Microwave Assisted One-Pot Synthesis of Pyrrolo[2,1-*b*]thiazol-6-ones from α-Aroyl Ketene-*N*,*S*-acetals

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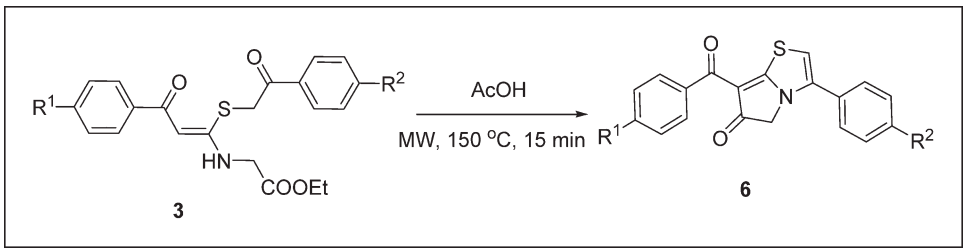
Received August 31, 2009
DOI 10.1002/jhet.334
Published online 4 March 2010 in Wiley InterScience (www.interscience.wiley.com).

This article is dedicated to our research guide Dr. C. V. Asokan who died on February 3, 2007.



α-Aroyl ketene-*N*,*S*-acetals **3** prepared by the reaction of β-oxothioamides **1** with phenacyl bromides **2**, underwent sequential cyclizations under microwave irradiation to afford pyrrolo[2,1-*b*]thiazol-6-ones **6** in good yields. A double cyclization takes place regioselectively in one pot and variety of functionalized pyrrolo[2,1-b]thiazol-6-ones were prepared by this protocol. The mode of cyclization under microwave condition is different from conventional heating.

J. Heterocyclic Chem., **47**, 430 (2010).

INTRODUCTION

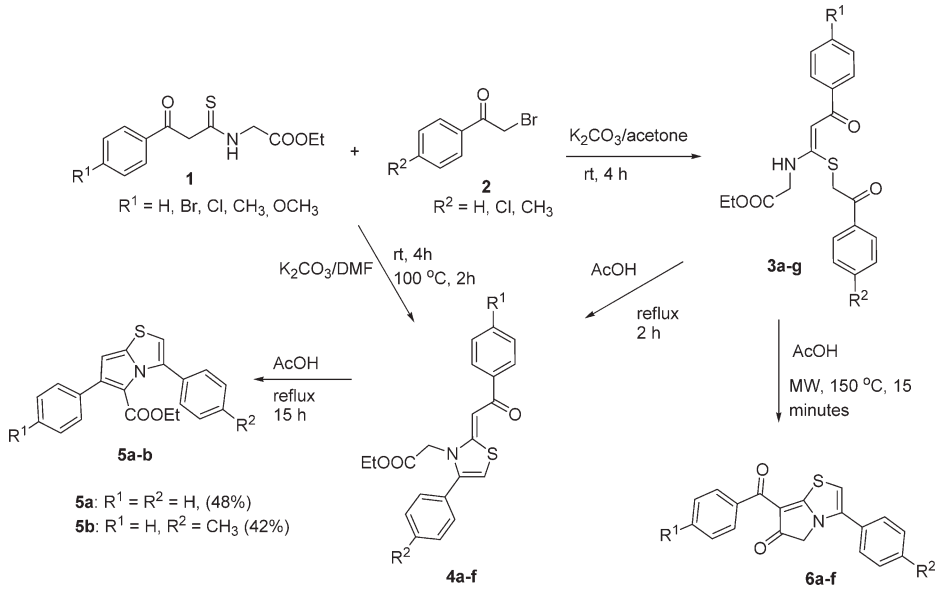
The structural diversity and biological importance exhibited by pyrrolothiazoles have made them attractive targets for synthesis [1]. Pyrrolo[2,1-*b*]thiazoles are known to display a wide range of biological activities such as antileukemic [2], platelet-activating factor antagonistic [3] and for prevention and treatment of various liver diseases [4]. The common strategy for their syntheses involves ring annelation of appropriately functionalized pyrroles [5,6] or thiazoles [7,8]. Other approaches are based on the cycloaddition reactions of thiazolium ylides [9], imidazo[2,1-*b*]thiazoles [10] or mesoionic thiazolo[3,2-*c*]oxazoles [2] with dimethyl acetylenedicarboxylate and related unsaturated acid derivatives. Recently, thiazadiene, an unsymmetrical polyhetropolyene, on sequential reaction with α-carbonyl bromide was converted into pyrrolo[2,1-*b*]thiazoles [11]. Ring contraction strategy is also used for constructing this heterobicyclic system [12]. All these reported methods needed multistep reaction sequences. Recently, microwave-assisted organic synthesis has attracted considerable attention due to enhanced reaction rates, high yields, improved selectivity, and cleaner products [13]. Herein, we report an efficient, microwave assisted, and environmentally benign one pot method for the preparation of pyrrolo[2,1-*b*]thiazol-6-ones **6** from easily accessible α-aroyl ketene-*N*,*S*-acetals **3**. To the best of our knowledge, this is the first report on the direct transformation of an open chain system into pyrrolo[2,1-*b*]thiazole derivative using a one pot strategy.

Direct alkylation of thioamides using alkyl halide affords ketene-*N*,*S*-acetals which is widely used as a synthon in heterocyclic synthesis [14]. Recently we have explored the synthetic potential of α-aroyl ketene-*N*,*S*-acetals prepared by the alkylation of β-oxothioamides **1** for the synthesis of functionalised pyrroles [15]. α-Aroyl ketene-*N*,*S*-acetals were previously prepared in our laboratory as an intermediate for the synthesis of functionalized thiophenes *via* alkylation of thioamides using 1,2-bielectrophiles in presence of base [16].

RESULTS AND DISCUSSION

Initially, alkylation of thioamide **1** with one equiv. of a 1,2-bielectrophile—phenacyl bromide in the presence of K_2CO_3 (2 equiv.) as the base in acetone at room temperature was carried out expecting monoalkylation at sulphur followed by *in situ* cyclization to form thiazole **4**, which could be further transformed into the pyrrolothiazoles. However, we isolated only the monoalkylated α-aroyl ketene-*N*,*S*-acetals **3** in nearly quantitative yields (Scheme 1, Table 1). The unexpected complex pattern of peaks observed in the ^{1}H NMR (360 MHz) spectrum of **3** is apparently due to the diastereotopic nature of the methylene protons. For example, in **3a**, ethyl moiety showed a triplet at δ 1.27 and two sets of doublets each at δ 3.40 and 3.50 (J = 12). Another doublet of doublet appeared at 3.79 (1H, J = 12 Hz) and 4.08 (1H, J = 12 Hz) due to SCH_2 moiety. The NCH_2 moiety showed a

Scheme 1



multiplet at δ 4.18–4.26 ppm. By recording the ^{1}H NMR spectrum at higher frequency (500 MHz), we further confirmed these sets of peaks as doublet of doublet rather than peaks arising from the possible geometrical isomeric forms.

Next, taking **3a** as a model substrate, its cyclization to thiazole **4a** was attempted. Initial experiments using K_2CO_3 as the base in acetone under reflux conditions failed to afford thiazole. Use of a strong base like KOH in ethanol or NaH in DMF afforded only intractable mixture of products. Further studies using acid catalysts showed that the ketene-*N*,*S*-acetals **3** can be easily transformed into thiazoles **4**. Thus, a solution of the ketene-*N*,*S*-acetal **3a** in acetic acid was heated at 70°C for 4 h; the thiazole **4a** was formed quantitatively. Using a similar protocol the thiazole **4b** was prepared (Table 2). Alternatively, when the alkylation of the thioamide **1a** was attempted in the presence of excess of K_2CO_3 (8 equiv.) in DMF, thiazole **4a** was formed in good yields. The same strategy was used for the preparation of thiazoles **4b–f** (Table 2).

Since the thiazole **4** containing structural units that can be easily transformed into pyrrolo[2,1-*b*]thiazoles, we attempted their pyrrole ring annulation studies. Similar cyclization has been previously reported by our group for the synthesis of pyrroles from ketene-*N*,*S*-acetals using Vilsmeier Haack reagent ($POCl_3$/DMF) [15]. Tverdokhlebov *et al*. used the same reagent for the synthesis of pyrrolo[2,1-*b*]thiazoles from thiazoles [17]. Attempts using base catalysts or Vilsmeier Haack reagent failed to afford pyrrolothiazoles. However, the thiazole **4a** or **4b** after heating under reflux in acetic acid for a period of 15 h, we observed the formation of pyrrolo[2,1-*b*]thiazoles **5a** and **5b** in 48% and 42% yields respectively (Scheme 1). To our surprise, other thiazoles (**4c–4f**) even after refluxing in acetic acid for 24 h, it was possible to isolate only the unreacted starting material. Failure of the above cyclization was apparently due to the unfavorable orientation of the aroyl moiety in the thiazole **4**.

The observation that the *N*,*S*-acetal **3a** underwent facile cyclization in presence of acetic acid prompted us to irradiate a solution of **3a** in acetic acid under

Table 1

Ketene-*N*,*S*-acetals **3** prepared from thioamide **1**.

Product	R^1	R^2	Yield (%)
3a	CH_3	H	92
3b	OCH_3	Cl	88
3c	H	Cl	92
3d	Br	Cl	94
3e	OCH_3	H	85
3f	Br	H	94
3g	H	H	96

Table 2

Thiazoles **4** prepared from thioamide **1** or from ketene-*N*,*S*-acetal **3**.

Product	R^1	R^2	Yield (%)
4a	H	H	88
4b	Br	H	87
4c	Cl	CH_3	85
4d	Cl	H	86
4e	OCH_3	CH_3	80
4f	H	CH_3	82

Table 3

Pyrrolo[2,1-*b*]thiazol-6-ones **6** prepared from ketene-*N*,*S*-acetal **3**.

Product	R^1	R^2	Yield (%)
6a	CH_3	H	81
6b	OCH_3	Cl	85
6c	H	Cl	82
6d	OCH_3	H	80
6d	Br	H	76
6f	H	H	84

microwave. Thus, by dissolving **3a** in acetic acid followed by microwave irradiation for 15 min at 150°C in a microwave synthesizer, transformation to the corresponding pyrrolo[2,1-*b*]thiazole **6a** was observed in 81% yield. Using a similar protocol we have prepared other pyrrolothiazoles (**6b–f**) in good yields (Table 3). Electron withdrawing or donating substituents have little effect on the mode of cyclization or on the overall yield of the pyrrolothiazoles **6** formed. When we reduced only the reaction time to 10 min, the reaction was incomplete and could be possible to isolate a mixture of the intermediate thiazole **4a** and the pyrrolothiazole **6a** in a ratio 1 : 3. In an independent experiment, transformation of **4a** to **6f** was observed under microwave heating. It is interesting to note that the mode of cyclization during pyrrole ring annelation step in conventional heating is different from that in microwave conditions. Thus, under microwave conditions pyrrolothiazoles **6** were formed which is structurally different form the pyrrolothiazoles **5**, formed during conventional heating. This is apparently due to the fact that under microwave conditions, the geometry of the exocyclic double bond present in the initially formed thiazole **4** was affected to a lesser extend and the ethyl carboxylate functionality underwent rapid conformational changes favoring the regioselective formation of pyrrolothiazoles **6**. While in conventional heating the reverse is true leading to the formation of pyrrolothiazole **5**.

In summary, we have developed a convenient and efficient one-pot procedure for the synthesis of a variety of pyrrolo[2,1-*b*]thiazoles from less expensive as well as easily accessible ketene-*N*,*S*-acetals under microwave conditions in a regioselective and efficient manner. The reaction is very fast and the product can be easily separated from the reaction medium by dilution using water followed by filtration.

EXPERIMENTAL

Thioamide **1** was prepared as reported [15(b)]. Microwave-assisted reactions were done in a multimode microwave reactor (Biotage Initiator™). Melting points were obtained on a Buchi-530 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 MHz or AM-360 MHz spectrometer in $CDCl_3$. Chemical shifts are expressed in parts per million. Coupling constants *J* are given in Hertz. Mass spectra-EIMS, FAB, were obtained on a Finngen-Mat 312, Jeol SX 102/Da-600 instruments respectively. Elemental analyses were recorded on an elementar vario EL III analyzer.

General procedure for the synthesis of α-aroyl ketene-*N*,*S*-acetals (3). A suspension of the thioamide **1** (10 mmol) and anhyd K_2CO_3 (20 mmol) in dry acetone (30 mL) was refluxed with stirring for 30 min. The mixture was cooled and phenacyl bromide **2** (10 mmol) was added followed by stirring at room temperature for 4 h. When the reaction was completed (TLC), the mixture was poured into ice-cold water and extracted using CH_2Cl_2 (2 × 50 mL). The organic layer was washed with water (2 × 100 mL), dried using anhyd Na_2SO_4 and evaporated. The crude product thus obtained was purified by column chromatography over silica gel using hexane: ethyl acetate (7 : 3) as eluent afforded the α-aroyl ketene-*N*,*S*-acetals **3a–g** (Table 1).

Ethyl[3-(4-methylphenyl)-3-oxo-1-(2-oxo-2-phenyl-ethylsulfanyl)-propenylamino]acetate (3a). White solid; mp 143–145°C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.27 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 2.39 (s, 3H, $ArCH_3$), 3.40 (1H, *J* = 12 Hz, CH_2CH_3), 3.50 (1H, *J* = 12 Hz, CH_2CH_3), 3.79 (1H, *J* = 12 Hz, SCH_2), 4.08 (1H, *J* = 12 Hz, SCH_2), 4.18–4.26 (m, 2H, NCH_2), 6.09 (s, 1H, vinylic), 7.21 (d, 2H, *J* = 8 Hz, 2H, ArH), 7. 39 (m, 3H, ArH), 7.59 (m, 2H, ArH), 7.77 (d, 2H, *J* = 8 Hz, ArH) ppm. ^{13}C NMR (90 MHz, $CDCl_3$): δ 14.5, 22.2, 48.1, 52.5, 62.3, 97.4, 126.4, 129.3, 129.7, 130.0, 133.7, 135.0, 141.9, 145.8, 156.5, 168.8, 195.9, 196.1. EIMS: *m*/*z* (%) 397.16 (M^+, 12), 379.16 (100), 306.15 (38), 246.14 (45), and 119.1 (70). Anal. Calcd. for $C_{22}H_{23}NO_4S$ (397.13): C, 66.48; H, 5.83; N, 3.52. Found: C, 66.35; H, 5.87; N, 3.58.

Ethyl{1-[2-(4-chlorophenyl-2-oxo-ethylsulfanyl]-3-(4-methoxyphenyl)-3-oxo-propenylamino}acetate (3b). White solid; mp 95–97°C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 3.36 (d, 1H, *J* = 12 Hz, CH_2CH_3), 3.43 (1H, *J* = 12 Hz, CH_2CH_3), 3.85 (d, 1H, *J* = 18 Hz, SCH_2), 3.84 (s, 3H, $ArOCH_3$), 4.05 (d, 1H, *J* = 18 Hz, SCH_2), 4.16–4.30 (m, 2H, NCH_2), 5.04 (bs, 1H, NH), 6.06 (s, 1H, vinylic), 6.91 (d, 2H, *J* = 8 Hz, 2H, ArH), 7. 38 (d, 3H, *J* = 8Hz, ArH), 7.55 (d, 2H, *J* = 8 Hz, ArH), 7.86 (d, 2H, *J* = 8 Hz, ArH) ppm. MS (FAB): *m*/*z* 448 (M^+ + H). Anal. Calcd. for $C_{22}H_{22}ClNO_5S$ (447.09): C, 58.99; H, 4.95; N, 3.13. Found: C, 58.76; H, 4.90; N, 3.17.

Ethyl{1-[2-(4-chloro-phenyl-2-oxo-ethylsulfanyl]-3-oxo-3-phenyl propenylamino}acetate (3c). White solid. mp 98–100°C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 3.39 (d, 1H, *J* = 10 Hz, CH_2CH_3), 3.47 (d, 1H, *J* = 10 Hz, CH_2CH_3), 3.77 (d, 1H, *J* = 18 Hz, SCH_2), 4.07 (d, 1H, *J* = 18 Hz, SCH_2), 4.15–4.32 (m, 2 H, NCH_2), 4.99 (bs, 1H, NH), 6.10 (s, 1H, vinylic), 7.39–7.45 (m, 3H, ArH), 7. 56 (d, *J* = 8Hz, 2H, ArH), 7.89 (d, 2H, *J* = 7 Hz, ArH) ppm. ^{13}C NMR (90 MHz, $CDCl_3$): δ 14.5, 44.8, 48.0, 63.1, 90.6, 96.2, 127.7, 128.5, 128.7, 129.1, 129.4, 131.8, 135.5, 139.3, 139.7, 166.1, 170.7, 187.7 ppm. MS (FAB): *m*/*z* 418 (M^+ + H). Anal. Calcd. for $C_{21}H_{20}ClNO_4S$ (417.08): C, 60.35; H, 4.82; N, 3.35. Found: C, 60.49; H, 4.91; N, 3.28.

Ethyl{3-(4-bromophenyl)-1-[2-(4-chloro-phenyl)-2-oxo-ethylsulfanyl]-3-oxo propenylamino}acetate (3d). White solid. mp 147–149°C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J* =

10 Hz, CH_2CH_3), 3.43 (q, 2H, J = 10 Hz, CH_2CH_3), 3.78 (d, 1H, J = 18 Hz, SCH_2), 4.08 (d, 1H, J = 18 Hz, SCH_2), 4.16–4.32 (m, 2 H, NCH_2), 4.99 (bs, 1H, N*H*), 6.10 (s, 1H, vinylic), 7.40 (d, J = 10 Hz, 2H, ArH), 7.55–7.57 (m, 4 H, ArH), 7.88 (d, 2H, J = 10 Hz, ArH) ppm. ^{13}C NMR (90 MHz, $CDCl_3$): δ 14.2, 49.0, 62.4, 95.9, 106.9, 125.1, 128.5, 129.4, 130.7, 131.5, 136.2, 138.3, 139.8, 164.3, 166.9, 181.8, 185.7 ppm. EIMS: *m/z* (%) 497.1 (M^+ + 2, 14), 479.1 (82), 406.1 (48), 324.2 (22), 240.2 (25), 183.1 (82) and 139.1 (100). Anal. Calcd. for $C_{21}H_{19}BrClNO_4S$ (494.99): C, 50.77; H, 3.85; N, 2.82. Found: C, 50.65; H, 3.89; N, 2.76.

Ethyl[3-(4-methoxyphenyl)-3-oxo-1-(2-oxo-2-phenyl-ethyl-sulfanyl)-propenylamino]acetate (3e). Pale yellow glass. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.26 (t, 3H, J = 7.2 Hz, CH_2CH_3), 3.38 (d, 1H, J = 14 Hz, CH_2CH_3), 3.49 (1H, J = 14 Hz, CH_2CH_3), 3.79 (d,1H, J = 18 Hz, SCH_2), 3.84 (s, 3H, $ArOCH_3$ + 1H, SCH_2), 4.06 (d, 1H, J = 18 Hz, SCH_2), 4.15–4.28 (m, 2H, NCH_2), 4.50 (bs, 1H, N*H*), 6.07 (s, 1H, vinylic), 6.92 (d, 2H, J = 9 Hz, 2H, ArH), 7. 41 (m, 3H, ArH), 7.61 (d, 2H, J = 7 Hz, ArH), 7.87 (d, 2H, J = 9 Hz, ArH). ^{13}C NMR (90 MHz, $CDCl_3$): δ 14.1, 44.3, 47.6, 55.3, 62.4, 89.6, 96.1, 113.4, 126.5, 128.7, 129.2, 132.1, 140.3, 162.1, 165.2, 170.3, 186.1, 187.1 ppm. EIMS ($CHCl_3/CH_3CN+H^+$): *m/z* (%) 414.1, (M^+ + H 12), 396.2 (100), 366.2 (18), 248.1 (35). Anal. Calcd. for $C_{22}H_{23}NO_5S$ (413.13): C, 63.90; H, 5.61; N, 3.39. Found: C, 63.82; H, 5.67; N, 3.43.

Ethyl[3-(4-bromophenyl)-3-oxo-1-(2-oxo-2-phenyl-ethylsul-fanyl) propenylamino]acetate (3f). White solid. mp 98–99°C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.27 (t, 3H, J = 7.2 Hz, CH_2CH_3), 3.43 (d, 1H, J = 10 Hz, CH_2CH_3), 3.53 (d, 1H, J = 10 Hz, CH_2CH_3), 3.81 (d, 1H, J = 18 Hz, SCH_2), 4.08 (d, 1H, J = 18 Hz, SCH_2), 4.20–4.30 (m, 2 H, NCH_2), 4.51 (s, 1H, N*H*), 6.03 (s, 1H, vinylic), 7.31 (d, 2H, J = 7 Hz, 2H, ArH), 7. 43 (m, 3H, ArH), 7.60 (m, 2H, ArH), 7.82 (d, 2H, J = 7 Hz, ArH) ppm. ^{13}C NMR (90 MHz, $CDCl_3$): δ 14.5, 44.8, 53.8, 62.7, 96.8, 126.9, 129.0, 129.3, 130.5, 131.9, 132.5, 138.6, 140.5, 166.9, 170.6, 182.6, 186.2 ppm. MS (FAB): *m/z* 462 (M^+ + H). Anal. Calcd. for $C_{21}H_{20}BrNO_4S$ (461.03): C, 54.55; H, 4.36; N, 3.03. Found: C, 54.62; H, 4.29; N, 3.06.

Ethyl[3-oxo-1-(2-oxo-2-phenyl-ethylsulfanyl)-3-phenyl-propenylamino]acetate (3g). White solid. mp 118–120°C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.29 (t, 3H, J = 7.2 Hz, CH_2CH_3), 3.42 (1H, J = 10 Hz, CH_2CH_3), 3.53 (1H, J = 10 Hz, CH_2CH_3), 3.81 (1H, J = 18 Hz, SCH_2), 4.11 (1H, J = 18 Hz, SCH_2), 4.18–4.32 (m, 2 H, NCH_2), 4.82 (s, 1H, N*H*), 6.11 (s, 1H, vinylic), 7.40–7.48 (m, 6H, ArH), 7.61 (d, 2H, ArH), 7.90 (d, 2H, J = 8 Hz, ArH) ppm. ^{13}C NMR (90 MHz, $CDCl_3$): δ 14.5, 44.8, 48.1, 62.9, 90.4, 97.6, 126.9, 127.7, 128.7, 129.3, 129.4, 131.7, 139.8, 140.6, 166.4, 170.8, 187.6 ppm. MS (FAB): *m/z* 385 (M^+ + H). Anal. Calcd. for $C_{21}H_{21}NO_4S$ (383.12): C, 65.78; H, 5.52; N, 3.65. Found: C, 65.86; H, 5.59; N, 3.60.

General procedure for the synthesis of thiazoles (4). Method (a): From ketene-*N*,*S*-acetal **3**: To a suspension of the ketene-*N*,*S*-acetal **3a** or **3b** (10 mmol) in glacial acetic acid (10 mL) was heated at 70°C with stirring for 4 h. The reaction mixture was cooled, diluted with water (50 mL), and the precipitated product was filtered, recrystallized from ethanol to afford the thiazole **4a** or **4b** in moderate yields.

Method (b): From thioamide **1**: To a suspension of the thioamide **1** (10 mmol) in anhyd DMF (30 mL) was added K_2CO_3 (80 mmol) followed by phenacyl bromide **2** (10 mmol). The mixture was stirred at room temperature for 4 h then at 100°C for 2 h. It was then cooled, poured into ice-cold water and extracted using ethyl acetate (2 × 50 mL). The organic layer was washed with water (2 × 100 mL), dried using anhyd Na_2SO_4 and evaporated. The crude product thus obtained was purified by column chromatography over silica gel using hexane: ethyl acetate (7 : 3) as eluent to give **4a–f** (Table 2).

Ethyl 2-{2-[(Z)-oxo(phenyl)ethylidene]-4-phenyl-1,3-thiazol-3-yl}acetate (4a). Pale yellow needles; mp. 130–131°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7 Hz, CH_2CH_3), 4.26 (q, 2H, J = 7 Hz, CH_2CH_3), 4.50 (s, 1H, NCH_2), 6.32 (s, 1H, vinylic), 6.40 (s, 1H, tzol C*H*), δ 7.42 (m, 6H, ArH), δ 7.94 (m, 4H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 48.9 (NCH_2), 62.2 (CH_2CH_3), 86.4 (tzol *C*H), 106.0 (vinylic), 126.8 (*C*4, tzol CH), 164.0 (*C*2, tzol), 128.1, 128.9, 129.3, 129.7, 129.9, 130.4, 139.6, 140.9 (ArC), δ 167.1 and 183.1 (carbonyl). EIMS: *m/z* (%) 365 (M^+, 82), 336 (41), 292 (51), 275 (15), 214 (33), 186 (36), 147 (54), 134 (58), and 105 (100). Anal. Calcd. for $C_{21}H_{19}NO_3S$ (365.45): C, 69.02; H, 5.24; N, 3.83. Found: C, 68.72; H, 5.36; N, 3.57.

Ethyl 2-{2-[(Z)-(4-bromophenyl)(oxo)ethylidene]-4-phenyl-1,3-thiazol-3-yl}acetate (4b). Pale yellow crystalline solid; mp 118–120°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, 3H, J = 7 Hz, CH_2CH_3), 4.20 (q, 2H, J = 7 Hz, CH_2CH_3), 4.53 (s, 1H, NCH_2), 6.46 (s, 1H, vinylic), 7.19 (s, 1H, tzol C*H*), 7.30–7.47 (m, 7H, ArH), 7.75 (d, 2H, J = 8 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2 (CH_2CH_3), 49.1 (NCH_2), 62.3 (CH_2CH_3), 86.2 (tzol *C*H), 106.4 (vinylic), 125.0 (*C*4, tzol), 164.5 (*C*2, tzol), 128.6, 128.3, 129.1, 129.5, 129.9, 131.4, 138.7, and 141.2 (ArC), 167.09 and δ 181.82 (carbonyl) ppm. EIMS: *m/z* (%) 443 (M^+, 50), 445 (M^+ + 2, 51), 411 (32), 260 (21), 216 (22), 185 (100), 157 (74), 134 (74), and 105 (51). Anal. Calcd. for $C_{21}H_{18}BrNO_3S$ (444.34): C, 56.76; H, 4.08; N, 3.15. Found: C, 56.52; H, 4.16; N, 3.02.

Ethyl 2-{2-[(Z)-(4-chlorophenyl)(oxo)ethylidene]-4-(4-methylphenyl)-1,3-thiazol-3-yl}acetate (4c). White crystalline solid; mp 148–149°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7 Hz, CH_2CH_3), 2.41 (s, 3H, CH_3), 4.28 (q, 2H, J = 7.2 Hz, CH_2CH_3), 4.51 (s, 1H, NH CH_2), 6.25 (s, 1H, vinylic), 6.40 (s, 1H, tzol CH), 7.27 (m, 4H, ArH), 7.37 (d, 2H, J = 8 Hz, ArH), 7.86 (d, 2H, J = 8 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) 14.2 (CH_2CH_3), 49.1 (NCH_2), 62.2 (CH_2CH_3), 86.3 (tzol *C*H), 106.0 (vinylic), 126.4 (*C*4, tzol), 164.5 (*C*2 tzol), 127.0, 128.4, 129.4, 129.8, 136.4, 138.3, 140.2, 141.3 (ArC), 167.2, and δ 181.6 (carbonyl) ppm. EIMS: *m/z* (%) 415 (M^+ + 2, 23), 413 (M^+, 72), 396 (41), 340 (38), 263 (15), 200 (26), 188 (34) and 139 (100). Anal. Calcd. for $C_{22}H_{20}ClNO_3S$ (413.92): C, 63.84; H, 4.87; N, 3.38. Found: C, 64.08; H, 4.56; N, 3.24.

Ethyl 2-{2-[(Z)-(4-chlorophenyl)(oxo)ethylidene]-4-phenyl-1,3-thiazol-3-yl}acetate (4d). White crystalline solid; mp 110–111°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7 Hz, CH_2CH_3), 4.27 (q, 2H, J = 7 Hz, CH_2CH_3), 4.51 (s, 1H, NCH_2), 6.26 (s, 1H, vinylic), 6.44 (s, 1H, tzol CH), 7.37–7.48 (m, 7H, ArH), 7.87 (d, 2H, J = 8 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$), 14.2 (CH_2CH_3), 48.1 (NCH_2), 62.3 (CH_2CH_3), 86.4 (tzol *C*H), 106.0 (vinylic), 126.8 (*C*4 tzol) 164.0 (*C*2 tzol), 127.7, 128.4, 129.2, 129.9, 136.4, 138.3, 141.2 (ArC), 167.1, and δ 181.6 (carbonyl) ppm. EIMS: *m/z* (%) 401, (M^+ +2, 28), 399 (M^+, 85), 382 (27), 326 (34), 298 (24), 249 (21), 183 (53), 141 (54), 139 (100), and 111 (100). Anal. Calcd. for

$C_{21}H_{18}ClNO_3S$ (399.89): C, 63.07; H, 4.54; N, 3.50. Found: C, 62.74; H, 4.78; N, 3.45.

Ethyl 2-{2-[(Z)-(4-methoxyphenyl)(oxo)ethylidene]-4-(4-methylphenyl)-1,3-thiazol-3-yl}acetate (4e). Pale yellow glass. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7 Hz, CH_2CH_3), 2.17 (s, 3H, CH_3), 4.27 (q, 2H, J = 7 Hz, CH_2CH_3), 4.69 (s, 1H, NCH_2), 6.46 ppm (s, 1H, vinylic), 6.48 ppm (s, 1H, tzol C*H*), 6.77 (d, 2H, J = 8 Hz, ArH), 6.90 (d, 2H, J = 8 Hz, ArH), 7.04 (d, 2H, J = 8 Hz, ArH), 7.28 (d, 2H, J = 8 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) 14.2 (CH_2CH_3), 21.3 (CH_3), 49.1 (NCH_2), 55.3 (OCH_3), 62.2 (CH_2CH_3), 86.1 (tzol *C*H), 105.5 (vinylic) 127.3 (*C*4 tzol), 161.6 (*C*2 tzol), 113.5, 128.8, 129.4, 129.7, 132.7, 139.9, 140.9, and 163.8 (ArC), 167.4 and 182.5 (carbonyl) ppm. EIMS: *m/z* (%) 409 (M^+, 78), 336 (32), 306 (15), 228 (25), 200 (16), 172 (11), 135 (100), and 121 (92). Anal. Calcd. for $C_{23}H_{23}NO_4S$ (409.50): C, 67.46; H, 5.66; N, 3.42. Found: C, 67.32; H, 5.73; N, 3.48.

Ethyl 2-{4-(4-methylphenyl)-2-[(Z)-oxo(phenyl)ethylidene]-1,3-thiazol-3-yl}acetate (4f). Pale yellow crystalline solid; mp 128–129°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7 Hz, CH_2CH_3), 2.41 (s, 3H, CH_3), 4.27 (q, 2H, J = 7 Hz, CH_2CH_3), 4.51 (s, 1H, NCH_2), 6.26–7.95 (m, 10H, ArH + tzol H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 21.3 (CH_3), 48.9 (NCH_2), 62.4 (CH_2CH_3), 90.0 (tzol *C*H), 105.8 (vinylic), 126.5 (*C*4 tzol), 165.9 (*C*2 tzol), 127.3, 128.3, 129.3, 129.7, 130.4, 131.2, 137.4, and 138.9 (ArC), 170.3 and 187.1 (carbonyl). EIMS: *m/z* (%) 379 (M^+, 84), 362 (31), 306 (51), 278 (18), 232 (13), 188 (16), 147 (34), 119 (58) and 105 (100). Anal. Calcd for $C_{22}H_{21}NO_3S$ (379.47): C, 69.63; H, 5.58; N, 3.69. Found: C, 69.32; H, 5.67; N, 3.76.

General procedure for the synthesis of pyrrolothiazoles (5). A suspension of the thiazole **3** (10 mmol) in glacial acetic acid (10 mL) was refluxed with stirring for 15 h. The mixture was cooled and poured into ice cold water and extracted using $CHCl_3$ (2 × 50 mL). The organic layer was washed with water (2 × 50 mL) and dried using anhyd Na_2SO_4. The solvent was evaporated and the crude product thus obtained was purified by column chromatography over silica gel using hexane: ethyl acetate as eluent (4 : 1) to afford **5a** or **5b**.

Ethyl 3,6-diphenylpyrrolo[2,1-b]-[1,3]thiazole-5-carboxylate (5a). Pale yellow glass. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (t, 3H, J = 7 Hz, CH_2CH_3), 3.45 (q, 2H, J =7 Hz, CH_2CH_3), 6.34 (s, 1H pyrrole CH), 6.52 (s, 1H, tzol CH(7.07–8.07 (m, 10H, ArH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.6, 59.0, 99.6 (tzol CH), 109.7, 112.3, 125.3, 126.2, 127.4, 127.5, 127.6, 128.8, 129.1, 131.7, 132.7, 135.6, 137.7 (ArH), 159.48. EIMS: *m/z* (%) 347 (M^+, 48), 302 (24), 275(100), 241 (18), 215 (15), 202 (12), 172 (15), 145 (20), and 102 (27). Anal. Calcd. for $C_{21}H_{17}NO_2S$ (347.43): C, 72.60; H, 4.93; N, 4.03. Found: C, 72.43; H, 4.86; N, 4.14.

Ethyl 3-(4-methylphenyl)-6-phenylpyrrolo[2,1-b][1,3]thiazole-5-carboxylate (5b). Pale yellow glass.^{1}H NMR (300 MHz, CDCl3) δ 0.68 (t, 3H, J = 7 Hz, CH_2CH_3), δ 3.50 (q, 2H, J = 7 Hz, CH_2CH_3), δ 2.30 (s, 3H, CH_3), δ 6.33 (s, 1H, pyrrole CH), δ 6.49 (s, 1H, tzol CH), δ 7.13–7.53 (m, 9H, ArH) ppm. ^{13}C NMR (75.5 MHz, CDCl3) δ 14.0, 21.7, δ 60.4, 101.0 (tzol CH). 110.6, 126.7, 127.6, 128.0, 128.9, 129.6, 130.2, 130.5, 134.0, 135.8, 137.8, 137.2, 139.0, 160.9. EIMS: *m/z* (%) 361 (M^+, 47), 316 (22), 289 (100), 273 (14), 210 (8), 145 (15), and 115 (31). Anal. Calcd. for $C_{22}H_{19}NO_2S$ (361.46): C, 73.10; H, 5.30; N, 3.88. Found: C, 73.28; H, 5.43; N, 3.74.

General procedure for the synthesis of pyrrole[2,1-*b*]thiazol-6-ones (6). To a 10 mL glass vial equipped with a small magnetic stirring bar, α-aroyl ketene-*N*,*S*-acetal **2** (1.0 mmol) was added followed by glacial acetic acid (3 mL). The mixture was then irradiated in a microwave synthesizer for 15 min at 150°C. After completion of the reaction, the vial was cooled to 50°C by air jet cooling before it was opened. It was then diluted with water (20 mL), and the precipitated product was collected by filtration, washed with cold water and recrystallized from ethyl acetate to afford **6a–f** (Table 3).

7-(4-Methyl-benzoyl)-3-phenyl-pyrrolo[2,1-b]thiazol-6-one (6a). White solid; mp 206–207°C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 2.40 (s, 3H $ArCH_3$), 4.62 (s, 2H, NCH_2), 6.80 (s, 1H tzol), 7.53 (s, 7H, ArH), 8.05 (d, 2H, J = 7 Hz, ArH). ^{13}C NMR (90 MHz, $CDCl_3$): δ 22.1, 59.3, 109.2, 127.7, 128.4, 128.9, 129.6, 129.9, 130.8, 135.5, 141.5, 142.7, 179.8, 185.4, 185.9. HRMS: calcd. for $C_{20}H_{15}NO_2S$ 333.0823, found 333.0809.

3-(4-Chloro-phenyl)-7-(4-methoxy-benzoyl)pyrrolo[2,1-b]thiazol-6-one (6b). White solid; mp 211–213°C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 3.84 (s, 3H, OCH_3), 4.93 (s, 2H, NCH_2), 6.99–7.01 (d, 2H, J = 7.2 Hz, ArH), 7.47 (s, 1H tzol), 7.61–7.63 (d, 2H, J = 7.2 Hz, ArH), 7.79–7.81 (d, 2H, J = 7.2 Hz, Ar*H*), 8.12–8.14 (d, 2H, J = 7.2 Hz, ArH). ^{13}C NMR (90 MHz, $CDCl_3$): δ 54.8, 59.9, 108.5, 127.6, 129.8, 131.0, 131.5, 135.1, 139.9, 162.4, 178.5, 183.0, 186.2. EIMS (THF/HCOOH): *m/z* (%) 384.1, M^+ + H 100), 316.4 (56), 288.4 (78), 244.3 (12), 166.2 (18). Anal. Calcd. for $C_{20}H_{14}ClNO_3S$ (383.04): C, 62.58; H, 3.68; N, 3.65. Found: C, 62.69; H, 3.74; N, 3.58.

7-Benzoyl-3-(4-chloro-phenyl)-pyrrolo[2,1-b]thiazol-6-one (6c). White solid. mp 200–202°C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 4.93 (s, 2H, NCH_2), 7.46–7.48 (m, 7H, ArH), 6.50 (s, 1H tzol), 7.61–7.63 (d, 2H, J = 7.2 Hz, ArH), 7.79–7.81 (d, 2H, J = 7.2 Hz, ArH), 7.97–7.99 (d, 2H, J = 7.2 Hz, ArH). ^{13}C NMR (90 MHz, $CDCl_3$): δ 59.7, 108.2, 127.4, 127.8, 128.2, 129.1, 129.4, 129.7, 130.1, 135.0, 138.5, 139.8, 178.0, 184.1, 186.3. MS (FAB): *m/z* 354 (M^+ + H). Anal. Calcd. for $C_{19}H_{12}ClNO_2S$ (353.03): C, 64.50; H, 3.42; N, 3.96. Found: C, 64.41; H, 3.38; N, 3.99.

7-(4-Methoxy-benzoyl)-3-phenyl-pyrrolo[2,1-b]thiazol-6-one (6d). White solid. mp 216–218 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 3.78 (s, 3H, OCH_3), 4.88 (s, 2H, NCH_2), 6.93–6.95 (d, 2H, J = 7.2 Hz, ArH), 7.36 (s, 1H tzol), 7.47 (s, 3H, ArH), 7.70 (s, 2H, ArH), 8.07–8.09 (d, 2H, J = 7.2 Hz, ArH). ^{13}C NMR (90 MHz, $CDCl_3$): δ 55.7, 59.7, 108.3, 127.9, 128.9, 129.3, 129.6, 130.9, 131.2, 131.4, 140.9, 162.2, 178.3, 182.8, 186.1. MS (FAB): *m/z* 350 (M^+ + H). Anal. Calcd. for $C_{20}H_{15}NO_3S$ (349.08): C, 68.75; H, 4.33; N, 4.01. Found: C, 68.62; H, 4.38; N, 4.07.

7-(4-Bromo-benzoyl)-3-phenyl-pyrrolo[2,1-b]thiazol-6-one (6e). White solid; mp 222–224°C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 4.63 (s, 2H, NCH_2), 6.84 (s, 1H tzol), 7.54–7.60 (m, 7H, ArH), 8.04 (d, 2H, J = 7.2 Hz, ArH). ^{13}C NMR (90 MHz, $CDCl_3$): δ 59.3, 109.2, 109.4, 126.9, 127.8, 128.3, 129.9, 129.9, 130.9, 131.4, 136.9, 141.6, 179.9, 184.6, 185.4. MS (FAB): *m/z* 398 (M^+ + H), 400 (M^+ + H + 2). Anal. Calcd. for $C_{19}H_{12}BrNO_2S$ (396.98): C, 57.30; H, 3.04; N, 3.52. Found: C, 57.18; H, 3.10; N, 3.55.

7-Benzoyl-3-phenyl-pyrrolo[2,1-b]thiazol-6-one (6f). White solid; mp 216–217°C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 4.62 (s, 2H, NCH_2), 6.80 (s, 1H tzol), 7.45–7.53 (m, 8H, ArH), 8.12 (d, 2H, J = 7.2 Hz, ArH). ^{13}C NMR (90 MHz, $CDCl_3$): δ

59.3, 109.2, 109.3, 127.7, 128.2, 128.4, 129.5, 129.9, 130.8, 132.2, 138.2, 141.6, 179.8, 185.4, 186.0. MS (FAB): *m*/*z* 320 ($M^+ + H$). Anal. Calcd. for $C_{19}H_{13}NO_2S$ (319.07): C, 71.45; H, 4.10; N, 4.39. Found: C, 71.58; H, 4.16; N, 4.32.

Acknowledgments. P.M. thank SAIF, CDRI, Lucknow, India for providing spectral and analytical data and the Kerala State Council for Science Engineering and Technology (KSCSTE), Kerala, India for financial support.

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