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

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

INTRODUCTION

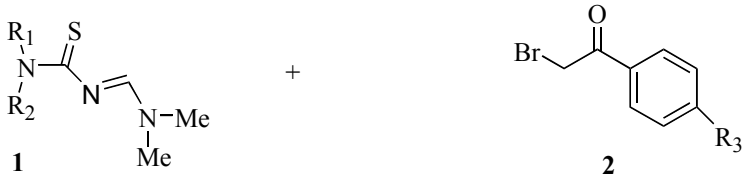
Substituted 1,3-thiazoles are ubiquitous structural motifs found in several compounds of biological interest. For example, 2-dialkyl-1,3-thiazoles serve as key intermediates in the synthesis of biologically interesting and pharmaceutically useful molecules such as dipeptidyl peptidase IV (DPP-IV) inhibitors, 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□ dienophile intermediates for [4+2] cycloadditions. For example, □,□-unsaturated thiaaldehydes and thiaketones selectively under go '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 Hartman[9] 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 quench 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.



1

2

a) R_1=R_2= -$(CH_2)_5$, R_3=H

b) R_1=R_2=-$CH_2)_2$-O-$(CH_2)_2$, R_3=H

c) R_1=R_2= Me, R_3=H

d) R_1=R_2= Et, R_3=H

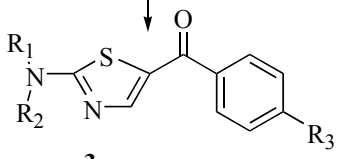
e) R_1=R_2= -CH-$(CH_2)_4$-CH-, R_3=H

1. anhydrous THF
reflux, 2h
2. H_2O

a) R_3 =H

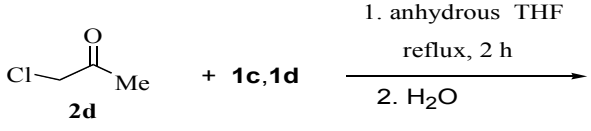
b) R_3 = Cl

c) R_3 = OMe



3a-q

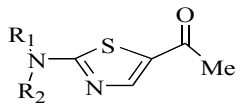
	Yield (%)		Yield (%)
a) R_1=R_2= -$(CH_2)_5$, R_3=H	97	**i**) R_1=R_2= Et, R_3=Cl	99
b) R_1=R_2=-$CH_2)_2$-O-$(CH_2)_2$, R_3=H	97	**j**) R_1=R_2= -CH-$(CH_2)_4$-CH-, R_3=Cl	98
c) R_1=R_2=Me, R_3=H	98	**k**) R_1=R_2= -$(CH_2)_5$, R_3=OMe	98
d) R_1=R_2= Et, R_3=H	96	**l**) R_1=R_2= -$(CH_2)_2$-O-$(CH_2)_2$, R_3=OMe	96
e) R_1=R_2= -CH-$(CH_2)_4$-CH-, R_3=H	96	**n**) R_1=R_2= Me, R_3=OMe	89
f) R_1=R_2= -$(CH_2)_5$, R_3=Cl	93	**m**) R_1=R_2= Et, R_3=OMe	96
g) R_1=R_2=-$(CH_2)_2$-O-$(CH_2)_2$, R_3=Cl	97	**o**) R_1=R_2= -CH-$(CH_2)_4$-CH-, R_3=OMe	93
h) R_1=R_2= Me, R_3=Cl	98		



2d

+ **1c**,**1d**

1. anhydrous THF
reflux, 2 h
2. H_2O



3p,3q

p) R_1=R_2= Me, 98

q) R_1=R_2= Et 97

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, ^{1}H NMR, ^{13}C 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]

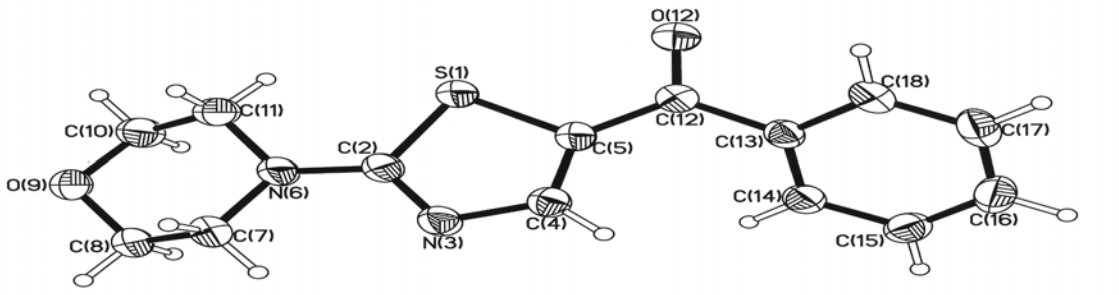


Figure 1. ORTEP of compound (**3a**)

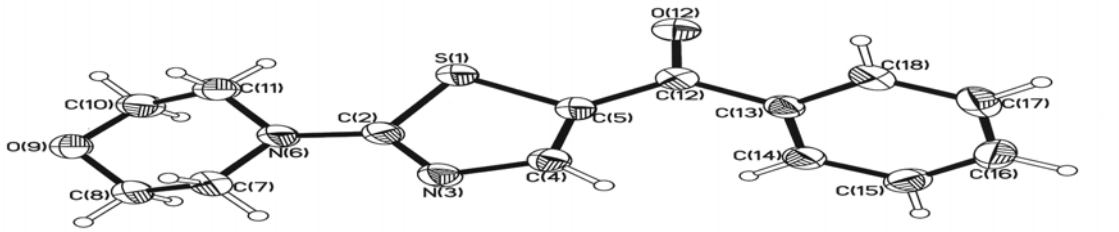


Figure 2. ORTEP of compound (**3b**)

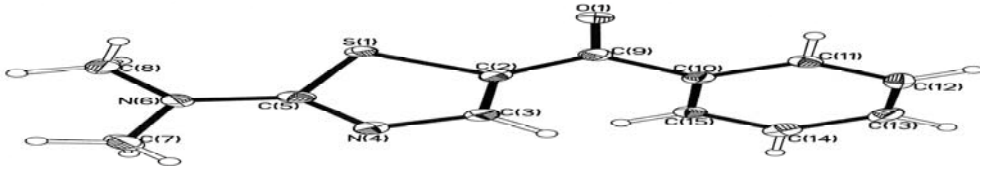
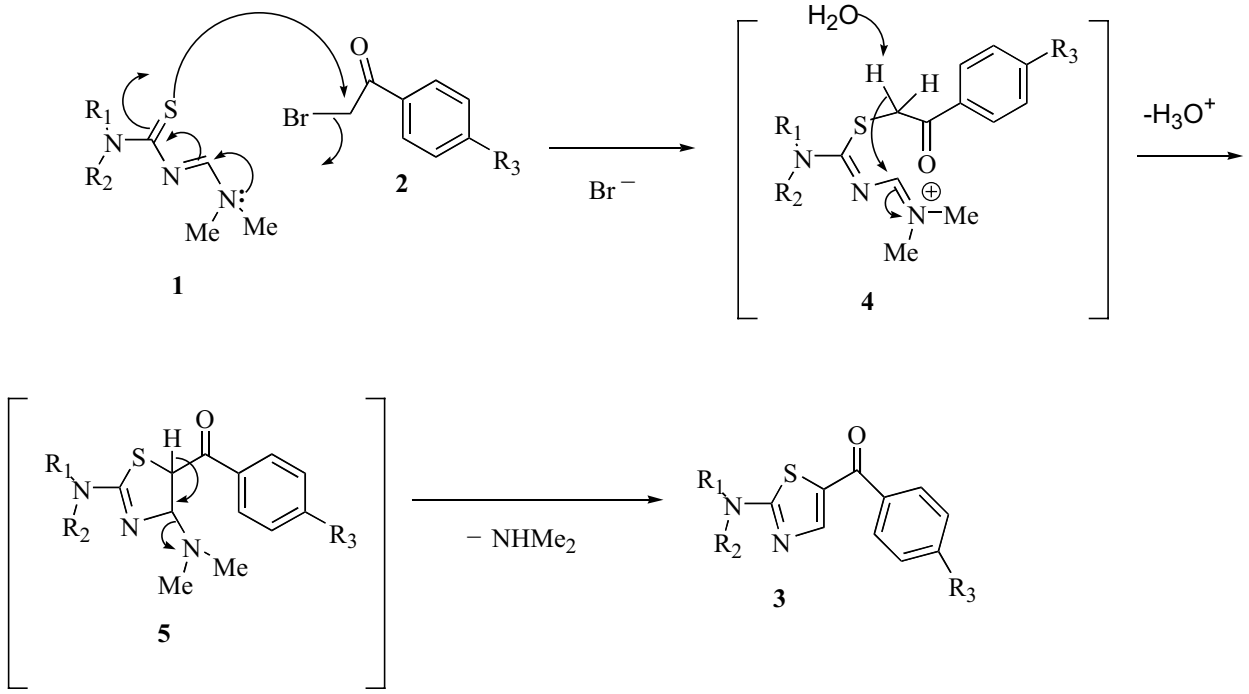


Figure 3. ORTEP of compound (**3c**)

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 thiaazadienes 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. ^{1}H NMR and ^{13}C 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 O_2–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 N^1,N^1-dimethyl-N^2-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. ^{1}H 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 $C_{15}H_{16}N_2O$: 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/ $CHCl_3$). ^{1}H 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 $C_{14}H_{14}N_2O_2S$: 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). ^{1}H 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 $C_{12}H_{12}N_2OS$: 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. ^{1}H 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 $C_{14}H_{16}N_2OS$: 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/ $CHCl_3$). ^{1}H 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 $C_{16}H_{20}N_2OS$: 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/ $CHCl_3$). ^{1}H 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, CD24.2 (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). Cl_3) δ *Anal*. Calcd for $C_{15}H_{15}N_2O_2Cl$ S: 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/ $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.7 , 66.3, 129.0, 129.2, 130.3, 137.0, 138.7, 150.6, 175.9, 185.6. *Anal*. Calcd for $C_{14}H_{13}N_2O_2Cl$ 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/ $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$). 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 $C_{12}H_{11}N_2OClS$: 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/ $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$). 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 $C_{14}H_{15}N_2OClS$: 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/ $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (t, *J* = 6.7 Hz, 12H), 4.03 (dd, *J* = 13.1, 6.6 Hz, 2H), 7.45 (d, *J* = 8.3Hz, 2H), 7.71 (s, 1H), 7.74 (d, J = 8.3Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{19}N_2OClS$: 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/ $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{18}N_2O_2S$: 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/ $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{15}H_{16}N_2O_3S$: 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/ $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{13}H_{14}N_2O_2S$: 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, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{15}H_{18}N_2O_2S$: 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, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$). 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 $C_{17}H_{22}N_2O_2S$: 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/ $CHCl_3$) (lit.,[9] 96–98 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.20 (s, 6H), 7.82 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1 (q), 40.6 (q), 129.5 (s), 148.8 (d), 175.8 (s), 189.2 (s). *Anal.* Calcd for $C_7H_{10}N_2OS$: 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, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_9H_{14}N_2OS$: C, 54.52; H, 7.12; N, 14.13. Found: C, 53.23; H, 7.09; N,13.49.

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REFERENCES

1. (a) M. Boehringer, D. Hunziker, H. Kuehne, B. M. Loeffler, R. Sarabu, and H. P. Wessel, Patent Wo 031037327 A1, 2003 (*Chem. Abstr.*, 2003, **138**, 368754); (b) A. T. Bach, P. K. Kapa, G. T. Lee, E. M. Loeser, M. L. Sabio, J. L. Stanton, and T. R. Vedananda, Patent Wo 031043985 A1, 2003 (*Chem. Abstr.,* 2003, **139**, 6767); (c) Y. Momose, T. Maekawa, and T. Yamano, *J. Med. Chem.,* 2002**, 45**, 1518; (d) R. J. Deorazio, S. S. Nikam, I. L. Scott, and B. A. Sherer, European Patent Ep1, 251128 A1, 2002 (*Chem. Abstr.*, 2002, **137**, 310908); (e) Y. Momose, T. Maekawa, H. Odaka, H.

Ikeda, and T. Sohda, *Chem. Pharm. Bull*., 2002, **50**, 100; (f) S. Takano, H. Imaizumi, T. Kajita, K. Takasima, K. Takezawa, M. Yotsutsuji, T. Hoda, A. Yotsutsuji, and H. Sakai, *Jpn. Kokai Tokyo Koho JP* 62178590, 1987 (*Chem. Abstr.,* 1988, **108**, 112450).

2. (a) H. H. Ruettinger, H. Dehne, and W. Schroth, *Pharmazie,* 1976**, 31***,* 218; (b) K. Hirai, H. Sugimoto, and T. Ishiba, *J. Org. Chem.,* 1980**, 45***,* 253.
3. (a) N. Antje and H. Horst, *Tetrahedron*, 2002, **58**, 21 37; (b) D. Kikelj and U. Urleb, *Synthesis,* 2002**, 11***,* 627.
4. (a) K. M. Marcantonio, L. F. Frey, J. A. Murry, and C. Chen, *Tetrahedron Lett.,* 2002, **43***,* 8845; (b) L. F. Frey, K. M. Marcantonio, C. Chen, D. J. Wallace, J. A. Murry, L. Tan, W. Chen, U. H. Dolling, and E. J. J., *Tetrahedron,* 2003, **59***,* 6363; (c) J. Lau, I. T. Christensen. P. B. Madsen, P. Bloch, C. Behrens, J. K. Kodra, and P. E. Nielsen, *PCT. Int. Appl.* 2004, W0 2004002480, *A1 20040108,* 210.
5. For reviews, see: (a) A. Dondoni and P. Merino, *Comprehensive Heterocyclic Chemistry II*, I. Shinkai, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Elsevier,Tarrytown, 1996, **3**, 373; (b) J. V. Metzger, *Comprehensive Heterocyclic Chemistry*; K. T. Potts, ed. by A. R. Katritzky and C. W. Rees, Pergamon, Elmsford, 1984, **6**, 235; (c) G. Vernin, *The Chemistry of Heterocyclic Compounds*; J. V. Metzger, ed. by A. Weissberger and E. C. Taylor, John Wiley & Sons, New York, 1979, **34**, Part 1.
6. (a) M. Al-Hariri, K. Joure, F. Pautet, M. Domard, B. Fenet, and H. Fillion, *J. Org., Chem.,* 1997, **62**, 405; (b) M. Al Hariri, O. Galley, F. Pautet, and H. Fillion, *Eur. J. Org. Chem.,* 1998, 593; (c) K. Jouve, F. Pautet, M. Domard, and H. Fillion, *Chem. Pharm. Bull*. 1999, **47**, 1064.
7. (a) M. Segi, M. Takahashi, T. Nakajima, and S. Suga, *Synth. Commun.,* 1989**, 19***,* 2431; (b) G. M. Li, S. Niu, M. Segi, K. Tanaka, T. Nakajima, R. A. Zingaro, J. H. Reibenspies, and M. B. Hall, *J. Org. Chem.,* 2000, **65***,* 6601.
8. (a) C. T. Gokou, T. P. Pradere, and H. Quiniou, *J. Org. Chem.,* 1985**, 50***,* 1545; (b) A. Harrison-Marchand, S. Collet, A. Guingant, J. P. Pradere, and L. Toupet, *Tetrahedron*, 2004, **60***,* 1827; (c) G. Trippe, J. Perron, A. Harrison-Marchand, V. Dupont, A. Guingant, J. P. Pradere, and L. Toupet, *Tetrahedron Lett*. 2002, **43**, 6067.
9. A. Noack and H. Hartman, *Tetrahedron,* 2002, **58**, 2137.
10. This results of this work was presented at the *60th American Chemical Society, Southwest Regional Meeting of the American Chemical Society*, Fort Worth, TX, U. S. A., 29 September–2 October, 2004.
11. R. Sathunuru and E. Biehl, *ARKIVOC*, 2004, (**IV**) 51.