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Unsymmetrical polyheteropolyene: a versatile building block for the preparation of pyrrolo[2,1-*b*]thiazoles and 2*H*-thiopyrano[2,3-*b*]pyridines

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Abstract—The synthesis of two classes of bisheterocyclic compounds, pyrrolothiazoles and thiopyranopyridines, is reported. The 4-dimethylamino-2-dimethylaminomethylenamino-1-thiabuta-1,3-diene **1** is used like a useful building block for the chemoselective synthesis of these heterocycles. Indeed, synthon **1** can react as thiazabutadiene or thiabutadiene form to afford either five- or six-membered ring monocyclic azadienes, themselves being precursors to the bicyclic structures. Semi-empirical calculations were undertaken to explain this efficient chemoselectivity.

1. Introduction

Pyrrolo[2,1-*b*]thiazoles and especially 2*H*-thiopyrano[2,3-*b*]pyridines are unusual ring systems, which may be of interest from a biological aspect. Since the first synthesis of the former was reported,[1] only few other preparations have sporadically been proposed,[2] despite di- and tetrahydroderivatives having attracted attention as potentially antineoplastic[3] or hypoglycemic agents,[4] or as modulators of dopaminergic neurotransmission in CNS in vivo[5] and as γ-lactam analogues of the penems.[6] To the best of our knowledge, few reports deal with the construction of 2*H*-thiopyrano[2,3-*b*]pyridines.[7] In the latest report, oxime ethers of these compounds were shown to display antihypertensive properties,[7c,d] and spirohydantoin derivatives were tested for their ability to inhibit aldose reductase.[7e]

In the course of our continued endeavour to expand the use of heterodienes in heterocyclic synthesis,[8] we describe herein a novel and simple methodology to access both of these heterocycles, using relatively low cost reactants. Moreover, this method involves a convenient common polyheteropolyenic precursor, namely the 4-dimethylamino-2-dimethylaminomethylenamino-1-thiabuta-1,3-diene **1**, constituted of a 1-thiabutadienic chain fused to a 1-thia-3-azabutadienic moiety and appropriately substituted with good leaving, strong electron-releasing groups. Using a similar methodology, we recently described a novel route to thiazolopyrimidines or imidazothiazines involving a double annulation reaction from an equivalent symmetrical polyheteropolyenic precursor.[9]

The use of such synthons has already been investigated by Liebscher and co-workers.[10] Their work, however, was restricted to the preparation of monocycles. As for us, our firm intention was to build bicyclic structures with an efficient chemoselectivity, in one or two steps, starting from a similar substrate and using various reagents.

2. Results and discussion

2.1. Synthesis of pyrrolo[2,1-*b*]thiazoles

The starting polyheteropolyenic precursor **1** was obtained in two steps in good yield by sulfhydration of 3-dimethylaminoacrylonitrile followed by condensation with *N*,*N*-dimethylformamide dimethylacetal. This 4-dimethylamino-2-dimethylaminomethylenamino-1-thiabuta-1,3-diene **1** was isolated as a mixture of stereoisomers and was used without further purification. This synthon can react as a thiazadiene or as an azadiene form for the first cyclization to give the heterocyclic compound.

With the aim of investigating the reactivity of the compound **1**, it was first subjected to alkylation with methyl bromoacetate and 2,4′-dibromoacetophenone (Scheme 1, Table 1).

Keywords: Cycloaddition; Bisheterocycles; Azadiene; Thiazadiene.
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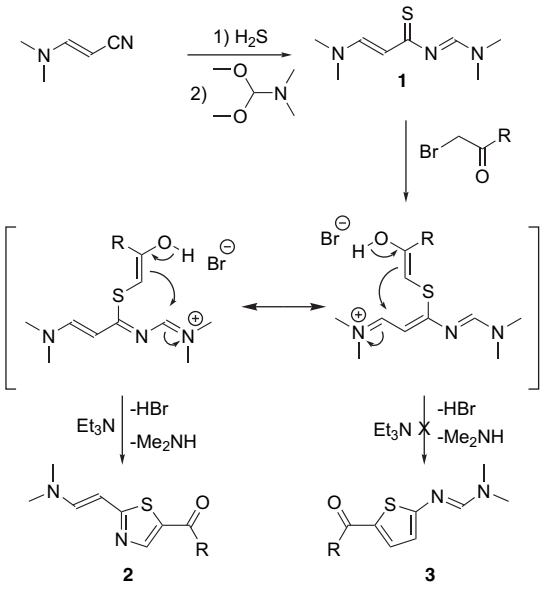
Treatment with triethylamine induced the expected intramolecular cyclization of the resulting *S*-alkylated salt by condensation of the enol with the amidinium moiety. The following spontaneous loss of dimethylamine provided good yields of thiazole derivatives **2** as the exclusive products, whereas the concurrent formation of thiophenes **3** might also have been expected as previously demonstrated by our group.[11] The proof of the thiazole structure, and therefore the total chemoselectivity, was given by the ^{1}H NMR spectra where we observed the loss of dimethylamino group and the presence of characteristic singlets.



Scheme 1. Synthesis of **2** and **3**.

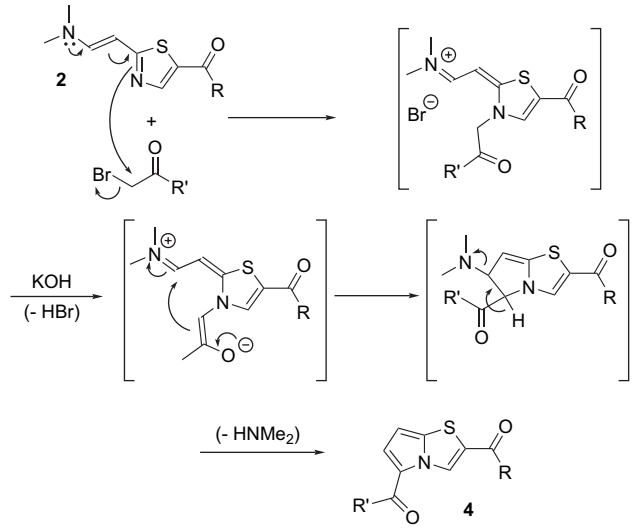
Table 1. Yields of compounds **2a,b**

Compounds	R	Yield (%)
2a	OCH_3	81
2b	*p*-BrC_6H_4	81

The isolated compounds **2**, which have now a 1-azadiene chain, were then allowed to react with another α-carbonyl bromide (Scheme 2, Table 2). The resulting *N*-alkylated salts were cyclized in situ by addition of KOH leading to pyrrolo[2,1-*b*]thiazoles **4**, by loss of dimethylamine, in modest to good yields. This result is somewhat surprising since Stanovnik and co-workers have failed to fuse a pyrrole to a similar dihydrothiazolium salt.[12]

2.2. Synthesis of 2*H*-thiopyrano[2,3-*b*]pyridines

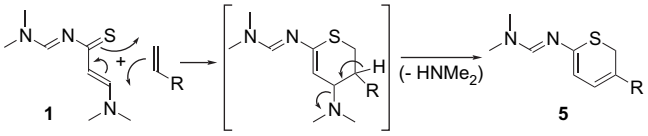
We continued our investigations by exposing polyheteropolyene **1** to acrylic dienophiles (Scheme 3, Table 3). The expected [4+2] cycloaddition occurred with faultless chemoselectivity to give, after deamination, the corresponding 2*H*-thiopyrane derivatives **5** without trace of 1,3-thiazines. This result corroborates previous related studies in which the 1-thiabuta-1,3-dienic chain was noticed to be significantly more reactive towards Diels–Alder reactions than the 1-thia-3-aza-1,3-butadienic derivative.[13]



Scheme 2. Reactions of compounds **2a,b** with α-carbonyl bromides.

Table 2. Yields of compounds **4a–f**

Compounds	R	R′	Yield (%)
4a	OCH_3	C_6H_5	77
4b	OCH_3	*p*-BrC_6H_4	85
4c	*p*-BrC_6H_4	OCH_3	70
4d	*p*-BrC_6H_4	OC_2H_5	67
4e	*p*-BrC_6H_4	*p*-ClC_6H_4	72
4f	*p*-BrC_6H_4	*p*-$NO_2C_6H_4$	55



Scheme 3. Reaction of polyheteropolyene **1** with acrylic dienophiles.

Table 3. Yields of compounds **5a–c**

Compounds	R	Yield (%)
5a	CN	61
5b	$COCH_3$	78
5c	$COOCH_3$	82

In order to understand this behaviour we have calculated the frontier molecular orbital (FMO) energies and MO coefficients by semi-empirical calculations.[14] For the polyheteropolyene **1** the electronic differences between C4 (N–*C*=C) and C9 (N–*C*=N) are not significant. It should be also noted that the HOMO-1 should be considered as the heterodiene HOMO because only that frontier orbital possesses the adequate coefficients and symmetry (vide infra) to react in a normal hetero-Diels–Alder cycloaddition. Both methods used by us (AM1[15] and PM3[16]) indicate a significant larger HOMO P_z coefficient for C4 than for C9 (Table 4), independent of the stereochemistry of the double bonds, in agreement with the experimental results.

Although acrylic dienophiles were always used in large excess, the reactivity of the generated 2-aza-1,3-dienic heterocycle **5** was low enough to ensure nearly complete

Table 4. Calculated AM1 MO coefficients for compound **1**

Eigenvalue HOMO	−8.17 eV
MO coefficient	
P_z C9 (N–*C*═N)	−0.09
P_z S	0.62
P_z C4 (N–*C*═C)	−0.24

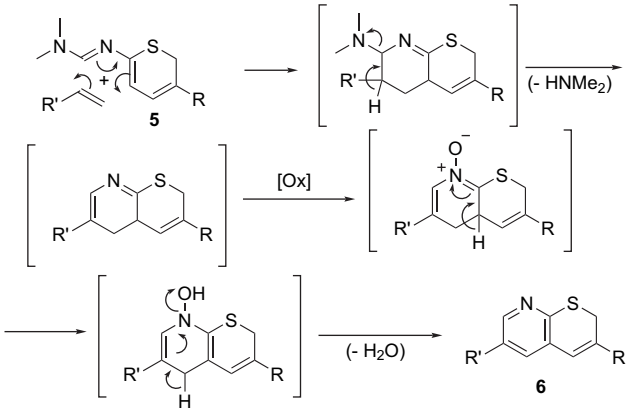
consumption of the starting material before double condensation could occur.

Subsequent [4+2] cycloadditions between the isolated 2*H*-thiopyranes **5**, bearing a 2-azadienic chain, and other dienophiles were performed using higher temperatures and longer reaction times, providing 2*H*-thiopyrano[2,3-*b*]pyridines **6** in modest to good yields (Table 5, method A: in two steps from **1**). Although the mechanistic details of the cyclization remain unknown, we suggest the loss of dimethylamine to lead to a 4a,5-dihydro-2*H*-thiopyrano[2,3-*b*]pyridine, which would then rearrange to the more stable unsaturated final product (Scheme 4). Oxidation probably occurred during the work-up procedure to give an intermediate *N*-oxide, itself undergoing a [1,4]-proton shift followed by dehydration. Furthermore, such rearrangements are precedented in the pyridinic series.[17]

Table 5. Yields of compounds **6a–f**

Compounds	R	R′	Yield (%)
6a	$COOCH_3$	CN	45[a]
6b	$COCH_3$	$COOCH_3$	54[a]
6c	$COOCH_3$	$COCH_3$	75[a]
6d	$COCH_3$	$COCH_3$	94[b]
6e	CN	CN	53[b]
6f	$COOCH_3$	$COOCH_3$	71[b]

[a] Compounds obtained by method A from **5**.
[b] Compounds obtained by method B from **1**.



Scheme 4. Synthesis of compounds **6**.

An attractive feature of this process is that 2*H*-thiopyrano[2,3-*b*]pyridines **6** could also be obtained directly from compound **1** in better overall yields (Table 5, method B: in one step from **1**). In this case, much harsher reaction conditions than for monocondensation were naturally required, and substituents R and R′ on the resulting heterocycle were identical. It is worth pointing out the excellent result obtained by this path with methyl vinyl ketone under relatively mild conditions.

In addition, the use of further reactants has been investigated in a view to extend the usefulness of our methodology. However, against all expectations, refluxing a solution of **2** in pure methyl vinyl ketone, conditions that might have provided a 5*H*-thiazolo[3,2-*a*]pyridine, resulted in none of the desired cycloadduct. Again, despite our attempts, neither ketenes nor sulfenes could undergo a successful cycloaddition with **1**, **2** or **5**. In most cases, starting material together with degraded products was recovered.

3. Conclusion

Thus we have demonstrated the 4-dimethylamino-2-dimethylaminomethylenamino-1-thiabuta-1,3-diene **1** to be a convenient precursor for the preparation of both pyrrolo[2,1-*b*]thiazoles **4** and 2*H*-thiopyrano[2,3-*b*]pyridines **6**, although some yields need to be optimized. We have shown that we have a faultless chemoselective control between the azadiene and thiadiene forms. We believe synthons of this type to be particularly applicable to solid-phase synthesis and combinatorial chemistry. Some of these possibilities are being examined in our laboratory, and these results will be published in due course.

4. Experimental

4.1. General comments

All reagents were purchased either from Acros Organics or Aldrich. Elemental analyses were performed by the C.N.R.S. Analysis Laboratory (Vernaison). Column chromatographies were conducted on silica gel 60 (40–63 μm), available from E. Merck. Thin layer chromatographies were performed on 0.5 mm×20 cm×20 cm E. Merck silica gel plates (60 F-254). Melting points were measured using a Reichert microscope. ^{13}C and ^{1}H NMR spectra were recorded at room temperature using a BRUKER AC 200 at 50 and 200 MHz, respectively. Chemical shifts (δ) are given in parts per million downfield from tetramethylsilane as internal standard. Mass spectra were determined with a Hewlett–Packard 5989 spectrometer. IR spectra were obtained using a BRUKER Vector 22 spectrometer. All chemicals were of reagent grade and used without further purification. THF was freshly distilled from Na/benzophenone, while CH_2Cl_2 was distilled over CaH_2. All reactions were carried in an Ar atmosphere.

4.1.1. 4-Dimethylamino-2-dimethylaminomethylenamino-1-thiabuta-1,3-diene (1).[18] To a suspension of 2-amino-4-dimethylamino-1-thiabuta-1,3-diene (10 mmol) in CH_2Cl_2 (20 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (11 mmol). The mixture was refluxed for 3 h. After removal of the solvent, the residue was diluted with CH_2Cl_2 (5 mL) and compound **2** was precipitated by addition of Et_2O (80 mL) and collected by filtration as ochre crystals (yield: 92%). Mp: 170 °C. IR (KBr): 1587, 1419, 1344, 1324, 1255, 1245, 1083 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.96 (br s, 6H), 3.14 (s, 3H), 3.17 (s, 3H), 5.94 (d, 1H,

J=12.0 Hz), 8.25 (d, 1H, J=12.0 Hz), 8.90 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 35.4, 37.3, 40.8, 44.8, 107.8, 158.8, 166.2, 206.4. MS *m/z*: 185 (100, M^+), 152 (39), 114 (43), 98 (20), 82 (39). Anal. calcd for $C_8H_{15}N_3S$: C, 51.86; H, 8.16; N, 22.68. Found: C, 51.99; H, 8.25; N, 22.47.

4.2. General procedure for the preparation of 2-(2-dimethylaminovinyl)thiazoles (2)

A solution of thiazadiene **1** (2 mmol) and methyl bromoacetate (2.1 mmol, for **2a**) or 2,4′-dibromoacetophenone (2.1 mmol, for **2b**) in CH_2Cl_2 (10 mL) was stirred at rt for 15 h (for **2a**) or 2 h (for **2b**). After addition of triethylamine (4.2 mmol), stirring was continued for 4 h. The solvent was then removed, and the residue was diluted with CH_2Cl_2 and chromatographed (using as eluent CH_2Cl_2/EtOAc 3/2 for **2a**, 9/1 for **2b**). Compounds **2** were crystallized from hexane/Et_2O (for **2a**) or Et_2O (for **2b**).

4.2.1. 2-(2-Dimethylaminovinyl)-5-methoxycarbonylthiazole (2a). Violet crystals (yield: 81%). Mp: 104 °C. IR (KBr): 1691, 1623, 1388, 1244, 1211, 1088 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.90 (s, 3H), 3.31 (s, 3H), 4.13 (s, 3H), 5.45 (d, 1H, J=12.8 Hz), 8.00 (d, 1H, J=12.8 Hz), 8.38 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 34.1, 38.3, 51.8, 89.5, 119.2, 148.0, 149.2, 161.7, 175.5. MS *m/z*: 212 (94, M^+), 197 (13), 180 (45), 170 (33), 152 (100), 138 (25). Anal. calcd for $C_9H_{12}N_2O_2S$: C, 50.93; H, 5.70; N, 13.20. Found: C, 50.80; H, 5.85; N, 13.42.

4.2.2. 5-*p*-Bromobenzoyl-2-(2-dimethylaminovinyl)thiazole (2b). Ochre crystals (yield: 81%). Mp: 163 °C. IR (KBr): 1626, 1602, 1437, 1380, 1315, 1262, 1214, 1107, 1008 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.99 (s, 6H), 5.45 (d, 1H, J=12.8 Hz), 7.58 (d, 1H, J=12.8 Hz), 7.59–7.72 (m, 4H), 7.88 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 40.8 (2C), 90.9, 126.7, 129.4 (2C), 131.8 (2C), 132.0, 137.6, 148.0, 151.1, 177.6, 185.5. MS *m/z*: 338/336 (79/78, M^+), 296/294 (18/19), 185/183 (40/38), 153 (100). Anal. calcd for $C_{14}H_{13}BrN_2OS$: C, 49.86; H, 3.89; N, 8.31. Found: C, 50.01; H, 4.10; N, 8.38.

4.3. General procedure for the preparation of pyrrolo[2,1-*b*]thiazoles (4)

A solution of 2-(2-dimethylaminovinyl)thiazole **2** (1 mmol) and α-carbonyl bromide (1.2 mmol of phenacyl bromide for **4a**, 2,4′-dibromoacetophenone for **4b**, 2-bromo-4′-chloroacetophenone for **4e**, 2-bromo-4′-nitroacetophenone for **4f**, 2 mmol of methyl acetate for **4c**, ethyl acetate for **4d**) in THF (10 mL) was heated for 24 h at 70 °C. After cooling to rt, the solvent was removed and the residue was diluted (20 mL) with MeOH (for **4a–c**) or EtOH (for **4d–f**). Powdered KOH (2 mmol) was added and the reaction mixture was further stirred for 24 h at rt and concentrated by rotary evaporation. The residue was then chromatographed using as eluent CH_2Cl_2. Compounds **4** were crystallized from Et_2O.

4.3.1. 5-Benzoyl-2-methoxycarbonylpyrrolo[2,1-*b*]thiazole (4a). Yellow crystals (yield: 77%). IR (KBr): 3134, 1707, 1616, 1564, 1443, 1427, 1385, 1301, 1191, 1090, 886, 746, 720 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 6.42 (dd, 1H, J=4.4 Hz, J=0.6 Hz), 7.27 (d, 1H, J=4.4 Hz), 7.44–7.87 (m, 5H), 9.43 (d, 1H, J=0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 52.8, 101.1, 123.2, 124.8, 128.0, 128.4 (2C), 128.9 (2C), 129.9, 131.6, 139.0, 141.5, 161.9, 183.0. MS *m/z*: 285 (100, M^+), 257 (16), 208 (38), 180 (14). Anal. calcd for $C_{15}H_{11}NO_3S$: C, 63.15; H, 3.89; N, 4.91. Found: C, 62.99; H, 3.83; N, 4.96.

4.3.2. 5-*p*-Bromobenzoyl-2-methoxycarbonylpyrrolo[2,1-*b*]thiazole (4b). Yellow crystals (yield: 85%). Mp: 146 °C. IR (KBr): 1724, 1610, 1568, 1425, 1406, 1396, 1260, 1091, 885, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 6.43 (dd, 1H, J=4.4 Hz, J=0.6 Hz), 7.23 (d, 1H, J=4.4 Hz), 7.60–7.74 (m, 4H), 9.39 (d, 1H, J=0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 52.9, 101.4, 123.4, 124.4, 126.4, 127.8, 129.7, 130.4 (2C), 131.7 (2C), 137.7, 141.8, 161.8, 181.6. MS *m/z*: 365/363 (100/98, M^+), 337/335 (9/9), 256 (17), 208 (47). Anal. calcd for $C_{15}H_{10}BrNO_3S$: C, 49.47; H, 2.77; N, 3.85. Found: C, 49.46; H, 2.85; N, 3.76.

4.3.3. 2-*p*-Bromobenzoyl-5-methoxycarbonylpyrrolo[2,1-*b*]thiazole (4c). Yellow crystals (yield: 70%). Mp: 201 °C. ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.38 (dd, 1H, J=4.4 Hz, J=0.6 Hz), 7.37 (d, 1H, J=4.4 Hz), 7.66–7.79 (m, 4H), 8.83 (d, 1H, J=0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 51.6, 100.8, 116.4, 124.6, 128.1, 129.9, 130.3 (2C), 132.4 (2C), 133.0, 136.0, 138.8, 160.9, 186.7. MS *m/z*: 365/363 (100/95, M^+), 334/332 (35/35), 307/305 (24/22), 185/183 (14/14). Anal. calcd for $C_{15}H_{10}BrNO_3S$: C, 49.47; H, 2.77; N, 3.85. Found: C, 49.41; H, 2.64; N, 3.74.

4.3.4. 2-*p*-Bromobenzoyl-5-ethoxycarbonylpyrrolo[2,1-*b*]thiazole (4d). Yellow crystals (yield: 67%). Mp: 122 °C. IR (KBr): 1693, 1638, 1523, 1419, 1306, 1213, 1178, 1122, 1109, 742. ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3H, J=7.2 Hz), 4.34 (q, 2H, J=7.2 Hz), 6.36 (dd, 1H, J=4.4 Hz, J=0.6 Hz), 7.36 (d, 1H, J=4.4 Hz), 7.65–7.78 (m, 4H), 8.83 (d, 1H, J=0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 14.5, 60.4, 100.6, 116.6, 124.4, 127.9, 129.8, 130.2 (2C), 132.2 (2C), 132.7, 135.9, 138.5, 160.4, 186.4. MS *m/z*: 379/377 (100/95, M^+), 351/349 (44/39), 307/305 (45/46), 185/183 (40/36). Anal. calcd for $C_{16}H_{12}BrNO_3S$: C, 50.81; H, 3.20; N, 3.70. Found: C, 50.73; H, 3.25; N, 3.79.

4.3.5. 2-*p*-Bromobenzoyl-5-*p*-chlorobenzoylpyrrolo[2,1-*b*]thiazole (4e). Yellow crystals (yield: 72%). Mp: 203 °C. IR (KBr): 1628, 1613, 1587, 1565, 1431, 1403, 1387, 1296, 1176, 1088, 999, 885, 838, 739 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.48 (dd, 1H, J=4.4 Hz, J=0.6 Hz), 7.29 (d, 1H, J=4.4 Hz), 7.46–7.82 (m, 8H), 9.26 (d, 1H, J=0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 101.9, 124.8, 128.4, 128.7, 128.9 (2C), 130.3 (2C), 130.4 (2C), 131.0, 132.5 (2C), 133.8, 135.8, 137.1, 138.2, 142.2, 181.8, 186.6. MS *m/z*: 447/445/443 (29/100/77, M^+), 331 (24), 185/183 (27/26). Anal. calcd for $C_{20}H_{11}BrClNO_2S$: C, 54.01; H, 2.49; N, 3.15. Found: C, 53.86; H, 2.62; N, 3.06.

4.3.6. 2-*p*-Bromobenzoyl-5-*p*-nitrobenzoylpyrrolo[2,1-*b*]thiazole (4f). Orange crystals (yield: 55%). Mp: 247 °C. IR (KBr): 1626, 1619, 1587, 1522, 1429, 1398, 1347, 1292, 1177, 848, 742 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.53 (dd, 1H, J=4.4 Hz, J=0.6 Hz), 7.27 (d, 1H, J=4.4 Hz), 7.70–8.39 (m, 8H), 9.27 (d, 1H, J=0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 102.5, 123.9 (2C), 124.5, 128.6, 129.1, 129.8 (2C), 130.4

(2C), 130.7, 132.5 (2C), 134.4, 135.7, 143.4, 144.3, 180.6, 183.7. MS *m/z*: 456/454 (100/99, M^+), 426/424 (36/30), 334/332 (33/31), 185/183 (76/75), 157/155 (49/51). Anal. calcd for $C_{20}H_{11}BrN_2O_4S$: C, 52.76; H, 2.44; N, 6.15. Found: C, 52.57; H, 2.60; N, 6.32.

4.4. General procedure for the preparation of *N*,*N*-dimethyl-*N*′-(6*H*-thiopyran-2-yl)formamidines (5)

A solution of thiazadiene **1** (2 mmol) in pure acrylonitrile (5 mL, for **5a**) or in a mixture of another dienophile (1 mL of methyl vinyl ketone for **5b**, 4 mL of methyl acrylate for **5c**) and CH_2Cl_2 (5 mL) was stirred for 16 h at 80 °C (for **5a**), at 40 °C (for **5b**) or at 50 °C (for **5c**). After cooling to rt, the mixture was concentrated and purified by chromatography (CH_2Cl_2/EtOAc 7/3 for **5a**,**b**, 9/1 for **5c**) and crystallization from Et_2O/hexane 1/1 (for **5b**) or hexane (for **5c**). Compound **5a** was isolated as an oil.

4.4.1. *N*′-(5-Cyano-6*H*-thiopyran-2-yl)-*N*,*N*-dimethylformamidine (5a). Red oil (yield: 61%). Hygroscopic. R_f=0.3 (EtOAc). ^{1}H NMR ($CDCl_3$) δ 3.14 (s, 3H), 3.15 (s, 3H), 3.53 (s, 2H), 6.14 (d, 1H, *J*=7.2 Hz), 6.89 (d, 1H, *J*=7.2 Hz), 7.80 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 27.7, 35.9, 41.5, 88.1, 109.1, 119.9, 142.4, 152.1, 155.7. MS *m/z*: 193 (28, M^+), 160 (16), 84 (68), 66 (63), 43 (100).

4.4.2. *N*′-(5-Acetyl-6*H*-thiopyran-2-yl)-*N*,*N*-dimethylformamidine (5b). Orange crystals (yield: 78%). Mp: 118 °C. IR (KBr): 1635, 1619, 1496, 1472, 1360, 1289, 1227, 1110 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.06 (s, 3H), 3.09 (s, 3H), 3.74 (s, 2H), 6.04 (d, 1H, *J*=7.2 Hz), 7.20 (d, 1H, *J*=7.2 Hz), 7.83 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 24.9 (2C), 35.1, 40.8, 109.2, 118.9, 139.5, 155.9, 156.8, 195.2. MS *m/z*: 210 (11, M^+), 167 (100). Anal. calcd for $C_{10}H_{14}N_2OS$: C, 57.12; H, 6.71; N, 13.32. Found: C, 57.01; H, 6.97; N, 13.45.

4.4.3. *N*′-(5-Methoxycarbonyl-6*H*-thiopyran-2-yl)-*N*,*N*-dimethylformamidine (5c). Orange crystals (yield: 82%). Mp: 95 °C. IR (KBr): 1665, 1621, 1503, 1443, 1353, 1288, 1266, 1229, 1194, 1163, 1107, 1084 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 3.08 (s, 3H), 3.72 (s, 2H), 3.76 (s, 3H), 6.03 (d, 1H, *J*=7.2 Hz), 7.31 (d, 1H, *J*=7.2 Hz), 7.81 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.2, 35.1, 40.9, 51.6, 109.3 (2C), 138.5, 154.6, 155.9, 166.8. MS *m/z*: 226 (100, M^+), 211 (59), 193 (39), 167 (77). Anal. calcd for $C_{10}H_{14}N_2O_2S$: C, 53.08; H, 6.24; N, 12.38. Found: C, 53.25; H, 6.44; N, 12.17.

4.5. General procedure for the preparation of 2*H*-thiopyrano[2,3-*b*]pyridines (6)

Method A: A solution of *N*,*N*-dimethyl-*N*′-(6*H*-thiopyran-2-yl)formamidine **5** (1 mmol) in a dienophile (5 mL) was heated at 70 °C for 24 h (for **6b**, **e**, **f**) or two days (for **6c**). After cooling to rt and removal of the solvent, the residue was diluted with CH_2Cl_2. Compounds **6** were isolated by chromatography (CH_2Cl_2 for **6e**, CH_2Cl_2/EtOAc 9/1 for **6b**, **c**, 5/1 for **6f**) followed by crystallization from Et_2O.

Method B: A solution of thiazadiene **1** (1 mmol) in a dienophile (5 mL) was heated at 70 °C for two days (for **6d**) or six days (for **6a**, **g**). After cooling to rt, the mixture was concentrated under reduced pressure. The resulting residue was chromatographed (CH_2Cl_2 for **6g**, CH_2Cl_2/EtOAc 9/1 for **6a**, 5/1 for **6d**). Then compounds **6** were crystallized from Et_2O.

4.5.1. 6-Cyano-3-methoxycarbonyl-2*H*-thiopyrano[2,3-*b*]pyridine (6a). Yellow crystals (yield: 45%). Mp: 134 °C. IR (KBr): 2234, 1717, 1584, 1426, 1390, 1256, 1228, 1115 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 4.02 (d, 2H, *J*=0.9 Hz), 7.43 (t, 1H, *J*=0.9 Hz), 7.61 (d, 1H, *J*=2.1 Hz), 8.52 (t, 1H, *J*=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 25.5, 52.9, 106.1, 116.1, 125.2, 127.0, 133.9, 138.5, 152.1, 164.1, 165.2. MS *m/z*: 232 (37, M^+), 217 (100), 173 (46). Anal. calcd for $C_{11}H_8N_2O_2S$: C, 56.89; H, 3.47; N, 12.06. Found: C, 56.76; H, 3.39; N, 11.83.

4.5.2. 3-Acetyl-6-methoxycarbonyl-2*H*-thiopyrano[2,3-*b*]pyridine (6b). Yellow crystals (yield: 54%). Mp: 148 °C. IR (KBr): 1726, 1669, 1588, 1427, 1389, 1313, 1237, 1214, 1139, 766 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 3.95 (s, 3H), 3.96 (d, 2H, *J*=0.9 Hz), 7.35 (t, 1H, *J*=0.9 Hz), 8.05 (d, 1H, *J*=2.1 Hz), 8.91 (t, 1H, *J*=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 24.4, 25.6, 52.6, 123.1, 126.7, 132.2, 135.5, 137.5, 151.4, 164.6, 165.3, 196.2. MS *m/z*: 249 (82, M^+), 206 (100), 147 (18). Anal. calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.69; H, 4.61; N, 5.64.

4.5.3. 6-Acetyl-3-methoxycarbonyl-2*H*-thiopyrano[2,3-*b*]pyridine (6c). Yellow crystals (yield: 75%). Mp: 173 °C. IR (KBr): 1720, 1684, 1647, 1581, 1391, 1309, 1253, 1223, 1196, 1135, 1061, 991, 731 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.87 (s, 3H), 4.00 (d, 2H, *J*=0.9 Hz), 7.51 (t, 1H, *J*=0.9 Hz), 7.93 (d, 1H, *J*=2.1 Hz), 8.82 (t, 1H, *J*=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 25.6, 26.6, 52.7, 124.2, 126.8, 129.7, 135.3, 135.7, 150.3, 164.1, 165.6, 195.5. MS *m/z*: 249 (42, M^+), 234 (100), 190 (37). Anal. calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.79; H, 4.48; N, 5.69.

4.5.4. 3,6-Diacetyl-2*H*-thiopyrano[2,3-*b*]pyridine (6d). Yellow crystals (yield: 94%). Mp: 205 °C. IR (KBr): 1689, 1665, 1620, 1577, 1383, 1303, 1216, 1130, 932 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 2.61 (s, 3H), 3.97 (d, 2H, *J*=0.9 Hz, SC*H*$_2$), 7.36 (t, 1H, *J*=0.9 Hz), 7.99 (d, 1H, *J*=2.1 Hz), 8.84 (t, 1H, *J*=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 24.5, 25.6, 26.7, 126.9, 129.6, 132.4, 135.6, 135.9, 150.6, 164.9, 195.5, 196.2. MS *m/z*: 233 (79, M^+), 218 (14), 190 (100), 147 (22). Anal. calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.66; H, 4.96; N, 6.17.

4.5.5. 3,6-Dicyano-2*H*-thiopyrano[2,3-*b*]pyridine (6e). Ochre crystals (yield: 53%). Mp: 180 °C. IR (KBr): 2234, 1627, 1583, 1421, 1388, 1128, 927, 747 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 4.11 (d, 2H, *J*=0.9 Hz), 7.49 (t, 1H, *J*=0.9 Hz), 8.13 (d, 1H, *J*=2.1 Hz), 8.75 (d, 1H, *J*=2.1 Hz). ^{13}C NMR (DMSO-d_6) δ 26.0, 105.6, 105.9, 116.5, 117.6, 126.0, 139.3, 139.7, 152.8, 161.9. MS *m/z*: 199 (91, M^+), 198 (100). Anal. calcd for $C_{10}H_5N_3S$: C, 60.29; H, 2.53; N, 21.09. Found: C, 60.45; H, 2.38; N, 21.23.

4.5.6. 3,6-Bis(methoxycarbonyl)-2*H*-thiopyrano[2,3-*b*]pyridine (6f). Yellow crystals (yield: 71%). Mp: 150 °C.

IR (KBr): 1726, 1646, 1584, 1441, 1396, 1311, 1243, 1210, 1142, 766 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H), 3.94 (s, 3H), 4.00 (d, 2H, J=0.9 Hz), 7.50 (t, 1H, J=0.9 Hz), 7.99 (d, 1H, J=2.1 Hz), 8.88 (t, 1H, J=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 25.6, 52.6, 52.7, 123.1, 124.1, 126.6, 135.3, 137.2, 151.1, 163.8, 165.3, 165.6. MS *m/z*: 265 (31, M^+), 250 (100), 206 (38), 147 (22), 146 (22). Anal. calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28. Found: C, 54.52; H, 4.35; N, 5.45.

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