

FACILE SYNTHESIS OF 5-ACYL-2-AMINO-1,3-THIAZOLE BY THE REACTION OF THIAAZADIENES WITH α -HALO KETONES

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Abstract – The reaction of thiaazadienes (**1a–e**) with α -halo ketones (**2a–d**) gives 5-acyl-2-amino-1,3-thiazole (**3a–q**) in high yields.

INTRODUCTION

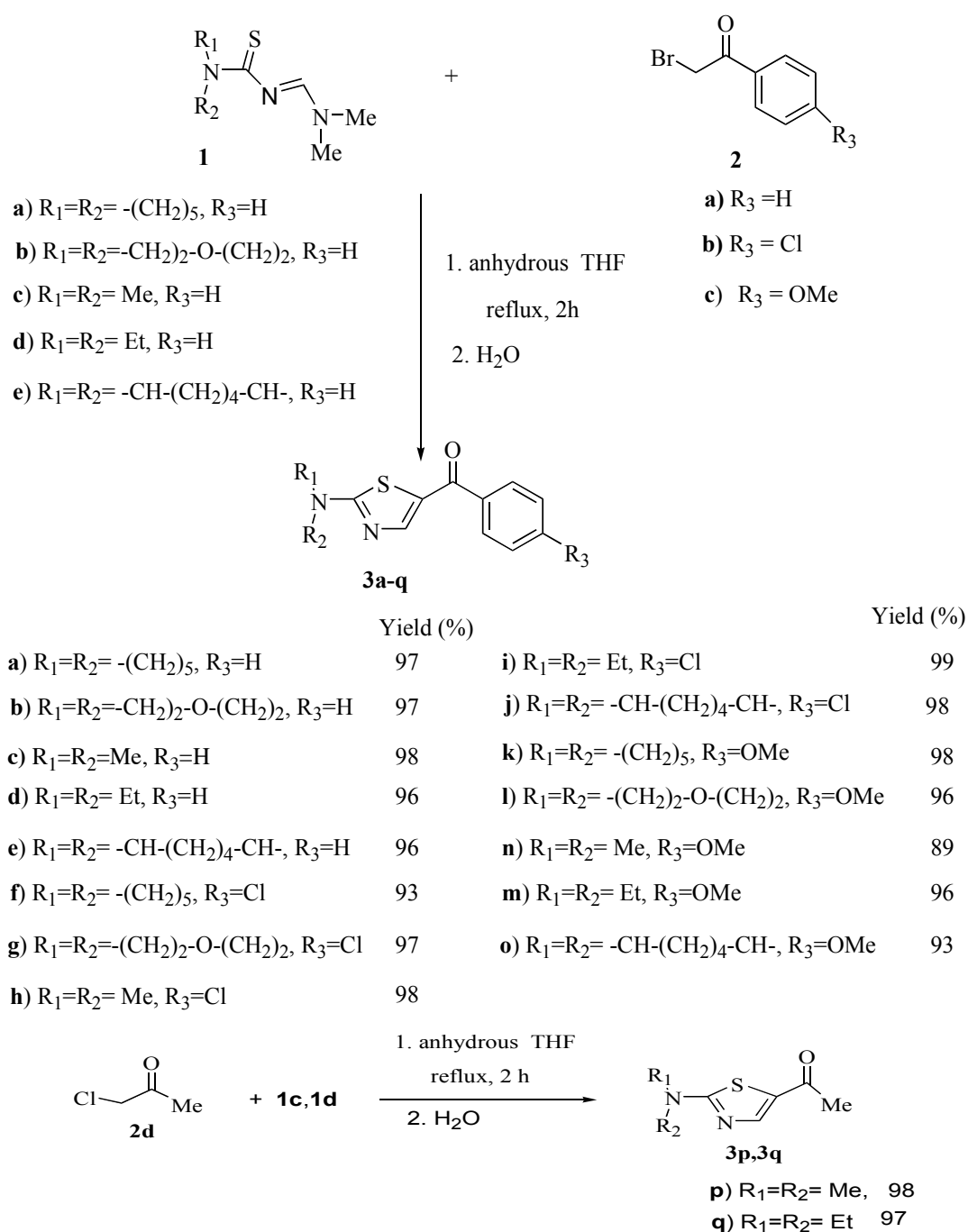
Substituted 1,3-thiazoles are ubiquitous structural motifs found in several compounds of biological interest. For example, 2-dialkyl-1,3-thiazoles serve as key intermediates in the synthesis of biologically interesting and pharmaceutically useful molecules such as dipeptidyl peptidase IV (DPP-IV) inhibitors, agonists of peroxisome proliferation-activated receptors (PPARs), subtype selective *N*-methyl-R-aspartate antagonists, glucose and lipid lowering agents and antifungal agents.¹⁻³ Consequently, several methods for the preparation of substituted 1,3-thiazoles have been developed.⁴⁻⁶ Although these methods allow ready accessibility to this class of compounds, their ability to prepare thiazoles with specific substitution patterns is limited and usually requires the design of new synthetic strategies.

Recently, the synthesis of sulfur heterocycles has been extensively studied using the carbon-sulfur double bond as 2 π dienophile intermediates for [4+2] cycloadditions. For example, α,β -unsaturated thialdehydes and thiaketones selectively undergo 'head-to-head' [4+2] dimerization to give six-membered cyclic dithianides.⁷ Furthermore, the reaction of *N*-thiaazadienes with dimethyl acetylenedicarboxylate (DMAD) affords six-membered ring 4*H*-thiazine that gets converted to a 4*H*-thianopyran by cycloreversion and recycloaddition with excess DMAD.⁸ Recently, Noack and Hartman⁹ prepared a series of 5-acyl-2-amino-1,3-thiazoles by allowing suitably substituted thiaazadines and haloacetophenones to react in a polar solvent such as acetonitrile or methanol to give vinanidinium salts which were converted *in situ* to by the addition of a suitable base (TEA or MeOK) and refluxing. During the course of our study on the biological activity of certain 1,3-thiazoles, we needed a supply of 5-acyl-2-

amino-1,3-thiazoles for testing purposes. We initially used the aforementioned method.⁹ However, we were able to modify the procedure with improved results which we report herein.¹⁰

RESULTS AND DISCUSSION

Five thiaazadienes (thiaacylamides) (**1a-e**), which were on hand from a previous study,¹¹ were treated with bromoacetophenones (**2a-c**) and chloroacetone (**2d**). We noted early on that the initially formed vinanidinium salts could simply be quenched with water to give the desired products (**3**). By eliminating the base/refluxing step, **3** were obtained in almost quantitative yields. The results are shown in Scheme 1.



Scheme 1

Accordingly, the reaction of bromoacetophenones (**2a-c**) with **1a-e** gave the 2-amino derivatives of 5-benzoyl-1,3-thiazoles (**3a-o**) in 89–99% yields and the reaction of chloroacetone (**2d**) with **1c,d** afforded 5-acyl-1,3-thiazoles (**p,q**) in 97–98% yields. Interestingly, the yields of **3c** (98%) and **3p** (98%) obtained in this study are significantly higher than the yields of **3c** (29%) and **3p** (13%) reported previously.⁹ The structures of **3a-q** were confirmed by GCMS, ¹H NMR, ¹³C NMR spectroscopy, and elemental analysis. In addition, the structures of **3a-c** were determined using X-Ray diffraction analysis (Figures 1–3). The X-Ray structure of **3c** was particularly important since its melting point reported here is much higher than that previously reported.⁹

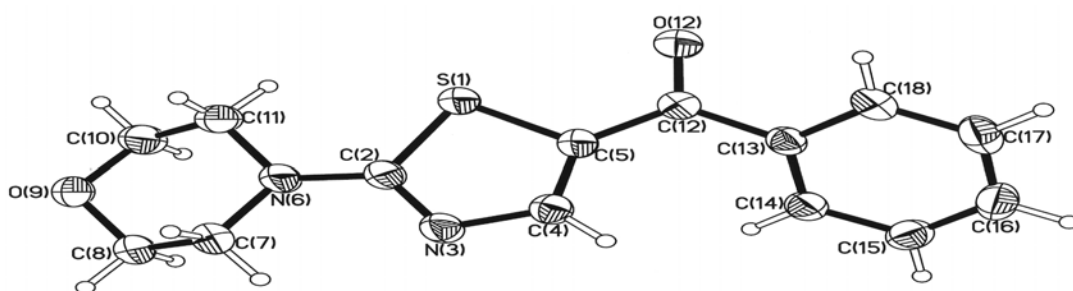


Figure 1. ORTEP of compound (**3a**)

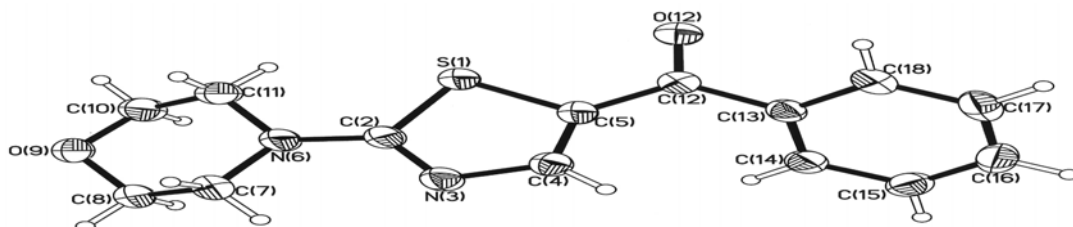


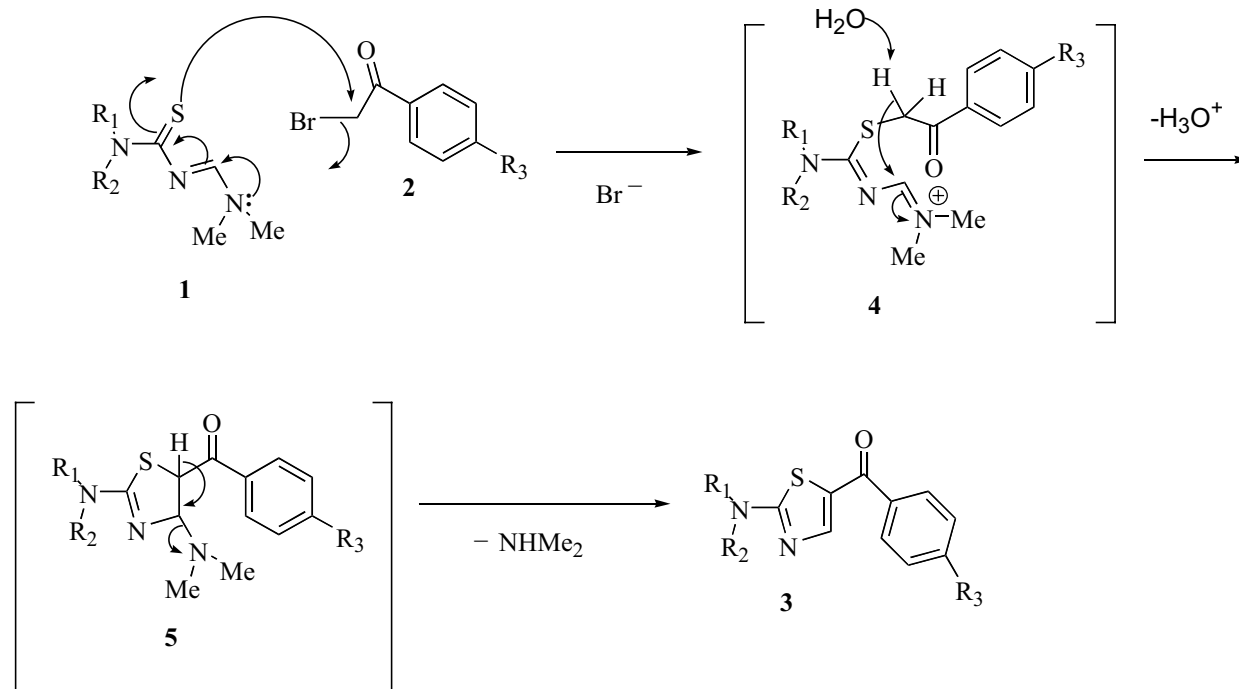
Figure 2. ORTEP of compound (**3b**)



Figure 3. ORTEP of compound (**3c**)

A possible mechanism for the formation of compounds (**3a-q**) is described in Scheme 2. The first step involves a S_N2 reaction involving the attack of the sulfur atom of a sulfuracylamidine (**1**) onto the α-

position of carbonyl carbon of **2** with the concomitant loss of Br⁻. The resulting adduct (**4**) then cyclizes to **5** from which dimethyl amine is eliminated to give the 5-acyl-2-amino-1,3-thiazole derivative (**3**).



Scheme 2

Conclusions

In this study, 2-amino-5-benzoyl-1,3-thiazoles and 5-acyl-2-amino-1,3-thiazoles were prepared in high yields by a one-pot reaction of thiazadienes and the appropriate α -halo ketones. The yields of the previously reported synthesis of 1,3-thiazoles were lower (significantly lower in some cases) than those reported here presumably due to the use of an additional base-mediated refluxing step in the latter. In that second step, undesired side reactions of starting materials, intermediates, or products presumably occur.

EXPERIMENTAL

General Data Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. ¹H NMR and ¹³C NMR spectra were recorded on a 400 MHz Bruker AVANCE DRX-400 Multi-nuclear NMR spectrometer. Chemical shifts are reported in reference to TMS as internal standard. Elemental analyses were carried out in the SMU Analytical Laboratory. The glassware was heated overnight in an oven at 125 °C prior to use. All the reactions were done under an atmosphere of dry O₂-free Ar *via* balloon.

General Procedure for the Synthesis of 5-Benzoyl-2-(piperidin-1-yl)-1,3-thiazole (**3a**)

2-Bromoacetophenone (**2a**) (0.75g, 3.8 mmol) was added to a stirred solution of N¹,N¹-dimethyl-N²-piperidinothiacarbonylformamidine (0.53 g, 2.5 mmol) in anhydrous tetrahydrofuran (50 mL) at rt under argon. The reaction mixture was refluxed for 2 h then cooled to rt during which time a solid appeared.

After the solvent was removed by distillation, the remaining solid was dissolved in water and stirred for 5 min. The mixture was extracted with ethyl acetate (2 X 50 mL) and the combined ethyl acetate extracts were washed with water (50 mL). The organic layer was separated, dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography on silica gel with cyclohexane: ethyl acetate (6:4) to give 5-benzoyl-2-(piperidine-1-yl)-1,3-thiazole (**3a**) (0.70g, 97%) as white crystals, mp 117–118 °C. ^1H NMR (400 MHz, CDCl_3) δ 1.73 (m, 6H), 3.65 (m, 4H), 7.49 (m, 2H), 7.55 (m, 1H), 7.72 (s, 1H), 7.79 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.3 (t), 25.5 (t), 50.0 (t), 128.3 (s), 128.8 (d), 128.9 (d), 132.0 (d), 139.0 (s), 151.3 (d), 175.7 (s), 187.0 (s). *Anal.* Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$: C, 66.15; H, 5.92; N, 10.29. Found: C, 66.39; H, 5.81; N, 10.30.

5-Benzoyl-2-(morpholin-1-yl)-1,3-thiazole (**3b**)

Colorless crystals, mp 144–145 °C (hexane/ CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 3.66 (m, 4H), 3.85 (m, 4H), 7.51 (m, 2H), 7.57 (m, 1H), 7.75 (s, 1H), 7.79 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 48.6 (t), 66.3 (t), 128.8 (d), 129.0 (d), 129.4 (s), 132.2 (d), 138.7 (s), 150.6 (d), 173.6 (s), 187.1 (s). *Anal.* Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.59; H, 5.14; N, 10.17.

5-Benzoyl-2-*N,N*-dimethylamino-1,3-thiazole (**3c**)

Light brown crystals, mp 72–73 °C (hexane/ CHCl_3) (lit.,⁹ 38–40 °C). ^1H NMR (400 MHz, CDCl_3) δ 3.25 (s, 6H), 7.49 (m, 2H), 7.57 (m, 1H), 7.75 (s, 1H), 7.79 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 40.7 (q), 128.8 (d), 128.9 (d), 129.1 (s), 132.0 (d), 138.9 (s), 151.3 (d), 174.2 (s), 187.0 (s). *Anal.* Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{OS}$: C, 62.04; H, 5.21; N, 12.06. Found: C, 62.01; H, 5.18; N, 11.87.

5-Benzoyl-2-*N,N*-diethylamino-1,3-thiazole (**3d**)

Colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 1.31 (t, $J = 7.1$ Hz, 6H), 3.61 (q, $J = 6.7$ Hz, 4H), 7.48 (m, 2H), 7.56 (m, 1H), 7.73 (s, 1H), 7.79 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 12.8 (q), 46.4 (t), 128.2 (d), 128.8 (d), 128.9 (d), 131.9 (s), 139.1 (s), 151.5 (d), 174.5 (s), 186.9 (s). *Anal.* Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{OS}$: C, 64.58; H, 6.19; N, 10.76. Found: C, 64.30; H, 6.24; N, 10.46.

5-Benzoyl-2-*N,N*-diisopropylamino-1,3-thiazole (**3e**)

Light yellow crystals, mp 82–84 °C (hexane/ CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 1.50 (t, $J = 6.7$ Hz, 12H), 4.03 (dd, $J = 13.1, 6.6$ Hz, 2H), 7.47 (m, 2H), 7.55 (m, 1H), 7.74 (s, 1H), 7.79 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 20.2 (q), 52.0 (d), 126.9 (s), 128.7 (d), 128.8 (d), 131.8 (d), 139.3 (s), 151.4 (d), 173.4 (s), 186.9 (s). *Anal.* Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{OS}$: C, 66.63; H, 6.99; N, 9.71. Found: C, 66.76; H, 7.04; N, 9.63.

5-(4'-Chlorobenzoyl)-2-piperidin-1,3-thiazole (**3f**)

Colorless crystals, mp 158–159 °C (hexane/ CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 1.66 (m, 6H), 3.65 (m, 4H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.69 (s, 1H), 7.74 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 24.2 (t),

25.5 (t) 50.0 (t), 127.9 (s), 129.0 (d), 130.3 (d), 137.3 (s), 138.1(s), 151.3 (d), 175.6 (s), 185.3 (s). Cl₃) δ
Anal. Calcd for C₁₅H₁₅N₂O₂ClS: C, 58.72; H, 4.93; N, 9.13. Found: C, 58.61; H, 4.92; N, 8.95.

5-(4'-Chlorobenzoyl)-2-(morpholin-1-yl)-1,3-thiazole (3g)

Colorless crystals, mp 180–181 °C (hexane/ CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 3.66 (m, 4H), 3.85 (m, 4H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.72 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 48.7, 66.3, 129.0, 129.2, 130.3, 137.0, 138.7, 150.6, 175.9, 185.6. *Anal.* Calcd for C₁₄H₁₃N₂O₂Cl S: C, 54.46; H, 4.24; N, 9.07. Found: C, 54.61; H, 4.26; N, 9.09.

5-(4'-Chlorobenzoyl)-2-*N,N*-dimethylamino-1,3-thiazole (3h)

Colorless crystals, mp 124–125 °C (hexane/ CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 3.25 (s, 6H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.72 (s, 1H), 7.74 (d, *J* = 8.3 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 40.6 (q), 128.6 (s), 129.0 (d), 130.2 (d), 137.2 (s), 138.0 (s), 151.2 (d), 175.7 (s), 185.1 (s). *Anal.* Calcd for C₁₂H₁₁N₂OClS: C, 54.03; H, 4.16; N, 10.50. Found: C, 54.45; H, 4.12; N, 10.50.

5-(4'-Chlorobenzoyl)-2-*N,N*-diethylamino-1,3-thiazole (3i)

Colorless crystals, mp 85–86 °C (hexane/ CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 1.31 (t, *J* = 7.1 Hz, 6H), 3.60 (q, *J* = 6.9 Hz, 4H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.70 (s, 1H), 7.74 (d, *J* = 8.1 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 12.7 (q), 46.4 (t), 127.7 (s), 129.0 (d), 130.2 (d), 137.3 (s), 138.0 (s), 151.4 (d), 174.4 (s), 185.1 (s). *Anal.* Calcd for C₁₄H₁₅N₂OClS: C, 57.04; H, 5.13; N, 9.50. Found: C, 57.56; H, 4.9; N, 9.47.

5-(4'-Chlorobenzoyl)-2-*N,N*-diisopropylamino-1,3-thiazole (3j)

Light yellow crystals, mp 109–110 °C (hexane/ CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 1.51 (t, *J* = 6.7 Hz, 12H), 4.03 (dd, *J* = 13.1, 6.6 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.71 (s, 1H), 7.74 (d, *J* = 8.3 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 20. (q), 52.1 (d), 126.5 (s), 128.9 (d), 130.2 (d), 137.5 (s), 137.8 (s), 151.3 (d), 173.4 (s), 185.1 (s). *Anal.* Calcd for C₁₆H₁₉N₂OClS: C, 59.52; H, 5.93; N, 8.68. Found: C, 59.88; H, 5.94; N, 8.64.

5-(4'-Methoxybenzoyl)-2-(piperidine-yl)-1,3-thiazole (3k)

Colorless crystals, mp 131–132 °C (hexane/ CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 1.73 (m, 6H), 3.64 (m, 4H), 3.89 (s, 3H), 6.98 (d, *J* = 8.6 Hz, 2H), 7.73 (s, 1H), 7.81 (d, *J* = 8.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 24.3 (d), 25.5 (d), 49.9 (d), 55.7 (q), 114.0 (d), 128.4 (s), 131.0 (d), 131.5 (s), 150.2 (d), 162.9 (s), 175.3 (s), 185.6 (s). *Anal.* Calcd for C₁₆ H₁₈N₂ O₂S: C, 63.55; H, 6.00; N, 9.26. Found: C, 63.56; H, 6.03; N, 9.23.

5-(4'-Methoxybenzoyl)-2-(morpholin-1-yl)-1,3-thiazole (3l)

Colorless crystals, mp 166–167 °C (hexane/ CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 3.65 (m, 4H), 3.85 (m, 4H), 3.91 (s, 3H), 6.99 (d, *J* = 8.6 Hz, 2H), 7.76 (s, 1H), 7.83 (d, *J* = 8.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 48.6 (d), 55.8 (q), 66.3 (t), 114.1 (d), 129.6 (s), 131.2 (d), 149.4 (d), 163.1 (s), 175.5 (s), 185.8 (s). *Anal.* Calcd for C₁₅H₁₆N₂O₃S: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.21; H, 5.30; N, 9.08.

5-(4'-Methoxybenzoyl)-2-*N,N*-dimethylamino-1,3-thiazole (3m)

Colorless crystals, mp 105-106 °C (hexane/ CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 3.24 (s, 6H), 3.90 (s, 3H), 6.98 (d, *J* = 6.8 Hz, 2H), 7.76 (s, 1H), 7.82 (d, *J* = 6.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 40.6 (q), 55.8 (q), 114.1 (d), 129.3 (s), 131.1 (d), 131.5 (s), 150.2 (d), 163.0 (s), 175.5 (s), 185.8 (s). Anal. Calcd for C₁₃H₁₄N₂O₂S: C, 59.52; H, 5.38; N, 10.68. Found C, 59.76; H, 5.42; N, 10.57.

5-(4'-Methoxybenzoyl)-2-*N,N*-diethylamino-1,3-thiazole (3n)

Colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 1.31 (t, *J* = 7.0 Hz, 6H), 3.60 (q, *J* = 6.8 Hz, 4H), 3.89 (s, 3H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.70 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 12.7 ((q), 46.4 (t), 55.8 (q), 114.0 (d), 128.3 (s), 131.0 (d), 131.6 (s), 150.4 (d), 162.9 (s), 174.1(s), 185.7 (s). Anal. Calcd for C₁₅H₁₈N₂O₂S: C, 62.04; H, 6.25; N, 9.65. Found: C, 62.51; H, 6.25; N, 9.36.

5-(4'-Methoxybenzoyl)-2-*N,N*-diisopropylamino-1,3-thiazole (3o)

Colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 1.43 (t, *J* = 6.8 Hz, 12H), 3.89 (s, 3H), 4.03 (dd, *J* = 13.2, 6.6 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 7.74 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 20.2 (q), 51.9 (d), 55.8 (q), 114.0 (d), 127.0 (s), 131.0 (d), 131.8 (s), 150.3 (d), 162.8 (s), 173.1(s), 185.8 (s). Anal. Calcd for C₁₇H₂₂N₂O₂S: C, 64.12; H, 6.96; N, 8.80. Found: C, 64.44; H, 6.85; N, 8.31.

5-Acetyl-2-*N,N*-dimethylamino-1,3-thiazole (3p)

Light brown crystals, mp 98 °C (hexane/ CHCl₃) (lit.,⁹96–98 °C). ¹H NMR (400 MHz, CDCl₃) δ 2.42 (s, 3H), 3.20 (s, 6H), 7.82 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 26.1 (q), 40.6 (q), 129.5 (s), 148.8 (d), 175.8 (s), 189.2 (s). Anal. Calcd for C₇H₁₀N₂OS: C, 49.39; H, 5.92; N, 16.46. Found: C, 50.08; H, 5.98; N, 16.38.

5-Acetyl-2-*N,N*-diethylamino-1,3-thiazole (3q)

Colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 1.27 (t, *J* = 7.1 Hz, 6H), 2.44 (s, 3H), 3.55 (q, *J* = 6.8 Hz, 4H), 7.81 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 12.6 (q), 26.0 (q), 46.3 (t), 128.5 (s), 149.0 (d), 174.4 (s), 189.1 (s). Anal. Calcd for C₉H₁₄N₂OS: C, 54.52; H, 7.12; N, 14.13. Found: C, 53.23; H, 7.09; N, 13.49.

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