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Efficient Synthesis of 5*H*-Thiazolo[3,2-*a*]pyrimidines from Reactions of 3,4-Dihydropyrimidine-thiones with α-Bromoacetone in Aqueous Media

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ABSTRACT: *An efficient and convenient method for thiazolo[3,2-a]pyrimidines from cyclization reaction of dihydropyrimidine-thiones with α-bromoacetone in aqueous media is described.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:149–153, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20386

INTRODUCTION

Although the acid-catalyzed one-pot condensation of aldehyde, ketoester, and urea (or thiourea) to afford 3,4-dihydropyrimidinone (DHPM), named as the Biginelli reaction after the name of its inventor, has been known for more than a century [1], the Biginelli-type 3,4-dihydropyrimidinones (DHPMs) were largely ignored in the early part of the 20th century [2]. In the past decades, the scope of the original cyclocondensation reaction was gradually extended by variation of all three building blocks, allowing access to a large number of structurelly diversified multifunctionalized DHPMs [3]. These nonplanar heterocyclic compounds have received considerable attention from the pharmaceutical industry because of their interesting multifaceted pharmacological profiles. Synthesis of DHPMs resulted in the discovery of calcium channel modulators, α_{1a}-adrenergic receptor antagonists, mitotic kinesin inhibitors, and hepatitis B virus replication inhibitors [4]. Furthermore, apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the DHPM core have recently been isolated [5]. Among these compounds, the batzelladine alkaloids A and B inhibit the binding of HIV gp120 human CD4 and, therefore, are potential new leads for AIDS therapy [6].

Among the synthetic and natural products containing DHPMs core, thiazolo[3,2-*a*]pyrimidine derivatives (**1**) are of interesting compounds because of their calcium channel blocking activity [3b]. Few methods have been contributed for the preparation of thiazolo[3,2-*a*]pyrimidine derivatives, and

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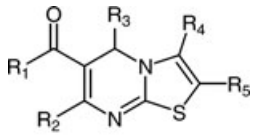

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FIGURE 1 Thiazolo[3,2-*a*]pyrimidine derivatives.

the existed methodologies required prolonged reaction times and strict reaction conditions in organic solvents [7,8]. Mishina et al. have completed the preparation of thiazolo[3,2-*a*]pyrimidines **1** (Fig. 1) by the reaction of enones with 2-aminothiazole in ethanol under refluxing for 2 days [7]. Recently, Balkan et al. have completed the synthesis of these compounds by refluxing 2-thioxo-1,2,3,4-tetrahydropyrimidine derivatives with phenacyl bromide in glacial acetic acid [8]. More recently, the reaction of dihydropyrimidine-2-thiones with α-bromophenylacetaldehyde in acetonitrile to afford thiazolo[3,2-*a*]pyrimidines has also been reported [9]. However, in spite of their potential utility in the preparation of this type of compounds, many of these methods involve organic solvent, long-reaction times, and unsatisfactory yields. Furthermore, to the best of our knowledge, there has been no report on the synthesis of thiazolo[3,2-*a*]pyrimidine analogs by the reaction of DHPMs with α-bromoacetone in aqueous media.

The use of water as a medium in organic reaction has received considerable attention because of its several advantages, such as it is the cheapest solvent available on the earth, nonhazardous to the environment, and nontoxic, and isolation of the organic products can be performed by simple phase separation. Also, there are beneficial effects of aqueous solvents on the rates and selectivity of important organic transformations, for example, the Diels–Alder reaction, aldol reaction, and Michael addition [10,11].

We herein report a methodology to efficiently prepare 5*H*-thiazolo[3,2-*a*]pyrimidines through a cyclization reaction of 3,4-dihydropyrimidine-2-thione and α-bromoacetone in aqueous media.

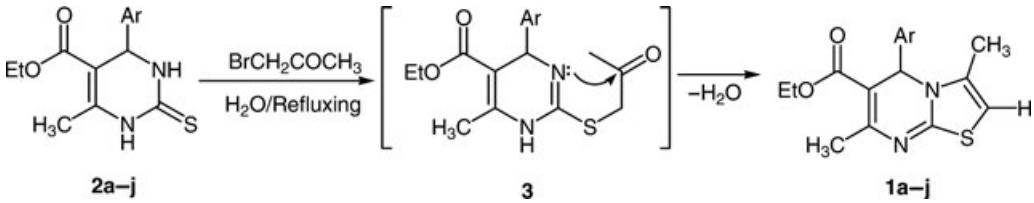
TABLE 1 Crystal and Experimental Data for Compound **1h**

Compound	**1h**
Formula	$C_{17}H_{17}ClN_2O_2S$
Formula weight	348
Crystal system	Monoclinic
Space group	*C* 2/*c*
Unit-cell dimensions (Å)	$a = 25.457(2)$, $b = 11.697(2)$, $c = 14.231(3)$
	$\alpha = 90.00^\circ$, $\beta = 106.808(16)^\circ$, $\gamma = 90.00^\circ$
Unit-cell volume, V (Å^3)	4056.54 (1964)
Formula per unit cell, Z	4
Calc. density D_{calcd} (g/cm^3)	1.296

RESULTS AND DISCUSSION

To study the reaction for thiazolo[3,2-*a*]pyrimidines **1**, we tested the reaction of **1a** with α-bromoacetone as simple model substrate and the results are shown in Table 1. First, α-bromoacetone was used in a molar excess (2:1) to test the reaction in the presence of K_2CO_3 as a base in refluxing water for 4 h. ^{1}H NMR and mass spectrometry indicated that during this reaction the desired product **1a** was obtained with good yield (90%). After experimentation with a variety of molar material, bases, temperatures, and reaction times, we quickly arrived at conditions where complete and clean conversion of the model substrate DHPM **1a** with α-bromoacetone could be achieved within 4 h under refluxing water. These optimized conditions were equal amount of starting material **1** and α-bromoacetone in refluxing water for 4 h.

Under the optimized conditions, 3,4-dihydropyrimidine-2-thiones (**2**) were treated with α-bromoacetone in refluxing water for 4 h to give thiazolo[3,2-*a*]pyrimidines (**1a–j)** in good yields (Scheme 1). To compare this procedure with the conventional method in organic solvent, we carried out the reaction for **1** by previously mentioned materials in acetone. This reaction can also be completed smoothly to afford the desired products. These results are listed in Table 1. It can be indicated that water is the optical solvent in this reaction from the environment friendly point of view.



2a–j **3** **1a–j**

SCHEME 1 Synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidines **1a–j** in water.

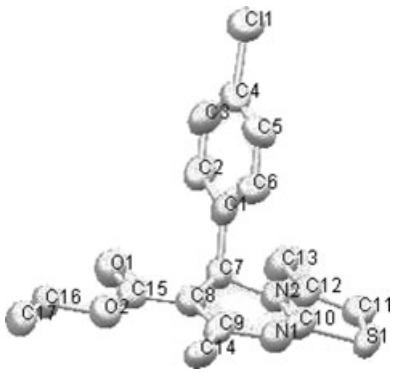


FIGURE 2 The ORTEP representation of the **1h**.

All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analyses. Comparing the ^{1}H NMR spectra with the data of DHPMs **2** and relative cyclization products **1** shows that peaks corresponding to the proton of *N*1 around δ 7.80 and *N*3 around δ 6.30 disappeared at the same time as the presence of the peaks corresponded to the proton of C=CH around δ 7.08. Meanwhile, the C_4–H comes as a singlet around δ 6.30 in the products, which is around δ 5.30 in DHPMs. The most distinct signal between IR absorption of DHPMs **2** and products thiazolo[3,2-*a*]pyrimidines **1** is the disappearance of two absorption around 3320 and 3118 cm^{-1}, with the disappearance of absorption bands around 1680 cm^{-1} corresponding to C=O. The single crystal X-ray crystallography of product **1h** also confirmed the structures of obtained products (Fig. 2; Tables 1 and 2). Crystallographic data for the structure analysis have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication (for **1h** CCDC No. CCDC 651561).

In this reaction, the nucleophilic addition of sulfur of dihydropyrimidine-thione to the α-position of α-bromoacetone gave **3**, followed by addition–elimination to give dihydropyrimidine-fused thiazole **1** (Table 3). The regioselectivity of the addition-cyclization step maybe due to a difference in the electron density at *N*3 and *N*1 position of 3,4-dihydropyrimidine-thione. The higher basisity of the former resulted in exclusive addition–cyclization at this position [12]. Our previous study also confirmed that the *N*3 atom possess higher reactivity than the *N*1 atom [13]. Moreover, it has been reported that 3,4-dihydropyrimidine-thiones reacted with 1,2-dichloroethane, affording thiazolo[3,2-*a*]pyrimidines [14].

In summary, 5*H*-thiazolo[3,2-*a*]pyrimidine can be efficiently prepared by the reaction of dihydropyrimidine-2-thione with α-bromoacetone only in water medium. The easy and efficacy of this method provides an attractive route to the synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidine derivatives. To the best of our knowledge, there has not been any report on the preparation of 5*H*-thiazolo[3,2-*a*]pyrimidine derivatives through the reaction of dihydropyrimidine-thione with α-bromoacetone, using water as the only solvent.

EXPERIMENTAL

All reagents were obtained commercially and used without further purification. Melting points were determined on an XT-4 electrothermal micromelting

TABLE 2 Bond Lengths (Å) and Angles (°) for Compound **1h**

C1–C2	1.397(6)	C8–C15	1.488(5)	C13–H13A	0.9600
C1–C6	1.381(5)	C9–N1	1.450(5)	C13–H13B	0.9600
C1–C7	1.587(5)	C9–C14	1.484(6)	C13–H13C	0.9600
C2–C3	1.374(6)	C10–N1	1.332(5)	C14–H14A	0.9600
C3–C4	1.398(6)	C10–N2	1.359(5)	C14–H14B	0.9600
C4–C5	1.395(6)	C10–S1	1.799(4)	C14–H14C	0.9600
C4–Cl1	1.781(4)	C11–C12	1.407(6)	C15–O1	1.241(4)
C5–C6	1.388(5)	C11–S1	1.801(4)	C15–O2	1.355(5)
C7–C8	1.538(5)	C12–N2	1.438(5)	C16–C17	1.503(5)
C7–N2	1.521(5)	C12–C13	1.504(5)	C16–O2	1.514(4)
C8–C9	1.414(5)				
C2–C1–C7	119.4(4)	C8–C9–N1	116.6(3)	N2–C7–C1	108.1(3)
C3–C2–C1	120.3(4)	C8–C9–C14	131.3(4)	C8–C7–C1	111.4(3)
C2–C3–C4	120.2(4)	N1–C10–N2	124.2(4)	C9–C8–C15	124.8(3)
C5–C4–C3	119.4(4)	N1–C10–S1	126.1(3)	C9–C8–C7	123.2(3)
C5–C4–Cl1	118.4(3)	N2–C10–S1	109.7(3)	C15–C8–C7	111.9(3)
C3–C4–Cl1	122.2(4)	C12–C11–S1	109.4(3)	O1–C15–O2	123.2(4)
C6–C5–C4	120.1(4)	C11–C12–N2	112.9(4)	O1–C15–C8	121.1(4)
C1–C6–C5	120.2(4)	C11–C12–C13	126.4(4)	O2–C15–C8	115.6(3)
C6–C1–C2	119.9(4)	N2–C12–C13	120.7(3)	C17–C16–O2	109.6(3)
C6–C1–C7	120.7(3)	N2–C7–C8	109.1(3)	C10–S1–C11	91.78(19)

TABLE 3 Synthesis of 5*H*-Thiazolo[3,2-*a*]pyrimidines **1a–j** in Water and Acetone

		Yield (%)[a]	
Product	**Ar**	*In Water*[b]	*In Acetone*[c]
1a	C_6H_5	89	91
1b	4-HOC_6H_4	85	86
1c	2-$CH_3OC_6H_4$	85	88
1d	4-$CH_3OC_6H_4$	94	93
1e	4-$NO_2C_6H_4$	81	82
1f	3-$NO_2C_6H_4$	83	86
1g	4-ClC_6H_4	84	86
1h	2-ClC_6H_4	86	88
1i	4-$CH_3C_6H_4$	90	90
1j	2-$CH_3C_6H_4$	92	92

[a]Determined based on DHPMs and on weight of isolated sample.
[b]Obtained by the reaction of DHPM with α-bromoacetone in water.
[c]Obtained by the reaction of DHPM with α-bromoacetone in acetone at 50°C for 4 h.

point apparatus and uncorrected. IR spectra were recorded using KBr pellets on a Digilab Merlin FT-IR spectrophotometer. NMR spectra were recorded at 400 (^{1}H) and 100 (^{13}C) MHz, respectively, on a Varian Mercury plus-400 instrument using $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal standard. Elemental analyses were performed on a Carlo-Erba 1106 elemental analysis instrument. Mass-spectra were recorded on a ZAB-HS instrument. Compounds **2a–j** were prepared by following the reported method [15].

Experimental Procedure

Bromoacetone (1.5 mmol) was added to a suspension of 3,4-dihydropyrimidine-thione **2a–j** (1 mmol) in water (5 mL). After the reaction mixture was stirred under refluxing for 4 h, the resulting mixture was cooled to room temperature. Then, the precipitate was filtered and washed with aqueous solution of NaOH (1%) and subsequently with water. The solid was recrystallization from ethanol–acetone to give a pure product in high yield.

*6-Ethoxycarbonyl-7-methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidine (**1a**)*

mp 242–243°C. IR (KBr) ν: 3106, 2986, 1668, 1572, 1602, 1491, 1242; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.30$ (t, $J = 7.2$ Hz, 3H), 2.26 (s, 3H), 2.63 (s, 3H), 4.16–4.28 (m, 2H), 6.33 (s, 1H), 7.05 (s, 1H), 7.27 (dd, $J = 6.0$ Hz, $J = 3.6$ Hz, 2H), 7.33 (dd, $J = 6.4$ Hz, $J = 3.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.49$, 14.15, 18.34, 59.09, 61.25, 102.93, 110.34, 126.67, 129.39, 129.63, 136.22, 139.08, 143.11, 160.57, 164.41; MS (FAB): $m/z = 315$ (M + 1); Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91. Found: C, 65.07; H, 5.71; N, 8.78.

*6-Ethoxycarbonyl-7-methyl-5-(4-hydroxyphenyl)-5H-thiazolo[3,2-a]pyrimidine (**1b**)*

mp 229–230°C. IR (KBr) ν: 3382, 3112, 2986, 1689, 1605, 1530, 1260; ^{1}H NMR (400 MHz, DMSO): $\delta = 1.17$ (t, $J = 7.2$ Hz, 3H), 2.19 (s, 3H), 2.39 (s, 3H), 4.02–4.13 (m, 2H), 6.27 (s, 1H), 6.74 (dd, $J = 8.4$ Hz, $J = 2.4$ Hz, 2H), 7.08 (s, 1H), 7.12 (bs, 1H), 7.15 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.49$, 14.15, 18.34, 59.09, 61.25, 102.93, 110.34, 126.67, 129.39, 129.63, 136.22, 139.08, 143.11, 160.57, 164.41; MS (FAB): $m/z = 331$ (M + 1); Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 61.98; H, 5.58; N, 8.37.

*6-Ethoxycarbonyl-7-methyl-5-(2-methoxyphenyl)-5H-thiazolo[3,2-a]pyrimidine (**1c**)*

mp 221–223°C. IR (KBr) ν: 3086, 2976, 1692, 1605, 1530, 1461, 1236; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.17$ (t, $J = 7.2$ Hz, 3H), 2.18 (s, 3H), 2.42 (s, 3H), 3.85 (s, 3H), 4.09 (q, $J = 7.0$ Hz, 2H, CH_2O), 6.28 (s, 1H), 6.84 (dd, 1 H, $J = 8$ Hz, 0.8 Hz), 6.91 (t, 1 H, $J = 0.8$ Hz), 7.03 (s, 1H), 7.22 (t, 1H, $J = 0.8$ Hz), 7.35–7.32 (dd, 1H, $J = 8$ Hz, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.5$, 14.2, 19.3, 59.0, 58.7, 61.6, 102.9, 110. 2, 121.3, 129.1, 129.7, 129.7, 136.1, 146.0, 155.8, 160.2, 165.4; MS (FAB): $m/z = 345$ (M + 1); $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13. Found: C, 63.01; H, 5.75; N, 8.33.

*6-Ethoxycarbonyl-7-methyl-5-(4-methoxyphenyl)-5H-thiazolo[3,2-a]pyrimidine (**1d**)*

mp 227–228°C. IR (KBr) ν: 3106, 2974, 1689, 1605, 1530, 1461, 1248; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.18$ (t, $J = 7.2$ Hz, 3H), 2.18 (s, 3H), 2.35 (s, 3H), 3.78 (s, 3H), 4.06–4.15 (m, 2H), 6.30 (s, 1H), 6.80 (d, $J = 8.8$ Hz, 2H), 7.05 (s, 1H), 7.23 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.6$, 14.7, 18.3, 59.0, 59.9, 61.1, 102.9, 108.6, 113.9, 127.8, 129.6, 136.1, 146.1, 163.6, 159.2, 164.7; MS (FAB): $m/z = 345$ (M + 1); $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.58; H, 5.99; N, 7.98.

*6-Ethoxycarbonyl-7-methyl-5-(4-nitrophenyl)-5H-thiazolo[3,2-a]pyrimidine (**2e**)*

mp 243–244°C. IR (KBr) ν: 3088, 1722, 1648, 1608, 1527, 1473, 1239; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 8.4$ Hz, 3H), 2.01 (s, 3H), 2.60 (s, 3H), 4.19–4.24 (m, 2H), 6.46 (s, 1H), 7.09 (s, 1H), 7.45 (d, $J = 8.4$, 2H), 7.33 (d, $J = 9.2$ Hz, 2H); ^{13}C NMR (100

MHz, $CDCl_3$): $\delta = 13.5$, 14.2, 18.6, 59.1, 61.8, 102.0, 111.3, 124.7, 127.9, 135.8, 144.4, 145.1, 148.4, 160.9, 164.3; MS (FAB): $m/z = 360$ (M + 1); Anal. Calcd for $C_{17}H_{17}N_3O_4S$: C, 56.81; H, 4.77; N, 11.69. Found C, 56.96; H, 4.71; N, 11.55.

*6-Ethoxycarbonyl-7-methyl-5-(3-nitrophenyl)-5H-thiazolo[3,2-a]pyrimidine (***2f***)*

mp 241–243°C. IR (KBr) ν: 3088, 1692, 1606, 1527, 1473, 1223; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.14$ (t, 3H, $J = 7.2$ Hz, CH_3CH_2O), 2.35 (s, 3H, CH_3), 2.60 (s, 3H), 4.01 (q, 2H, $J = 7.2$ Hz, CH_3CH_2O), 6.42 (s, 1H), 7.09 (s, 1H), 7.75–7.64 (m, 2H), 8.14–8.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.5$, 14.2, 18.6, 58.5, 61.7, 103.0, 111.3, 120.7, 125.8, 130.7, 135.6, 138.8, 145.2, 148.5, 155.5, 160.7, 164.3; MS (FAB): $m/z = 360$ (M + 1); Anal. Calcd for $C_{17}H_{17}N_3O_4S$: C, 56.81; H, 4.77; N, 11.69. Found C, 56.98; H, 4.65; N, 11.80.

*6-Ethoxycarbonyl-7-methyl-5-(4-chlorophenyl)-5H-thiazolo[3,2-a]pyrimidine (***1g***)*

mp 241–242°C. IR (KBr) ν: 3112, 2986, 1683, 1638, 1608, 1524, 1494, 1269; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.22$ (t, $J = 7.2$ Hz, 3H), 2.00 (s, 3H), 2.55 (s, 3H), 4.10–4.21 (m, 2H), 6.27 (s, 1H), 7.10 (s, 1H), 7.14–7.24 (m, 2H), 7.26–7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.4$, 14.1, 18.3, 58.4, 61.3, 102.6, 111.1, 128.1, 129.5, 135.6, 135.9, 137.5, 143.2, 160.4, 164.2; MS (FAB): $m/z = 349$ (M + 1); Anal. Calcd for $C_{17}H_{17}ClN_2O_2S$: C, 58.53; H, 4.91; N, 8.03; Found: C, 58.74; H, 5.12; N, 7.88.

*6-Ethoxycarbonyl-7-methyl-5-(2-chlorophenyl)-5H-thiazolo[3,2-a]pyrimidine (***1h***)*

mp 243–245°C. IR (KBr) ν: 3088, 2991, 1692, 1649, 1606, 1527, 1473, 1223; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.13$ (t, 3H, $J = 7.2$ Hz, CH_3CH_2O), 2.43 (s, 3H, CH_3), 2.60 (s, 3H), 4.05–3.99 (m, 2H, CH_2O), 6.46 (s, 1H), 7.08 (s, 1H), 7.31–7.18 (m, 3H), 7.51 (dd, 1H, $J = 8$ Hz, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 19.6, 22.9, 59.5, 61.7, 103.0, 110.1, 126.3, 128.5, 129.6, 133.6, 134.8, 140.1, 143.4, 154.5, 161.0, 165.1; MS (FAB): $m/z = 349$ (M + 1); Anal. Calcd for $C_{17}H_{17}ClN_2O_2S$: C, 58.53; H, 4.91; N, 8.03. Found C, 58.72; H, 4.99; N, 8.23.

*6-Ethoxycarbonyl-7-methyl-5-(4-methylphenyl)-5H-thiazolo[3,2-a]pyrimidine (***1i***)*

mp 251–253°C. IR (KBr) ν: 3088, 2976, 1694, 1645, 1604, 1532, 1254, 1103; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.17$ (t, $J = 7.2$ Hz, 3H), 2.24 (s, 3H), 2.36 (s, 3H), 2.48 (s, 3H), 4.17–4.20 (m, 2H), 6.31 (s, 1H), 6.80 (d, $J = 8.8$ Hz, 2H), 6.82 (s, 1H), 7.05 (s, 1H), 7.24 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 14.3, 18.6, 19.1, 59.5, 61.8, 103.7, 110.2, 127.1, 129.5, 134.7, 136.5, 138.2, 141.3, 160.1, 164.5; MS (FAB): $m/z = 329$ (M + 1); Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.98; H, 5.99; N, 8.38.

*6-Ethoxycarbonyl-7-methyl-5-(2-methylphenyl)-5H-thiazolo[3,2-a]pyrimidine (***1j***)*

mp 252–253°C. IR (KBr) ν: 3110, 2977, 1688, 1649, 1603, 1534, 1254, 1105; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.27$ (t, $J = 7.2$ Hz, 3H), 2.21 (s, 3H), 2.55 (s, 3H), 2.62 (s, 3H), 4.17–4.20 (m, 2H), 6.51 (s, 1H), 6.85 (s, 1H), 7.18–7.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.8$, 14.2, 18.5, 19.2, 56.6, 61.3, 103.4, 109.2, 127.7, 128.5, 129.6, 131.4, 134.7, 136.7, 138.2, 142.2, 160.6, 164.7; MS (FAB): $m/z = 329$ (M + 1); Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.67; H, 5.98; N, 8.70.

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