Microwave mediated syntheses of β-enamino thioic acid derivatives

Alan R. Katritzky,* Hui Tao, and Kostyantyn Kirichenko

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

Submitted to honor the 65th Anniversary of Professor Alain Krief

Abstract

Reaction of di(benzotriazole-1-yl)methanethione **1** with imines **2a**–**f** gave air and moisture stable benzotriazolyl β-enaminothiones **3a**–**f**. The thioacylbenzotriazoles **3a**–**f** enable simple and efficient preparation of β-enamino thioic acid derivatives (thioamides, thioesters and dithioesters) in 74–99% yields *via* microwave mediated nucleophilic substitution of the benzotriazolyl moiety. *C*-Thioacylation with 1-thioacyl-6-nitrobenzotriazoles **7a**–**c** is also discussed.

Keywords: Microwave, benzotriazole, β-enaminothiones, 1-thioacyl-6-nitrobenzotriazoles, *C*-thioacylation

Introduction

Organosulfur compounds possess a rich and varied chemistry, and diverse biological properties.[1,2,3] Among them, β-enaminothioic acids are important building blocks for heterocycle construction e.g., pyrazoles,[4] 4-aminoquinolines,[5] dihydrothiopyrans,[6,7] thiazoline,[8] thiazolin-4-one,[8] 1,3-thiazolin-4-one,[8] 6*H*-1,3-thiazines,[9] as well as useful precursors for liquid crystals[10] and β-keto thioic acid derivatives.[11] β-Enaminothioic acids are reported as good 1-thia-1,3-dienes[Error! Bookmark not defined.,12,13,14] and Michael acceptors.[15]

Despite the importance of β-enaminothioic acids, existing methods for their preparation are limited to: i) the reaction of β-enaminones with phosphorus pentasulfide or other O/S exchange reagents, such as Lawesson's reagents;[16] ii) the cycloaddition of unactivated 2-aza-1,3-dienes to isothiocyanates to give 1,2-dihydropyrimidin-4(3*H*)-thiones, followed by reduction with $LiAlH_4$ to provide β-enamino thioamides;[11] iii) the reaction of β-enaminones with aryl isothiocyanates at 90 °C;[17,18] and iv) the reaction of cyclopentanones and 2-substituted cyclopentanones with

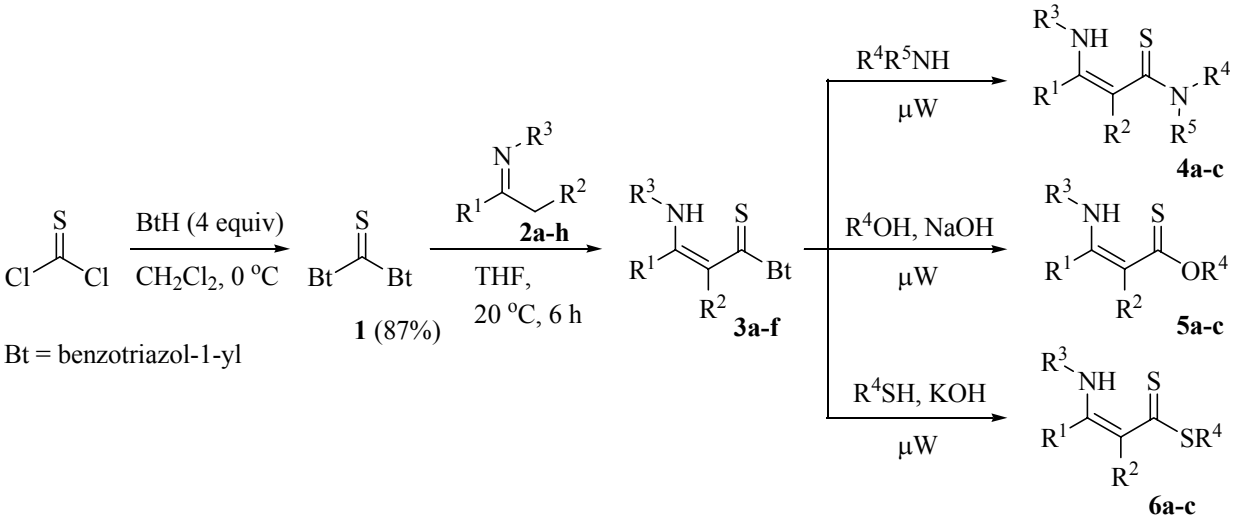
carbon disulphide and ammonia at 0 °C.[19] The first method involves foul smelling starting materials and/or intermediates, while the other methods are limited to specific substrates.

We now disclose a novel and efficient synthetic protocol for benzotriazolyl enaminothiones **3a**–**f** from dibenzotriazolylmethanethione **1** and the application of these products to the preparation of β-enamino thioamides **4a**–**c**, thioesters **5a**–**c**, and dithioesters **6a**–**c**.

Results and Discussion

The reaction of thiophosgene with four equivalents of benzotriazole in methylene chloride at 0 °C gave dibenzotriazolylmethanethione **1** in 87% yield (Scheme 1).[20]

The use of twofold excess of benzotriazole advantageously avoids the precursory generation of either 1-trimethylsilyl benzotriazole[21] or the sodium salt of benzotriazole,[20] required in the previously reported protocols. Excess of benzotriazole and low reaction temperature appear to be essential for successful preparation of **1**.[20]



Scheme 1

Dibenzotriazolylmethanethione **1** reacted with equimolar ketimines **2a**–**f** in THF at 20 °C to give benzotriazolyl enaminothiones **3a**–**f** (78–97%) (Table 1). The treatment of **1** with a twofold excess of ketimine **2a**–**f** resulted in exclusive formation of **3a**–**f**. Attempted reactions of **1** with aldimines **2g**,**h** and 1-cyclohexenylpyrrolidine (not shown) failed.

Structures **3a**–**f** were supported by their ^{1}H and ^{13}C NMR spectra, and elemental analyses (see Experimental Section). In the ^{1}H NMR spectra of benzotriazolyl enaminothiones **3a**–**f**, the broad singlet signals in the range 13.21–14.95 ppm and the singlet signals at 7.16–7.21 ppm (for compounds **3a**,**b**,**e**) corresponding to NH and CH of enamine fragment, respectively, confirmed exclusive existence in the Z-enamine form, resulting from N···H···S chelation.

Treatment of compounds **3a**,**b** under microwave irradiation at 80 °C with secondary amines gave β-enamino thioamides **4a**–**c** (92–95%) (Scheme 1, Table 1). Similar treatment of **3a**,**b** with alcohols or thiols in the presence of sodium or potassium hydroxide afforded thioesters **5a**–**c** (74–99%) and dithioesters **6a**–**c** (85–92%), respectively.

Table 1. Microwave-mediated synthesis of β-enamino thioic acid derivatives **3**–**6**

Entry	Product	R^1	R^2	R^3	R^4	R^5	Yield, %
1	**3a**	Ph	H	Bu	–	–	95
2	**3b**	4-Py	H	Bu	–	–	94
3	**3c**	Ph	Me	Bu	–	–	83
4	**3d**	-$(CH_2)_4$-		Bu	–	–	78
5	**3e**	-$(CH_2)_4$-		Bn	–	–	95
6	**3f**	Et	H	Bu	–	–	78
7	**3g**	H	vinyl	Ph	–	–	0
8	**3h**	H	Et	Bn	–	–	0
9	**4a**	Ph	H	Bu	–$C_2H_4OC_2H_4$–		91
10	**4b**	Ph	H	Bu	–$(CH_2)_5$–		95
11	**4c**	4-Py	H	Bu	–$C_2H_4OC_2H_4$–		92
12	**5a**	Ph	H	Bu	Me	–	95
13	**5b**	Ph	H	Bu	Pr	–	94
14	**5c**	4-Py	H	Bu	Me	–	74
15	**6a**	Ph	H	Bu	*n*-C_6H_{13}	–	85
16	**6b**	Ph	H	Bu	Ph	–	87
17	**6c**	4-Py	H	Bu	Ph	–	92

As with compounds **3a**,**b**, the ^{1}H NMR spectra of products **4**–**6** showed the presence of a broad singlet in the range 11.44–13.16 ppm corresponding to NH proton suggesting exclusive Z-enaminothione configuration (Scheme 1).

However, under the same conditions, treatment of benzotriazolyl enaminothiones **3c**–**f** with alcohols, thiols or amines resulted in the recovery of **3c**–**f**. Attempted treatments of **3c**–**f** with sodium methoxide in methanol under microwave irradiation caused decomposition of the starting materials, while no reaction occurred upon stirring at room temperature for 48 h.

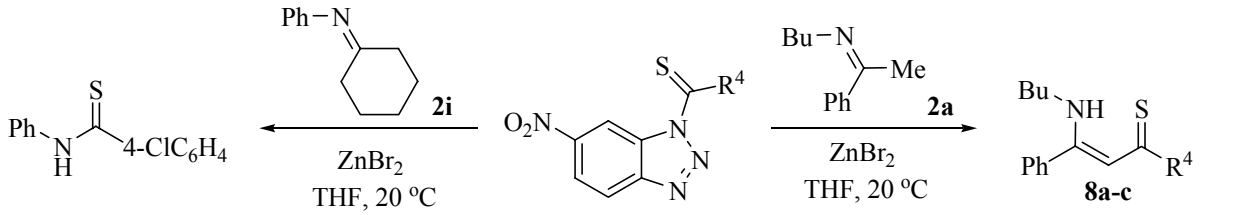
When group R^1 is aryl or heteroaryl group (compounds **3a**,**b**), which behave as electron withdrawing groups, the electrophilicity of thioacyl group increases, making the benzotriazolyl β-enaminothione reactive toward secondary amines, alcohols and thiols. However, when R^1 is an alkyl group (compounds **3d**–**f**), which behave as electron donating groups, the electrophilicity of the thioacyl group decreases, resulting in no reaction under same reaction conditions. Compound **3c** was also unreactive toward secondary amines, alcohols and thiols.

The attempted reaction of benzotriazolyl enaminothione **3a** with hydrazine under microwave irradiation at 80 °C failed and resulted in a complex set of polar products. Treatment of **3a** with

nitromethane or acetonitrile at 20 °C or heating up to 80 °C under microwave irradiation in the presence of sodium hydroxide gave no reaction.

Synthesis of β-enaminothiones

Thioacyl-6-nitrobenzotriazoles **7a-c** reacted with ketimine **2a** in THF in the presence of $ZnBr_2$ at 20 °C for **3** d to give β-enamino thiones **8a-c** in moderate to good yield (Scheme 2). Unfortunately, similar reactions of thioacylbenzotriazoles **7a** with ketimine **2i** produced under the same reaction conditions thioamide **9** in low 35% yield instead of the expected β-enamino thione **8** (Scheme 2), while the reactions with imines **2e** and **2h** resulted in complex mixtures of products. It is possible that the formation of complex mixtures is due to the concurrent addition of ionized thioacylbenzotriazole **7** to the imine bond, followed by hydrolysis to thioamides, such as **9**.



Scheme 2

Structures **8a**–**c** were supported by their ^1H and ^{13}C NMR spectra, and by elemental analyses (see Experimental Section).

The order of addition significantly influences the chemical yield. Thus, the best results were obtained when the appropriate thioacylbenzotriazole **7** in THF was first treated with $ZnBr_2$, followed by slow addition of the corresponding imine **2**, in contrast to low yields upon the initial addition of the Lewis acid to a solution of ketimine **2a** in THF.

After screening a series of nucleophiles, including Grignard, organozinc, organolithium reagents, enolates, silyl enol ethers, allyl trimethyl silane, and active methylenes, enamines and aldimines, ketimines were the only nucleophiles found to be effectively thioacylated by 1-thioacylbenzotriazoles **7**.

Conclusions

In conclusion, a novel and general approach to β-enamino thioic acid derivatives has been developed. The procedure described appears to be general and represents an efficient, simple and alternative route to β-enamino thioic acid derivatives **4**–**6**.

Experimental Section

General Procedures. Melting points were determined on a hot-stage apparatus equipped with a digital thermometer and are uncorrected. NMR spectra were recorded on a Varian Gemini 300 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz) unless otherwise stated. The elemental analyses were performed on a Carlo Erba EA–1108 instrument. Anhydrous THF was used freshly distilled from sodium/benzophenone. Column chromatography was conducted on silica gel 200-245 meshes.

Imines **2a–i** were prepared according to the published procedures: butyl(1-phenylethylidene)amine (**2a**), colorless oil (91%);[22] butyl[1-(pyridin-4-yl)ethylidene]amine (**2b**), colorless oil (78%);[23] butyl(1-phenylpropylidene)amine (**2c**), colorless oil (88%);[24] butyl(cyclohexylidene)amine (**2d**), colorless oil (83%);[25] benzyl(cyclohexylidene)amine (**2e**), colorless oil (85%);[26] butyl(butan-2-ylidene)amine (**2f**), colorless oil (88%);[22] *N*-(3-butenylidene)aniline (**2g**), colorless oil (73%); benzyl(butylidene)amine (**2h**), colorless oil (78%);[27] *N*-(cyclohexylidene)aniline (**2i**), colorless oil (61%).[28]

1-Thioacyl-6-nitrobenzotriazoles **7a-c** were prepared according to published procedures:[29] (6-nitrobenzotriazol-1-yl)(2-thienyl)methanethione (7b), gray microcrystals (40%), mp 132–134 °C (lit.[29] mp 133–134 °C); (6-nitrobenzotriazol-1-yl)(2-furyl)methanethione (**7c**), orange microcrystals (80%), mp 162–163 °C (lit.[29] mp 161–162 °C).

(6-Nitrobenzotriazol-1-yl)-4-chlorophenylmethanethione (7a). Recrystallized from hexanes to give pink microcrystals (93%), mp 161–163 °C; ^1H NMR δ 9.49 (d, *J* = 1.9 Hz, 1H), 8.48 (dd, *J* = 8.9 , 2.1 Hz, 1H), 8.34 (d, *J* = 8.9 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR δ 199.4, 149.1, 140.2, 132.9, 132.1, 128.7, 121.9, 121.4, 112.2. Anal. Calcd for $C_{13}H_7ClN_4O_2S$: C, 48.99; H, 2.21; N, 17.58. Found: C, 49.11; H, 2.19; N, 16.22.

Procedure for the preparation of dibenzotriazolylmethanethione (1). Thiophosgene (11.5 g, 10 mmol) was added dropwise to a solution of benzotriazole (4.77 g, 40 mmol) in dichloromethane (50 mL) at 0 ºC. The reaction mixture was stirred at the same temperature for 3h. The mixture was filtered, and the solid residue was washed with dichloromethane (3×30 mL). The filtrate was washed with 5% aqueous Na_2CO_3 (3×50 mL). The solvent was removed under vacuum to dryness, and the residue was recrystallized from dichloromethane to give di-(1*H*-benzotriazol-1-yl)methanethione in 87% yield as yellow microcrystals, mp 171 °C (lit.[21] mp 170–172 °C).

General procedure for the preparation of benzotriazolyl β-enaminothiones 3a–h

To a solution of dibenzotriazolylmethanethione **1** (280 mg, 1 mmol) in THF (50 mL), appropriate imine **2** (1 mmol) was added at room temperature. The reaction mixture was stirred at the same temperature for 6 h, and then concentrated under vacuum. The residue was dissolved in ethyl acetate (50 mL), and was washed with 5% aqueous Na_2CO_3 (3×30 mL), followed by

brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was either recrystallized from dichloromethane/hexanes or purified by flash chromatography (hexanes/ethyl acetate 5:1) on silica gel to give **3a**–**h**.

(*Z*)-1-(1*H*-Benzotriazol-1-yl)-3-(butylamino)-3-phenyl-2-propene-1-thione (3a). Recrystallized from dichloromethane to give yellow microcrystals (95%), mp 94–96 °C; ^{1}H NMR δ 13.36 (br s, 1H), 8.82 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.58–7.38 (m, 7H), 7.21 (s, 1H), 3.47–3.40 (m, 2H), 1.73–1.64 (m, 2H), 1.53–1.41 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 179.3, 169.4, 147.0, 135.1, 132.5, 130.3, 128.8, 128.5, 127.3, 124.7, 119.8, 115.7, 106.5, 45.7, 32.1, 19.9, 13.5. Anal. Calcd for $C_{19}H_{20}N_4S$: C, 67.83; H, 5.99; N, 16.65. Found: C, 67.80; H, 6.04; N, 16.74.

(*Z*)-1-(1*H*-Benzotriazol-1-yl)-3-(butylamino)-3-(4-pyridinyl)-2-propene-1-thione (3b). Recrystallized from hexanes to give yellow microcrystals (94%), mp 100–102 °C; ^{1}H NMR δ 13.21 (br s, 1H), 8.85–8.80 (m, 3H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.61–7.56 (m, 1H), 7.46–7.38 (m, 3H), 7.19 (s, 1H), 3.40–3.34 (m, 2H), 1.73–1.64 (m, 2H), 1.54–1.42 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 181.5, 165.8, 150.6, 147.0, 142.8, 132.5, 129.0, 125.0, 121.7, 120.0, 115.7, 104.8, 45.6, 32.1, 19.9, 13.5. Anal. Calcd for $C_{18}H_{19}N_5S$: C, 64.07; H, 5.68; N, 20.75. Found: C, 64.33; H, 5.69; N, 20.72.

(*Z*)-1-(1*H*-Benzotriazol-1-yl)-3-(butylamino)-2-methyl-3-phenyl-2-propene-1-thione (3c). Orange oil (83%); ^{1}H NMR δ 15.22 (br s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.56–7.46 (m, 4H), 7.39–7.27 (m, 3H), 3.28–3.22 (m, 2H), 1.71–1.60 (m, 2H), 1.51–1.35 (m, 5H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 175.0, 172.6, 145.3, 133.2, 132.0, 129.5, 129.0, 127.4, 125.9, 123.7, 119.1, 115.5, 112.1, 46.2, 31.4, 19.7, 19.2, 13.2. Anal. Calcd for $C_{20}H_{22}N_4S$: C, 68.54; H, 6.33; N, 15.99. Found: C, 68.68; H, 6.40; N, 15.62.

1*H*-Benzotriazol-1-yl[2-(butylamino)-1-cylohexen-1-yl]methanethione (3d). Viscous red oil (78%); ^{1}H NMR δ 14.94 (br s, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.39 –7.34 (m, 1H), 3.57–3.50 (m, 2H), 2.67 (t, *J* = 6.7 Hz, 2H), 2.20 (t, *J* = 6.4 Hz, 2H), 1.89–1.74 (m, 4H), 1.66–1.56 (m, 2H), 1.52–1.44 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 173.0, 171.5, 145.2, 131.8, 127.3, 123.7, 119.1, 118.5, 111.8, 43.8, 30.3, 27.8, 27.5, 21.8, 20.7, 20.0, 13.4. Anal. Calcd for $C_{17}H_{22}N_4S$: C, 64.93; H, 7.05; N, 17.82. Found: C, 65.14; H, 7.29; N, 18.17.

1*H*-Benzotriazol-1-yl[2-(benzylamino)-1-cyclohexen-1-yl]methanethione(3e). Recrystallized from dichloromethane//hexanes to give orange microcrystals (95%), mp 89–91 °C; ^{1}H NMR δ 15.24 (br s, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.52–7.36 (m, 7H), 4.73 (d, *J* = 5.8 Hz, 2H), 2.67 (t, *J* = 6.7 Hz, 2H), 2.21 (t, *J* = 6.4 Hz, 2H), 1.76–1.68 (m, 2H), 1.50–1.42 (m, 2H); ^{13}C NMR δ 175.2, 171.9, 145.4, 134.7, 132.2, 129.2, 128.3, 127.8, 127.5, 124.2, 119.4, 118.9, 112.2, 47.8, 28.2, 27.9, 22.0, 20.9. Anal. Calcd for $C_{20}H_{20}N_4S$: C, 68.94; H, 5.78; N, 16.08. Found: C, 68.71; H, 5.90; N, 16.35.

(*Z*)-1-(1*H*-Benzotriazol-1-yl)-3-(butylamino)-2-pentene-1-thione (3f). Recrystallized from hexanes to give light yellow microcrystals (78%), mp 58–60 °C; ^{1}H NMR δ 13.30 (br s, 1H), 8.77 (d, *J* = 8.2 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.56–7.51 (m, 1H), 7.43–7.37 (m, 1H), 7.16

(s, 1H), 3.57–3.51 (m, 2H), 2.55 (q, *J* = 7.6 Hz, 2H), 1.82–1.75 (m, 2H), 1.65–1.54 (m, 2H), 1.31 (t, *J* = 7.6 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 178.4, 173.4, 147.0, 132.6, 128.3, 124.6, 119.7, 115.6, 104.8, 43.6, 31.4, 27.3, 20.2, 13.6, 12.1.

General procedure for the preparation of β-enamino thioamides 4a–c from benzotriazolyl β-enaminothiones 3

Benzotriazolyl β-enaminothione **3** (0.3 mmol) was dissolved in secondary amine (2 mL). The mixture was exposed to microwave irradiation (80 Watts, 80 ºC) for 0.5 h. The solvent was removed under vaccuum. The residue was dissolved in dichloromethane (10 mL) and washed with 5% aqueous Na_2CO_3 (3×10 mL), followed by brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (hexanes/ethyl acetate 5:1) on silica gel to give **4a–c**.

(*Z*)-3-(Butylamino)-1-morpholino-3-phenyl-2-propene-1-thione (4a). Light yellow oil (91%); ^{1}H NMR δ 11.97 (br s, 1H), 7.43–7.41 (m, 3H), 7.34–7.33 (m, 2H), 5.14 (s, 1H), 3.99–3.91 (m, 4H), 3.71 (t, *J* = 5.1 Hz, 4H), 3.15–3.08 (m, 2H), 1.55–1.48 (m, 2H), 1.41–1.34 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 187.0, 164.1, 137.9, 128.9, 128.3, 127.4, 93.3, 66.5, 47.7, 44.6, 32.5, 20.0, 13.6. Anal. Calcd for $C_{17}H_{24}N_2OS$: C, 67.07; H, 7.95; N, 9.20. Found: C, 66.80; H, 7.97; N, 9.08.

(*Z*)-3-(Butylamino)-3-phenyl-1-piperidino-2-propene-1-thione (4b). Yellow oil (95%); ^{1}H NMR δ 11.79 (br s, 1H), 7.42–7.33 (m, 5H), 5.15 (s, 1H), 3.92 (br s, 4H), 3.11–3.05 (m, 2H), 1.69–1.47 (m, 8H), 1.40–1.33 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 185,7, 163.2, 138.3, 128.6, 128.2, 127.6, 93.4, 49.1, 44.5, 32.6, 25.8, 24.6, 20.0, 13.6. Anal. Calcd for $C_{18}H_{26}N_2S$: C, 71.47; H, 8.66; N, 9.26. Found: C, 71.54; H, 8.87; N, 9.33.

(*Z*)-3-(Butylamino)-1-morpholino-3-(4-pyridinyl)-2-propene-1-thione (4c). Light yellow oil (92%); ^{1}H NMR δ 11.85 (br s, 1H), 8.69 (d, *J* = 6.1 Hz, 2H), 7.26 (d, *J* = 6.4 Hz, 2H), 5.07 (s, 1H), 3.96 (br s, 4H), 3.74–3.71 (m, 4H), 3.10–3.04 (m, 2H), 1.58–1.48 (m, 2H), 1.43–1.31 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 187.7, 160.8, 150.2, 145.6, 122.3, 93.0, 66.5, 47.9, 44.8, 32.6, 20.0, 13.6. Anal. Calcd for $C_{16}H_{23}N_3OS$: C, 62.92; H, 7.59; N, 13.76. Found: C, 63.17; H, 7.88; N, 13.38.

General procedure for the preparation of β-enamino thioesters 5a–c

Benzotriazolyl β-enaminothione **3** (0.3 mmol) was dissolved in 2N alcoholic sodium hydroxide (2 mL). The reaction mixture was exposed to microwave irradiation (80 Watts, 80 ºC) for 0.5 h. The solvent was removed under vacuum to dryness. The residue was dissolved in dichloromethane (10 mL) and the solution was washed with 5% aqueous Na_2CO_3 (3×10 mL), followed by brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4. the solvent was removed under vacuum, and the residue was purified by flash chromatography (hexanes/ethyl acetate 5:1) on silica gel to give **5a–c**.

***O*-Methyl (*Z*)-3-(butylamino)-3-phenyl-2-propenethioate (5a).** Light yellow oil (95%); ^{1}H NMR δ 11.44 (br s, 1H), 7.43–7.41 (m, 3H), 7.36–7.31 (m, 2H), 5.49 (s, 1H), 3.97 (s, 3H), 3.21

(q, *J* = 6.2 Hz, 2H), 1.60–1.50 (m, 2H), 1.44–1.34 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 202.2, 166.0, 136.4, 129.4, 128.4, 127.4, 100.0, 55.1, 44.8, 32.5, 19.9, 13.6. Anal. Calcd for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68; N, 5.62. Found: C, 67.41; H, 7.59; N, 5.93.

***O*-Propyl (*Z*)-3-(butylamino)-3-phenyl-2-propenethioate (5b).** Light yellow oil (94%); ^{1}H NMR δ 11.46 (br s, 1H), 7.43–7.41 (m, 3H), 7.36–7.32 (m, 2H), 5.49 (s, 1H), 4.35 (t, *J* = 6.7 Hz, 2H), 3.23–3.16 (m, 2H), 1.78–1.71 (m, 2H), 1.60–1.50 (m, 2H), 1.44–1.32 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 201.9, 136.5, 129.3, 128.6, 128.4, 127.4, 100.3, 69.6, 44.8, 32.5, 22.0, 19.9, 13.6, 10.5. Anal. Calcd for $C_{16}H_{23}NOS$: C, 69.27; H, 8.36; N, 5.05. Found: C, 69.48; H, 8.51; N, 4.89.

***O*-Methyl (*Z*)-3-(butylamino)-3-(4-pyridinyl)-2-propenethioate (5c).** Yellow oil (74%); ^{1}H NMR δ 11.29 (br s, 1H), 8.73–8.70 (m, 2H), 7.27–7.26 (m, 2H), 5.40 (s, 1H), 3.98 (s, 3H), 3.18–3.12 (m, 2H), 1.60–1.50 (m, 2H), 1.42–1.32 (m, 2H), 0.89 (t, = 7.3 Hz, 3H); ^{13}C NMR δ 162.4, 150.5, 150.2, 144.2, 122.1, 99.7, 55.4, 44.9, 32.5, 19.9, 13.6. Anal. Calcd for $C_{13}H_{18}N_2OS$: C, 62.36; H, 7.25; N, 11.19. Found: C, 62.07; H, 7.70; N, 11.50.

General procedure for the preparation of β-enamino dithioesters 6a–c

Benzotriazolyl β-enaminothione **3** (0.3 mmol) and potassium hydroxide (0.2 g) were dissolved in appropriate thiol (2 mL). The reaction mixture was exposed to microwave irradiation (80 Watts, 80 ºC) for 0.5 h. The solvent was removed under vacuum and the residue was dissolved in dichloromethane (10 mL), and the solution was washed with 5% aqueous Na_2CO_3 (3×10 mL), followed by brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue purified by flash chromatography (hexanes/ethyl acetate, 5:1) on silica gel to give **6a**–**c**.

Hexyl (*Z*)-3-(butylamino)-3-phenyl-2-propenedithioate (6a). Light yellow oil (85%); ^{1}H NMR δ 12.85 (br s, 1H), 7.45–7.43 (m, 3H), 7.36–7.33 (m, 2H), 6.11 (s, 1H), 3.26–3.16 (m, 4H), 1.72–1.51 (m, 4H), 1.44–1.26 (m, 8H), 0.91–0.84 (m, 6H); ^{13}C NMR δ 203.4, 163.6, 135.6, 129.6, 128.6, 127.4, 109.6, 44.9, 33.0, 32.3, 31.4, 28.8, 28.7, 22.5, 19.9, 14.0, 13.5. Anal. Calcd for $C_{19}H_{29}NS_2$: C, 68.00; H, 8.71; N, 4.17. Found: C, 67.71; H, 9.03; N, 4.14.

Phenyl (*Z*)-3-(butylamino)-3-phenyl-2-propenedithioate (6b). Recrystallized from ethyl acetate/hexanes to give yellow microcrystals (87%), mp 76–78 °C; ^{1}H NMR δ 13.16 (br s, 1H), 7.54–7.50 (m, 2H), 7.41–7.38 (m, 6H), 7.26–7.22 (m, 2H), 5.88 (s, 1H), 3.27–3.21 (m, 2H), 1.60–1.50 (m, 2H), 1.43–1.32 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 201.7, 165.0, 135.6, 135.2, 132.2, 129.9, 129.5, 129.2, 128.6, 127.3, 108.6, 45.2, 32.1, 19.9, 13.5. Anal. Calcd for $C_{19}H_{21}NS_2$: C, 69.68; H, 6.46; N, 4.28. Found: C, 69.78; H, 6.54; N, 4.04.

Phenyl (*Z*)-3-(butylamino)-3-(4-pyridinyl)-2-propenedithioate (6c). Orange oil (92%); ^{1}H NMR δ 13.04 (br s, 1H), 8.70–8.68 (m, 2H), 7.52–7.47 (m, 2H), 7.42–7.40 (m, 3H), 7.19–7.17 (m, 2H), 5.79 (s, 1H), 3.21–3.14 (m, 2H), 1.59–1.49 (m, 2H), 1.43–1.32 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 204.8, 161.3, 150.3, 142.8, 135.6, 131.7, 129.8, 129.2, 121.6, 107.3, 45.1, 32.1, 19.8, 13.4.

General procedure for the preparation of β-enaminothiones 8a–c

The appropriate (6-nitrobenzotriazol-1-yl)methanethione **7a**–**c** (1.0 mmol) and $ZnBr_2$ (2.0 mmol) was dissolved in THF (20 mL) and stirred at room temperature for 1 h. A solution of ketimine **2a** (1.0 mmol) in THF (10 mL) was added dropwise during 5 min, and the mixture was allowed to stir at room temperature for **3d**. The completion of reaction was monitored by TLC. The reaction was quenched with 5% aqueous KOH (20 mL) and the product was extracted with dichloromethane (3×15 mL). The extract was washed with brine (2×15 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuum to give the crude product, which was purified by flash chromatography on silica gel using chloroform to give **8a**–**c**.

(*Z*)-3-(Butylamino)-1-(4-chlorophenyl)-3-phenyl-2-propene-1-thione (8a). Red oil (91%); ^{1}H NMR δ 14.49 (br s, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.51–7.46 (m, 3H), 7.43–7.38 (m, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.54 (s, 1H), 3.37 (q, *J* = 6.8 Hz, 2H), 1.70–1.61 (m, 2H), 1.48–1.39 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 199.7, 167.8, 146.9, 135.4, 135.2, 130.1, 128.8, 128.2, 128.0, 127.3, 113.0, 45.3, 32.1, 20.1, 13.6. Anal. Calcd for $C_{19}H_{20}ClNS$: C, 69.18; H, 6.11; N, 4.25. Found: C, 68.92; H, 6.41; N, 3.89.

(*Z*)-3-(Butylamino)-1-(2-thienyl)-3-phenyl-2-propene-1-thione (8b). Red oil (76%); ^{1}H NMR δ 14.04 (br s, 1H), 7.50–7.40 (m, 7H), 7.02–6.99 (m, 1H), 6.65 (s, 1H), 3.33 (q, *J* = 6.4 Hz, 2H), 1.67–1.47 (m, 2H), 1.46–1.39 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 189.6, 167.3, 154.4, 135.6, 130.9, 129.9, 128.8, 127.8, 127.3, 124.6, 109.9, 45.3, 32.1, 20.0, 13.5. Anal. Calcd for $C_{17}H_{19}NS_2$: C, 67.73; H, 6.35; N, 4.65. Found: C, 68.09; H, 6.48; N, 4.25.

(*Z*)-3-(Butylamino)-1-(2-furyl)-3-phenyl-2-propene-1-thione (8c). Red oil (45%); ^{1}H NMR δ 14.16 (br s, 1H), 7.42–7.40 (m, 3H), 7.34–7.31 (m, 3H), 7.12 (d, *J* = 3.7 Hz, 1H), 6.72 (s, 1H), 6.36 (dd, *J* = 3.4, 1.5 Hz, 1H), 3.27 (q, *J* = 6.4 Hz, 2H), 1.58–1.51 (m, 2H), 1.39–1.31 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 183.0, 167.8, 158.9, 143.6, 135.6, 129.9, 128.7, 127.3, 113.9, 112.7, 109.0, 45.3, 32.1, 20.0, 13.5. Anal. Calcd for $C_{17}H_{19}NOS$: C, 71.54; H, 6.71; N, 4.91. Found: C, 71.28; H, 7.02; N, 4.53.

4-Chloro-*N*-phenyl-thiobenzamide (9). Was obtained from the reaction of **7a** with imine **2i**, following the procedure for **8a**–**c**. Recrystallization from dichloromethane//hexanes gave light yellow microcrystals (35%), mp 153–155 °C (lit.[30] mp 157–158 °C); ^{1}H NMR (DMSO-d_6) δ 11.83 (br s, 1H), 7.87–7.80 (m, 4H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 195.9, 141.2, 139.9, 135.5, 129.3, 128.5, 128.0, 126.4, 124.2.

References

1. Cremlyn, R. J. *An Introduction to Organosulfur Chemistry*; John Wiley & Sons: New York, 1996.
2. Vedejs, E.; Krafft, G. A. *Tetrahedron* **1982**, *38*, 2857.

3. Wilde, T. G.; Billheimer, J. T.; Germain, S. J.; Hausner, E. A.; Meunier, P. C.; Munzer, D. A.; Stoltenborg, J. K.; Gillies, P. J.; Burcham, D. L.; Huang, S. M.; Klackiewick, J. D.; Ko, S. S.; Wexler, R.R. *Bioorg. Med. Chem.* **1996**, *4*, 1493.
4. Missio, L. J.; Braibante, H. S.; Braibante, M. E. F. *J. Heterocycl. Chem.* **1996**, *33*, 1243.
5. Palacios, F.; Aparicio, D.; Garcia, J. *Tetrahedron* **1997**, *53*, 2931.
6. Al-Badri, H.; Collignon, N.; Maddalino, J.; Masson, S. *Tetrahedron* **2000**, *56*, 3909.
7. Bogdanowicz-Szwed, K.; Budzowski, A. *Monatsh. Chem.* **2001**, 132, 947.
8. Coen, S.; Ragonnet, B.; Vieillescazes, C.; Roggero, J. *Heterocycles* **1985**, *23*, 1225.
9. Meslin, J. C.; Reliquet, A.; Reliquet, F.; Quiniou, H. *Synthesis* **1980**, 453.
10. Cativiela, C.; Serrano, J. L.; Zurbano, M. M. *J. Org. Chem.* **1995**, *60*, 3074.
11. Barluenga, J.; Gonzalez, F. J.; Gotor, V.; Fustero, S. *J. Chem. Soc., Perkin. Trans. 1* **1988**, 1739.
12. Adiwidjaja, G.; Proll, T.; Walter, W. *Tetrahedron Lett.* **1981**, *22*, 3175.
13. Kascheres, A.; Kascheres, C.; Braga, A.C.H. *J. Org. Chem.* **1993**, *58*, 1702.
14. Saito, T.; Takekawa, K.; Takahashi, T. *Chem. Commun.* **1999**, 1001.
15. Sosnicki, J. G.; Jagodzinski, T. S.; Hansen, P. E. *Tetrahedron* **2001**, 8705.
16. Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.
17. Albert, R.; Knecht, H.; Andersen, E.; Hungerford, V.; Schreier, M. H.; Papagerogiou, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2203.
18. Braibante, M. E. F.; Braibante, H. S.; Missio, L.; Andricopulo, A. *Synthesis* **1994**, 898.
19. Ramadas, S. R.; Srinivasan, P. S.; Ramachandran, J.; Sastry, V. V. S. K. *Synthesis* **1983**, 605.
20. Orth, R. E.; Soedigdo, S. *J. Heterocycl. Chem.* **1965**, *2*, 486.
21. Larsen, C.; Steliou, K.; Harpp, D. N. *J. Org. Chem.* **1978**, *43*, 337.
22. Smith, J. K.; Bergbreiter, D. E.; Newcomb, M. *J. Am. Chem. Soc.* **1983**, *105*, 4396.
23. Boduszek, B. *Tetrahedron* **1996**, *52*, 12483.
24. Asinger, F.; Offermanns, H.; Köhler, H.-D. *Tetrahedron Lett.* **1967**, *8*, 631.
25. Liao, S.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 15114.
26. Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319.
27. Baricordi, N.; Benetti, S.; Biondini, G.; De Risi C.; Pollini, G. P. *Tetrahedron Lett.* **2004**, *45*, 1373.
28. Varma, R. S.; Dahiya, R. *Tetrahedron* **1998**, *54*, 6293.
29. Katritzky, A. R.; Witek, R. M.; Rodriguez-Garcia, V.; Mohapatra, P. P.; Rogers, J. W.; Cusido, J.; Abdel-Fattah, A. A. A.; Steel, P. J. *J. Org. Chem.* **2005**, *70*, 7866.
30. Waisser, K.; Houngbedji, N.; Machacek, M.; Sekera, M.; Urban, J.; Odlerova, Z. *Collect. Czech. Chem. Commun.* **1990**, *55*, 307.