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XANTHATE MEDIATED GENERATION OF THE BENZOTRIAZOL-1-YL-METHYL RADICAL AND ITS SUBSEQUENT ADDITION TO A VARIETY OF OLEFINS

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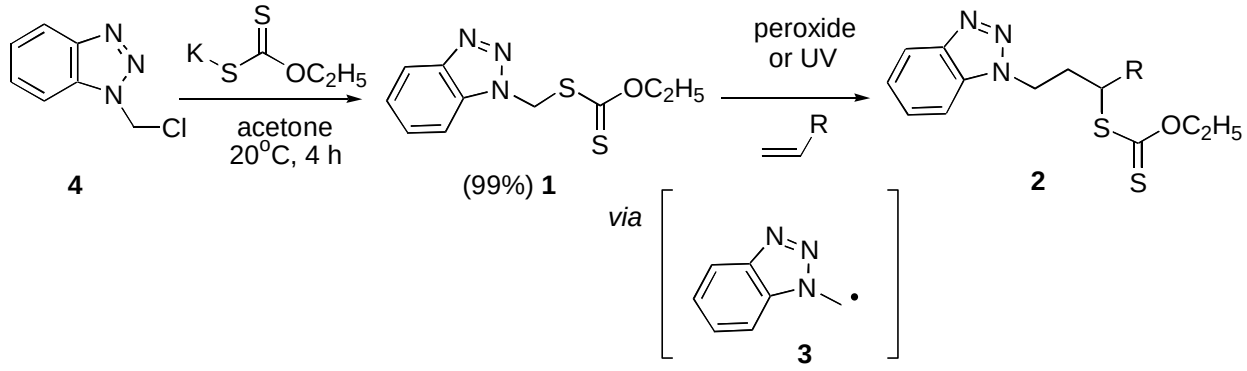
Abstract - The first generation of the benzotriazol-1-ylmethyl radical (**3**) is reported from *S*-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-*O*-ethylcarbonodithioate (**1**). Subsequent additions of radical (**3**) to a variety of olefins are demonstrated.

The use of free radicals as important and versatile synthetic intermediates in organic synthesis has been extensively documented.[1] However, due to their high reactivity, the use of radicals is often hampered by many side-reactions (dimerisation, disproportionation). The application of xanthates (dithiocarbonates) is one way of minimising this problem, favouring the radical process by depressing side reactions.[2,3] Xanthates readily undergo carbon-sulfur bond scission upon chemical or photochemical initiation. Use of lauroyl peroxide as an initiator allows for the cheap, clean and efficient production of xanthate and carbon-centered radicals. This mild approach to radical generation has many advantages as demonstrated by the addition of xanthates to activated and unactivated olefins in the presence of a wide range of sensitive functional groups.[4] Thus, radical additions of xanthates to olefins have been utilised for the synthesis of indolines and indanes,[5] α-tetralones,[6] piperidine and pyridines,[7] tetrazoles[4] and bicyclic β-lactams.[8] In all these cases, the xanthate reagents fragment to give the xanthate radical as well as a carbon-centered radical.

Benzotriazole is a useful synthetic auxiliary.[9] However, reports of benzotriazole-substituted radicals are rare.[10] To the best of our knowledge, no evidence for the existence of the parent benzotriazol-1-ylmethyl radical (**3**) has been provided to date. The appropriate benzotriazol-1-ylmethyl xanthate (**1**) should allow for the convenient production of the desired benzotriazol-1-ylmethyl radical (**3**) following chemical or photochemical initiation (Scheme 1), and, by trapping **3** with an olefin, for synthesis of new benzotriazole substituted xanthates such as **2** (Scheme 1). The benzotriazole-xanthates of type (**2**) could undergo further

radical reaction sequences.

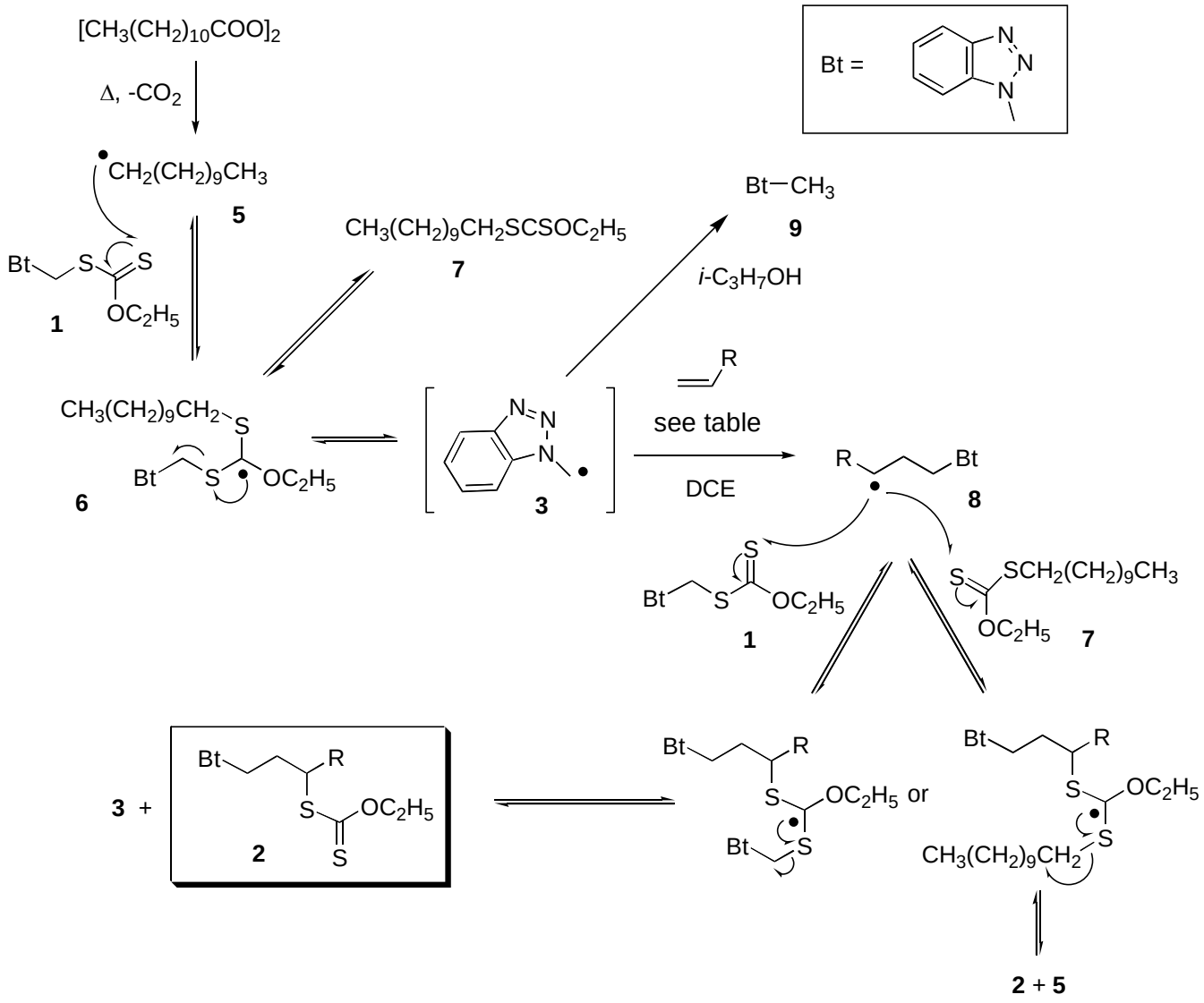


Scheme 1

RESULTS AND DISCUSSION

Commercially available potassium-*O*-ethyl xanthate and chloromethylbenzotriazole[11] (**4**) were stirred together in acetone at 20°C to give *S*-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-*O*-ethylcarbonodithioate (**1**) (99%) as a white crystalline solid (Scheme 1). The benzotriazol-1-ylmethyl radical (**3**) was formed either by heating a solution of *S*-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-*O*-ethylcarbonodithioate **1** in 1,2-dichloroethane under reflux, or by UV photo-irradiation. The lauroyl peroxide initiator was added gradually to a deoxygenated solution of substrate (**1**) and an olefin, thus preventing the build up of radical species. After addition of 21–33% of the initiator the consumption of the starting material was complete and the desired alkene addition products (**2**) were formed in good yield (Scheme 2). A range of olefins afforded the benzotriazole substituted xanthates (**2a**-**f**) in 51–71% isolated yields (Table), with crude yields substantially higher as indicated by NMR analysis. The addition of the radical was regiospecific with the benzotriazol-1-ylmethyl moiety linked to the unsubstituted side of the double bond. Interestingly, the ability of compound (**1**) to generate radical pairs is not affected by the introduction of nitrogen atom in the α-position to the xanthate residue: previously described substrates of type (**1**) all contain carbon-carbon bonds adjacent to sulfur.

The proposed mechanism is highlighted for the reaction with mono-substituted olefins (Scheme 2), it involves peroxide initiation using dilauroyl peroxide, loss of carbon dioxide and reaction of radical (**5**) with *S*-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-*O*-ethylcarbonodithioate **1**. Intermediate radical (**6**) fragments to the desired benzotriazol-1-ylmethyl radical (**3**) and a new xanthate (**7**). The benzotriazol-1-ylmethyl radical **3** is captured by an olefin to afford new radical (**8**) which subsequently reacts with either xanthate (**1**) or (**7**), to give desired xanthate (**2**) after two reversible steps, regenerating radical (**3**) or (**5**).

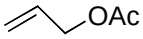
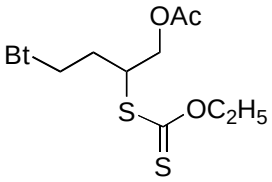
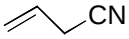
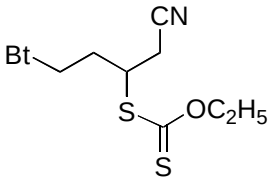
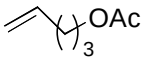
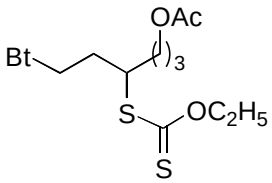
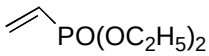
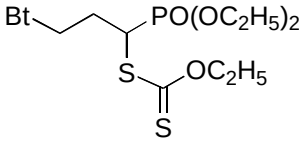
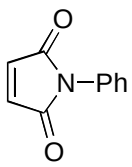
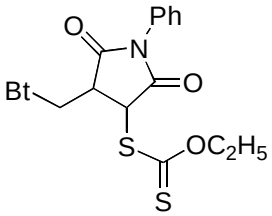
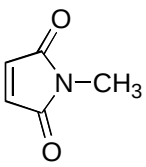
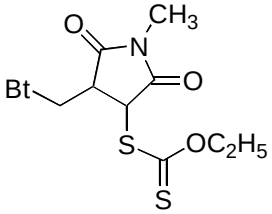


Scheme 2

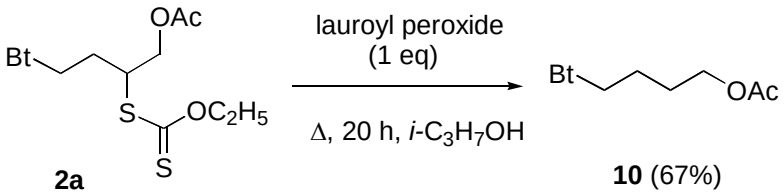
To help verify the mechanism highlighted in Scheme 2, an attempt was made to observe the benzotriazol-1-ylmethyl radical intermediate (**3**) using EPR (Electron Paramagnetic Resonance) spectroscopy. Although a signal was observed upon UV irradiation of a sample of xanthate (**1**), the intensity was very weak. This signal was observed irrespectively of irradiation time and therefore did not verify the formation or presence of any carbon-centered radical (**3**).

Surprisingly, NMR analysis did not enable us to detect the presence of any benzotriazol-1-ylmethyl dimers, even when no olefin was added to the reaction mixture. However, xanthate (**7**) was produced as a major by-product following fragmentation of **6**, observed by NMR and easily removed by column chromatography. IsoPropanol was used as both solvent and hydrogen source in an attempt to quench radical (**3**) to obtain methylbenzotriazole (**9**),[12] together with expected by-product (**7**). Methyl-benzotriazole (**9**) was indeed observed by NMR and MS, thus supporting the presence of radical (**3**) (Scheme 2).

Table. Radical addition of benzotriazol-1-ylmethyl xanthate (**1**) to a range of olefins

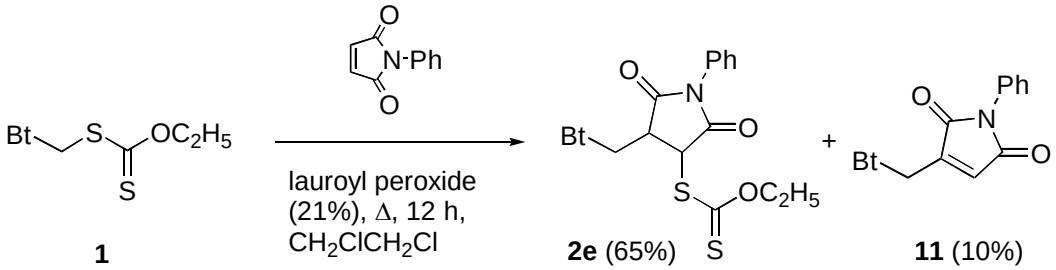
Olefin	Lauroyl Peroxide (%)	Reaction Time (h)	Xanthate Product	**2**	Yield (%)
	21	10.5		**a**	60
	33	16.5		**b**	51
	24	12		**c**	55
	21	10.5		**d**	71
	21	10.5		**e**	65
	24	12		**f**	55

The xanthate moiety was easily removed from (**2a**) by reductive homolytic cleavage using a stoichiometric amount of lauroyl peroxide (Scheme 3). Here, xanthate (**2a**) and equimolar amount of the initiator (added in 5% portions) were refluxed in isopropanol to afford **10** in 67% yield after column chromatography.



Scheme 3

It was observed that following the reaction of *N*-phenylmaleimide with xanthate (**1**), a small amount of benzotriazol-1-ylmethyl substituted *N*-phenylmaleimide (**11**), as characterised by ^{1}H NMR, was present (Scheme 4).



Scheme 4

The radical addition of **1** to allyl acetate to give **2a** was also demonstrated using photochemical initiation with a mercury lamp.

In conclusion, a novel synthesis of benzotriazole xanthates (**2a-f**) was demonstrated using a clean, efficient and non-toxic xanthate radical process. This provides the first evidence of the simple unsubstituted benzotriazol-1-ylmethyl carbon-centered radical.

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EXPERIMENTAL

General Comments. Melting points were determined using a Kofler hot stage apparatus without correction. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Gemini-300

spectrometer in $CDCl_3$ with TMS as the internal standard. Microanalyses were performed on a CarboErba 1106 elemental analyser. Column chromatography was carried out on Fisher silica gel (200-425 mesh).

***S*-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-*O*-ethylcarbonodithioate (1)**. *O*-Ethylxanthic acid potassium salt (2g, 12 mmol) was added to a solution of benzotriazol-1-ylmethyl chloride (1.9g, 12 mmol) in acetone (30 mL) and stirred for 4 hours at room temperature. The KCl was filtered off and solvent removed to yield the desired compound in 99% crude yield as pale yellow crystals. This was recrystallised from carbon tetrachloride to give white crystals. mp 72 ^{o}C. ^{1}H NMR ($CDCl_3$): δ 1.45 (t, *J* = 7.2 Hz, 3H), 4.70 (q, *J* = 7.2 Hz, 2H), 6.41 (s, 2H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.7, 51.9, 71.3, 110.2, 120.2, 124.3, 127.8, 132.3, 146.2, 210.3. *Anal*. Calcd for $C_{10}H_{11}N_3OS_2$: C, 47.41; H, 4.38; N, 16.59. Found: C, 47.02; H, 4.18; N, 16.56.

General procedure for the formation of 2a-f following the addition of *S*-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-*O*-ethylcarbonodithioate (**1**) **to olefins**. A solution of *S*-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-*O*-ethyl carbonodithioate (**1**) (0.5g, 2 mmol) and an olefin (6 mmol) in degassed dichloroethane (8 mL) was heated to reflux under an argon atmosphere. To this solution was added lauroyl peroxide (3%) every 1.5 h until the reaction was complete, as monitored by the disappearance of the starting xanthate from TLC or NMR spectroscopy. The solvent was removed under reduced pressure and the residue purified by column chromatography to give the desired compounds (**2a-f**).

4-(1*H*-1,2,3-Benzotriazol-1-yl)-2-[(ethoxycarbothioyl)sulfanyl]butyl acetate (2a). The compound was obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.34 (t, *J* = 7.2 Hz, 3H), 2.05 (s, 3H), 2.24–2.37 (m, 1H), 2.55–2.67 (m, 1H), 3.88–3.96 (m, 1H), 4.22–4.39 (m, 2H), 4.48–4.64 (m, 2H), 4.82 (t, *J* = 7.1 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.47–7.56 (m, 2H), 8.07 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.5, 20.6, 30.7, 45.2, 46.3, 65.1, 70.4, 109.0, 119.9, 123.8, 127.3, 132.8, 145.7, 170.3, 211.4. FAB POS, exp for $C_{15}H_{20}N_3O_3S_2$; 354.0946. Found: 354.0946.

***S*-[3-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(cyanomethyl)propyl]-*O*-ethylcarbonodithioate (2b)**. The compound was obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.35 (t, J = 7.2 Hz, 3H), 2.38–2.50 (m, 1H), 2.58–2.69 (m, 1H), 2.94 (t, *J* = 5.1Hz, 2H), 3.82 (m, 1H), 4.50–4.60 (m, 2H), 4.83 (t, *J* = 6.6 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 8.1 Hz, 2H), 8.04 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.4, 23.7, 31.9, 43.2, 44.6, 70.5, 108.9, 116.5, 119.7, 123.9, 127.4, 132.6, 145.5, 210.3. FAB POS, exp for $C_{14}H_{17}N_4OS_2$; 321.0844. Found: 321.0846.

6-(1*H*-1,2,3-Benzotriazol-1-yl)-4-[(ethoxycarbothioyl)sulfanyl]hexyl acetate (2c). The compound was obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H), 1.70–1.88 (m, 4H), 2.04 (s, 3H), 2.25–2.38 (m, 1H), 2.46–2.58 (m, 1H), 3.68–3.76 (m, 1H), 4.05 (t, *J* = 5.6 Hz, 2H), 4.44–4.60 (m, 2H), 4.76–4.83 (m, 2H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.46–7.55 (m, 2H), 8.07 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.6, 20.8, 25.8, 31.0, 34.3, 45.4, 47.9, 63.7, 70.1, 109.1, 119.9, 123.8, 127.3, 132.9, 145.8, 170.9, 212.8. FAB POS, exp for $C_{17}H_{24}N_3O_3S_2$; 382.1259. Found: 382.1257.

Diethyl 3-(1*H*-1,2,3-benzotriazol-1-yl)-1-[(ethoxycarbothioyl)thio]propyl phosphonate (2d). The compound was obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.30–1.38 (m, 9H), 2.38–2.54 (m, 1H), 2.77–2.93 (m, 1H), 4.09–4.24 (m, 5H), 4.49–4.62 (m, 2H), 4.90 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.6, 16.4, 30.4, 41.2, 43.1, 45.2, 63.3, 71.3, 109.3, 120.0, 123.9, 127.3, 133.0, 145.9, 211.2. FAB POS, exp for $C_{16}H_{24}N_3O_4PS_2$; 418.1024. Found: 418.1033.

***S*-[4-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-2,5-dioxo-1-phenyltetrahydro-1*H*-pyrrol-3-yl]-*O*-ethylcarbonodithioate (2e)**. The compound was obtained as orange crystals. mp 148-149 ^{o}C. ^{1}H NMR ($CDCl_3$): δ 1.38 (t, *J* = 7.1 Hz, 3H), 4.02–4.07 (m, 1H), 4.54–4.66 (m, 3H), 5.14 (dd, *J* = 14.4, 3.9 Hz,1H), 5.28 (dd, *J* = 14.7, 4.5 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.34–7.45 (m, 4H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.5, 44.9, 46.8, 47.3, 71.0, 109.3, 120.0, 124.4, 126.0, 128.1, 128.8, 129.0, 131.3, 133.1, 145.6, 170.6, 173.5, 209.7. *Anal.* Calcd. for $C_{20}H_{18}N_4O_3S_2$: C, 56.32; H, 4.25; N 13.14. Found: C, 56.12; H, 4.04; N, 13.00. By-product (**11**) was also obtained (*ca.* 10%), it crystallised in the test tubes following column chromatography on (**2e**) and was isolated by filtration.

3-(1*H*-1,2,3-benzotriazol-1-ylmethyl)-1-phenyl-Δ^{3}-pyrrolin-2,5-dione (11). ^{1}H NMR ($CDCl_3$): δ 4.18 (d, *J* = 2.4 Hz, 2H), 7.40-7.47 (m, 3H), 7.54 (t, *J* = 7.5 Hz, 3H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.41 (d, *J* = 2.4 Hz, 1H).

***S*-[4-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-1-methyl-2,5-dioxotetrahydro-1*H*-pyrrol-3-yl]-*O*-ethylcarbonodithioate (2f)**. The compound was obtained as white crystals. mp 116-117 ^{o}C. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, *J* = 7.1 Hz, 3H), 2.97 (s, 3H), 3.81–3.87 (m, 1H), 4.47 (d, *J* = 6.6 Hz, 1H), 4.57 (q, *J* = 7.2 Hz, 2H), 5.10 (dd, *J* = 14.7, 4.2 Hz, 1H), 5.21 (dd, *J* = 14.7, 4.8 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.6, 25.8, 44.9, 47.4, 47.6, 70.9, 109.3, 120.0, 124.3, 128.0, 133.1, 145.5, 171.6, 174.1, 209.0. *Anal.* Calcd for $C_{15}H_{16}N_4O_3S_2$: C, 49.43; H, 4.43; N 15.37. Found: C, 49.62; H, 4.27; N, 15.04.

4-(2,3-Dihydro-1*H*-1,2,3-benzotriazol-1-yl)butyl acetate (10). 4-(1*H*-1,2,3-Benzotriazol-1-yl)-2-[(ethoxycarbothioyl)sulfanyl]butyl acetate (**2a**) (0.25g, 1 mmol) was dissolved in 2-propanol (10 mL) under an inert atmosphere. To this was added lauroyl peroxide (5%) every 1 h until the complete consumption of the starting xanthate could be seen by either TLC or NMR spectroscopy (100% over 20 h). The solvent was removed *in vacuo* to yield the desired product as a clear oil in 67% yield following column chromatography in hexanes / ethyl acetate 10:3. ^{1}H NMR ($CDCl_3$): δ 1.65–1.74 (m, 2H), 2.03 (s, 3H), 2.05–2.14 (m, 2H), 4.10 (t, *J* = 6.3 Hz, 2H), 4.69 (t, *J* = 7.1 Hz, 2H), 7.38 (dd, *J* = 8.1, 6,6 Hz, 1H), 7.45–7.56 (m, 2H), 8.07 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 20.9, 25.8, 26.2, 47.5, 63.3, 109.1, 120.0, 123.8, 127.2, 132.8, 145.8, 170.9. *Anal.* Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.77; H, 6.49; N 18.02. Found; C, 61.98; H, 6.61; N, 18.41.

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