A Facile Access to Imidazo[2,1-*b*]thiazole and Thiazolo[3,2-*a*]pyrimidine Derivatives

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Abstract: A new and efficient method for the synthesis of 2,3-dihydroimidazo[2,1-*b*]thiazoles **3**, 2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **4** and 2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidines **5** has been developed. The reactions of *N*′-(4,5-dihydrothiazol-2-yl)-*N*,*N*-dimethylamidines **1** with α-halogenoketones, acid chlorides or acrylic dienophiles were performed, leading to the title products.

Keywords: bicyclic compounds, heterocycles, acylations, alkylations, Diels–Alder reactions

Imidazo[2,1-*b*]thiazole and thiazolo[3,2-*a*]pyrimidine derivatives are important heterocycles found in numerous biologically active compounds. Particularly, Levamisole[1] is well known as a potent immuno-modulating agent, while Ritanserin[2] finds application in several psychopharmacological fields. Furthermore, Andreani and coworkers[3] have explored the widespread activities of various imidazo[2,1-*b*]thiazoles displaying herbicidal,[3a] antiarrhythmic[3b] and antitumor[3c] properties and have shown that some of them have an interesting potential for the treatment of human neurodegenerative diseases.[3d] Diaryl derivatives of these heterocycles have also been found to possess anti-arthritic and anti-inflammatory properties,[4] and to be interesting intermediates for the preparation of trisubstituted imidazoles.[5] On the other hand, some thiazolo[3,2-*a*]pyrimidines were recently reported to be active against HIV-1 as annulated analogues of HEPT,[6] while another series of these compounds have been successfully tested as anti-inflammatory agents by Tozkoparan and coworkers.[7]

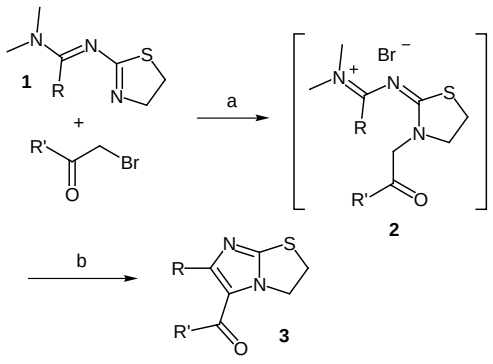
Several methods have been published for the construction of these structures. Both may be obtained via the alkylation of a cyclic thiourea by an appropriate dielectrophile. However, this route induces the formation of two regioisomers in certain cases.[8] Thiazolo[3,2-*a*]pyrimidines are generally prepared by subjecting 2-aminothiazoles to cyclization with difunctionalized reagents.[9] The most common preparation of imidazo[2,1-*b*]thiazoles remains the well-known Hantzch type synthesis.[10] Consequently, derivatives are synthesized by substitutions of previously known compounds.[11]

These considerations as well as our strong background in heterocyclic chemistry[12] led us to develop an alternative approach to build these systems. In previous papers,[12a,c] we described the versatility of cationic diazadienes as stable synthons for the preparation of various monocycles. As a consequence, we planned to investigate the syntheses of fused ring systems applying these methods to analogous heterocyclic diazadienes.

The use of such substrates is not unprecedented since several teams have mentioned their reaction with isothiocyanates,[13] diphenylketene[14] or diketene.[15] Furthermore, Stanovnik and coworkers[16] have widely exploited a similar synthetic sequence leading to fused imidazoles. This path consisted of the alkylation of this type of amidines by a bromide possessing an activated methylene group, followed by intramolecular cyclization. These works, however, were not specifically directed to the synthesis of the title compounds.

The method starts with the preparation of the heterocyclic diazadienes **1**, which was carried out according to literature[13] by heating a CH_2Cl_2 solution of 2-amino-Δ^2-thiazoline and *N*,*N*-dimethylformamide dimethyl acetal or *N*,*N*-dimethylacetamide dimethyl acetal.

As shown in Scheme 1, amidines **1** were first subjected to alkylation with α-halogenoketones leading to amidinium bromides **2**. Treatment with a base generated the enolate, which underwent intramolecular condensation with the iminium group, followed by spontaneous elimination of dimethylamine to give imidazo[2,1-*b*]thiazoles **3** in moderate to good yields (Table 1).



Scheme 1 *Reagents and conditions:* (a) THF, 78 °C, 20 h; (b) Et_3N, r.t., 24 h or KOH/EtOH, 78 °C, 18 h

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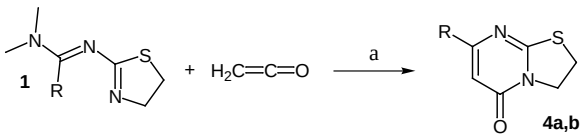
Table 1 Yields of Amidinium Bromides **2** and 2,3-Dihydroimidazo[2,1-*b*]thiazoles **3** Prepared

R	R′	Product	Yield (%)	Product	Yield (%)
H	*p*-BrC_6H_4	**2a**	79	**3a**	79[a]
H	*p*-ClC_6H_4	–	–	**3b**	32
CH_3	*p*-BrC_6H_4	–	–	**3c**	78
H	*p*-$CH_3C_6H_4$	**2d**	73	**3d**	40[a]

[a] Yields based on compounds **2**.

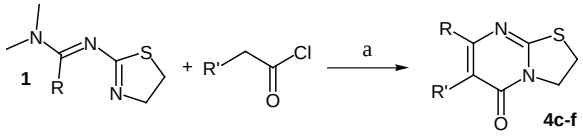
Salts **2** were found to be stable but quite hygroscopic. When bromides **2** could not be isolated, deprotonation was performed in situ by addition of two equivalents of Et_3N; in the other case, treatment with an ethanolic solution of KOH was preferred. The use of other bases (e.g., NaH, EtONa) did not significantly increase the yield of cyclization. Thus, we were able to prepare imidazo[2,1-*b*]thiazoles bearing an electron-withdrawing group in position 5, similarly to those obtained by Iwata et al.,[17] but with the benefit that position 6 is not occupied by an amino group and therefore may be used as a candidate for a later substitution.

The synthetic value of compounds **1** was then emphasized by three further cyclization reactions. The [4+2] cycloaddition with ketene, prepared according to Vogel[18] by cracking of acetone, was first examined. As expected, cyclization took place followed by deamination of the intermediary cycloadduct leading to 6-unsubstituted thiazolo[3,2-*a*]pyrimidin-5-ones **4a**,**b** (Scheme 2).



Scheme 2 *Reagents and conditions:* (a) CH_2Cl_2, r.t., 1 h

The 6-substituted analogues **4c**–**f** were then obtained in good yields by condensation of **1** with acid chlorides (Scheme 3, Table 2). Acylation of **1** occurred smoothly and cyclization of the resulting non-isolated salt was achieved by addition of 2 equivalents of Et_3N. We assume that the reaction proceeds by a classical [4+2] cycloaddition with the ketenes generated by dehydrohalogenation of acid chlorides, since the same results were obtained when Et_3N was added first.



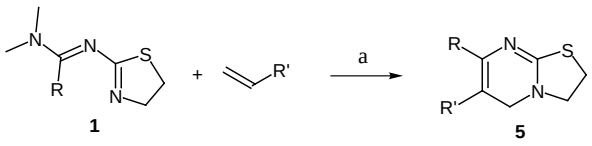
Scheme 3 *Reagents and conditions:* (a) CH_2Cl_2, r.t., 4 h then Et_3N, CH_2Cl_2, r.t., 16 h

Table 2 Yields of 2,3-Dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **4** Prepared

Product	R	R′	Yield (%)
4a[19,20]	H	H	33
4b[19]	CH_3	H	61
4c	H	$COOCH_3$	89
4d	CH_3	$COOCH_3$	56
4e[19–21]	H	$COOC_2H_5$	98
4f[21,22]	H	C_6H_5	63

Most of these compounds were accessible by previous methods,[19–22] like treatment of 2-aminothiazoline with ethoxymethylenemalonic esters. However, theses procedures provided in some cases a mixture of both the 5- and 7-oxoisomers. Our pathway excludes any regioisomeric ambiguity: indeed, the ^{1}H NMR deshielding effect observed for the 3-methylene group signal is unambiguously attributed to the proximity of the 5-carbonyl function. Moreover, this regioselective route seems simpler and more general than the one proposed by Bernáth and coworkers,[23] involving the retrodiene decomposition of the corresponding norbornene-fused derivatives.

We continued our investigations towards thiazolo[3,2-*a*]pyrimidines by exposing dienes **1** to acrylic dienophiles (Scheme 4). The [4+2] cycloaddition with acrolein, methyl vinyl ketone or methyl acrylate proceeded as expected, followed once again by spontaneous deamination, affording 2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidines **5** in modest to excellent yields (Table 3). Both ^{1}H NMR spectra of **5b** and **5e** present a singlet due to the methyl group in position 7, allowing us to rule out an unlikely rearrangement leading to the 7*H*-isomer. It should be noticed that this methodology is somewhat complementary to the precedent since position 5 of the furnished compounds is not occupied by a carbonyl function.



Scheme 4 *Reagents and conditions:* (a) $CHCl_3$, 20 h, for **5a**,**b**; neat, 20 h, r.t. for **5c**,**e**; or Δ for **5d**

In conclusion, a reliable and regiocontrolled alternative route to imidazo[2,1-*b*]thiazoles **3**, 5*H*-imidazo[3,2-*a*]pyrimidin-5-ones **4** and 5*H*-imidazo[3,2-*a*]pyrimidines **5** has been established. We believe the present methodology to have a broad applicability to the synthesis of biologically active derivatives.

All reagents were purchased either from Acros Organics or Aldrich. The elemental analyses were performed at the C.N.R.S. Analysis Laboratory (Vernaison). Column chromatography was conducted

Table 3 Yields of 2,3-Dihydro-5*H*-thiazolo[3,2-*a*]pyrimidines **5** Prepared

Product	R	R′	Yield (%)
5a	H	CHO	88
5b	CH_3	CHO	64
5c	H	$COCH_3$	61
5d	H	$COOCH_3$	23
5e	CH_3	$COCH_3$	51

on silica gel 60 (40–63 μm), available from E. Merck. TLC was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60 F-254). Mps (uncorrected) were measured using a Reichert microscope. ^{13}C and ^1H NMR spectra were recorded at r.t. using a Bruker AC 200 at 50 MHz and 200 MHz, respectively. Chemical shifts (δ) are given in ppm downfield from TMS as internal standard. Mass spectra were recorded with a Hewlett Packard 5989 spectrometer. The IR spectra were obtained using a Bruker Vector 22 spectrometer. All chemicals were reagent grade and used without further purification. THF was freshly distilled from Na/benzophenone ketyl, while CH_2Cl_2 was distilled over CaH_2. All reactions were carried in a N_2 atm.

Amidines 1; General Procedure

A suspension of 2-amino-Δ^2-thiazoline (10 mmol) and *N*,*N*-dimethylformamide dimethylacetal (11 mmol, for **1a**) or *N*,*N*-dimethylacetamide dimethylacetal (13 mmol, for **1b**) in CH_2Cl_2 (10 mL) was refluxed for 4 h. Compound **1a** was obtained by filtration through cotton, evaporation of the solvent and crystallization from Et_2O. Compound **1b** was obtained as an oil by chromatography (CH_2Cl_2–EtOH, 5:1).

***N′*-(4,5-Dihydrothiazol-2-yl)-*N*,*N*-dimethylformamidine (1a)[13]**

Yield: 96%; white crystals.

Mp 72 °C (Lit.[13] mp 70–72 °C).

IR (KBr): 1639, 1559, 1419, 1362, 1113, 1022 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.04, 3.06 [2s, 6 H, $(NCH_3)_2$], 3.36 (t, 2 H, *J* = 7.8 Hz, SCH_2), 4.11 (t, 2 H, *J* = 7.8 Hz, NCH_2), 7.91 (s, 1 H, C*H*).

^{13}C NMR ($CDCl_3$): δ = 33.9 (SCH_2), 34.4, 40.2 [$(NCH_3)_2$], 59.7 (NCH_2), 158.4 (*C*H), 168.2 (S*C*N).

MS (EI): *m/z* (%) = 157 (M^+, 55), 124 (12), 110 (95), 98 (89), 83 (58), 42 (100).

***N′*-(4,5-Dihydrothiazol-2-yl)-*N*,*N*-dimethylacetamidine (1b)**

Yield: 97%; yellow oil.

R_f = 0.4 (EtOH–CH_2Cl_2, 1:1).

IR (film): 1597, 1419, 1399, 1312, 1163, 1013 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.15 (s, 3 H, CH_3), 3.03 [s, 6 H, $(NCH_3)_2$], 3.39 (t, 2 H, *J* = 7.8 Hz, SCH_2), 4.14 (t, 2 H, *J* = 7.8 Hz, NCH_2).

^{13}C NMR ($CDCl_3$): δ = 11.8 (CCH_3), 31.2 (SCH_2), 33.6 [$(NCH_3)_2$], 57.0 (NCH_2), 156.0 (CCH_3), 164.4 (S*C*N).

MS (EI): *m/z* (%) = 171 (M^+, 43), 138 (14), 124 (100), 112 (33), 97 (21).

Amidinium Bromides 2 and Imidazo[2,1-*b*]thiazoles 3; General Procedure

A solution of α-bromoketone (2.2 mmol) (2,4′-dibromoacetophenone for **3a**,**c**, 2-bromo-4′-chloroacetophenone for **3b**, 2-bromo-4′-methylacetophenone for **3d**) and amidine **1** (2 mmol) in THF (10 mL) was refluxed for 20 h.

Method A

After cooling to r.t., Et_3N (4.4 mmol) was added. The reaction mixture was further stirred at r.t. for 24 h, then concentrated in vacuo. The resulting residue was purified by chromatography (CH_2Cl_2–EtOAc, 9:1) to furnish compounds **4b**,**c**, which were crystallized from Et_2O.

Method B

The solvent was evaporated and amidinium bromides **2a**, **d** were precipitated with Et_2O, collected by filtration and dried. A solution of compound **2** (1.5 mmol) and KOH (3 mmol) in EtOH (20 mL) was refluxed for 18 h. The mixture was cooled to r.t., diluted with CH_2Cl_2 (100 mL) and washed with H_2O (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (CH_2Cl_2–EtOAc, 9:1), followed by precipitation with Et_2O, furnished compounds **3a**,**d** as white crystals.

Amidinium Bromide (2a)

Yield: 79%; white crystals; hygroscopic.

^1H NMR (DMSO-d_6): δ = 3.01, 3.28 [2s, 6 H, $N(CH_3)_2$], 3.68 (t, 2 H, *J* = 7.8 Hz, SCH_2), 4.10 (t, 2 H, *J* = 7.8 Hz, NCH_2), 5.38 (s, 2 H, NCH_2CO), 7.78–8.00 (m, 4 H, Ar*H*), 8.35 (s, 1 H, NC*H*).

^{13}C NMR (DMSO-d_6): δ = 28.1 (SCH_2), 36.3, 41.9 [$N(CH_3)_2$], 53.7, 53.8 (2 × NCH_2), 128.3 (Ar*C*), 130.1, 132.0 (4 × Ar*C*H), 133.2 (Ar*C*), 163.0 (N*C*H), 176.9 (S*C*N), 191.3 (*C*O).

5-*p*-Bromobenzoyl-2,3-dihydroimidazo[2,1-*b*]thiazole (3a)

Yield:79%; white crystals.

Mp 216 °C.

IR (KBr): 1623, 1585, 1510, 1366, 1243, 1166, 902, 753 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.02 (t, 2 H, *J* = 7.6 Hz, SCH_2), 4.52 (t, 2 H, *J* = 7.6 Hz, NCH_2), 7.62 (s, 1 H, NC*H*), 7.74–7.76 (m, 4H, Ar*H*).

^{13}C NMR (DMSO-d_6): δ = 35.1 (SCH_2), 47.0 (NCH_2), 126.3, 129.9, 136.5 (N*C*CO, 2 × Ar*C*), 130.5, 131.8 (4 × Ar*C*H), 144.5 (N*C*H), 168.7 (S*C*N), 181.2 (*C*O).

MS (EI): *m/z* (%) = 310/308 (M^+, 100/99), 229 (7), 185/183 (48/51), 157/155 (26/28), 125 (13).

Anal. Calcd for $C_{12}H_9BrN_2OS$ (309.2): C, 46.62; H, 2.93; N, 9.06. Found: 46.48; H, 2.79; N, 9.17.

5-*p*-Chlorobenzoyl-2,3-dihydroimidazo[2,1-*b*]thiazole (3b)

Yield: 32%; white crystals.

Mp 212 °C.

IR (KBr): 1624, 1404, 1366, 1246, 1166, 904, 755 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.95 (t, 2 H, *J* = 7.6 Hz, SCH_2), 4.62 (t, 2 H, *J* = 7.6 Hz, NCH_2), 7.39–7.86 (m, 4 H, Ar*H*). 7.55 (s, 1 H, NC*H*).

^{13}C NMR ($CDCl_3$): δ = 35.2 (SCH_2), 47.1 (NCH_2), 126.3, 129.6, 137.5 (N*C*CO, 2 × Ar*C*), 129.2, 130.8 (4 × Ar*C*H), 142.5 (N*C*H), 163.5 (S*C*N), 181.7 (*C*O).

MS (EI): *m/z* (%) = 266/264 (M^+, 41/100), 153 (18), 141/139 (33/96), 125 (15), 113/111 (18/55), 97 (21).

Anal. Calcd for $C_{12}H_9ClN_2OS$ (264.7): C, 54.44; H, 3.43; N, 10.58. Found: 55.08; H, 3.29; N, 10.76.

6-Methyl-5-*p*-bromobenzoyl-2,3-dihydroimidazo[2,1-*b*]thiazole (3c)
Yield: 78%; yellow crystals.

Mp 161 °C.

IR (KBr): 1606, 1584, 1507, 1360, 1312, 1251, 941, 757 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.03 (s, 3 H, CH_3), 3.88 (t, 2 H, *J* = 7.8 Hz, SCH_2), 4.50 (t, 2 H, *J* = 7.8 Hz, NCH_2), 7.55–7.65 (m, 4 H, Ar*H*).

^{13}C NMR ($CDCl_3$): δ = 17.2 (C*C*H_3), 35.4 (S*C*H_2), 47.5 (N*C*H_2), 126.9, 127.8, 137.8 (N*C*CO, 2 × Ar*C*), 130.2, 131.8 (4 × Ar*C*H), 153.3 (*C*CH_3), 175.8 (S*C*N), 184.4 (*C*O).

MS (EI): *m/z* (%) = 324/322 (M^+, 100/98), 243 (62), 185/183 (36/38), 167 (20), 157/155 (35/34), 139 (21).

Anal. Calcd for $C_{13}H_{11}BrN_2OS$ (323.2): C, 48.31; H, 3.43; N, 8.67. Found: 48.43; H, 3.38; N, 8.60.

Amidinium Bromide (2d)
Yield: 73%; white crystals; hygroscopic.

^1H NMR (DMSO-d_6): δ = 2.39 (s, 3 H, CH_3), 3.00, 3.29 [2s, 6 H, N(CH_3)$_2$], 3.68 (t, 2 H, *J* = 7.8 Hz, SCH_2), 4.11 (t, 2 H, *J* = 7.8 Hz, NCH_2), 5.35 (s, 2 H, NCH_2CO), 7.36–7.94 (m, 4 H, Ar*H*), 8.34 (s, 1 H, NC*H*).

^{13}C NMR (DMSO-d_6): δ = 21.2 (*C*H_3), 28.1 (S*C*H_2), 36.2, 41.9 [N(*C*H_3)$_2$], 53.7, 54.0 (2 × N*C*H_2), 128.2, 129.5 (4 × Ar*C*H), 131.8, 144.8 (2 × Ar*C*), 163.0 (N*C*H), 176.9 (S*C*N), 191.3 (*C*O).

5-*p*-Toluoyl-2,3-dihydroimidazo[2,1-*b*]thiazole (3d)
Yield: 40%; white crystals.

Mp 180 °C.

IR (KBr): 1621, 1603, 1512, 1402, 1359, 1241, 1157, 902, 751 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 3.93 (t, 2 H, *J* = 7.6 Hz, SCH_2), 4.62 (t, 2 H, *J* = 7.6 Hz, NCH_2), 7.27–7.78 (m, 4 H, Ar*H*), 7.56 (s, 1 H, NC*H*).

^{13}C NMR ($CDCl_3$): δ = 21.2 (*C*H_3), 35.4 (S*C*H_2), 46.8 (N*C*H_2), 128.4, 128.8 (4 × Ar*C*H), 130.2, 134.8 (2 × Ar*C*), 142.8 (N*C*CO), 143.9 (N*C*H), 156.8 (S*C*N), 182.9 (*C*O).

MS (EI): *m/z* (%) = 244 (M^+, 100), 229 (14), 119 (66), 91 (39), 65 (19).

Anal. Calcd for $C_{13}H_{12}N_2OS$ (244.3): C, 63.91; H, 4.95; N, 11.47. Found: 63.83; H, 4.79; N, 11.35.

Thiazolo[3,2-*a*]pyrimidin-5-ones 4; General Procedure
Method A
Ketene (CAUTION), produced by cracking of acetone, was bubbled into a solution of amidine **1** (4 mmol) in CH_2Cl_2 (150 mL) until complete consumption of the starting material, as monitored by TLC (approx. 1 h). After evaporation of the solvent, the residue was dissolved in a small amount of CH_2Cl_2 and subjected to flash chromatography (EtOAc–acetone, 9:1 for **4a**; EtOAc–CH_2Cl_2, 5:1 for **4b**). Compounds **4a**,**b** were crystallized from Et_2O.

2,3-Dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (4a)[19,20]
Yield: 33%; yellow crystals.

Mp 110 °C (Lit.[19] mp 107–108 °C).

IR (KBr): 1684, 1570, 1493, 1451, 1377, 1148, 833 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.46 (t, 2 H, *J* = 7.7 Hz, SCH_2), 4.45 (t, 2 H, *J* = 7.7 Hz, NCH_2), 6.15 (d, 1 H, *J* = 6.7 Hz, C*H*CO), 7.73 (d, 1 H, *J* = 6.7 Hz, NC*H*).

^{13}C NMR ($CDCl_3$): δ = 26.3 (S*C*H_2), 48.8 (N*C*H_2), 110.4 (*C*HCO), 153.9 (N*C*H), 160.9 (N*C*O), 165.6 (S*C*N).

MS (EI): *m/z* (%) = 154 (M^+, 100), 126 (22), 108 (8), 95 (24), 80 (13).

Anal. Calcd for $C_6H_6N_2OS$ (154.2): C, 46.74; H, 3.92; N, 18.17. Found: 46.86; H, 3.99; N, 18.24.

7-Methyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (4b)[19]
Yield: 61%; white crystals.

Mp 128 °C (Lit.[19] mp 127–128 °C).

IR (KBr): 1678, 1581, 1516, 1446, 1404, 1123, 865 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.23 (s, 3 H, CH_3), 3.44 (t, 2 H, *J* = 7.8 Hz, SCH_2), 4.45 (t, 2 H, *J* = 7.8 Hz, NCH_2), 6.00 (s, 1 H, C*H*).

^{13}C NMR ($CDCl_3$): δ = 23.5 (*C*CH_3), 26.2 (S*C*H_2), 48.5 (N*C*H_2), 107.6 (*C*H), 161.0 (N*C*O), 164.2, 164.7 (S*C*N, *C*CH_3).

MS (EI): *m/z* (%) = 168 (M^+, 100), 140 (17), 122 (6), 109 (34), 94 (7).

Anal. Calcd for $C_7H_8N_2OS$ (168.2): C, 49.98; H, 4.79; N, 16.65. Found: 50.07; H, 4.87; N, 16.75.

Method B
A solution of amidine **1** (2 mmol) and acid chloride (2.4 mmol) (methyl malonyl chloride for **4c**,**d**, ethyl malonyl chloride for **4e**, or phenylacetyl chloride for **4f**) in CH_2Cl_2 (10 mL) was stirred at r.t. for 4 h. After cooling to 0 °C, Et_3N (4.8 mmol) was added and stirring was continued at r.t. for 16 h. After removal of the solvent, the residue was chromatographed using CH_2Cl_2–EtOAc (1:1 for **4c**, **e**, 5:1 for **4d**,**f**). Compounds **4c**–**f** were crystallized from Et_2O.

6-Methoxycarbonyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (4c)
Yield: 89%; white crystals.

Mp 127 °C.

IR (KBr): 1735, 1496, 1119 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.53 (t, 2 H, *J* = 7.9 Hz, SCH_2), 3.88 (s, 3 H, OCH_3), 4.56 (t, 2 H, *J* = 7.9 Hz, NCH_2), 8.53 (s, 1 H, C*H*).

^{13}C NMR ($CDCl_3$): δ = 27.5 (S*C*H_2), 50.3 (N*C*H_2), 53.1 (O*C*H_3), 113.0 (*C*CO), 158.2 (N*C*O), 160.9 (N*C*H), 165.1 (S*C*N), 171.2 (*C*OO).

MS (EI): *m/z* (%) = 212 (M^+, 35), 181 (100), 154 (23), 113 (21).

Anal. Calcd for $C_8H_8N_2O_3S$ (212.2): C, 45.28; H, 3.80; N, 13.20. Found: 45.35; H, 3.85; N, 13.31.

6-Methoxycarbonyl-7-methyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (4d)
Yield: 56%; white crystals.

Mp 109 °C.

IR (KBr): 1700, 1675, 1496, 1254, 1129 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.36 (s, 3 H, CH_3), 3.47 (t, 2 H, *J* = 7.9 Hz, SCH_2), 3.90 (s, 3 H, OCH_3), 4.49 (t, 2 H, *J* = 7.9 Hz, NCH_2).

^{13}C NMR ($CDCl_3$): δ = 22.8 (*C*CH_3), 26.3 (S*C*H_2), 49.1 (N*C*H_2), 52.4 (O*C*H_3), 113.8 (*C*CO), 158.0 (N*C*O), 165.3, 165.6, 165.9 (*C*CH_3, S*C*N, *C*OO).

MS (EI): *m/z* (%) = 226 (M^+, 28), 195 (100), 168 (11), 127 (44), 67 (46).

Anal. Calcd for $C_9H_{10}N_2O_3S$ (226.2): C, 47.78; H, 4.45; N, 12.38. Found: 47.65; H, 4.52; N, 12.46.

6-Ethoxycarbonyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (4e)[19,20,21]
Yield: 98%; white crystals.

Mp 174 °C (Lit.[19] mp 174–176 °C).

IR (KBr): 1730, 1653, 1496, 1286, 1127, 799 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.36 (t, 3 H, *J* = 7.2 Hz, CH_2CH_3), 3.53 (t, 2 H, *J* = 7.9 Hz, SCH_2), 4.35 (q, 2 H, *J* = 7.2 Hz, OCH_2), 4.56 (t, 2 H, *J* = 7.9 Hz, NCH_2), 8.51 (s, 1 H, C*H*).

^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 26.4 (SCH_2), 49.1 (NCH_2), 60.8 (OCH_2), 112.1 (*C*CO), 157.0 (N*C*O), 159.3 (N*C*H), 163.3 (S*C*N), 170.2 (*C*OO).

MS (EI): *m/z* (%) = 226 (M^+, 25), 181 (100), 154 (87), 113 (22).

Anal. Calcd for $C_9H_{10}N_2O_3S$ (226.2): C, 47.78; H, 4.45; N, 12.38. Found: 47.88; H, 4.53; N, 12.45.

6-Phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (4f)[21,22]
Yield: 63%; white crystals.

Mp 180 °C (Lit.[22] mp 181 °C).

IR (KBr): 1653, 1517, 1465, 1394, 786, 696 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.51 (t, 2 H, *J* = 7.7 Hz, SCH_2), 4.56 (t, 2 H, *J* = 7.7 Hz, NCH_2), 7.33–7.65 (m, 5 H, Ar*H*), 7.92 (s, 1 H, NC*H*).

^{13}C NMR ($CDCl_3$): δ = 26.5 (SCH_2), 49.0 (NCH_2), 122.5 (*C*CO), 123.0, 128.2, 128.3 (5 × Ar*C*H), 132.9 (Ar*C*), 151.4 (N*C*H), 159.9 (N*C*O), 163.8 (S*C*N).

MS (EI): *m/z* (%) = 230 (M^+, 100), 202 (9), 174 (6), 142 (10), 102 (22), 63 (7).

Anal. Calcd for $C_{12}H_{10}N_2OS$ (230.3): C, 62.59; H, 4.38; N, 12.16. Found: 62.48; H, 4.36; N, 12.23.

Thiazolo[3,2-a]pyrimidines 5: General Procedure
A mixture of amidine **1** (4 mmol) and dienophile [acrolein (10 mmol) in $CHCl_3$ (10 mL) for **5a**,**b**; methyl acrylate (5 mL) for **5d**; methyl vinyl ketone (5 mL) for **5c**,**e**] was stirred for 20 h at r.t. (**5a**–**c**, **e**) or at reflux (**5d**), then evaporated under reduced pressure and chromatographed (EtOAc–acetone, 7:3 for **5a**,**b**; 9:1 for **5c**; 5:1 for **5e**; CH_2Cl_2–EtOAc, 7:3 for **5d**). Compounds **5** were crystallized from Et_2O (except for **5e**, which was isolated as an oil).

6-Formyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine (5a)
Yield: 88%; yellow crystals.

Mp 135 °C.

IR (KBr): 1646, 1612, 1513, 1380, 1132, 1055 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.35 (t, 2 H, *J* = 7.6 Hz, SCH_2), 3.73 (t, 2 H, *J* = 7.6 Hz, NCH_2CH_2), 4.21 (s, 2 H, NCH_2), 7.18 (s, 1 H, NC*H*), 9.33 (s, 1 H, C*H*O).

^{13}C NMR ($CDCl_3$): δ = 25.7 (SCH_2), 44.0 (NCH_2), 53.8 (NCH_2CH_2), 114.3 (*C*CO), 155.9 (N*C*H), 171.8 (S*C*N), 188.5 (*C*HO).

MS (EI): *m/z* (%) = 168 (M^+, 100), 167 (52), 140 (23), 112 (37).

Anal. Calcd for $C_7H_8N_2OS$ (168.2): C, 49.98; H, 4.79; N, 16.65. Found: 49.77; H, 4.82; N, 16.72.

6-Formyl-7-methyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine (5b)
Yield: 64%; orange crystals.

Mp 162 °C.

IR (KBr): 1628, 1600, 1526, 1387, 1188, 1022 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.23 (s, 3 H, C*H*$_3$), 3.32 (t, 2 H, *J* = 7.6 Hz, SCH_2), 3.74 (t, 2 H, *J* = 7.6 Hz, NCH_2CH_2), 4.12 (s, 2 H, NCH_2), 9.85 (s, 1 H, C*H*O).

^{13}C NMR ($CDCl_3$): δ = 19.1 (*C*C*H*$_3$), 25.7 (S*C*H$_2$), 44.4 (N*C*H$_2$), 54.1 (N*C*H$_2$C*H*$_2$), 109.1 (*C*CO), 162.1 (*C*C*H*$_3$), 170.4 (S*C*N), 187.1 (*C*HO).

MS (EI): *m/z* (%) = 182 (M^+, 100), 181 (60), 154 (16), 126 (21).

Anal. Calcd for $C_8H_{10}N_2OS$ (182.2): C, 52.73; H, 5.53; N, 15.37. Found: 52.59; H, 5.44; N, 15.49.

6-Acetyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine (5c)
Yield: 61%; yellow crystals.

Mp 151 °C.

IR (KBr): 1627, 1521, 1394, 1309, 1262, 1138 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.27 (s, 3 H, COC*H*$_3$), 3.32 (t, 2 H, *J* = 7.5 Hz, SC*H*$_2$), 3.69 (t, 2 H, *J* = 7.5 Hz, NC*H*$_2$CH$_2$), 4.17 (s, 2 H, NC*H*$_2$), 7.37 (s, 1 H, NC*H*).

^{13}C NMR ($CDCl_3$): δ = 24.3 (CO*C*H$_3$), 25.7 (S*C*H$_2$), 45.0 (N*C*H$_2$), 53.8 (N*C*H$_2$CH$_2$), 112.8 (*C*CO), 148.3 (N*C*H), 170.2 (S*C*N), 195.1 (*C*O).

MS (EI): *m/z* (%) = 182 (M^+, 100), 181 (61), 154 (25), 139 (29).

Anal. Calcd for $C_8H_{10}N_2OS$ (182.2): C, 52.73; H, 5.53; N, 15.37. Found: 52.88; H, 5.69; N, 15.29.

6-Methoxycarbonyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine (5d)
Yield: 23%; yellow crystals.

Mp 150 °C.

IR (KBr): 1689, 1623, 1533, 1405, 1296, 1136, 1095 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.30 (t, 2 H, *J* = 7.5 Hz, SC*H*$_2$), 3.64 (t, 2 H, *J* = 7.5 Hz, NC*H*$_2$CH$_2$), 3.73 (s, 3 H, OC*H*$_3$), 4.19 (s, 2 H, NC*H*$_2$), 7.37 (s, 1 H, NC*H*).

^{13}C NMR ($CDCl_3$): δ = 25.8 (S*C*H$_2$), 45.4 (N*C*H$_2$), 51.3 (O*C*H$_3$), 53.8 (N*C*H$_2$CH$_2$), 102.7 (*C*CO), 146.5 (N*C*H), 166.7 (*C*O), 170.0 (S*C*N).

MS (EI): *m/z* (%) = 198 (M^+, 30), 197 (50), 183 (100), 167 (14), 139 (11).

Anal. Calcd for $C_8H_{10}N_2O_2S$ (198.2): C, 48.47; H, 5.08; N, 14.13. Found: 48.63; H, 5.24; N, 14.30.

6-Acetyl-7-methyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine (5e)
Yield: 51%; yellow oil.

R_f = 0.2 (acetone).

IR (KBr): 1653, 1621, 1525, 1416, 1377, 1318, 1276, 1194 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.29 (s, 3 H, C*H*$_3$), 2.36 (s, 3 H, COC*H*$_3$), 3.30 (t, 2 H, *J* = 7.6 Hz, SC*H*$_2$), 3.67 (t, 2 H, *J* = 7.6 Hz, NC*H*$_2$CH$_2$), 4.12 (s, 2 H, NC*H*$_2$).

^{13}C NMR ($CDCl_3$): δ = 24.2, 25.7, 31.1 (CO*C*H$_3$, S*C*H$_2$, C*C*H$_3$), 46.6 (N*C*H$_2$), 53.9 (N*C*H$_2$CH$_2$), 109.1 (*C*CO), 155.8 (*C*CH$_3$), 168.4 (S*C*N), 195.9 (*C*O).

MS (EI): *m/z* (%) = 196 (M^+, 44), 195 (100), 181 (27), 153 (12), 127 (32).

Although the purity of this compound was confirmed by TLC (only one spot was present after purification by flash chromatography), we did not obtain the desirable result by elemental analyses.

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