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From Thiourea to Bicyclic Structures: An Original Route to Imidazo[2,1-*b*]thiazoles, 5*H*-Thiazolo[3,2-*a*]pyrimidines, 7*H*-Imidazo[2,1-*b*][1,3]thiazines, and 2*H*,6*H*-Pyrimido[2,1-*b*][1,3]thiazines†

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We report an example of an efficient regioselective synthesis of biheterocyclic compounds using thiourea as starting material. In fact, *N*,*N*′-bis(dimethylaminomethylene)thiourea (**1**), easily prepared by double condensation of *N*,*N*-dimethylformamide dimethyl acetal with thiourea, can be reacted with haloketones or acrylic dienophiles to give thiazolic (**2**) and thiazinic (**3**) diazadienes, respectively, themselves undergoing cyclization reactions to yield imidazo[2,1-*b*]thiazoles, 5*H*-thiazolo[3,2-*a*]pyrimidines, 7*H*-imidazo[2,1-*b*][1,3]thiazines, and 2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazines without any regioisomeric ambiguity. This straightforward route represents an original and unambiguously regioselective pathway to these valuable heterocycles.

Introduction

In recent years, the synthesis of bicyclic compounds possessing an alkylthioamidine central core has been the focus of great interest. This is due, in part, to the broad spectrum of biological properties of these compounds.[1−4] Imidazo[2,1-*b*]thiazole derivatives are of considerable interest because of their activities as antiarthritic,[1a,b] immunomodulating,[1c] herbicidal,[1d] cardiotonic,[1e] antiarrhythmic[1f] and antitumor agents.[1g,h] One recent paper has shown them to be effective against tuberculosis.[1i] Thiazolo[3,2-*a*]pyrimidines are also of pharmacological interest due to their antiinflammatory,[2a,b] psychopharmacological,[2c] bactericidal,[2d] and antiviral activity as inhibitors of HIV-1 reverse transcriptase.[2e] On the other hand, imidazo[2,1-*b*][1,3]thiazines and pyrimido[2,1-*b*]-[1,3]thiazines have prompted less interest, although some of these compounds proved to be biologically active as benzodiazepine substitutes[3] and antiinflammatory agents, respectively.[4]

Numerous methods for the synthesis of these heterocycles involve approaches based on either (i) alkylations of cyclic thioureas by appropriate 1,2- or 1,3-dielectrophiles[5] or (ii) condensations of 2-aminothiazoles or thiazines with 1,2- or 1,3-difunctionalized units, such as α,*β*-unsaturated esters or lactam acetals.[6] Although frequently used, both routes can give mixtures of regiosiomers.[7] Known regioselective syntheses of these structures involve the retrodiene decomposition of the corresponding norbornene-fused derivatives[8] or the condensation of 2-(cyanoimino)thiazolidine with acyl chlorides,[9] 2-aminothiazoles with α-halogenoketones,[10] isothiocyanato-2-

† Dedicated to the memory of Dr. Alain Reliquet.

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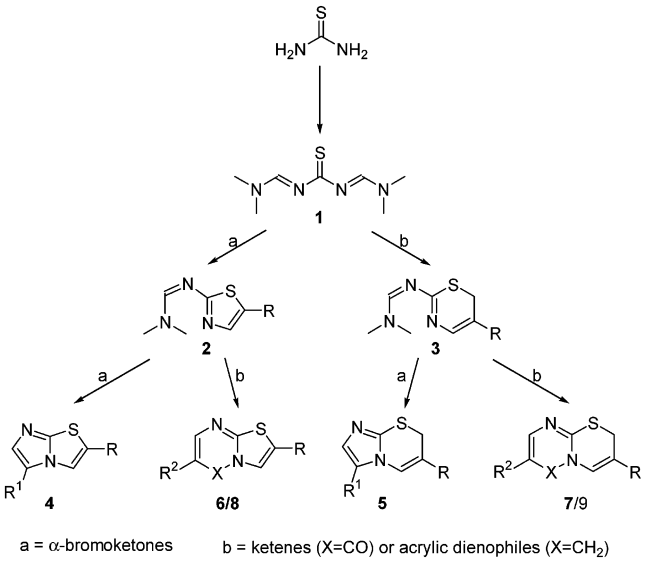
SCHEME 1. Preparation of Bicyclic Structures



propenium salts with α-aminoketones[11] or other specific reactants.[12] The methods mentioned above offer variable versatility and convenience.

New routes to these structures would be of great interest, and recently we published efficient synthetic procedures involving heterocyclic diazadienes.[13e,f] We showed that such amidines, prepared by condensation of 2-aminothiazoline or 2-amino-4,6,6-trimethyl-6*H*-1,3-thiazine with *N*,*N*-dimethylacetamide or formamide dimethyl acetal, were useful building blocks for the regioselective synthesis of these heterocycles. As part of our continuing study on the reactivity of polyheteropolyenes,[13] we now report that title compounds can be conveniently prepared in three steps starting from thiourea. By this method, we recently described a novel acces to thiazolopyrimidine and imidazo-1,3-thiazine derivatives involving compound **1**.[13j] Our method utilizes *N*,*N*′-bis(dimethylaminomethylene)thiourea (**1**) as a common intermediate, undergoing cyclization reactions to afford either five- (**2**) or six-membered-ring (**3**) monocyclic diazadienes, themselves being precursors to the bicyclic structures (Scheme 1).

Results and Discussion

Compound **1** was easily prepared in 95% yield by double condensation of commercially available *N*,*N*-dimethylformamide dimethyl acetal and thiourea in dichloromethane. It is worth noting that monocondensation was favored when methanol was employed as the solvent.[13c]

TABLE 1. Yields of Compounds 2a−d and 3a,b

compd	R	yield (%)
2a	$COOCH_3$	81
2b[13j]	COC_6H_4Br-*p*	74
2c	COC_6H_4Cl-*p*	82
2d	$COC_6H_4CH_3$-*p*	72
3a	CHO	48
3b[13j]	$COCH_3$	45

With gram quantities of precursor (**1**) in hand, initial work focused on exploring its reactivity toward various electrophiles. First, treatment of *N*,*N*′-bis(dimethylaminomethylene)thiourea (**1**) with α-bromoketones or methyl bromoacetate gave nonisolated *S*-alkyl salts, which underwent cyclization when treated with a base via condensation of the generated enolate with one of the amidinium moieties. Spontaneous deamination of the intermediary cycloadduct afforded *N*,*N*-dimethyl-*N*′-(thiazol-2-yl)amidines (**2**) in high yields (Table 1, Scheme 2). This mirrors work described by Knoll and Liebscher;[14] however, these authors did not make any attempts toward further cyclizations.

We then decided to investigate the feasibility of a reaction between *N*,*N*′-bis(dimethylaminomethylene)thiourea (**1**) and acrylic dienophiles. This reaction gave *N*,*N*-dimethyl-*N*′-(6*H*-1,3-thiazin-2-yl)formamidines (**3**) in only moderate yields after loss of dimethylamine (Table 1, Scheme 2). In accordance with the literature, we assume that the reaction proceeds by a classical hetero-Diels−Alder reaction rather than a conjugate addition/alkylation.[15] When acrolein was used as the dienophile, partial degradation (20−30%) of the product amidine side chain was observed during the workup procedure, leading to the undesired 5-formyl-2-formylamino-6*H*-1,3-thiazine. Whereas with methyl vinyl ketone the main problem was double condensation resulting from second [4 + 2] cycloaddition between this dienophile and the resulting thiazine **3b**, occurring before complete consumption of the starting material. Consequently bicycle **9c** was observed as a major side product (15%). Compounds **3** were unambiguously characterized by spectroscopy techniques. The proof of the thiazine structure, so the total regioselectivity, was given by the ^{1}H NMR spectra where we observed the loss of dimethylamino group and the presence of two singlets (3.68 and 7.52 for S-CH_2 and N-CH, respectively).

We have previously demonstrated 4,5-dihydrothiazole amidines to be useful heterodienes.[13e] It therefore seemed reasonable to investigate the feasibility of cycloadducts **2** to act as heterodienes, their aromaticity being clearly decreased by the presence of an electron-withdrawing group in the 5-position. Moreover, the same consideration

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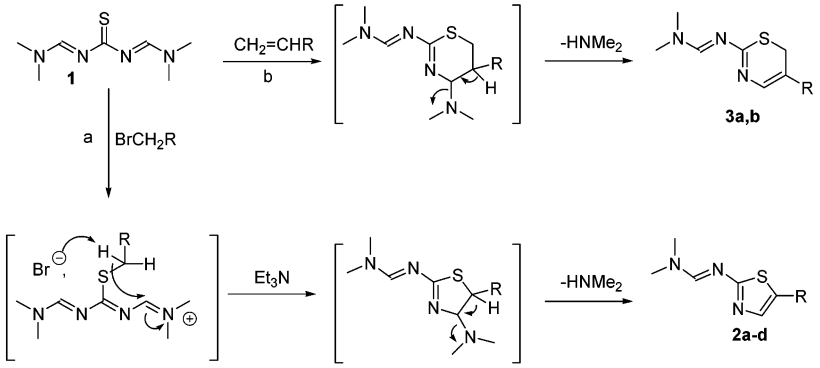
SCHEME 2. Synthesis of 2 and 3[a]

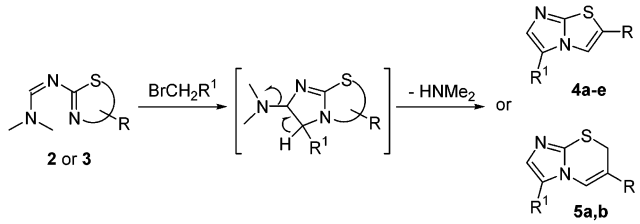


[a] Reagents and conditions: (a) CH_2Cl_2, rt, 15 min then TEA, rt, 20 h; (b) CH_2Cl_2, rt, 18 h.

TABLE 2. Yields of Compounds 4a−e and 5a,b

compd	R	R^1	yield (%)
4a	CO_2CH_3	COC_6H_4Cl-*p*	68
4b	COC_6H_4Br-*p*	COC_6H_4Br-*p*	74
4c	COC_6H_4Br-*p*	$COC_6H_4CH_3$-*p*	73
4d	$COC_6H_4CH_3$-*p*	COC_6H_4Cl-*p*	87
4e	COC_6H_4Cl-*p*	$COC_6H_4CH_3$-*p*	82
5a	CHO	COC_6H_4Br-*p*	41
5b[13j]	$COCH_3$	COC_6H_4Br-*p*	49

SCHEME 3. Synthesis of 4a−e and 5a,b[a]



[a] Reagents and conditions: THF, reflux, 6 or 20 h then TEA, rt, 24 h.

could be applied to compounds **3**, which should react in a similar way as the thiazine amidines previously studied by our group.[13f]

Initially the reaction of amidines **2** and **3** with α-bromoketones was examined. As expected, the resulting *N*-alkyl salts, whose isolations were not encouraged, were converted in situ by addition of triethylamine, leading after spontaneous deamination to the corresponding imidazo[2,1-*b*]thiazoles (**4**) and 7*H*-imidazo[2,1-*b*][1,3]-thiazines (**5**) (Table 2, Scheme 3).

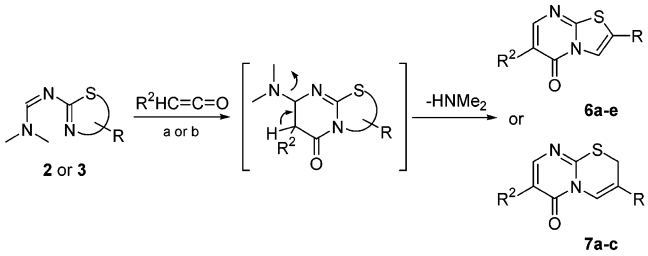
Treatment of compounds **2** and **3** with a range of ketenes led to a [4 + 2] cyclocondensation which gave 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones (**6**) and 2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-ones (**7**), respectively, by loss of dimethylamine (Table 3, Scheme 4). Our pathway excludes any regioisomeric ambiguity: indeed, the ^{1}H NMR deshielding effect observed for the proton signal in position 3 (for **6a−e**) or 4 (for **7a−c**) is unambiguously attributed to the proximity of the carbonyl function of pyrimidinic ring. Moreover, the final step that consisted of deamination of the supposed intermediary cycloadduct was not possible for the unlikely isomer.

Finally, to complete this study, we decided to investigate the behavior of amidines **2** and **3** with acrylic dienophiles (either as neat liquids or in chloroform). The

TABLE 3. Yields of Compounds 6a−e and 7a−c

compd	R	R^2	yield (%)
6a	COC_6H_4Cl-*p*	H	55
6b	COC_6H_4Br-*p*	CO_2CH_3	77
6c	COC_6H_4Cl-*p*	CO_2CH_3	86
6d	$COC_6H_4CH_3$-*p*	CO_2CH_3	65
6e	COC_6H_4Cl-*p*	$CO_2C_2H_5$	63
7a	$COCH_3$	H	58
7b	CHO	$CO_2C_2H_5$	51
7c	$COCH_3$	$CO_2C_2H_5$	59

SCHEME 4. Synthesis of 6a−e and 7a−c[a]



[a] Reagents and conditions: (a) R^2 = H, CH_2Cl_2, rt, 1 h; (b) $R^2 \neq$ H, CH_2Cl_2, rt, 4 h, then TEA, 0 °C → rt, 16 h.

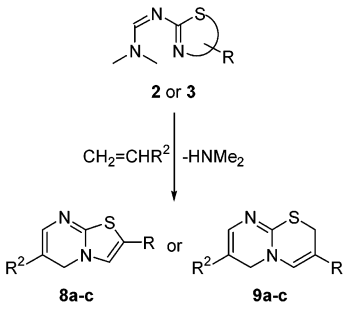
TABLE 4. Yields of Compounds 8a−c and 9a−c

compd	R	R^2	yield (%)
8a[13j]	COC_6H_4Br-*p*	$COCH_3$	47
8b	COC_6H_4Cl-*p*	$COCH_3$	53
8c	$COC_6H_4CH_3$-*p*	$COCH_3$	46
9a	CHO	$COCH_3$	48
9b	$COCH_3$	CHO	53
9c[13j]	$COCH_3$	$COCH_3$	52

tandem [4 + 2] cycloaddition/deamination process occurred as expected, furnishing 5*H*-thiazolo[3,2-*a*]pyrimidines (**8**) and 2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazines (**9**) respectively, albeit in moderate yields (Table 4, Scheme 5). It is worth noting that this synthetic sequence makes it possible to obtain regioisomers **9a** and **9b**, both bearing an acetoxy and a formyl group, in a regiocontrolled manner. Similarly, the expected derivatives **8** and **9** were obtained with an absolute regioselectivity. The ^{1}H NMR spectra of **8a−c** and **9a−c** showed a singlet due to the methylene group in position 5 or 6, respectively, and thus excluded the regioisomeric substituted structure.

In conclusion, we have demonstrated *N*,*N*′-bis(dimethylaminomethylene)thiourea **1** to be a suitable building

SCHEME 5. Synthesis of 8a−c and 9a−c[a]



[a] Reagents and conditions: neat or $CHCl_3$, reflux, 6 h or 4 days.

block for the synthesis of imidazo[2,1-*b*]thiazoles (**4**), 5*H*-thiazolo[3,2-*a*] pyrimidines (**6** and **8**), 7*H*-imidazo[2,1-*b*]-[1,3]thiazines (**5**) and 2*H*,6*H*-pyrimido[2,1-*b*] [1,3]thiazines (**7** and **9**). This straightforward route represents an original and unambiguously regioselective pathway to these valuable heterocycles.

Experimental Section

***N,N*-Dimethyl-*N*′-(thiazol-2-yl)amidines (2).** The α-carbonylated bromide (5 mmol) (methyl bromoacetate for **2a**, *p*-bromophenacyl bromide for **2b**,[13j] *p*-chlorophenacyl bromide for **2c**, *p*-toluoylacyl bromide for **2d**) was added to a solution of *N*,*N*′-bis(dimethylaminomethylene)thiourea **1** (5 mmol) in dichloromethane (10 mL). After 15 min of stirring at room temperature, the triethylamine (10 mmol) was added. The reaction mixture was further stirred for 20 h, and then the solvent was evaporated. The residue, diluted with dichloromethane, was purifed by chromatography (elution dichloromethane/ethyl acetate 1/9 for **2a**, 4/1 for **2b**, 3/2 for **2c**, 3/1 for **2d**). Compounds **2** were recrystallized from ether.

***N*′-(5-Methoxycarbonylthiazol-2-yl)-*N,N*-dimethylformamidine (2a).** Yellow crystals (yield 81%). Mp: 104.5−105.5 °C. IR (KBr): 3087, 1703, 1621, 1401, 1318, 1249 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.11 (s, 3H), 3.14 (s, 3H), 3.85 (s, 3H), 7.98 (s, 1H), 8.35 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 34.9, 40.9, 51.7, 120.9, 147.0, 156.0, 162.4, 179.7. MS *m*/*z*: 213 (52, M^+), 153 (86), 42 (100). Anal. Calcd for $C_8H_{11}N_3O_2S$: C, 45.06; H, 5.20; N, 19.70. Found: C, 44.87; H, 5.06; N, 19.53.

***N*′-(5-*p*-Chlorobenzoylthiazol-2-yl)-*N,N*-dimethylformamidine (2c).** Yellow crystals (yield 82%). Mp: 159−160 °C. IR (KBr): 2918, 1632, 1608, 1448 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.15 (s, 3H), 3.17 (s, 3H), 7.44−7.78 (m, 4H), 7.81 (s, 1H), 8.36 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 35.0, 40.9, 128.7 (2), 130.1 (2), 131.9, 136.6, 138.1, 149.0, 156.4, 181.1, 185.8. MS *m*/*z*: 295/293 (40/100, M^+), 154 (87). Anal. Calcd for $C_{13}H_{12}ClN_3OS$: C, 53.15; H, 4.12; N, 14.30. Found: C, 53.01; H, 3.91; N, 14.15.

***N,N*-Dimethyl-*N*′-(5-*p*-toluoylthiazol-2-yl)formamidine (2d).** Yellow crystals (yield 72%). Mp: 146−148 °C. IR (KBr): 1610, 1442, 1371, 1283, 1100 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.44 (s, 3H), 3.14 (s, 3H), 3.17 (s, 3H), 7.26−7.76 (m, 4H), 7.84 (s, 1H), 8.35 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.5, 35.2, 41.1, 128.9 (2), 129.1 (2), 132.5, 135.6, 142.6, 148.6, 156.4, 180.1, 187.0. MS *m*/*z*: 273 (100, M^+), 154 (59), 119 (41). Anal. Calcd for $C_{14}H_{15}N_3OS$: C, 61.52; H, 5.53; N, 15.37. Found: C, 61.40; H, 5.76; N, 15.51.

***N,N*-Dimethyl-*N*′-(5-formyl-6*H*-1,3-thiazin-2-yl)formamidine (3a).** The *N*,*N*′-bis(dimethylaminomethylene)thiourea **1** (4 mmol) was added to a solution of acroleine (20 mmol) in dichloromethane (10 mL). The reaction mixture was stirred for 18 h at room temperature, diluted with acetone (80 mL), and filtered through a short pad of Celite. The solvent was evaporated, and the residue was diluted with dichloromethane. Compounds **3a** was isolated as a yellow oil by chromatography (elution ethyl acetate/acetone 3/2) (yield 48%). R_f (acetone) = 0.2. IR: 2928, 1618, 1453, 1108 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.16 (s, 3H), 3.20 (s, 3H), 3.68 (s, 2H), 7.52 (s, 1H), 8.40 (s, 1H), 9.46 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.9, 35.7, 41.7, 114.5, 157.3, 158.3, 171.7, 190.1. MS *m*/*z*: 197 (52, M^+), 168 (100), 115 (64). Anal. Calcd for $C_8H_{11}N_3OS$: C, 48.71; H, 5.62; N, 21.30. Found: C, 48.63; H, 5.76; N, 21.18.

Imidazo[2,1-*b*]thiazoles (4). Compounds **4** were prepared using the same procedure described above for the synthesis of **2**.

5-*p*-Chlorobenzoyl-2-methoxycarbonylimidazo[2,1-*b*]-thiazole (4a). Colorless crystals (yield 68%). Mp: 180.5−181.5 °C. IR (KBr): 1726, 1264 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.98 (s, 3H), 7.50−7.88 (m, 4H), 7.97 (s, 1H), 9.12 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 53.2, 124.5, 127.3, 129.2 (2), 130.1 (2), 136.0, 139.2, 145.0 (2), 156.5, 161.2, 181.7. MS *m*/*z*: 322/320 (39/100, M^+), 209 (76), 141/139 (12/37), 113/111 (16/51). Anal. Calcd for $C_{14}H_9ClN_2O_3S$: C, 52.43; H, 2.83; N, 8.73. Found: C, 52.61; H, 3.02; N, 8.58.

2,5-Bis(*p*-bromobenzoyl)imidazo[2,1-*b*]thiazole (4b). Colorless crystals (yield 74%). Mp: 253−255 °C. IR (KBr): 2362, 1629, 1618, 1585, 1438, 1400 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.67−7.83 (m, 8H), 8.01 (s, 1H), 8.95 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 127.5, 127.9, 129.3 (2), 130.1 (2), 130.4 (2), 130.7 (2), 134.3, 134.4, 134.9, 135.1, 144.2, 145.0, 156.4, 181.9, 182.6. MS *m*/*z*: 492/490/488 (52/92/46, M^+), 335/333 (35/36), 185/183 (95/100), 157/155 (70/73). Anal. Calcd for $C_{19}H_{10}Br_2N_2O_2S$: C, 46.56; H, 2.06; N, 5.72. Found: C, 46.77; H, 2.14; N, 5.59.

2-*p*-Bromobenzoyl-5-*p*-toluoylimidazo[2,1-*b*]thiazole (4c). Colorless crystals (yield 73%). Mp: 193−196 °C. IR (KBr): 1632, 1620, 1587, 1380 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.47 (s, 3H), 7.33−7.84 (m, 8H), 8.03 (s, 1H), 8.97 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.6, 127.1, 128.1, 128.7 (2), 129.5 (2), 130.2 (2), 132.3 (2), 129.5, 134.2, 134.6, 135.1, 143.7, 145.0, 156.2, 182.8, 186.1. MS *m*/*z*: 426/424 (63/59, M^+), 185/183 (47/48), 119 (66), 91 (100). Anal. Calcd for $C_{20}H_{13}BrN_2O_2S$: C, 56.48; H, 3.08; N, 6.59. Found: C, 56.27; H, 3.22; N, 6.38.

5-*p*-Chlorobenzoyl-2-*p*-toluoylimidazo[2,1-*b*]thiazole (4d). Colorless crystals (yield 87%). Mp: 184.5−185.5 °C. IR (KBr): 2358, 1652, 1645, 1373, 897 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.49 (s, 3H), 7.36−7.88 (m, 8H), 8.00 (s, 1H), 8.96 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.6, 126.7, 127.5, 129.0 (2), 129.1 (2), 129.7 (2), 129.9 (2), 133.6, 135.1, 135.7, 139.1, 144.4, 145.2, 156.7, 181.6, 186.6. MS *m*/*z*: 382/380 (31/70, M^+), 269 (19), 119 (100), 91 (74). Anal. Calcd for $C_{20}H_{13}ClN_2O_2S$: C, 63.08; H, 3.44; N, 7.36. Found: C, 63.25; H, 3.29; N, 7.54.

2-*p*-Chlorobenzoyl-5-*p*-toluoylimidazo[2,1-*b*]thiazole (4e). Colorless crystals (yield 82%). Mp: 160.5−161.5 °C. IR (KBr): 1636, 1620, 1380, 1302, 899 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.47 (s, 3H), 7.33−7.80 (m, 8H), 8.02 (s, 1H), 8.97 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.5, 127.0, 128.1, 128.3 (2), 128.4 (2), 128.4 (2), 130.1 (2), 130.1, 134.1, 134.6, 139.8, 143.7, 145.0, 156.1, 182.7, 185.8. MS *m*/*z*: 382/380 (42/100, M^+), 291/289 (9/22), 141/139 (16/52), 119 (45), 91 (59). Anal. Calcd for $C_{20}H_{13}ClN_2O_2S$: C, 63.08; H, 3.44; N, 7.36. Found: C, 63.21; H, 3.63; N, 7.60.

3-*p*-Bromobenzoyl-6-formyl-7*H*-imidazo[2,1-*b*][1,3]-thiazine (5a). The *p*-bromophenacyl bromide (1.1 mmol) was added to a solution of amidine **3** (1 mmol) in tetrahydrofuran (10 mL). The reaction mixture was refluxed for 6 h. After the mixture was cooled to room temperature, triethylamine (2.2 mmol) was added. The mixture was further stirred for 24 h. The solvent was then evaporated, and the residue, diluted with dichloromethane, was purifed by chromatography (elution dichloromethane/ethyl acetate 9/1). Compound **5** was recrystallized from ether. Colorless crystals (yield 41%). Mp: 144−146 °C. IR (KBr): 1685, 1646, 1623, 1422, 1336, 894 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.88 (d, 2H, J = 0.9 Hz), 7.63 (s, 1H), 7.64−7.76 (m, 4H), 8.50 (t, 1H, J = 0.9 Hz), 9.65 (s, 1H). ^{13}C NMR

($CDCl_3$) δ: 20.4, 120.6, 128.3, 129.8, 136.5, 130.4 (2), 132.3 (2), 141.3, 142.6, 150.4, 183.0, 188.3. MS *m*/*z*: 350/348 (35/33, M^+), 185/183 (99/100), 157/155 (56/58). Anal. Calcd for $C_{14}H_9BrN_2O_2S$: C, 48.15; H, 2.60; N, 8.02. Found: C, 48.23; H, 2.49; N, 7.98.

5*H*-Thiazolo[3,2-*a*]pyrimidin-5-ones (6). Method A. Ketene (CAUTION!) produced by cracking of acetone, was bubbled into a solution of thiazolylamidine **2c** (2 mmol) in dichloromethane (100 mL) until complete consumption of the starting material, as monitored by TLC (1 h). The solvent was then evaporated, and the resulting residue was diluted with dichloromethane and purifed by chromatography (elution ethyl acetate/dichloromethane 5/1).

Method B. The acyl chloride (2.4 mmol) (methyl malonyl chloride for **6b**,**c**,**d**, ethyl malonyl chloride for **6e**) was added to a solution of amidine **2b**−**d** (2 mmol) in dichloromethane (10 mL). After 4 h of stirring at room temperature, the reaction mixture was cooled to 0 °C and triethylamine (4.8 mmol) was added. The mixture was stirred at room temperature for further 16 h, and then the solvent was evaporated. The residue was diluted with dichloromethane and purifed by chromatography (elution dichloromethane/ethyl acetate 9/1). Compounds **6b**−**e** were recrystallized from ether.

2-*p*-Chlorobenzoyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (6a). Yellow foam (yield 55%). IR (KBr): 1689, 1635, 1587, 1323, 1222, 1091, 817 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 6.36 (d, 1H, J = 6.6 Hz), 7.54−7.88 (m, 4H), 8.05 (d, 1H, J = 6.6 Hz), 8.43 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 106.9, 127.5, 129.4, 129.7 (2), 130.5 (2), 134.0, 140.7, 154.3, 158.5, 163.3, 185.2. MS *m*/*z*: 292/290 (36/97, M^+), 141/139 (34/100), 113/111 (12/35). Anal. Calcd for $C_{13}H_7ClN_2O_2S$: C, 53.71; H, 2.43; N, 9.64. Found: C, 53.51; H, 2.49; N, 10.01.

2-*p*-Bromobenzoyl-6-methoxycarbonyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (6b). Colorless crystals (yield 77%). Mp: 177−179 °C. IR (KBr): 1749, 1491, 1313 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.94 (s, 3H), 7.76−7.78 (m, 4H), 8.54 (s, 1H), 8.85 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 52.3, 108.5, 127.7, 129.6, 130.4 (2), 132.6 (2), 130.5, 133.9, 154.8, 159.3, 164.0, 166.7, 184.7. MS *m*/*z*: 394/392 (67/68, M^+), 363/361 (100/94), 185/183 (69/69), 157/155 (52/53). Anal. Calcd for $C_{15}H_9BrN_2O_4S$: C, 45.82; H, 2.31; N, 7.12. Found: C, 45.68; H, 2.46; N, 7.01.

2-*p*-Chlorobenzoyl-6-methoxycarbonyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (6c). Colorless crystals (yield 86%). Mp: 179.5−180.5 °C. IR (KBr): 1747, 1492, 1371, 1312, 1191 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.94 (s, 3H), 7.55−7.89 (m, 4H), 8.53 (s, 1H), 8.84 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 52.4, 108.5, 127.8, 129.7 (2), 130.5 (2), 130.6, 133.6, 140.9, 154.9, 159.3, 164.1, 166.8, 184.6. MS *m*/*z*: 350/348 (29/66, M^+), 319/317 (47/100), 251/249 (12/30). Anal. Calcd for $C_{15}H_9ClN_2O_4S$: C, 51.66; H, 2.60; N, 8.03. Found: C, 51.47; H, 2.49; N, 7.94.

6-Methoxycarbonyl-2-*p*-toluoyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (6d). Colorless crystals (yield 65%). Mp: 158−161 °C. IR (KBr): 1712, 1699, 1487, 1320, 1126 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.49 (s, 3H), 3.94 (s, 3H), 7.36−7.84 (m, 4H), 8.55 (s, 1H), 8.84 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.8, 52.4, 108.4, 127.5, 129.3 (2), 130.0 (2), 131.2, 132.7, 145.5, 155.0, 159.3, 164.3, 167.0, 185.3. MS *m*/*z*: 328 (80, M^+), 297 (100), 119 (85), 91 (81). Anal. Calcd for $C_{16}H_{12}N_2O_4S$: C, 58.53; H, 3.68; N, 8.53. Found: C, 58.42; H, 3.76; N, 8.77.

2-*p*-Chlorobenzoyl-6-ethoxycarbonyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (6e). Yellow crystals (yield 63%). Mp: 135−137 °C. IR (KBr): 1745, 1477, 1131 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.40 (t, 3H, J = 7.2 Hz), 4.40 (q, 2H, J = 7.2 Hz), 7.55−7.88 (m, 4H), 8.54 (s, 1H), 8.83 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 14.3, 61.4, 108.9, 127.9, 129.7 (2), 130.5 (2), 130.5, 133.6, 140.9, 154.9, 159.1, 163.5, 166.7, 184.6. MS *m*/*z*: 364/362 (12/28, M^+), 292/290 (41/100), 141/139 (27/79), 113/111 (15/46). Anal. Calcd for $C_{16}H_{11}ClN_2O_4S$: C, 52.97; H, 3.06; N, 7.72. Found: C, 53.19; H, 3.25; N, 7.81.

2*H*,6*H*-Pyrimido[2,1-*b*][1,3]thiazin-6-ones (7). Compounds **7** were prepared using the same procedure described above for the synthesis of **6**.

3-Acetyl-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one (7a). Colorless crystals (yield 58%). Mp: 159.5−160.5 °C. IR (KBr): 1696, 1673, 1409, 1401. ^1H NMR ($CDCl_3$) δ: 2.51 (s, 3H), 3.83 (d, 2H, J = 0.9 Hz), 6.27 (d, 1H, J = 6.6 Hz), 7.73 (d, 1H, J = 6.6 Hz), 8.43 (t, 1H, J = 0.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.4, 25.5, 111.2, 122.1, 132.1, 152.5, 158.3, 158.8, 194.5. MS *m*/*z*: 208 (100, M^+), 165 (47), 112 (59). Anal. Calcd for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45. Found: C, 51.84; H, 3.93; N, 13.60.

7-Ethoxycarbonyl-3-formyl-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one (7b). Colorless crystals (yield 51%). Mp: 150.5−151.5 °C. IR (KBr): 1745, 1663, 1496. ^1H NMR ($CDCl_3$) δ: 1.38 (t, 3H, J = 7.2 Hz), 3.85 (d, 2H, J = 0.9 Hz), 4.38 (q, 2H, J = 7.2 Hz), 8.34 (t, 1H, J = 0.9 Hz), 8.48 (s, 1H), 9.70 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 14.3, 21.0, 61.7, 113.2, 122.2, 138.0, 155.1, 162.8, 163.5, 157.6, 188.2. MS *m*/*z*: 266 (86, M^+), 221 (99), 220 (100), 194 (98). Anal. Calcd for $C_{11}H_{10}N_2O_4S$: C, 49.62; H, 3.79; N, 10.52. Found: C, 49.68; H, 3.89; N, 10.77.

3-Acetyl-7-ethoxycarbonyl-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one (7c). Colorless crystals (yield 59%). Mp: 109−111 °C. IR (KBr): 1710, 1487 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.39 (t, 3H, J = 7.2 Hz), 2.51 (s, 3H), 3.86 (d, 2H, J = 0.9 Hz), 4.38 (q, 2H, J = 7.2 Hz), 8.46 (t, 1H, J = 0.9 Hz), 8.49 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 14.3, 21.4, 25.6, 61.6, 112.7, 121.8, 131.9, 155.6, 163.0, 163.7, 157.5, 194.3. MS *m*/*z*: 280 (26, M^+), 234 (100). Anal. Calcd for $C_{12}H_{12}N_2O_4S$: C, 51.42; H, 4.31; N, 9.99. Found: C, 51.64; H, 4.48; N, 10.15.

5*H*-Thiazolo[3,2-*a*]pyrimidines (8). A solution of amidine **2b**−**d** (4 mmol) in methyl vinyl ketone (7 mL) was heated under reflux for 4 days. The excess methyl vinyl ketone was evaporated, and then the residue was diluted with dichloromethane and purifed by chromatography (elution ethyl acetate). Compounds **8** were recrystallized from dichloromethane (for **8a**[13j]) or dichloromethane/ether (for **8b**,**c**).

5-Acetyl-2-*p*-chlorobenzoyl-5*H*-thiazolo[3,2-*a*]pyrimidine (8b). Yellow crystals (yield 53%). Mp: 219−221 °C. IR (KBr): 1617, 1592, 1496, 1250 cm^{-1}. ^1H NMR (CF_3CO_2D) δ: 2.56 (s, 3H), 5.28 (s, 2H), 7.59−7.90 (m, 4H), 7.76 (s, 1H), 8.09 (s, 1H). ^{13}C NMR (CF_3CO_2D) δ: 25.1, 48.8, 115.3, 132.1 (2), 132.4 (2), 133.4, 134.6, 136.0, 138.6, 145.5, 165.7, 188.5, 201.6. MS *m*/*z*: 320/318 (36/100, M^+), 141/139 (16/48), 113/111 (12/40). Anal. Calcd for $C_{15}H_{11}ClN_2O_2S$: C, 56.52; H, 3.48; N, 8.79. Found: C, 56.37; H, 3.32; N, 8.63.

5-Acetyl-2-*p*-toluoyl-5*H*-thiazolo[3,2-*a*]pyrimidine (8c). Yellow crystals (yield 46%). Mp: 224−227 °C. IR (KBr): 1617, 1604, 1506, 1253. ^1H NMR (CF_3CO_2D): 2.53 (s, 3H), 2.57 (s, 3H), 5.30 (s, 2H), 7.46−7.88 (m, 4H), 7.78 (s, 1H), 8.11 (s, 1H). ^{13}C NMR (CF_3CO_2D): 22.7, 25.5, 49.1, 115.6, 131.8 (2), 132.7 (2), 133.8, 134.2, 136.4, 139.1, 151.2, 166.1, 189.7, 202.0. Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.57; H, 4.81; N, 9.49.

2*H*,6*H*-Pyrimido[2,1-*b*][1,3]thiazines (9). Thiazinylamidine **3** (1 mmol) was added to methyl vinyl ketone (5 mL) for **9a**,**c** or to a solution of acrolein (8 mmol) in chloroform (10 mL) for **9b**. The reaction mixture was stirred for 6 h at 45 °C (for **9a**), at 60 °C (for **9b**), and for 4 h under reflux (for **9c**[13j]). The mixture was then diluted with acetone (60 mL) and filtered through a short pad of Celite. The solvent was evaporated, the residue was diluted with dichloromethane, and compounds **9** were isolated after chromatography (elution dichloromethane/ethyl acetate 1/1 for **9a**, ethyl acetate/acetone 19/1 for **9b**, ethyl acetate for **9c**). Compound **9a** was isolated as an oil; compounds **9b**,**c** were recrystallized from ether.

7-Acetyl-3-formyl-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazine (9a). Yellow oil (yield 48%). R_f (EtOAc) = 0.4. IR (KBr): 2924, 1641, 1499, 1259, 1208, 1143. ^1H NMR ($CDCl_3$) δ: 2.32 (s, 3H), 3.68 (d, 2H, J = 0.9 Hz), 4.53 (d, 2H, J = 1.2 Hz), 6.79 (t, 1H, J = 0.9 Hz), 7.36 (t, 1H, J = 1.2 Hz), 9.40 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.0, 24.9, 48.7, 117.5, 118.8, 144.2, 148.2, 163.2, 187.0, 195.3. MS *m*/*z*: 222 (75, M^+), 43 (100). Anal. Calcd for

$C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 54.26; H, 4.61; N, 12.48.

7-Formyl-3-acetyl-2*H*,6*H*-pyrimido[2,1-*b*][1,3]-thiazine (9b). Yellow crystals (yield 53%). Mp: 159.5−160.5 °C. IR (KBr): 1653, 1472, 1223 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.37 (s, 3H), 3.72 (d, 2H, $J = 0.9$ Hz), 4.52 (d, 2H, $J = 1.2$ Hz), 6.97 (t, 1H, $J = 0.9$ Hz), 7.22 (t, 1H, $J = 1.2$ Hz), 9.44 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.9, 25.1, 48.1, 118.2, 119.0, 141.6, 151.6, 162.2, 188.8, 193.4. MS *m*/*z*: 222 (100, M^+), 43 (69). Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 53.87; H, 4.63; N, 12.52.

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Supporting Information Available: General procedures, detailed experimental procedures for compounds **1**, **4**, and **7**, spectroscopic data for **1**, **2b**, **3b**, **5b**, **8a**, and **9c**, and copies of ^1H and ^{13}C NMR for all compounds (except ^1H for **8b** and ^{13}C for **4b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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