Microwave mediated syntheses of β-enamino thioic acid derivatives

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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 6H-1,3-thiazines,9 as well as useful precursors for liquid crystals10 and β-keto thioic acid derivatives.11 β-Enaminothioic acids are reported as good 1-thia-1,3-dienes12,13,14 and Michael acceptors.15

Despite the importance of β-enaminothioic acids, existing methods for their preparation are limited to: i) the reaction of β- enamionones with phosphorus pentasulfide or other O/S exchange reagents, such as Lawesson’s reagents;16 ii) the cyloaddition of unactivated 2-aza-1,3-dienes to isothiocyanates to give 1,2-dihydropyrimidin-4(3H)-thiones, followed by reduction with LiAlH4 to provide β-enamino thioamides;11 iii) the reaction of β- enamionones 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 ºC. 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 ºC gave dibenzotriazolylmethanethione 1 in 87% yield (Scheme 1).

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

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{Bt} & \quad \text{Cl} \\
\text{Bt} & \quad \text{Bt} \\
\text{2a-h} & \quad \text{2a-h} \\
\text{THF, 20 ºC, 6 h} & \quad \text{THF, 20 ºC, 6 h} \\
\text{1 (87%)} & \quad \text{3a-f} \\
\end{align*}
\]

\( \text{Bt} = \text{benzotriazol-1-yl} \)

Scheme 1

Dibenzotriazolylmethanethione 1 reacted with equimolar ketimines 2a–f in THF at 20 ºC 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>Yield, %</th>
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<tr>
<td>1</td>
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<td>Bu</td>
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<td>–</td>
<td>95</td>
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<tr>
<td>2</td>
<td>3b</td>
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<td>H</td>
<td>Bu</td>
<td>–</td>
<td>–</td>
<td>94</td>
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<tr>
<td>3</td>
<td>3c</td>
<td>Ph</td>
<td>Me</td>
<td>Bu</td>
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<tr>
<td>4</td>
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<td>–</td>
<td>–</td>
<td>78</td>
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<tr>
<td>5</td>
<td>3e</td>
<td>-(CH₂)₄-</td>
<td>Bn</td>
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<tr>
<td>6</td>
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<td>Bu</td>
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<td>Bu</td>
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<td>H</td>
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<td>–C₂H₄OC₂H₄–</td>
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<td>Ph</td>
<td>–</td>
<td>92</td>
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</tbody>
</table>

As with compounds 3a, b, the ¹H 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 3e–f with alcohols, thiols or amines resulted in the recovery of 3e–f. Attempted treatments of 3e–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 R¹ 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 R¹ 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 3e 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 ZnBr₂ 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](image)

**Scheme 2**

Structures 8a–c were supported by their ¹H and ¹³C 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 ZnBr₂, 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 aldimes, 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 CDCl₃ with tetramethylsilane as the internal standard for ¹H (300 MHz) or solvent as the internal standard for ¹³C (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); ¹³C NMR δ 199.4, 149.1, 140.2, 132.9, 132.1, 128.7, 121.9, 121.4, 112.2. Anal. Calcd for C₁₃H₂ClN₄O₂S: 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 °C. 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 Na₂CO₃ (3×50 mL). The solvent was removed under vacuum to dryness, and the residue was recrystallized from dichloromethane to give di-(1H-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 Na₂CO₃ (3×30 mL), followed by
brine (30 mL). The organic layer was dried over anhydrous Na₂SO₄, 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-(1H-Benzotriazol-1-yl)-3-(butylamino)-3-phenyl-2-propene-1-thione (3a). Recrystallized from dichloromethane to give yellow microcrystals (95%), mp 94–96 °C; ¹H 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); ¹³C 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 C₁₉H₂₀N₄S: C, 67.83; H, 5.99; N, 16.65. Found: C, 67.80; H, 6.04; N, 16.74.

(Z)-1-(1H-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; ¹H 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); ¹³C 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 C₁₈H₁₉N₅S: C, 64.07; H, 5.68; N, 20.75. Found: C, 64.33; H, 5.69; N, 20.72.

(Z)-1-(1H-Benzotriazol-1-yl)-3-(butylamino)-2-methyl-3-phenyl-2-propene-1-thione (3c). Orange oil (83%); ¹H 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); ¹³C 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 C₂₀H₂₂N₄S: C, 68.54; H, 6.33; N, 15.99. Found: C, 68.68; H, 6.40; N, 15.62.

1H-Benzotriazol-1-yl[2-(butylamino)-1-cylohexen-1-yl]methanethione (3d). Viscous red oil (78%); ¹H 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); ¹³C 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 C₁₇H₂₂N₄S: C, 64.93; H, 7.05; N, 17.82. Found: C, 65.14; H, 7.29; N, 18.17.

1H-Benzotriazol-1-yl[2-(benzylamino)-1-cylohexen-1-yl]methanethione (3e). Recrystallized from dichloromethane/hexanes to give orange microcrystals (95%), mp 89–91 °C; ¹H 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); ¹³C 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 C₂₀H₂₀N₄S: C, 68.94; H, 5.78; N, 16.08. Found: C, 68.71; H, 5.90; N, 16.35.

(Z)-1-(1H-Benzotriazol-1-yl)-3-(butylamino)-2-pentene-1-thione (3f). Recrystallized from hexanes to give light yellow microcrystals (78%), mp 58–60 °C; ¹H 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
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 °C) for 0.5 h. The solvent was removed under vacuum. The residue was dissolved in dichloromethane (10 mL) and washed with 5% aqueous Na₂CO₃ (3×10 mL), followed by brine (10 mL). The organic layer was dried over anhydrous Na₂SO₄. 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%); ¹H 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); ¹³C NMR δ 187.0, 164.1, 137.9, 128.9, 128.3, 93.3, 66.5, 47.7, 44.6, 32.5, 20.0, 13.6. Anal. Calcd for C₁₇H₂₄N₂O: 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%); ¹H 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), 1.40–1.33 (m, 2H), 1.40–1.33 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H); ¹³C NMR δ 185.7, 163.2, 138.6, 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 C₁₈H₂₆N₂S: 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%); ¹H 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); ¹³C 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 C₁₆H₂₃N₃OS: 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 °C) 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 Na₂CO₃ (3×10 mL), followed by brine (10 mL). The organic layer was dried over anhydrous Na₂SO₄. 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%); ¹H 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 $\delta$ 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 $\delta$ 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); $^{13}$C NMR $\delta$ 201.9, 136.5, 129.3, 128.6, 128.4, 127.4, 100.3, 69.6, 44.8, 32.5, 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 $\delta$ 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, $J = 7.3$ Hz, 3H); $^{13}$C NMR $\delta$ 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$_2$OS: 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$_2$CO$_3$ (3×10 mL), followed by brine (10 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$. 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 $\delta$ 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 $\delta$ 203.4, 163.6, 135.6, 129.6, 128.6, 127.4, 109.6, 44.9, 33.0, 32.3, 31.4, 28.8, 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 ºC; $^1$H NMR $\delta$ 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 $\delta$ 204.8, 161.3, 150.3, 142.8, 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$_{21}$N$_2$OS: C, 69.78; 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 $\delta$ 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 $\delta$ 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 ZnBr₂ (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 3 d. 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 MgSO₄ 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%); ¹H 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); ¹³C 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 C₁₉H₂₀ClNS: 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%); ¹H 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); ¹³C 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 C₁₇H₁₉NS₂: 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%); ¹H 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); ¹³C 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 C₁₇H₁₉NOS: 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); ¹H NMR (DMSO-d₆) 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); ¹³C NMR (DMSO-d₆) δ 195.9, 141.2, 139.9, 135.5, 129.3, 128.5, 128.0, 126.4, 124.2.

References


