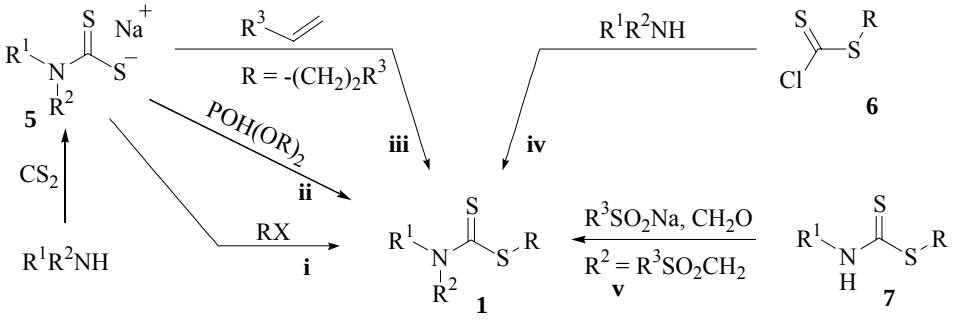
3



4

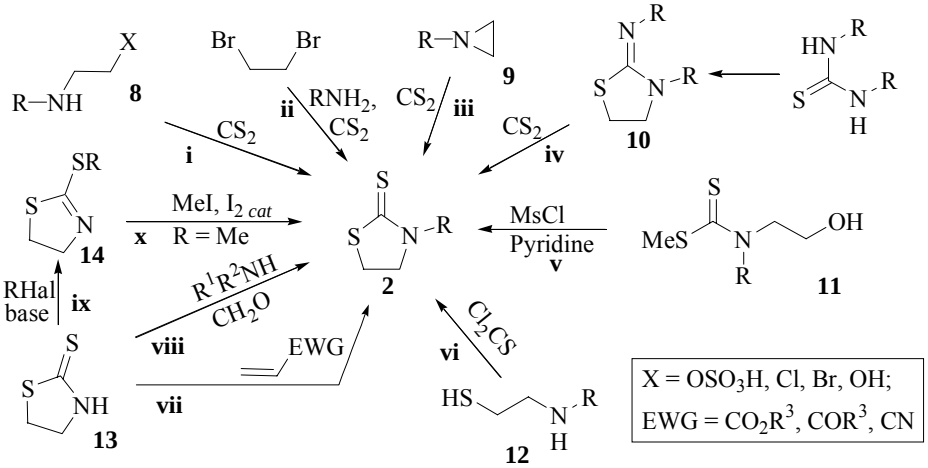
Major approaches to the preparation of N,N-dialkyl dithiocarbamates **1** (Scheme 1) utilize reactions of dithiocarbamic acid salts **5** (accessible, or generated in situ from amines with carbon

disulfide) (i) with alkyl halides,[3,13,18–25] (ii) with dialkyl phosphates,[26] or (iii) by addition to electron-deficient olefins.[27,28] Acylation of amines with less easily available chlorodithioformates **6** (Scheme 1, Route iv) provides another access to dithiocarbamates **1**.[18] N-Arylsulfonylmethyl dithiocarbamates **1** ($R^2 = R^3SO_2CH_2$) were prepared by the N-alkylation of dithiocarbamates **7** with sodium *p*-toluenesulfinate and formaldehyde.[29]



Scheme 1

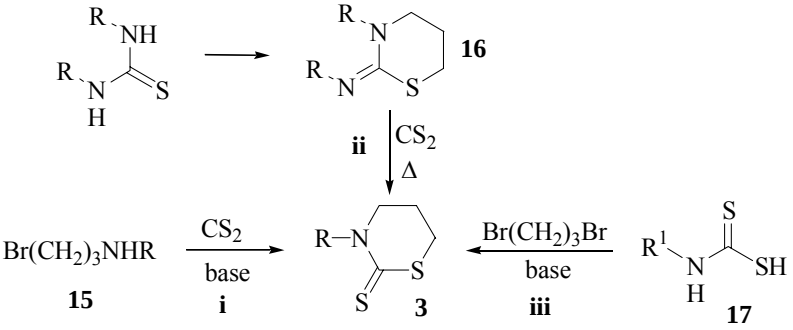
Reported preparations of N-alkyl thiazolidine-2-thiones **2** (Scheme 2) employ reactions of carbon disulfide (i) with 2-aminoethanols **8** (X = OH),[16,17] 2-aminoethyl sulfates **8** (X = OSO_3H),[30] and 2-aminoethyl halides **8** (X = Cl, Br);[31,32] (ii) with primary amines and 1,2-dibromoethane in the presence of a base;[18,19] (iii) with aziridines **9**;[30,33] (iv) with 2-iminothiazolidines **10**.[34] The preparation of compounds **2** via cyclization of methyl β-hydroxyalkyldithiocarbamates **11** upon treatment with mesyl chloride in pyridine (Scheme 2, Route v)[24] and via cyclization of 2-alkylaminoethanethiols **12** with thiophosgene in the presence of a base (Route vi)[33] have also been reported. The alkylation of thiazolidine-2-thiones **13** with alkyl halides in the presence of a base gives 2-alkylthiothiazoles **14** (Scheme 2, Route ix).[31,35] 2-Methylthiothiazoles **14** (R = Me) are thermally isomerized by catalytic methyl iodide and iodine into the corresponding *N*-methylthiazolidine-2-thiones **2** (Scheme 2, Route x).[30]



Scheme 2

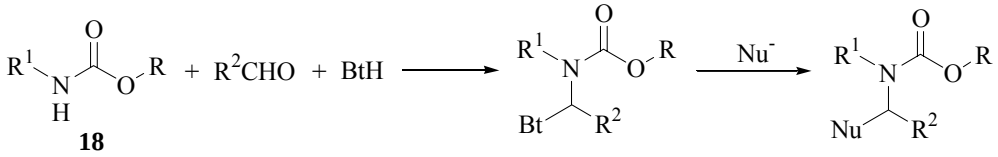
The aminoalkylation of thiazolidine-2-thiones **13** (first erroneously reported as giving products of S-alkylation)[35,36] succeeded for formaldehyde[37,38] (Scheme 2, Route viii) but attempts with higher aldehydes failed.[38] N-Alkylated thiazolidine-2-thiones also resulted from Michael- type addition of unsubstituted thiazolidine-2-thiones **13** to electron-deficient olefins (Scheme 2, Route vii).[39,40]

N-Alkyl-1,3-thiazine-2-thiones **3** have been prepared in similar ways from 3-bromopropylamines **15**[41] (Scheme 3, Route i) or 2-imino-1,3-thiazines **16**[42] (Route ii) with carbon disulfide, and from dithiocarbamic acids **17** with 1,3-dibromopropane (Route iii).[8]



Scheme 3

However, we have located no reports of the introduction of functionalized N-substituents into either open-chain- or cyclic- dithiocarbamates. Our group has previously functionalized carbamates **18** (Scheme 4) via benzotriazolylalkylation[43–45] followed by nucleophilic displacement of benzotriazole with diverse nucleophiles,[46–54] such as organozinc reagents,[48,51] ester enolates,[54] or ammonia.[46,47,49] This approach also includes condensation of carbamates **18** and benzotriazole with aliphatic and aromatic aldehydes.[47,48,53–56] We have now applied similar methodology to functionalize dithiocarbamates **13**, **25** and **29** providing a new route to diverse *N*-(1-sulfanylalkyl) **23a–l**, **27a–c** and **31a–e** and *N*-[1-(dialkylphosphono)alkyl] dithiocarbamates **24a–e**, **28a,b** and **32a–d** in good overall yields (Schemes 5, 6 and 7).



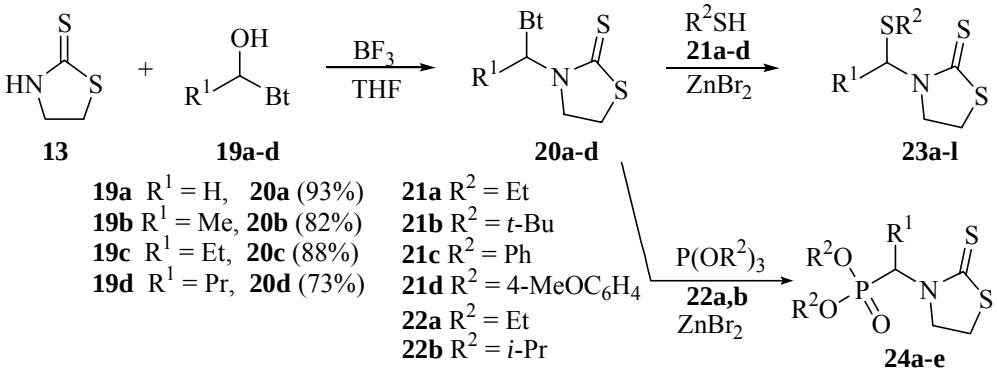
Scheme 4

Results and Discussion

The 1-(1-hydroxyalkyl)benzotriazoles **19a–d** were prepared from benzotriazole and the corresponding aldehydes in excellent yields according to the published procedure.[57] The reaction

of 1-(1-hydroxyalkyl)benzotriazoles **19a–d** with thiazolidine-2-thione **13** in the presence of boron trifluoride in THF at 25 °C gave the 3-(1-benzotriazolylalkyl)thiazolane-2-thiones **20a–d** in good isolated yields (Scheme 5). Structures **20a–d** were supported by their ^{1}H- NMR and ^{13}C-NMR spectra. The NMR spectra of **20a–d** showed sets of signals in the ranges 7.38–7.60 ppm and 7.91–8.07 ppm in the ^{1}H- and about 111, 120, 125, 128, 133 and 146 ppm in the ^{13}C- spectra, characteristic of N-(1-amidoalkyl) benzotriazoles (see Experimental Section).[47,48,50,53–55,58]

Nucleophilic substitution of the benzotriazolyl group in the 3-(1-benzotriazolylalkyl)-thiazolane-2-thiones **20b–d** with thiols **21a–d** in the presence of $ZnBr_2$ in refluxing diethyl ether for 12 h gave thio- derivatives **23a–l** of 1,3-thiazolidine-2-thione in excellent isolated yields (Scheme 5, Table 1). Structures **23a–l** were confirmed by their ^{1}H- NMR and ^{13}C- NMR spectra. Their NMR spectra no longer showed distinctive signals associated with the benzotriazole ring in the ^{1}H- NMR range 7.38–8.07 ppm or at 111, 120, 125, 133 and 146 ppm in the ^{13}C- spectra. The NMR spectra of **23a–l** showed the appearance of a new set of signals corresponding to the introduced alkyl- or aryl-sulfanyl group (R^2), as well as upfield shifts in the position of the signals corresponding to the α-CH of the N-alkyl chain from 7.57–7.80 ppm for **20b–d** to 6.09–6.54 ppm for **23a–l** (^{1}H- NMR) and from 64.5–69.0 ppm to 56.5–66.8 ppm (^{13}C- NMR).



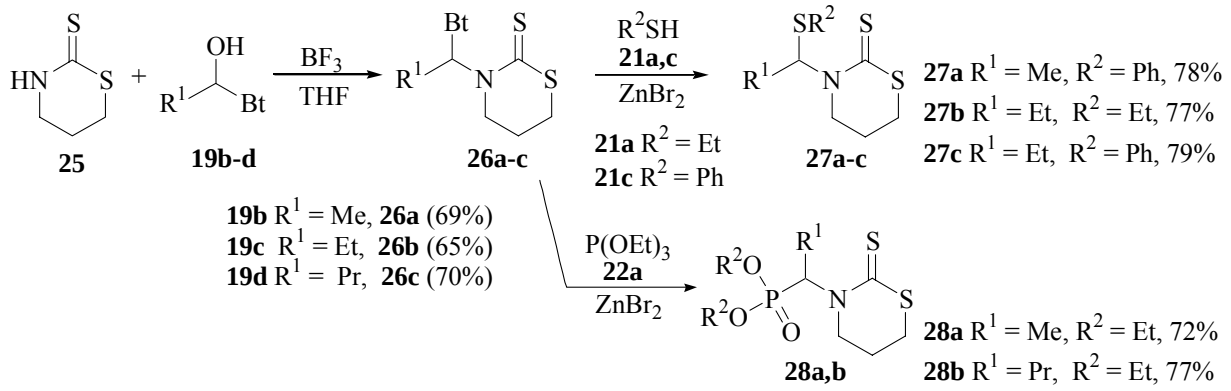
Scheme 5

Table 1. Preparation of functionalized thiazolidine-2-thiones **23a–l** and **24a–e**

Product	R^1	R^2	Yields, %	Product	R^1	R^2	Yields, %
23a	Me	Et	96	**23j**	Me	4-$MeOC_6H_4$	99
23b	Et	Et	95	**23k**	Et	4-$MeOC_6H_4$	92
23c	Pr	Et	93	**23l**	Pr	4-$MeOC_6H_4$	91
23d	Me	*t*-Bu	89	**24a**	Me	Et	79
23e	Et	*t*-Bu	94	**24b**	Et	Et	81
23f	Pr	*t*-Bu	91	**24c**	Et	*i*-Pr	78
23g	Me	Ph	99	**24d**	Pr	Et	76
23h	Et	Ph	95	**24e**	Pr	*i*-Pr	88
23I	Pr	Ph	98				

Reaction of the 3-(1-benzotriazolylalkyl)thiazolane-2-thiones **20b–d** with trialkyl phosphites **22a,b** in the presence of $ZnBr_2$ in refluxing dichloromethane gave 1-(2-thioxo-1,3-thiazolidin-3-yl)alkylphosphonates **24a–e** in good isolated yields (Scheme 5, Table 1). Structures **24a–e** were supported by their ^{1}H- NMR and ^{13}C- NMR spectra, which showed the disappearance of signals assigned to the benzotriazolyl group of **20b–d** and the appearance of a new set of signals corresponding to dialkyl phosphonate (see Experimental Section). As with **23a–l**, the signals for α-CH (between the phosphorus and thiazolidinyl nitrogen) of the dialkyl phosphonates **24a–e** appeared in the ranges 5.44–5.67 ppm in the ^{1}H- and 49.3–55.7 ppm (doublet, J = 152.9–155.7 Hz) in the ^{13}C- NMR spectra.

1,3-Thiazinane-2-thione **25** was prepared in 78% yield by the reaction of 3-bromopropylamine hydrobromide with carbon disulfide according to a published procedure.[41] In analogy to the preparation of **20a–d**, condensation of compound **25** with 1-(1-hydroxyalkyl)benzotriazoles **19b–d** in the presence of boron trifluoride in THF at 25 °C gave 3-(1-benzotriazolylalkyl)thiazine-2-thiones **26a–c** in good isolated yields (Scheme 6).



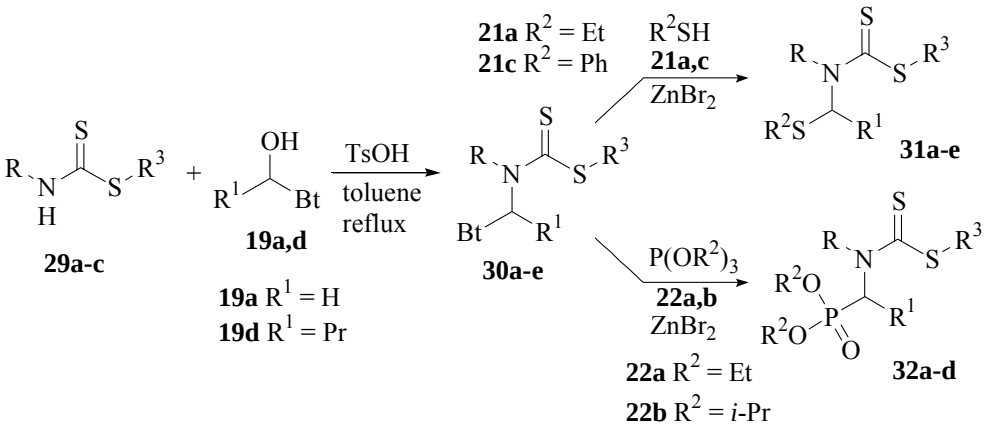
Scheme 6

Nucleophilic substitution of the benzotriazolyl group in the 3-(1-benzotriazolylalkyl)-1,3-thiazinane-2-thiones **26a,b** by thiols **21a,c** in the presence of $ZnBr_2$ in refluxing diethyl ether gave 3-[1-(substituted-sulfanyl)alkyl]-1,3-thiazinane-2-thiones **27a–c** in 77–79% yields (Scheme 6).

Reaction of 1,3-thiazinane-2-thiones **26a,c** with trialkyl phosphite **22a** in the presence of $ZnBr_2$ in refluxing dichloromethane gave 1-(2-thioxo-1,3-thiazinan-3-yl)alkylphosphonates **28a,b** in 72–77% yields (Scheme 6). Compounds **26a–c**, **27a–c** and **28a,b** were characterized by elemental analyses and their ^{1}H- and ^{13}C- NMR spectra.

Reaction of alkyl *N*-alkyldithiocarbamates **29a–c** with 1-(1-hydroxyalkyl)benzotriazoles **19a,d** in the presence of *p*-toluenesulfonic acid in toluene under reflux for 24 h gave *N*-[1-(benzotriazol-1-yl)alkyl]-*N*-alkyldithiocarbamates **30a–d** in good isolated yields (Scheme 7, Table 2). Owing to difficulties with isolation, crude compound **30e** was used for the further preparation of **31d,e**.

Nucleophilic substitution of the benzotriazolyl group in **30b,d,e** by thiols **21a,c** in the presence of $ZnBr_2$ in refluxing diethyl ether gave excellent yields of the alkyl *N*-thioalkyl dithiocarbamates **31a–e** (Scheme 7, Table 2).



Scheme 7

Reaction of intermediates **30b,d** with trialkyl phosphites **22a,b** (R^2 = Et) in the presence of $ZnBr_2$ in refluxing dichloromethane gave the dialkyl phosphonates **32a–d** in 83–89% yields (Scheme 7, Table 2). Compounds **30a–d**, **31a–e** and **32a–d** were characterized by elemental analyses and by their ^{1}H- and ^{13}C- NMR spectra.

Table 2. Preparation of dithiocarbamates **30a–e**, **31a–e** and **32a–d**

Product	R	R^1	R^2	R^3	Yields, %	Product	R	R^1	R^2	R^3	Yields, %
30a	Me	H	–	Et	56	**31c**	Et	Pr	Et	Me	95
30b	Me	Pr	–	Et	61	**31d**	Bu	Pr	Ph	Et	98
30c	Et	H	–	Me	61	**31e**	Bu	Pr	Et	Et	95
30d	Et	Pr	–	Me	63	**32a**	Me	Pr	Et	Et	86
30e	Bu	Pr	–	Et	–[a]	**32b**	Me	Pr	*i*-Pr	Et	83
31a	Me	Pr	Ph	Et	97	**32c**	Et	Pr	Et	Me	89
31b	Et	Pr	Ph	Me	98	**32d**	Et	Pr	*i*-Pr	Me	80

[a] Not isolated, used as crude material for the preparation of **31d,e**.

However, attempted nucleophilic substitution of the benzotriazolyl group in *N*-(1-benzotriazolylmethyl)- thiazolane-2-thione **20a** and *N*-alkyldithiocarbamates **30a,c** with thiols **21** and trialkyl phosphites **22** failed.

In summary, an efficient route has been developed to functionalized *N*-[1-(dialkylphosphono)alkyl]- and *N*-(1-sulfanylalkyl)- dithiocarbamates via substitution of benzotriazole by thiols and trialkyl phosphites in intermediate *N*-(1-

benzotriazolylalkyl)dithiocarbamates. The protocol provides high overall yields of functionalized dithiocarbamates, both in the open-chain series and the cyclic analogs.

Experimental Section

General Procedures. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were obtained in $CDCl_3$ with TMS as the internal standard for ^1H (300 MHz) or with the solvent as the internal standard for ^{13}C (75 MHz). THF and diethyl ether were dried over sodium / benzophenone, dichloromethane was dried over calcium hydride and used freshly distilled. Column chromatography was conducted on silica gel 200–425 mesh. All of the chemicals were employed as supplied.

General procedure for the preparation of 3-(1-benzotriazolylalkyl)thiazolane-2-thiones 20a–d

Boron trifluoride etherate (3.8 mL, 30 mmol) was added to a solution of thiazolidine-2-thione **13** (1.79 g, 15 mmol) and the 1-(1-hydroxyalkyl)benzotriazole **19a–d** (15 mmol) in anhydrous THF (25 mL) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. Ethyl acetate was added, and the organic layer was washed with 10% aqueous sodium carbonate. The organic layer was separated, dried over magnesium sulfate, and then solvent was removed under reduced pressure. The crude product was recrystallized from ethyl acetate to give **20a–d**.

3-(Benzotriazol-1-ylmethyl)-1,3-thiazolane-2-thione (20a). White microcrystals from ethyl acetate (93%), mp 176–177 °C; ^1H NMR δ 3.24 (t, *J* = 7.8 Hz, 2H), 4.15 (t, *J* = 7.8 Hz, 2H), 6.59 (s, 2H), 7.38–7.43 (m, 1H), 7.50–7.55 (m, 1H), 8.02–8.06 (m, 2H); ^{13}C NMR δ 27.2, 54.7, 58.1, 111.1, 119.8, 124.7, 128.4, 132.2, 146.0, 200.2. Anal. Calcd for $C_{10}H_{10}N_4S_2$: C, 47.98; H, 4.03; N, 22.38. Found: C, 48.49; H, 3.86; N, 22.14%.

3-[1-(Benzotriazol-1-yl)ethyl]-1,3-thiazolane-2-thione (20b). White microcrystals from ethyl acetate (65%), mp 135–136 °C; ^1H NMR δ 2.19 (d, *J* = 6.9 Hz, 3H), 3.09 (dt, *J* = 11.0, 8.8 Hz, 1H), 3.24 (ddd, *J* = 11.0, 8.1, 5.8 Hz, 1H), 3.75 (ddd, *J* = 11.3, 8.4, 5.8 Hz, 1H), 4.22 (dt, *J* = 11.3, 8.4 Hz, 1H), 7.40–7.45 (m, 1H), 7.51–7.56 (m, 1H), 7.80 (q, *J* = 6.9 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 16.8, 27.6, 50.7, 64.5, 110.7, 119.7, 124.7, 128.2, 132.5, 145.7, 198.6. Anal. Calcd for $C_{11}H_{12}N_4S_2$: C, 49.98; H, 4.58; N, 21.19. Found: C, 50.26; H, 4.65; N, 21.12%.

3-[1-(Benzotriazol-1-yl)propyl]-1,3-thiazolane-2-thione (20c). White microcrystals from ethyl acetate (88%), mp 147–148 °C; ^1H NMR δ 1.07 (t, *J* = 7.4 Hz, 3H), 2.52–2.66 (m, 1H), 2.68–2.83 (m, 1H), 3.12 (dt, *J* = 11.0, 8.4 Hz, 1H), 3.26 (ddd, *J* = 11.1, 8.2, 6.1 Hz, 1H), 3.91 (ddd, *J* = 11.3, 8.4, 6.1 Hz, 1H), 4.24 (dt, *J* = 11.3, 8.3 Hz, 1H), 7.39–7.44 (m, 1H), 7.51–7.55 (m, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 9.7, 24.7, 27.7, 51.1, 69.0, 110.8, 119.7, 124.7, 128.2, 133.0, 145.5, 199.3. Anal. Calcd for $C_{12}H_{14}N_4S_2$: C, 51.77; H, 5.07; N, 20.12. Found: C, 51.49; H, 5.18; N, 19.90%.

3-[1-(Benzotriazol-1-yl)butyl]-1,3-thiazolane-2-thione (20d). White microcrystals from ethyl acetate (73%), mp 144–145 °C; ^{1}H NMR δ 1.04 (t, *J* = 7.4 Hz, 3H), 1.43 (sextet, *J* = 7.5 Hz, 2H), 2.46–2.58 (m, 1H), 2.65–2.77 (m, 1H), 3.11 (dt, *J* = 11.0, 8.4 Hz, 1H), 3.25 (ddd, *J* = 11.1, 8.2, 6.1 Hz, 1H), 3.93 (ddd, *J* = 11.3, 8.4, 6.1 Hz, 1H), 4.24 (dt, *J* = 11.3, 8.3 Hz, 1H), 7.39–7.44 (m, 1H), 7.51–7.56 (m, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 13.5, 18.5, 27.7, 33.1, 51.1, 67.6, 110.8, 119.7, 124.7, 128.2, 133.0, 145.5, 199.1. Anal. Calcd for $C_{13}H_{16}N_4S_2$: C, 53.40; H, 5.51; N, 19.16. Found: C, 53.80; H, 5.57; N, 19.10%.

General procedure for the preparation of 3-[1-(sulfanyl)alkyl]-1,3-thiazolidine-2-thione 23a–l

To a solution of 3-(1-benzotriazolylalkyl) thiazolane-2-thiones **20b–d** (2 mmol) and thiols **21a–d** (8 mmol) in anhydrous diethyl ether (25 mL) under nitrogen was added anhydrous zinc bromide (2 mmol). The mixture was heated under reflux for 12h, and then cooled to room temperature. A precipitate was filtered off and washed with diethyl ether. The filtrate (plus washings) was washed with 5 % aqueous sodium hydroxide (2 x 25 mL) and water (2 x 25 mL). The ethereal solution was dried over magnesium sulfate and solvent was evaporated in vacuum. The product was purified by column chromatography on silica gel (hexanes / ethyl acetate 9:1).

3-[1-(Ethylsulfanyl)ethyl]-1,3-thiazolane-2-thione (23a). Colorless oil (96%); ^{1}H NMR δ 1.29 (t, *J* = 7.3 Hz, 3H), 1.46 (d, *J* = 7.0 Hz, 3H), 2.43–2.55 (m, 1H), 2.57–2.69 (m, 1H), 3.22–3.37 (m, 2H), 3.90–3.99 (m, 1H), 4.38–4.47 (m, 1H), 6.39 (q, *J* = 7.0 Hz, 1H); ^{13}C NMR δ 15.1, 18.8, 25.3, 27.7, 50.4, 57.5, 196.6. Anal. Calcd for $C_7H_{13}NS_3$: C, 40.54; H, 6.32; N, 6.75. Found: C, 41.19; H, 6.37; N, 7.21%.

3-[1-(Ethylsulfanyl)propyl]-1,3-thiazolane-2-thione (23b). Colorless oil (95%); ^{1}H NMR δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.29 (t, *J* = 7.3 Hz, 3H), 1.63–1.90 (m, 2H), 2.44–2.55 (m, 1H), 2.58–2.70 (m, 1H), 3.24–3.39 (m, 2H), 3.84–3.93 (m, 1H), 4.37–4.45 (m, 1H), 6.20 (dd, *J* = 8.8, 6.6 Hz, 1H); ^{13}C NMR δ 11.0, 15.2, 25.0, 26.6, 27.8, 50.6, 63.2, 197.2. Anal. Calcd for $C_8H_{15}NS_3$: C, 43.40; H, 6.83; N, 6.33. Found: C, 43.68; H, 6.87; N, 6.67%.

3-[1-(Ethylsulfanyl)butyl]-1,3-thiazolane-2-thione (23c). Colorless oil (93%); ^{1}H NMR δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.29 (t, *J* = 7.4 Hz, 3H), 1.34–1.55 (m, 2H), 1.61–1.80 (m, 2H), 2.43–2.55 (m, 1H), 2.58–2.70 (m, 1H), 3.23–3.38 (m, 2H), 3.84–3.93 (m, 1H), 4.36–4.45 (m, 1H), 6.28 (dd, *J* = 8.6, 6.8 Hz, 1H); ^{13}C NMR δ 13.6, 15.2, 19.6, 25.0, 27.8, 35.2, 50.6, 61.5, 197.0. Anal. Calcd for $C_9H_{17}NS_3$: C, 45.91; H, 7.28; N, 5.95. Found: C, 46.18; H, 7.40; N, 6.01%.

3-[1-(*tert*-Butylsulfanyl)ethyl]-1,3-thiazolane-2-thione (23d). Colorless oil (89%); ^{1}H NMR δ 1.37 (s, 9H), 1.44 (d, *J* = 7.1 Hz, 3H), 3.18–3.34 (m, 2H), 3.89–3.99 (m, 1H), 4.53–4.61 (m, 1H), 6.31 (q, *J* = 7.1 Hz, 1H); ^{13}C NMR δ 19.7, 27.4, 31.2, 44.8, 51.1, 56.5, 194.6. Anal. Calcd for $C_9H_{17}NS_3$: C, 45.91; H, 7.28; N, 5.95. Found: C, 46.40; H, 7.47; N, 5.89%.

3-[1-(*tert*-Butylsulfanyl)propyl]-1,3-thiazolane-2-thione (23e). Colorless oil (94%); ^{1}H NMR δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.38 (s, 9H), 1.63–1.85 (m, 2H), 3.19–3.34 (m, 2H), 3.82–3.91 (m, 1H), 4.50–4.58 (m, 1H), 6.09 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 11.0, 27.5, 27.6, 31.4, 44.6, 51.5, 62.2,

195.2. Anal. Calcd for $C_{10}H_{19}NS_3$: C, 48.15; H, 7.68; N, 5.61. Found: C, 48.60; H, 7.94; N, 5.91%.

3-[1-(*tert*-Butylsulfanyl)butyl]-1,3-thiazolane-2-thione (23f). Colorless oil (91%); ^{1}H NMR δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.37 (s, 9H), 1.43–1.77 (m, 4H), 3.18–3.33 (m, 2H), 3.82–3.92 (m, 1H), 4.50–4.58 (m, 1H), 6.17 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 13.5, 19.6, 27.6, 31.4, 36.2, 44.6, 51.5, 60.7, 194.9. Anal. Calcd for $C_{11}H_{21}NS_3$: C, 50.14; H, 8.03; N, 5.32. Found: C, 50.24; H, 8.22; N, 5.58%.

3-[1-(Phenylsulfanyl)propyl]-1,3-thiazolane-2-thione (23h). Colorless oil (95%); ^{1}H NMR δ 1.06 (t, *J* = 7.4 Hz, 3H), 1.76–2.04 (m, 2H), 3.00–3.19 (m, 2H), 3.84–3.93 (m, 1H), 4.35–4.43 (m, 1H), 6.46 (dd, *J* = 8.5, 6.7 Hz, 1H), 7.22–7.32 (m, 3H), 7.41–7.45 (m, 2H); ^{13}C NMR δ 11.1, 26.6, 27.8, 51.0, 65.6, 127.7, 129.0, 131.8, 131.9, 197.3. Anal. Calcd for $C_{12}H_{15}NS_3$: C, 53.49; H, 5.61; N, 5.20. Found: C, 53.57; H, 5.57; N, 5.42%.

3-[1-(Phenylsulfanyl)butyl]-1,3-thiazolane-2-thione (23i). Colorless oil (98%); ^{1}H NMR δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.33–1.62 (m, 2H), 1.73–1.92 (m, 2H), 2.99–3.18 (m, 2H), 3.84–3.93 (m, 1H), 4.34–4.43 (m, 1H), 6.54 (dd, J = 8.1, 6.9 Hz, 1H), 7.22–7.31 (m, 3H), 7.42–7.45 (m, 2H); ^{13}C NMR δ 13.6, 19.7, 27.8, 35.1, 50.9, 64.1, 127.8, 129.0, 131.8, 131.9, 197.1. Anal. Calcd for $C_{13}H_{17}NS_3$: C, 55.08; H, 6.04; N, 4.94. Found: C, 55.43; H, 6.12; N, 5.37%.

3-[1-(4-Methoxyphenylsulfanyl)ethyl]thiazolidine-2-thione (23j). Colorless oil (99%); ^{1}H NMR δ 1.52 (d, *J* = 6.9 Hz, 3H), 3.05–3.20 (m, 2H), 3.77 (s, 3H), 3.88–3.98 (m, 1H), 4.36–4.44 (m, 1H), 6.48 (q, *J* = 6.9 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 18.4, 27.8, 50.8, 55.4, 61.0, 114.7, 122.1, 135.0, 160.1, 196.6. HRMS Calcd. for $C_{12}H_{15}NOS_3$: [M^+]: 285.0316, Found: 285.0323.

3-[1-(4-Methoxyphenylsulfanyl)propyl]thiazolidine-2-thione (23k). White microcrystals (99%); ^{1}H NMR δ 1.03 (t, *J* = 7.3 Hz, 3H), 1.73–1.98 (m, 2H), 3.05–3.21 (m, 2H), 3.78 (s, 3H), 3.82–3.92 (m, 1H), 4.37–4.45 (m, 1H), 6.33 (dd, *J* = 8.6, 6.4 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 11.3, 26.7, 28.0, 51.0, 55.4, 66.8, 114.7, 122.1, 135.2, 160.1, 197.3. HRMS Calcd. for $C_{13}H_{17}NOS_3$ [M^+]: 299.0472, Found: 299.0469.

3-[1-(4-Methoxyphenylsulfanyl)butyl]thiazolidine-2-thione (23l). Colorless oil (91%); ^{1}H NMR δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.34–1.51 (m, 2H), 1.70–1.86 (m, 2H), 3.02–3.18 (m, 2H), 3.75 (s, 3H), 3.85 (dd, *J* = 19.6, 9.1 Hz, 1H), 4.34–4.42 (m, 1H), 6.38 (dd, *J* = 8.4, 6.7 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 13.6, 19.7, 27.8, 34.9, 50.8, 55.2, 65.0, 114.4, 121.8, 135.1, 159.9, 196.8. HRMS Calcd. for $C_{14}H_{19}NOS_3$ [M^+]: 313.0629, Found: 313.0628.

General procedure for the preparation of 1-(2-thioxo-1,3-thiazolidin-3-yl)alkylphosphonates 24a–e

To a solution of 3-(1-benzotriazolylalkyl)thiazolane-2-thione **20b–d** (2 mmol) in anhydrous dichloromethane (20 mL) at 20–25 °C was added anhydrous zinc bromide (4 mmol) followed by the appropriate trialkyl phosphite **22a,b** (4 mmol). The reaction mixture was heated under reflux for 16 h. The reaction mixture was cooled to 20–25 °C, quenched with a 10% aqueous solution

of sodium carbonate and extracted with dichloromethane. The combined organic layers were washed with brine and dried over magnesium sulfate. The solvent was removed in vacuum and the product was purified by column chromatography on silica gel (hexanes / ethyl acetate 2:1).

Diethyl 1-(2-thioxo-1,3-thiazolan-3-yl)ethylphosphonate (24a). Colorless oil (78%); ^{1}H NMR δ 1.34 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.49 (dd, *J* = 16.3, 7.3 Hz, 3H), 3.20–3.38 (m, 2H), 3.99–4.08 (m, 1H), 4.10–4.25 (m, 4H), 4.41–4.49 (m, 1H), 5.61 (dq, *J* = 17.7, 7.3 Hz, 1H); ^{13}C NMR δ 12.3, 16.3 (d, *J* = 5.2 Hz, 1C), 16.4 (d, *J* = 5.1 Hz, 1C), 27.7, 49.3 (d, *J* = 155.7 Hz, 1C), 52.7, 62.7 (d, *J* = 10.9 Hz, 1C), 62.8 (d, *J* = 10.9 Hz, 1C), 197.6. Anal. Calcd for $C_9H_{18}NO_3PS_2$: C, 38.15; H, 6.40; N, 4.94. Found: C, 38.18; H, 6.67; N, 5.13%.

Diethyl 1-(2-thioxo-1,3-thiazolan-3-yl)propylphosphonate (24b). Colorless oil (81%); ^{1}H NMR δ 0.97 (t, *J* = 7.4 Hz, 3H), 1.33 (dt, *J* = 7.0, 4.1 Hz, 6H), 1.80–2.12 (m, 2H), 3.22–3.39 (m, 2H), 3.96 (dt, *J* = 11.4, 8.2 Hz, 1H), 4.08–4.24 (m, 4H), 4.42 (ddd, *J* = 11.4, 8.0, 6.3 Hz, 1H), 5.49 (ddd, *J* = 18.0, 11.5, 4.4 Hz, 1H); ^{13}C NMR δ 10.8 (d, *J* = 14.3 Hz, 1C), 16.3 (d, *J* = 5.7 Hz, 1C), 16.4 (d, *J* = 5.7 Hz, 1C), 20.7, 27.8, 52.6, 55.2 (d, *J* = 152.9 Hz, 1C), 62.7 (d, *J* = 5.1 Hz, 1C), 62.8 (d, *J* = 5.1 Hz, 1C), 198.3 (d, *J* = 7.4 Hz, 1C). Anal. Calcd for $C_{10}H_{20}NO_3PS_2$: C, 40.39; H, 6.78; N, 4.71. Found: C, 40.10; H, 6.87; N, 5.03%.

Diisopropyl 1-(2-thioxo-1,3-thiazolan-3-yl)propylphosphonate (24c). Colorless oil (78%); ^{1}H NMR δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.32–1.37 (m, 12 H), 1.77–2.11 (m, 2H), 3.21–3.37 (m, 2H), 3.95 (dt, *J* = 11.4, 8.4 Hz, 1H), 4.42 (ddd, *J* = 11.4, 8.0, 6.3 Hz, 1H), 4.65–4.81 (m, 2H), 5.44 (ddd, *J* = 18.4, 11.4, 4.3 Hz, 1H); ^{13}C NMR δ 10.8 (d, *J* = 14.9 Hz, 1H), 20.7, 23.7–24.2 (m, 4C), 27.7, 52.5, 55.7 (d, *J* = 154.6 Hz, 1C), 71.6 (d, *J* = 6.9 Hz, 2C), 198.2 (d, *J* = 7.4 Hz, 1C). Anal. Calcd for $C_{12}H_{24}NO_3PS_2$: C, 44.29; H, 7.43; N, 4.30. Found: C, 43.90; H, 7.48; N, 4.40%.

Diethyl 1-(2-thioxo-1,3-thiazolan-3-yl)butylphosphonate (24d). Colorless oil (76%); ^{1}H NMR δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.31–1.42 (m, 8H), 1.85–1.96 (m, 2H), 3.21–3.38 (m, 2H), 3.96 (dt, *J* = 11.5, 8.1 Hz, 1H), 4.08–4.24 (m, 4H), 4.40 (ddd, *J* = 14.6, 8.0, 6.6 Hz, 1H), 5.50–5.67 (m, 1H); ^{13}C NMR δ 13.4, 16.2 (d, *J* = 5.7 Hz, 1C), 16.3 (d, *J* = 5.7 Hz, 1C), 19.1 (d, *J* = 13.7 Hz, 1C), 27.8, 28.9, 52.5, 53.4 (d, *J* = 152.9 Hz, 1C), 62.6 (d, *J* = 5.7 Hz, 2C), 197.0 (d, *J* = 6.9 Hz, 1C). Anal. Calcd for $C_{11}H_{22}NO_3PS_2$: C, 42.43; H, 7.12; N, 4.50. Found: C, 42.38; H, 7.29; N, 4.78%.

Diisopropyl 1-(2-thioxo-1,3-thiazolan-3-yl)butylphosphonate (24e). Colorless oil (88%); ^{1}H NMR δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.25–1.41 (m, 14H), 1.82–1.92 (m, 2H), 3.20–3.36 (m, 2H), 3.91–4.00 (m, 1H), 4.36–4.44 (m, 1H), 4.67–4.79 (m, 2H), 5.45–5.56 (m, 1H); ^{13}C NMR δ 13.8, 19.4 (d, *J* = 14.3 Hz, 1C), 24.0–24.4 (m, 4C), 28.0, 29.3 (d, *J* = 1.4 Hz, 1C), 52.8, 54.3 (d, *J* = 154.3 Hz, 1C), 71.7 (d, *J* = 7.5 Hz, 1C), 71.8 (d, *J* = 6.9 Hz, 1C), 198.1 (d, *J* = 7.5 Hz, 1C). Anal. Calcd for $C_{13}H_{26}NO_3PS_2$: C, 46.00; H, 7.72; N, 4.13. Found: C, 45.88; H, 8.08; N, 3.99%.

General procedure for the preparation of 3-(1-benzotriazolylalkyl)thiazine-2-thiones 26a–c

Boron trifluoride etherate (3.8 mL, 30 mmol) was added to a solution of 1,3-thiazinane-2-thione **25** (2 g, 15 mmol) and the 1-(1-hydroxyalkyl)benzotriazole **19b–d** (15 mmol) in anhydrous THF (25 mL) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. Ethyl acetate

was added, and the organic layer was washed with 10% aqueous sodium carbonate (2 x 25 mL). The organic layer was separated, dried over magnesium sulfate, and solvent removed under reduced pressure. The crude product was recrystallized from an appropriate solvent.

3-[1-(Benzotriazol-1-yl)ethyl]-1,3-thiazinane-2-thione (26a). White microcrystals from ethyl acetate (69%), mp 156–157 °C; ^{1}H NMR δ 1.73–1.86 (m, 1H), 2.08–2.17 (m, 1H), 2.17 (d, *J* = 6.9 Hz, 3H), 2.78–2.85 (m, 1H), 2.92–3.00 (m, 1H), 3.10 (ddd, *J* = 13.6, 7.6, 2.2 Hz, 1H), 3.57 (ddd, *J* = 13.6, 8.5, 2.3 Hz, 1H), 7.40–7.46 (m, 1H), 7.52–7.57 (m, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.74 (q, *J* = 6.9 Hz, 1H); ^{13}C NMR δ 15.8, 22.8, 31.9, 42.9, 66.9, 110.7, 119.8, 124.8, 128.4, 132.5, 145.8, 194.2. Anal. Calcd for $C_{12}H_{14}N_4S_2$: C, 51.77; H, 5.07; N, 20.12. Found: C, 52.09; H, 5.03; N, 19.69%.

3-[1-(Benzotriazol-1-yl)propyl]-1,3-thiazinane-2-thione (26b). White microcrystals from ethyl acetate (65%), mp 166–167 °C; ^{1}H NMR δ 1.13 (t, *J* = 7.3 Hz, 3H), 1.73–1.86 (m, 1H), 2.11–2.23 (m, 1H), 2.52–2.67 (m, 1H), 2.70–2.85 (m, 2H), 2.92–3.00 (m, 1H), 3.30 (ddd, *J* = 13.7, 7.6, 2.2 Hz, 1H), 3.60 (ddd, *J* = 13.7, 8.8, 2.5 Hz, 1H), 7.40–7.45 (m, 1H), 7.51–7.57 (m, 1H), 8.04 (dd, *J* = 15.0, 8.2 Hz, 2H), 8.59 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR δ 9.7, 22.8, 23.9, 31.9, 43.5, 71.2, 111.0, 119.7, 124.7, 128.3, 133.0, 145.6, 195.1. Anal. Calcd for $C_{13}H_{16}N_4S_2$: C, 53.40; H, 5.51; N, 19.16. Found: C, 53.70; H, 5.57; N, 18.95%.

3-[1-(Benzotriazol-1-yl)butyl]-1,3-thiazinane-2-thione (26c). White microcrystals from ethyl acetate (70%),mp 93–94 °C; ^{1}H NMR δ 1.05 (t, *J* = 7.4 Hz, 3H), 1.40–1.62 (m, 2H), 1.74–1.86 (m, 1H), 2.11–2.23 (m, 1H), 2.43–2.56 (m, 1H), 2.68–2.84 (m, 2H), 2.92–3.00 (m, 1H), 3.32 (ddd, *J* = 13.6, 7.3, 2.3 Hz, 1H), 3.62 (ddd, *J* = 13.7, 8.7, 2.3 Hz, 1H), 7. 39–7.44 (m, 1H), 7.51–7.56 (m, 1H), 8.01–8.07 (m, 2H), 8.65 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 13.9, 18.6, 23.0, 32.1, 32.5, 43.8, 70.0, 111.1, 119.8, 124.9, 128.5, 133.2, 145.8, 195.0. Anal. Calcd for $C_{14}H_{18}N_4S_2$: C, 54.87; H, 5.92; N, 18.28. Found: C, 55.13; H, 5.89; N, 18.28%.

General procedure for the preparation of 3-[1-(substituted- sulfanyl)alkyl]-1,3-thiazinane-2-thiones 27a–c

To a solution of the 3-(1-benzotriazolylalkyl)-1,3-thiazinane-2-thione **26a–c** (2 mmol) and thiol **21a,c** (8 mmol) in anhydrous diethyl ether (25 mL) under nitrogen was added anhydrous zinc bromide (2 mmol). The mixture was heated under reflux for 12h, and then cooled to room temperature. A precipitate was filtered off and washed with diethyl ether. The filtrate (plus washings) was washed with 5 % aqueous sodium hydroxide (2 x 25 mL) and water (2 x 25 mL). The ethereal solution was dried over magnesium sulfate and solvent was removed in vacuum. The product was purified by column chromatography on silica gel (hexanes / ethyl acetate 9:1).

3-[1-(Phenylsulfanyl)ethyl]-1,3-thiazinane-2-thione (27a). Colorless oil (78%); ^{1}H NMR δ 1.52 (d, *J* = 6.9 Hz, 3H), 1.78–1.91 (m, 1H), 2.14–2.25 (m, 1H), 2.70–2.77 (m, 1H), 2.92 (ddd, *J* = 11.8, 9.5, 4.8 Hz, 1H), 3.31 (ddd, *J* = 13.5, 9.5, 2.8 Hz, 1H), 3.96 (ddd, *J* = 13.5, 6.9, 2.8 Hz, 1H), 7.20–7.32 (m, 3H), 7.40–7.43 (m, 2H), 7.64 (q, *J* = 6.9 Hz, 1H); ^{13}C NMR δ 17.9, 23.3, 32.3, 43.4, 62.7, 127.5, 129.2, 130.7, 132.6, 193.3. Anal. Calcd for $C_{12}H_{15}NS_3$: C, 53.49; H, 5.61; N, 5.20. Found: C, 53.34; H, 5.63; N, 5.17%.

3-[1-(Ethylsulfanyl)propyl]-1,3-thiazinane-2-thione (27b). Colorless oil (77%); ^{1}H NMR δ 1.01 (t, *J* = 7.4 Hz, 3H), 1.31 (t, *J* = 7.4 Hz, 3H), 1.65–1.81 (m, 2H), 2.08–2.22 (m, 1H), 2.33–2.44 (m, 1H), 2.52 (dq, *J* = 20.3, 7.4 Hz, 1H), 2.70 (dq, *J* = 20.5, 7.4 Hz, 1H), 2.90–2.97 (m, 1H), 3.07 (ddd, *J* = 11.7, 10.0, 4.7 Hz, 1H), 3.21 (ddd, *J* = 12.4, 9.8, 2.3 Hz, 1H), 3.92–3.99 (m, 1H), 7.20–7.25 (m, 1H); ^{13}C NMR δ 10.9, 15.4, 23.1, 24.9, 26.1, 32.2, 43.1, 66.4, 193.1. Anal. Calcd for $C_9H_{17}NS_3$: C, 45.91; H, 7.28; N, 5.95. Found: C, 46.07; H, 7.66; N, 5.85%.

3-[1-(Phenylsulfanyl)propyl]-1,3-thiazinane-2-thione (27c). Colorless oil (79%); ^{1}H NMR δ 1.09 (t, *J* = 7.4 Hz, 3H), 1.79–1.92 (m, 3H), 2.18–2.29 (m, 1H), 2.72–2.79 (m, 1H), 2.94 (ddd, *J* = 11.8, 9.7, 5.0 Hz, 1H), 3.25 (ddd, *J* = 12.0, 9.5, 2.5 Hz, 1H), 3.94–4.01 (m, 1H), 7.21–7.32 (m, 3H), 7.44–7.48 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR δ 11.0, 23.1, 26.3, 32.1, 43.6, 68.2, 127.4, 129.0, 131.0, 132.3, 193.7. Anal. Calcd for $C_{13}H_{17}NS_3$: C, 55.08; H, 6.04; N, 4.94. Found: C, 55.25; H, 6.06; N, 4.83%.

General procedure for the preparation of 1-(2-thioxo-1,3-thiazinan-3-yl)alkylphosphonates (28a,b)

To a solution of 3-(1-benzotriazolylalkyl)-1,3-thiazinane-2-thione **26a,c** (2 mmol) in anhydrous dichloromethane (20 mL) at 20–25 °C was added anhydrous zinc bromide (4 mmol) followed by triethyl phosphite **22a** (4 mmol). The reaction mixture was heated under reflux for 14 h, then cooled to 20–25 °C, quenched with a 10% aq. sodium carbonate (20 mL) and extracted with dichloromethane (2 x 25 mL). The combined organic layers were washed with brine and dried over magnesium sulfate. The solvent was evaporated and the residue purified by column chromatography on silica gel (hexanes / ethyl acetate 2:1).

Diethyl 1-(2-thioxo-1,3-thiazinan-3-yl)ethylphosphonate (28a). Colorless oil (72%); ^{1}H NMR δ 1.28 (td, *J* = 7.1, 1.4 Hz, 6H), 1.42 (dd, *J* = 16.3, 7.4 Hz, 3H), 2.17–2.24 (m, 2H), 2.86–3.01 (m, 2H), 3.41–3.49 (m, 1H), 3.86 (dt, *J* = 13.7, 4.9 Hz, 1H), 4.00–4.18 (m, 4H), 6.54 (ddd, *J* = 19.1, 14.7, 7.3 Hz, 1H); ^{13}C NMR δ 12.0, 16.2 (d, *J* = 5.7 Hz, 1C), 16.3 (d, *J* = 4.0 Hz, 1C), 23.0, 32.2, 46.0, 51.76 (d, *J* = 152.9 Hz, 1C), 62.5 (d, *J* = 6.9 Hz, 1C), 62.67 (d, *J* = 6.9 Hz, 1C), 193.2 (d, *J* = 8.0 Hz, 1C). Anal. Calcd for $C_{10}H_{20}NO_3PS_2$: C, 40.39; H, 6.78; N, 4.71. Found: C, 40.35; H, 7.03; N, 4.61%.

Diethyl 1-(2-thioxo-1,3-thiazinan-3-yl)butylphosphonate (28b). Colorless oil (77%); ^{1}H NMR δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.32–1.48 (m, 8H), 1.83–2.01 (m, 2H), 2.24–2.32 (m, 2H), 2.93–3.08 (m, 2H), 3.40–3.48 (m, 1H), 3.90 (dt, *J* = 13.6, 4.8 Hz, 1H), 4.10–4.26 (m, 4H), 6.61 (ddd, *J* = 19.1, 10.3, 5.1 Hz, 1H); ^{13}C NMR δ 13.7, 16.2 (d, *J* = 5.2 Hz, 1C), 16.3 (d, *J* = 5.7 Hz, 1C), 19.2 (d, *J* = 13.8 Hz, 1C), 23.0, 28.9, 32.2, 46.0, 56.1 (d, *J* = 150.0 Hz, 1C), 62.5 (d, *J* = 1.7 Hz, 1C), 62.6 (d, *J* = 1.7 Hz, 1C), 193.9 (d, *J* = 7.4 Hz, 1C). Anal. Calcd for $C_{12}H_{24}NO_3PS_2$: C, 44.29; H, 7.43; N, 4.30. Found: C, 44.35; H, 7.77; N, 4.54%.

General procedure for the preparation of alkyl *N*-[1-(benzotriazol-1-yl)alkyl]-*N*-ethyl dithiocarbamates 30a–e

The methyl *N*-ethyldithiocarbamate **29a–c** (10 mmol), 1-(1-hydroxy-alkyl)benzotriazole **19a,d** (10 mmol) and *p*-toluenesulfonic acid (0.1 g, as catalyst) in toluene (50 mL) were heated under reflux in a Dean-Stark apparatus for 24 h. The reaction mixture was concentrated in vacuum to give the crude products **30a–e**. The products **30a–d** were purified by column chromatography on silica gel; **30e** was used in the crude state.

Ethyl *N*-(benzotriazol-1-ylmethyl)-*N*-methylcarbamodithioate (30a). Colorless oil (56%); ^{1}H NMR δ 1.38 (t, *J* = 7.4 Hz, 3H), 3.32 (q, *J* = 7.4 Hz, 2H), 3.54 (br s, 3H), 6.89 (br s, 2H), 7.39–7.42 (m, 2H), 7.87–7.92 (m, 2H); ^{13}C NMR δ 13.2, 29.7, 32.3, 70.6, 118.5, 127.0, 144.6, 202.4. Anal. Calcd for $C_{11}H_{14}N_4S_2$: C, 49.60; H, 5.30; N, 21.03. Found: C, 50.22; H, 5.43; N, 20.85%.

Ethyl *N*-[1-(benzotriazol-1-yl)butyl]-*N*-methylcarbamodithioate (30b). White microcrystals from ethyl acetate (61%), mp 49–50 °C; ^{1}H NMR δ 1.04 (t, *J* = 7.3 Hz, 3H), 1.37 (t, *J* = 7.3 Hz, 3H), 1.39–1.57 (m, 2H), 2.45–2.58 (m, 1H), 2.66–2.78 (m, 1H), 3.17 (s, 3H), 3.26–3.38 (m, 2H), 7.37–7.42 (m, 1H), 7.48–7.53 (m, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.58 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 13.2, 13.7, 18.4, 31.6, 32.9, 33.0, 71.5, 110.9, 119.7, 124.5, 128.0, 133.1, 145.6, 201.2. Anal. Calcd for $C_{14}H_{20}N_4S_2$: C, 54.51; H, 6.54; N, 18.16. Found: C, 54.79; H, 6.62; N, 18.10%.

Methyl *N*-(benzotriazol-1-ylmethyl)-*N*-ethylcarbamodithioate (30c). White microcrystals from ethyl acetate (61%), mp 104–105 °C; ^{1}H NMR δ 1.17 (t, *J* = 7.1 Hz, 3H), 2.70 (s, 3H), 3.91 (q, *J* = 7.1 Hz, 2H), 6.98 (s, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 8.1 Hz, 1H), 8.04–8.10 (m, 2H); ^{13}C NMR δ 11.8, 20.3, 45.2, 62.0, 111.4, 119.7, 124.5, 128.0, 132.4, 146.0, 202.3. Anal. Calcd for $C_{11}H_{14}N_4S_2$: C, 49.60; H, 5.30; N, 21.03. Found: C, 49.94; H, 5.41; N, 21.03%.

Methyl *N*-[1-(benzotriazol-1-yl)butyl]-*N*-ethylcarbamodithioate (30d). White microcrystals from ethyl acetate (63%), mp 91–92 °C; ^{1}H NMR δ 0.70 (t, *J* = 7.0 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H), 1.36–1.55 (m, 2H), 2.40–2.52 (m, 1H), 2.71 (s, 3H), 2.76–2.88 (m, 1H), 3.78–3.84 (m, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 8.63 (br s, 1H); ^{13}C NMR δ 13.1, 13.6, 18.4, 20.1, 32.9, 41.6, 72.0, 110.7, 119.7, 124.6, 128.1, 133.3, 145.5, 201.2. Anal. Calcd for $C_{14}H_{20}N_4S_2$: C, 54.51; H, 6.54; N, 18.16. Found: C, 54.94; H, 6.60; N, 18.21%.

General procedure for the preparation of alkyl *N*-thioalkyl dithiocarbamates 31a–e

To a solution of either **30b,d,** or **e** (2 mmol) and a thiol **21a** or **c** (8 mmol) in anhydrous diethyl ether (25 mL) under nitrogen was added anhydrous zinc bromide (0.45 g, 2 mmol). The mixture was heated under reflux for 12 h, and then cooled to room temperature. The precipitate was filtered off and washed with diethyl ether. The filtrate (plus washings) was washed with 5 % aqueous sodium hydroxide (2 x 25 mL) and water (2 x 25 mL). The ethereal solution was dried over magnesium sulfate, the solvent was evaporated in vacuum, and the residue purified by column chromatography on silica gel (hexanes / ethyl acetate 9:1).

Ethyl *N*-methyl-*N*-[1-(phenylsulfanyl)butyl]carbamodithioate (31a). Colorless oil (97%); ^{1}H NMR δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.25 (1.10) (t, *J* = 7.3 Hz, 3H), 1.33–1.54 (m, 2H), 1.76–1.89 (m, 2H), 3.00–3.24 (m, 2H), 3.27 (3.48) (s, 3H), 7.22–7.28 (m, 3H), 7.41–7.44 (m, 2H), 7.46 (6.14) (t, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 13.5, 13.7, 13.7, 13.8, 19.6 (19.7), 29.7, 31.2, 33.4, 35.2, 35.7, 36.9, 68.7, 70.1, 127.4, 128.6, 128.8, 128.9, 132.1, 132.5, 134.5, 199.7. Anal. Calcd for $C_{14}H_{21}NS_3$: C, 56.14; H, 7.07; N, 4.68. Found: C, 55.50; H, 6.99; N, 4.76%.

Methyl *N*-ethyl-*N*-[1-(phenylsulfanyl)butyl]carbamodithioate (31b). Colorless oil (98%); ^{1}H NMR δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.25–1.38 (m, 3H), 1.40–1.64 (m, 2H), 1.79–1.89 (m, 2H), 2.59 (2.45) (s, 3H), 3.99–4.26 (3.72–3.84) (m, 2H), 7.19–7.26 (m, 3H), 7.37–7.40 (m, 2H), 7.48 (6.15) (t, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 13.1, 13.5, 13.7, 14.2, 19.7, 19.8, 35.8, 36.1, 42.1, 44.6, 69.4, 70.6, 126.8, 127.5, 128.2, 128.7, 130.6, 132.0, 132.5, 133.3, 133.6, 198.6, 199.9. Anal. Calcd for $C_{14}H_{21}NS_3$: C, 56.14; H, 7.07; N, 4.68. Found: C, 56.61; H, 7.16; N, 4.87%.

Methyl *N*-ethyl-*N*-[1-(ethylsulfanyl)butyl]carbamodithioate (31c). Colorless oil (95%); ^{1}H NMR δ 0.94 (t, *J* = 7.3 Hz, 3H), 1.26 (t, *J* = 7.3 Hz, 3H), 1.32–1.43 (m, 4H), 1.46–1.58 (m, 1H), 1.66–1.80 (m, 2H), 2.36–2.48 (m, 1H), 2.55–2.61 (m, 1H), 2.66 (s, 3H), 3.95–4.12 (3.69–3.81) (m, 2H), 7.29 (5.95) (t, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 13.3, 13.7, 13.9, 14.5, 15.0, 15.4, 19.8, 20.0, 24.8, 36.0, 36.2, 41.6, 44.3, 66.9, 67.4, 198.0, 200.2. Anal. Calcd for $C_{10}H_{21}NS_3$: C, 47.76; H, 8.42; N, 5.57. Found: C, 48.52; H, 8.61; N, 5.91%.

Ethyl *N*-butyl-*N*-[1-(phenylsulfanyl)butyl]carbamodithioate (31d). Colorless oil (98%); ^{1}H NMR δ 0.92–1.02 (m, 6H), 1.26 (1.12) (t, *J* = 7.3 Hz, 3H), 1.34–1.66 (m, 5H), 1.72–1.89 (2.02–2.15) (m, 3H), 3.12–3.31 (2.99–3.08) (m, 2H), 3.87–4.14 (3.57–3.67) (m, 2H), 7.16–7.25 (m, 3H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.49 (6.18) (t, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 13.5, 13.6, 13.7, 19.8, 19.9, 20.4, 29.4, 30.7, 31.2, 35.9, 36.2, 47.5, 49.6, 69.2, 70.6, 127.0, 128.3, 128.8, 131.0, 132.1, 133.3, 133.8, 197.9, 199.3. Anal. Calcd for $C_{17}H_{27}NS_3$: C, 59.77; H, 7.97; N, 4.10. Found: C, 60.09; H, 8.21; N, 4.51%.

Ethyl *N*-butyl-*N*-[1-(ethylsulfanyl)butyl]carbamodithioate (31e). Colorless oil (95%); ^{1}H NMR δ 0.92–1.00 (m, 6H), 1.26 (t, *J* = 7.4 Hz, 3H), 1.31–1.75 (m, 10H), 1.89–2.03 (m, 1H), 2.37–2.48 (m, 1H), 2.51–2.66 (m, 1H), 3.24–3.38 (m, 2H), 3.80–3.97 (3.53–3.64) (m, 2H), 7.29 (5.98) (t, *J* = 7.1 Hz, 1H); ^{13}C NMR δ 13.3 (13.4), 13.6, 13.7, 15.3 (14.9), 19.7, 20.4, 24.7, 29.4 (29.6), 30.8, 31.3, 35.9 (36.1), 47.0, 49.1, 66.9 (66.5), 199.3 (197.2). Anal. Calcd for $C_{13}H_{27}NS_3$: C, 53.19; H, 9.27; N, 4.77. Found: C, 53.30; H, 9.50; N, 5.01%.

General procedure for the preparation of dialkyl 1-[ethyl(methylsulfanylthiocarbonyl) amino]butylphosphonates (32a–d)

To a solution of **30b,** or **d** (2 mmol) in anhydrous dichloromethane (20 mL) at 20–25 °C was added anhydrous zinc bromide (0.9 g, 4 mmol) followed by a trialkyl phosphite **22a,** or **b** (4 mmol). The mixture was heated under reflux for 16 h and cooled to 20–25 °C. It was then quenched with a 10% aqueous solution of sodium carbonate (20 mL) and the product was extracted with dichloromethane (2 x 25 mL). The combined organic layers were washed with

brine and dried over magnesium sulfate. The solvent was evaporated and the residue purified by column chromatography on silica gel (hexanes / ethyl acetate 2:1).

Diethyl 1-{[(ethylsulfanyl)carbothioyl](methyl)amino}butylphosphonate (32a). Colorless oil (86%); ^{1}H NMR δ 0.93–0.99 (m, 3H), 1.27–1.41 (m, 11H), 1.82–2.00 (m, 2H), 3.22–3.33 (m, 2H), 3.35 (3.48) (s, 3H), 4.06–4.23 (m, 4H), 6.55 (5.04) (ddd, *J* = 20.2, 10.7 & 4.1 Hz, 1H); ^{13}C NMR δ 13.3, 13.6, 13.8, 16.3 (d, *J* = 5.2 Hz, 1C), 16.4 (d, *J* = 5.8 Hz, 1C), 19.2 (d, *J* = 13.7 Hz, 1C), 29.9 (29.6), 32.0, 35.3 (38.8), 57.9 (58.8) (d, *J* = 150.6 Hz, 1C), 62.4 (d, *J* = 6.9 Hz, 1C), 62.5 (d, *J* = 7.0 Hz, 1C), 200.7 (d, *J* = 7.4 Hz, 1C). Anal. Calcd for $C_{12}H_{26}NO_3PS_2$: C, 44.02; H, 8.00; N, 4.28. Found: C, 44.01; H, 8.25; N, 4.82%.

Diisopropyl 1-{[(ethylsulfanyl)carbothioyl](methyl)amino}butylphosphonate (32b). Colorless oil (83%); ^{1}H NMR δ 0.85–0.91 (m, 3H), 1.19–1.32 (m, 17H), 1.72–1.96 (m, 2H), 3.07–3.26 (m, 2H), 3.27 (3.40) (s, 3H), 4.58–4.73 (m, 2H), 6.43 (4.91) (ddd, *J* = 19.6, 10.2 &5.1, 1H); ^{13}C NMR δ 13.1, 13.4, 13.5, 13.6, 13.8, 19.2 (d, *J* = 13.7 Hz, 1C), 23.7, 23.8, 23.9, 24.0, 24.0, 24.1, 24.1, 24.2, 24.3, 29.7, 29.8, 31.8, 31.9, 35.2, 38.8, 58.4 (59.2) (d, *J* = 152.3 Hz, 1C), 71.1, 71.2, 71.3, 71.4, 71.9, 72.0, 200.4 (d, *J* = 7.4 Hz, 1C). Anal. Calcd for $C_{14}H_{30}NO_3PS_2$: C, 47.30; H, 8.51; N, 3.94. Found: C, 47.88; H, 8.95; N, 4.15%.

Diethyl 1-[ethyl(methylsulfanylcarbothioyl)amino]butylphosphonate (32c). Colorless oil (89%); ^{1}H NMR δ 0.93–1.00 (m, 3H), 1.27–1.46 (m, 11H), 1.93 (p, *J* = 7.1 Hz, 2H), 2.68 (2.65) (s, 3H), 3.85–4.05 (m, 2H), 4.07–4.22 (m, 4H), 6.58–6.72 (m, 1H); ^{13}C NMR δ 12.5, 13.6 (d, *J* = 8.6 Hz, 1C), 16.1 (d, *J* = 1.7 Hz, 1C), 16.2 (d, *J* = 1.7 Hz, 1C), 19.1 (d, *J* = 13.7 Hz, 1C), 20.3, 29.8 (d, *J* = 1.7 Hz, 1C), 43.6, 58.7 (d, *J* = 150.6 Hz, 1C), 62.2 (d, *J* = 7.4 Hz, 1C), 62.3 (d, *J* = 7.4 Hz, 1C). Anal. Calcd for $C_{12}H_{26}NO_3PS_2$: C, 44.02; H, 8.00; N, 4.28. Found: C, 44.46; H, 8.27; N, 4.44%.

Diisopropyl 1-{ethyl[(methylsulfanyl)carbothioyl]amino}butylphosphonate (32d). Colorless oil (80%); ^{1}H NMR δ 0.93–1.00 (m, 3H), 1.26–1.46 (m, 17H), 1.85–1.95 (m, 2H), 2.67 (2.64) (s, 3H), 3.84–4.07 (4.24–4.36) (m, 2H), 4.66–4.78 (m, 2H), 4.89–5.00 (ddd, *J* = 20.6, 10.2 & 3.8 Hz, 0.28H), 6.59 (dt, *J* = 20.3 & 7.4 Hz, 0.72H); ^{13}C NMR δ 12.6, 13.7, 13.8, 13.9, 19.2, 19.4, 19.6, 20.3, 20.5, 23.5, 23.6, 23.7, 23.8, 23.8, 23.9, 24.0, 24.1, 24.1, 24.1, 24.2, 24.3, 30.1, 30.1, 43.7, 46.5, 59.6 (59.9) (d, *J* = 154.6 Hz, 1C), 71.1 (71.2) (d, *J* = 3.4 Hz, 1C), 71.3 (71.8) (d, *J* = 7.4 Hz, 1C), 201.2 (199.3) (d, *J* = 6.9 Hz, 1C). Anal. Calcd for $C_{14}H_{30}NO_3PS_2$: C, 47.30; H, 8.51; N, 3.94. Found: C, 47.14; H, 8.75; N, 4.10%.

References

1. Rieche, A.; Martin, D.; Schade, W. *Arch. Pharm.* **1963**, *296*, 770.
2. Schorr, M.; Duerckheimer, W.; Klatt, P.; Laemmler, G.; Nesemann, G.; Schrinner, E. *Arzneim.-Forsch.* **1969**, *19*, 1807.
3. Bruer, H.; Treuner, U. D. US Pat. 3855211, 1974; *Chem. Abstr.* **1975**, *83*, 8845.
4. El-Shorbagi, A.-N. *Arch. Pharm.* **2000**, *333*, 281.

5. Farbwerke Hoechst A.-G. Fr. Pat. 2015026, 1970; *Chem. Abstr.* **1971**, *75*, 5534.
6. Schorr, M.; Duerckheimer, W.; Behrendt, L.; Duewel, D. Ger. Pat. 1 947 746, 1971; *Chem. Abstr.* **1971**, *75*, 5531.
7. D'Amico, J. J.; Harman, M. W. Br. Pat. 769222, 1957; *Chem. Abstr.* **1957**, *51*, 68492.
8. Hanefeld, W. *Arch. Pharm.* **1977**, *310*, 409.
9. Hussein, M. A.; El-Shorbagi, A.-N.; Khallil, A.-R. *Arch. Pharm.* **2001**, *334*, 305.
10. Aboul-Fadl, T.; Hussein, M. A.; El-Shorbagi, A.-N.; Khallil, A.-R. *Arch. Pharm.* **2002**, *335*, 438.
11. Zsolnai, T. *Zentralblatt fur Bakteriologie. 1. Abt. Originale. A: Medizinische Mikrobiologie, Infektionskrankheiten und Parasitologie* **1980**, *247*, 410.
12. Nishimura, K.; Yasunaga, T.; Kanada, S.; Katayama, S. Jpn. Pat. 53-029932, 1978; *Chem. Abstr.* **1978**, *89*, 101949.
13. (Ciba-Geigy AG) Br. Pat. 1301032, 1972.
14. (Henkel) Fr. Pat. 1600071, 1970; *Chem. Abstr.* **1971**, *74*, 98852.
15. Richards, L. M. (E. I. du Pont de Nemours) US Pat. 2423520, 1947; *Chem. Abstr.* **1947**, *41*, 30335.
16. Sullivan, F. A. V.; Lindaw, A. C. (American Cyanamid Co.) US Pat. 3215703, 1965; *Chem. Abstr.* **1966**, *64*, 11503.
17. Kinstler, R. C. (American Cyanamid Co.) US Pat. 3215704, 1965; *Chem. Abstr.* **1966**, *64*, 19347.
18. Braun, J. V. *Chem. Ber.* **1902**, *35*, 3368.
19. Hirano, H. *Yakugaku Zasshi* **1955**, *75*, 249.
20. Beck, G.; Heitzer, H. (Bayer A.-G.) US Pat. 4 125 723, 1978; *Chem. Abstr.* **1978**, *89*, 109560.
21. Gotthardt, H.; Reiter, F. *Liebigs Ann. Chem.* **1979**, 650.
22. Barzen, R.; Schunack, W. *Arch. Pharm.* **1980**, *313*, 544.
23. Ahlbrecht, H.; Kornetzky, D. *Synthesis* **1988**, 775.
24. Agami, C.; Couty, F.; Hamon, L.; Venier, O. *Bull. Soc. Chim. Fr.* **1995**, *132*, 808.
25. Kanie, K.; Mizuno, K.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1973.
26. Smith, T. D. *J. Chem. Soc.* **1961**, 3164.
27. Hook, E. O.; Beegle, L. C.; Wystrach, V. P. (American Cyanamid Co.) US Pat. 2786866, 1957; *Chem. Abstr.* **1957**, *51*, 66859.
28. Perjési, P.; Sohar, P. *Monatsh. Chem.* **1991**, *122*, 1047.
29. van der Werf, S.; Engberts, J. B. F. N. *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 423.
30. Bafford, R. A.; Chanon, F.; Chanon, M.; Metzger, J. *Bull. Soc. Chim. Fr.* **1973**, 808.
31. Johnston, T. P.; Stringfellow, C. R., Jr.; Piper, J. R. *J. Med. Chem.* **1968**, *11*, 1256.
32. Schubart, R.; Eholzer, U. (Bayer A.-G.) US Pat. 4148800, 1979.
33. Shomina, F. N.; Etlis, V. S.; Sineokov, A. P. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1973**, 1105.
34. Bradsher, C. K.; Brown, F. C.; Sinclair, E. F. *J. Am. Chem. Soc.* **1956**, *78*, 6189.

35. Goddin, A. H.; Searle, N. E. (E. I. du Pont de Nemours & Co.) US Pat. 2516313, 1950; *Chem. Abstr.* **1951**, *45*, 4680.
36. Scott, W. US Pat. 2353593, 1944; *Chem. Abstr.* **1944**, *38*, 44062.
37. Elslager, E. F.; Gavrilis, Z. B.; Phillips, A. A.; Worth, D. F. *J. Med. Chem.* **1969**, *12*, 357.
38. Fisher, M. P.; Lauter, W. M. *J. Am. Pharm. Assoc.* **1956**, *45*, 531.
39. Gaul, R. J.; Fremuth, W. J.; O'Connor, M. N. *J. Org. Chem.* **1961**, *26*, 5106.
40. Jurek, J.; Rodewald, W. J. *J. Prakt. Chem.* **1992**, *334*, 350.
41. Felder, E.; Fumaġalli, L.; Pitré, D. *Helv. Chim. Acta* **1963**, 752.
42. Hanefeld, W.; Bercin, E. *Arch. Pharm.* **1981**, *314*, 413.
43. Locher, C.; Peerzada, N. *ARKIVOC* **2000**, *(i)*, 12.
44. Pernak, J.; Rogoża, J. *ARKIVOC* **2000**, *(i)*, 889.
45. Katritzky, A. R.; Zhang, Y.; He, H.-Y. *ARKIVOC* **2002**, (*v)*, 161.
46. Katritzky, A. R.; Urogdi, L.; Mayence, A. *J. Chem. Soc., Chem. Commun.* **1989**, 337.
47. Katritzky, A. R.; Urogdi, L.; Mayence, A. *J. Org. Chem.* **1990**, *55*, 2206.
48. Katritzky, A. R.; Harris, P. A. *Tetrahedron Asymmetry* **1992**, *3*, 437.
49. Sherrill, R. G.; Sugg, E. E. *J. Org. Chem.* **1995**, *60*, 730.
50. Katritzky, A. R.; Cobo-Domingo, J.; Yang, B.; Steel, P. J. *Tetrahedron Asymmetry* **1999**, *10*, 255.
51. Katritzky, A. R.; Luo, Z.; Fang, Y. *Tetrahedron Lett.* **2000**, *41*, 9691.
52. Katritzky, A. R.; Luo, Z. *Heterocycles* **2001**, *55*, 1467.
53. Katritzky, A. R.; Qiu, G. *J. Org. Chem.* **2001**, *66*, 2862.
54. Katritzky, A. R.; Kirichenko, K.; Elsayed, A. M.; Ji, Y.; Fang, Y. *J. Org. Chem.* **2002**, *67*, 4957.
55. Katritzky, A. R.; Yannakopoulou, K. *Synthesis* **1989**, 747.
56. Katritzky, A. R.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1853.
57. Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 791.
58. Katritzky, A. R.; Shobana, N.; Harris, P. A.; Hill, J. B.; Ager, D. J. *Org. Prep. Proced. Int.* **1992**, *24*, 121.