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The Methyl Group as a Source of Structural Diversity in Heterocyclic Chemistry: Side Chain Functionalization of Picolines and Related Heterocycles

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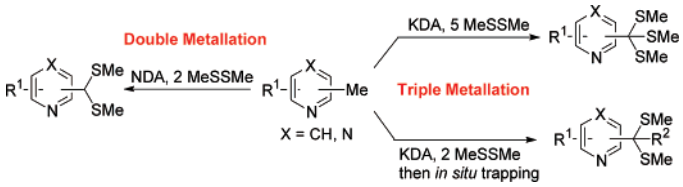

The reaction of 2-picoline at the methyl group with NDA and KDA followed by dimethyldisulfide trapping furnished, respectively, dithioacetals and trithioortho esters with high selectivity. The method was successfully applied to other methyl-substituted pyridines, quinolines, and pyrazines. Dithioketals were prepared by a one-pot procedure involving the reaction of metalated 2-picoline with 2 equiv of dimethyldisulfide followed by in situ trapping with a second electrophile. All of the generated thio-substituted compounds were efficiently transformed in presence of mercury salts or under oxidizing conditions to other functional groups comprising aldehydes, ketones, ketals, thiol esters, orthoesters, and esters.

Introduction

The need for functionalized pyridine derivatives is still growing because they are extensively used in several fields such as pharmaceutical chemistry,[1] asymmetric catalysis,[2] and coordination chemistry for the preparation of new materials with defined properties.[3] The construction of the pyridine ring[4] and its metalation represent the main approaches for obtaining substituted pyridines. Among metallations, the halogen-metal exchange is still the method of choice when the parent halopyridines are available.[5] In some cases, the direct metalation represents a straightforward alternative route to functional derivatives.[6] In previous works, our group described the synthesis of substituted picolines by direct metalation at the pyridine ring with the superbase *n*-BuLi-LiDMAE (lithium dimethylaminoethanolate) leaving the methyl group unchanged (Figure 1).[7] We now report a new efficient approach for the synthesis of functionalized pyridines from commercial or easily

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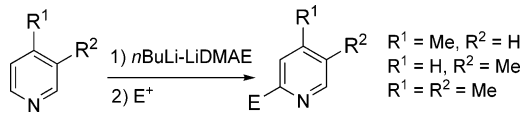

FIGURE 1. Ring selective lithiation of methylpyridines.

available picolines[8] and methyl-substituted *N*-heterocycles by selective transformation of the methyl group to dithioacetals, dithioketals, and trithioortho esters. Further reactions on these thio-substituted derivatives can generate aldehydes, esters, orthoesters, thiol esters, ketones, and ketals.

The role of dithioacetals in organic synthesis is well recognized since they can serve as reactive protecting groups.[9] For instance, the dithioacetal group was used in pyridine derivatives to induce a conjugate 1,4-addition on α,*β*-unsaturated ketones before removal by reduction with Raney Ni.[10] Although some reports described the direct synthesis of dithioacetal substituted pyridine derivatives, the trithioortho ester derivatives were unknown. Apart from the dithioacetalization of aldehydes,[11] the most common strategy used to introduce the dithioacetal functionality on the pyridine ring is based on the nucleophilic addition of lithiated dithianes on activated pyridines.[12] The direct double metalation of picoline derivatives at the methyl group and electrophilic trapping with disulfides was less studied. In 1975, Finch and Gemenden reported the synthesis of 2-bis(*tert*-butylthio)methylpyridine, although in low yield.[13] Later, Quéguiner and co-workers described the double metalation and PhSSPh trapping in the bipyridine series.[14] Subsequent deprotection furnished the aldehyde. It is worth noting that this methodology has been also applied for the functionalization of *o*-toluate derivatives.[15] In 1996, Tazaki and co-workers performed a systematic study on the formation of pyridyl-1,3-dithianes from 2- and 4-picolines and dithiolanes. Although the reaction proceeded smoothly, the need of a 2.5-fold excess of picoline is a limiting factor for its applicability (Figure 2).[16]

Results and Discussion

In connection to our previous work concerning the use of pyridine derivatives for the synthesis of polycyclic heterocycles,[17] we were interested in the transformation of the methyl group of picolines to functional groups such as aldehydes and ketones. In this context, the direct preparation of dithioacetals from picolines was attractive since they can serve as intermediates for aldehydes by deprotection and for ketones by alkylation−deprotection sequence.[18]

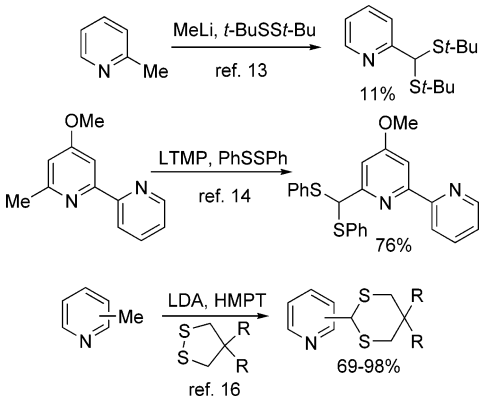

FIGURE 2. Dithioacetals from double metalation and disulfide trapping.

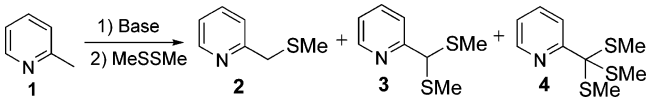

FIGURE 3. Metalation and MeSSMe trapping of 2-picoline **1**.

Metalation of Methyl-Substituted Pyridines and Azines (Table 1). To find the best conditions to achieve the selective formation of dithioacetal derivatives, we started our study on 2-picoline **1** by reacting it with different bases and by quenching the generated anions with MeSSMe (Figure 3 and Table S1 in Supporting Information).

The use of a non-nucleophilic base such as LDA seemed to us to be the best starting point for the synthesis of dithioacetal derivative **3**.[19] To our surprise, when we used 2.5 equiv of LDA and 2 equiv of MeSSMe, we observed that along with the major product **3**, small amounts of (methylthio)methylpyridine **2** (12%) and more interestingly of the new trithioortho ester derivative **4** (5%) were also observed. We raised the amount of base and electrophile and observed that compound **4** was now the major product, but still the reaction was not selective (68% of **4** and 32% of **3**). Previous studies have shown that NDA and KDA (respectively, sodium and potassium diisopropylamide) were suitable bases for the metalation of methyl-substituted picolines.[20] We then examined the reaction of 2-picoline **1** with 2.5 equiv of NDA followed by 2 equiv of MeSSMe and were pleased to see that **3** was formed as the sole product in this reaction, yielding 85% of isolated product after chromatography (Table 1, entry 1). Note that the amount of electrophile is very important and should not exceed 2 equiv to avoid over-functionalization. In the same conditions, KDA was proven to be less selective for the formation of **3** since compound **4** was also formed. We then increased the amount of base in order to obtain selectively the trithioortho ester **4**. While 5 equiv of NDA and MeSSMe led to incomplete and nonselective reaction (85% conversion with 15% of **3**), we found that 5 equiv of KDA followed by 5 equiv of MeSSMe produced exclusively compound **4**, which was isolated after chromatography with 81%

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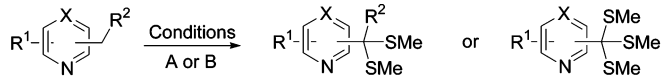
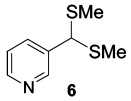
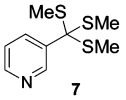
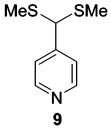
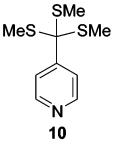
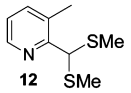
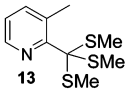
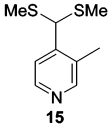
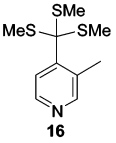
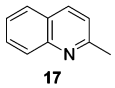
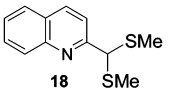
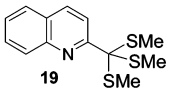
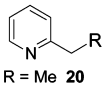
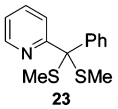
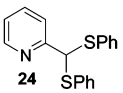
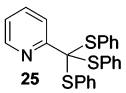
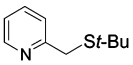
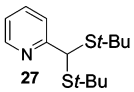
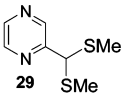
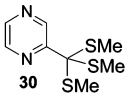
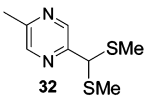
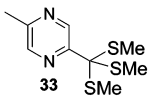
TABLE 1. Synthesis of Dithioacetals and Trithiortho Esters



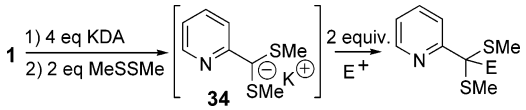
Entry	Substrate	Product (Conditions A)[a]	Yield (%)[c]	Entry	Product (Conditions B)[b]	Yield (%)[c]
1	**1**	**3**	85	2	**4**	81
3	 **5**	 **6**	0	4	 **7**	26
5	 **8**	 **9**	71	6[d]	 **10**	68
7	 **11**	 **12**	89	8[e]	 **13**	46
9[f]	 **14**	 **15**	55	10[d]	 **16**	54
11	 **17**	 **18**	57	12[d]	 **19**	68
13[g]	 R = Me **20** R = Ph **21**	 **22**	75	14[g]	 **23**	88
15	**1**	 **24**	76	16[d]	 **25**	70
17	**1**	 **26**	77	18	 **27**	34[h]
19	 **28**	 **29**	51	20[d]	 **30**	54
21	 **31**	 **32**	36	22[e]	 **33**	81

[a] Conditions A: (i) substrate (2 mmol), NDA (2.5 equiv), −78 °C; (ii) RSSR (2 equiv), −78 °C; (iii) H_2O, −78 °C to rt. [b] Conditions B: (i) substrate (2 mmol), KDA (5 equiv), −78 °C; (ii) RSSR (5 equiv), −78 °C to *T*; (iii) H_2O, *T* to rt. [c] Isolated yields after chromatography on silica gel. [d] $T = -50$ °C. [e] 4 equiv KDA, 4 equiv MeSSMe, −78 °C. [f] 3 equiv KDA, 3 equiv MeSSMe, −78 °C. [g] 3 equiv KDA, 3 equiv. MeSSMe, −78 to −60 °C. [h] Along with 25% of **26**.

yield (Table 1, entry 2). Taking into account these results, we decided to choose NDA for the preparation of dithioacetals (conditions A) and KDA for the formation of trithioortho esters (conditions B) from various methyl-substituted *N*-heterocyclic derivatives (Table 1). In contrast to 2-picoline **1**, 3-picoline **5** did not react well with either NDA or KDA. The dithioacetal **6** could not be isolated (entry 3), and the trithioortho ester compound **7** was obtained in low yield (entry 4). In both

experiments we observed essentially deterioration products with no recovery of the starting material. 4-Picoline **8** reacted smoothly to furnish, respectively, **9** and **10** in good yields (entries 5 and 6). The complete conversion to **10** was achieved by raising the temperature of the reaction mixture after addition of the electrophile (entry 6). The observed difference in reactivity between 2- and 3-picolines **1** and **5** and between 3- and 4-picolines **5** and **8**, which is in agreement with the known pK_a values of the methyl group of picolines,[21] allowed us to perform the selective methyl functionalization of lutidines. 2,3-Lutidine **11** reacted selectively at the 2-position to give **12** in good yield (entry 7) and **13** in moderate yield (entry 8). 3,4-Lutidine **14** was more reactive at the 4-position furnishing **15** and **16** in acceptable yields (entries 9 and 10). For the synthesis of **15**, a better result was obtained when using 3 equiv of KDA and 3 equiv of MeSSMe. Quinaldine **17** proved to be a good substrate for the reaction, leading selectively **18** and **19** in reasonable yields (entries 11 and 12). The efficiency of the reaction was not affected by the presence of another substitutent on the methyl group. Indeed, 2-ethylpyridine **20** and 2-benzylpyridine **21** reacted well with KDA and MeSSMe to give, respectively, compounds **22**[19] and **23** in good yields (entries 13 and 14). Other disulfide electrophiles were tested in the reaction with 2-picoline **1**, and it appeared that the phenylthio group PhS could be introduced easily twice to give compound **24** in good yield (entry 15). The introduction of the third PhS group was more difficult compared to MeS, and raising the temperature to −50 °C was necessary to achieve complete conversion furnishing compound **25** in 70% yield (entry 16). Under conditions A (footnote a), the bulky *tert*-butylthio group (*t*-BuS) could be introduced only once to furnish **26**[22] in good yield (entry 17). We did succeed in incorporating two *t*-BuS groups when applying conditions B (footnote b) only after raising the temperature to ambient. In that case, compound **27**[13] was isolated with 34% yield along with the monosubstituted product **26**, but no trace of the tris-functionalized derivative was observed (entry 18). We finally turned our attention to the functionalization of methylpyrazines **28** and **31**. The pyrazine ring functionalization is more challenging than in the pyridine series because it undergoes easily nucleophilic addition in the presence of bases. Therefore methods to obtain substituted pyrazines from simple starting material are not numerous, and our method can be a good alternative to the directed metalation methodology.[23] Although dithioacetal-functionalized compounds of pyrazine were recently obtained in good yields by the reaction of dichloropyrazines and metalated dithiane,[24] the trithioortho ester derivatives were unkown. Methylpyrazine **28** reacted smoothly under our conditions to furnish **29** and **30** in moderate yields (entries 19 and 20). The selective functionalization of one methyl group in 2,5-dimethylpyrazine **31** was successful despite the identical initial reactivity of both methyl groups.[25] Whereas dithioacetal **32** was obtained with only 36% yield (entry 21), the trithioortho ester **33** was produced with an excellent yield of 81% (entry 22). The structural identitification of two new trithioortho ester derivatives **13** and **25** was supported by single-crystal X-ray diffraction (see Supporting Information for details).

TABLE 2. Direct Formation of Dithioketals from 2-Picoline 1



entry	E^+	E	product	yield (%)[a]
1	H_2O	H	**3**	68 (82)[b]
2	MeI	Me	**22**	63
3	allylBr	allyl	**35**	72
4	BnBr	Bn	**36**	56
5	PhCOCN	COPh	**37**	55

[a] Isolated yields. [b] ^{1}H NMR yield in parentheses.

One-Pot Synthesis of Dithioketals. Because KDA gave good results for the formation of tris-functionalized compounds, we decided to use it to generate in a one-pot procedure dithiomethyl-protected ketones. Indeed, by using an excess of KDA at the beginning of the reaction, we could expect to realize a successive trapping of metalated **1** with 2 equiv of MeSSMe and 1 equiv of a second electrophile (Table 2).

In a test reaction we showed that after addition of 2 equiv of MeSSMe and quenching of the reaction mixture with water the dithioacetal **3** was obtained in 82% NMR yield indicating that the bis(dimethylthio)pyridine anion **34** was preponderant in the reaction mixture (entry 1). Thus, by reacting **34** with different electrophiles we could obtain in one pot several protected ketones. Compound **22** which was already prepared from 2-ethylpyridine **20** (Table 1, entry 13) has been prepared in good yield from 2-picoline **1** (entry 2). This method allowed us to prepare the allyl derivative **35** in good yield (entry 3). Note that this compound could hardly be synthesized by other methods, for instance by dithioketalization of the parent carbonyl compound, due to the probable migration of the double bond. Benzyl and benzoyl groups were introduced efficiently to give compounds **36** and **37** in moderate yields (entries 4 and 5).

Transformation of Dithioacetal and Trithiortho Ester Derivatives. To show the interest of our new methodology, we explored the possibilities of structural transformations of dithioacetal derivatives and more importantly of the previously unknown trithioortho ester compounds. In this context, mercury salts were found to effect selective transformations depending on the solvent used in the reaction. Some examples of hydrolysis and dithioketal/ketal interchange of the bis(dimethylthio) function are given in Scheme 1. Whereas the deprotection of compounds **22** and **23** to give, respectively, ketones **39** and **40** was relatively fast (less than 10 h), derivatives **3** and **37** required longer reaction times (48 h) and more $HgCl_2$ and $CaCO_3$ to produce aldehyde **38** and diketone **41**[26] (Method A, Scheme 1). We could realize efficiently the bis(dimethylthio)ketal/bis(dimethyl)ketal interchange in compounds **22** and **23** by using $HgCl_2$ and HgO in methanol, generating **42**[27] and **43** in excellent yields.

(21) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232−3234.

(22) Canovese, L.; Visentin, F.; Uguagliati, P.; Chessa, G.; Pesce, A. *J. Organomet. Chem.* **1998**, *566*, 61−71.

(23) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489−4505.

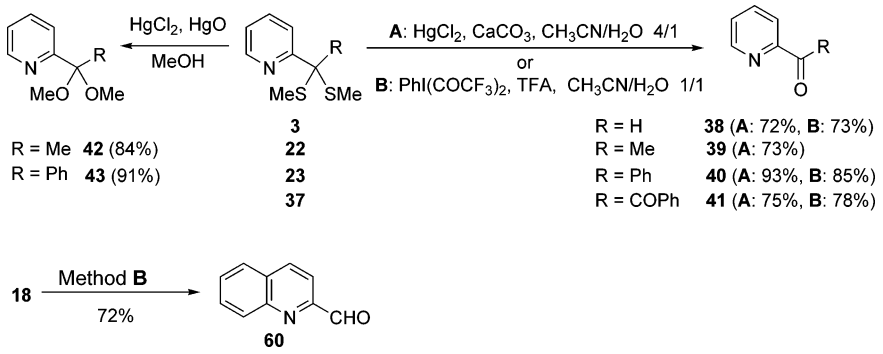
(24) Torr, J. E.; Large, J. M.; Horton, P. N.; Hursthouse, M. B.; McDonald, E. *Tetrahedron Lett.* **2006**, *47*, 31−34.

(25) After the first metallation−trapping sequence, the hydrogen in the -CH_2-SMe group becomes more acidic than that in the methyl group. The second metallation−trapping then occurs preferentially on the -CH_2-SMe group to give **32** in which the hydrogen of the -$CH(SMe)_2$ group is much more acidic than that in the methyl group. When 5 equiv of MeSSMe are used, the third thiomethyl group is introduced to furnish **33**.

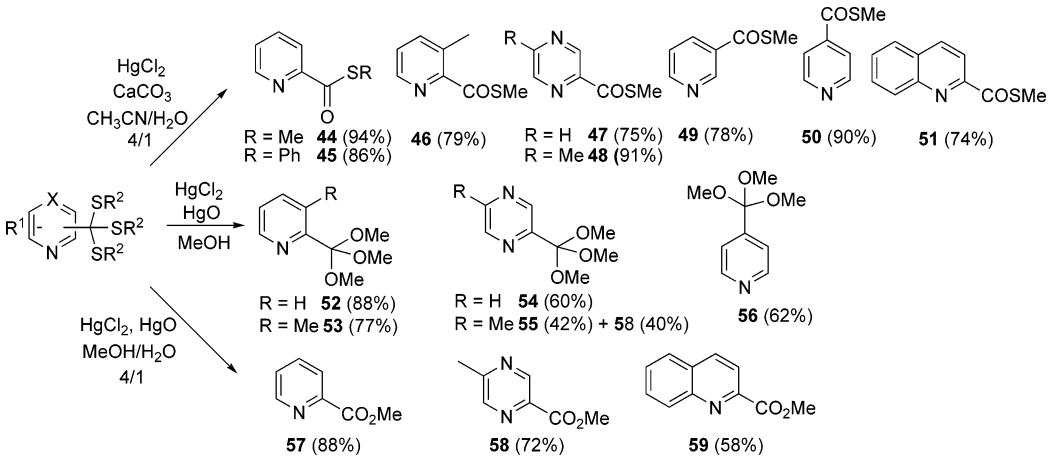
(26) Katritzki, A. R.; Lang, H.; Wang, Z.; Zhang, Z.; Song, H. *J. Org. Chem.* **1995**, *60*, 7619−7624.

(27) Brambilla, R.; Friary, R.; Ganguly, A.; Puar, M. S.; Sunday, B. R.; Wright, J. J.; Onan, K. D.; McPhail, A. T. *Tetrahedron* **1981**, *37*, 3615−3625.

SCHEME 1. Transformations of Some Dithioacetal Compounds



SCHEME 2. Preparation of Thiol Esters, Orthoesters, and Esters from Trithioortho Esters



Analogously the trithioortho ester derivatives could be selectively transformed to esters, orthoesters, and thiol esters in the presence of mercuric salts. Among these functionalities, orthoesters of pyridine and pyrazine are unkown and methods for obtaining thiol esters are very limited. They usually require the initial activation of the carboxylic group.[28] The good reactivity of the C−S bond toward transition metals[29] makes the thiol ester an interesting function for the elaboration of α-aryl pyridyl and pyrazyl ketone derivatives. We found that several trithioortho ester derivatives undergo a facile transformation to either the ester group by using $HgCl_2$/HgO system in a methanol−water mixture, to orthoesters by omitting water in the precedent system, or to thiol esters by using $HgCl_2$ and $CaCO_3$ in an acetonitrile−water solvent mixture. As shown in Scheme 2 the yields are generally good whatever the heterocycle implicated in the reaction.

Because of the high toxicity of mercuric compounds we then focused our research on more environmentally friendly methods. We started our work on the hydrolysis of compounds which were less reactive in presence of mercuric salts namely dithioacetal **3** and dithioketal **37**. Among the methods tested we found that the one developed by Fleming and co-workers on the deprotection of dithiane-containing alkaloids was well adapted to our compounds.[30] The combination of bis(trifluoroacetoxy)iodobenzene and trifluoroacetic acid in an acetonitrile−water mixture allowed fast reaction in comparison with $HgCl_2$−$CaCO_3$ system. Aldehyde **38** and diketone **41** were obtained in good yields after 3 h of reaction. Analogously, dithioketal **23** and dithioacetal **18** generated, respectively, ketone **40** and quinoline-2-carbaldehyde **60** in good yields (Method B, Scheme 1). The same procedure applied to trithioortho ester **4** furnished the desired thiol ester **44** in an excellent yield of 88%.

Conclusion

The methodology reported here allowed an easy two-step access to a wide range of functionalized heterocycles. The efficiency of the method was due to the facile double and triple deprotonation of methyl-substituted *N*-heterocycles, which allowed the selective introduction of two or three thiomethyl groups. Dithioketals were prepared in a one-pot procedure by the successive trapping of metalated 2-picoline with MeSSMe and a second electrophile. Dithiocetal, dithioketal, and orthothioester derivatives reacted well in the presence of mercuric salts or under oxidizing conditions and were transformed depending on the solvent to aldehydes, ketones, acetals, thiol esters, orthoestersn and esters. The present study reveals the possibility to generate functional diversity from simple starting materials, and our group is pursuing the search for other functional transformations and for applying this new methodology to a broader range of heterocycles.

Experimental Section

Representative Procedure for the Synthesis of Dithioacetals: Preparation of 2-Bis(methylthio)methylpyridine (3). *t*-BuONa (5 mmol, 480.5 mg) was dried for 2 h at 100 °C in vacuo.

(28) (a) Katritzky, A. R.; Shestopalov, A. A.; Suzuki, K. *Synthesis* **2004**, 1806−1813. (b) Jew, S.; Park, B.; Lim, D.; Kim, M.; Chung, I.; Kim, J.; Hong, C.; Kim, J.; Park, H.; Lee, J.; Park, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 609−612.

(29) Dubbaka, S. R.; Vogel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7674−7684.

(30) Fleming, F. F.; Funk, L.; Altundas, R.; Tu, Y. *J. Org. Chem.* **2001**, *66*, 6502−6504.

THF (5 mL) and diisopropylamine (5 mmol, 0.7 mL) were added and the mixture was cooled to −78 °C. *n*-BuLi (1.6 M in hexane, 5 mmol, 3.15 mL) was added dropwise and the mixture was stirred for 15 min at the same temperature. 2-Picoline **1** (2 mmol, 200 μL) dissolved in THF (2 mL) was added dropwise and the resulting orange solution was stirred for 15 min at −78 °C. MeSSMe (4 mmol, 355 μL) in THF (4 mL) was added dropwise and the mixture was stirred for another 15 min, after which time TLC analysis showed complete conversion. Water (2 mL) was added at −78 °C and the temperature was raised to ambient temperature. The product was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. After filtration and solvent evaporation, the crude product was purified by chromatography on silica gel (hexanes/ethyl acetate 9/1) to furnish 315 mg (85% yield) of a pale yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.13 (s, 6H), 4.95 (s, 1H), 7.17 (dd, J = 6.2, 5.2 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.68 (dd, J = 7.8, 6.2 Hz, 1H), 8.52 (d, J = 4.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 57.7, 121.3, 122.0, 136.4, 148.4, 158.8. MS (EI) *m*/*z* 186 ([M + 1]$^+$, 46%), 138 (100), 106 (32), 93 (35), 79 (40).

Spectroscopic data of compounds prepared analogously can be found in Supporting Information.

Representative Procedure for the Synthesis of Trithioortho Esters: Preparation of 2-Tris(methylthio)methyl Pyridine (4). *t*-BuOK (10 mmol, 1.12 g) was dried for 2 h at 100 °C in vacuo. THF (10 mL) and diisopropylamine (10 mmol, 1.4 mL) were added and the mixture was cooled to −78 °C. *n*-BuLi (1.6 M in hexane, 10 mmol, 6.25 mL) was added dropwise and the mixture was stirred for 15 min at the same temperature. 2-Picoline **1** (2 mmol, 200 μL) dissolved in THF (2 mL) was added dropwise and the resulting orange solution was stirred for 15 min. MeSSMe (10 mmol, 890 μL) in THF (10 mL) was added dropwise and the mixture was stirred at −78 °C for another 15 min, after which time TLC analysis showed complete conversion. Water (2 mL) was added and the temperature was raised to ambient temperature. The product was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. After filtration and solvent evaporation, the crude product was purified by chromatography on silica gel (hexanes/ethyl acetate 95/5) to give 373 mg (81%) of a pale yellow solid, mp 45 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.98 (s, 9H), 7.20 (dd, J = 6.2, 4.8 Hz, 1H), 7.77 (dd, J = 8, 6.2 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H), 8.50 (d, J = 5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 76.1, 122.0, 122.4, 136.6, 146.8, 160.0. MS (EI) *m*/*z* 231 (M$^+$, 88%), 184 (100), 136 (80), 122 (35), 78 (57). Anal. Calcd for $C_9H_{13}NS_3$ (231.02): C, 46.71; H, 5.66; N, 6.05; S, 41.57. Found: C, 46.88; H, 5.74; N, 6.37; S, 42.13.

Spectroscopic data of compounds prepared analogously can be found in Supporting Information.

General Procedure for the Synthesis of Dithioketals: Preparation of 2-[1,1-Bis(methylthio)]but-3-enylpyridine (35). *t*-BuOK (8 mmol, 896 mg) was dried for 2 h at 100 °C in vacuo. THF (8 mL) and diisopropylamine (8 mmol, 1.12 mL) were added and the mixture was cooled to −78 °C. *n*-BuLi (1.6 M in hexane, 8 mmol, 5 mL) was added dropwise and the mixture was stirred for 15 min at the same temperature. 2-Picoline **1** (2 mmol, 200 μL) dissolved in THF (2 mL) was added dropwise and the resulting orange solution was stirred for 15 min. MeSSMe (4 mmol, 355 μL) in THF (4 mL) was added dropwise and the mixture was stirred at −78 °C for 30 min. Allyl bromide (6 mmol, 520 μL) was added dropwise and the mixture was stirred at −78 °C for 30 min. Water (2 mL) was added and the temperature was raised to ambient temperature. The product was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. After filtration and solvent evaporation, the crude product was purified by chromatography on silica gel (hexanes/ethyl acetate mixtures). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.95 (s, 6H), 2.98 (d, J = 6.8 Hz, 2H), 4.95 (dd, J = 5.8, 1 Hz, 1H), 5.02 (d, J = 12.8 Hz, 1H), 5.66 (m, 1H), 7.15 (t, J = 5.2 Hz, 1H), 6.60−7.80 (m, 2H), 8.56 (d, J = 4.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.7, 42.1, 66.9, 117.1, 121.6, 132.4, 135.9, 147.7, 159.9. MS (EI) *m*/*z* 225 (M$^+$, 13%), 210 (32), 178 (47), 162 (42), 131 (100), 78 (52).

Spectroscopic data of compounds prepared analogously can be found in Supporting Information.

General Procedure for Hydrolysis of Dithioacetals, Dithioketals, and Trithioortho Esters: Preparation of Pyridine-2-carbothioic Acid *S*-Methyl Ester[19] (44). Trithiortho ester **4** (1 mmol) was dissolved in acetonitrile (12 mL). Water (3 mL), $HgCl_2$ (2.2 mmol, 598 mg), and $CaCO_3$ (2.2 mmol, 220 mg) were added and the mixture was stirred at room temperature overnight. The mixture was filtered over celite and dichloromethane was added until no spot of product appeared on TLC. More water was added and the organic phase was separated and dried over $MgSO_4$. After solvent evaporation the residue was purified by chromatography on silica gel (hexanes/ethyl acetate 4/1) to give 145 mg of a white powder (94%), mp 58 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.53 (dt, J = 4.8, 1.2 Hz, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 8.69 (d, J = 4.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.4, 120.1, 127.6, 137.0, 149.0, 151.7, 193.9. MS (EI) *m*/*z* 153 (M$^+$, 5%), 125 (10), 111 (19), 106 (30), 78 (100), 51 (37). Anal. Calcd for C_7H_7NOS (153.02): C, 54.88; H, 4.61; N, 9.14; S, 20.93. Found: C, 54.85; H, 4.71; N, 8.84; S, 20.37.

Spectroscopic data of compounds prepared analogously can be found in Supporting Information.

General Procedure for Formation of Ketals and Ortho Esters: Preparation of 2-(1,1-Dimethoxy-ethyl)-pyridine (42). The substrate (0.5 mmol, 99.5 mg) was dissolved in methanol (5 mL). $HgCl_2$ (1.65 mmol, 448 mg) and HgO (0.83 mmol, 180 mg) were added and the mixture was stirred at room temperature overnight. The mixture was filtered over celite and dichloromethane was added until no spot of product appeared on TLC. After solvent evaporation the residue was purified by chromatography on silica gel (hexanes/ethyl acetate/triethylamine 6/3/1) to give 70 mg of a colorless syrup. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.64 (s, 3H), 3.23 (s, 6H), 7.22 (ddd, J = 6.7, 4.8, 1.7 Hz, 1H), 7.60−7.80 (m, 2H), 8.67 (d, J = 4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.9, 49.0, 101.5, 121.2, 136.1, 149.0, 160.4. MS (EI) *m*/*z* 152 ([M − CH_3]$^+$, 14%), 136 (47), 122 (28), 104 (33), 89 (100), 78 (36), 51 (27).

Spectroscopic data of compounds prepared analogously can be found in Supporting Information.

General Procedure for Ester Formation: Preparation of 5-Methyl-pyrazine-2-carboxylic Acid Methyl Ester (58). The substrate (0.46 mmol, 113 mg) was dissolved in methanol (6 mL). Water (1.5 mL), $HgCl_2$ (1.52 mmol, 412 mg), and HgO (0.76 mmol, 164 mg) were added and the mixture was stirred at room temperature overnight. The mixture was filtered over celite and dichloromethane was added until no spot of product appeared on TLC. More water was added and the organic phase was separated and dried over $MgSO_4$. After solvent evaporation the residue was purified by chromatography on silica gel (hexanes/ethyl 4/1)to give 50 mg of a white solid, mp 92 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.69 (s, 3H), 4.04 (s, 3H), 8.60 (s, 1H), 9.20 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.6, 52.6, 140.1, 143.9, 145.0, 157.6, 164.3. MS (EI) *m*/*z* 152 (M$^+$, 8%), 122 (35), 94 (100), 66 (24), 53 (30). Anal. Calcd for $C_7H_8N_2O_2$ (152.06): C, 55.26; H, 5.30; N, 18.41. Found: C, 55.28; H, 5.20; N, 18.26.

Spectroscopic data of compounds prepared analogously can be found in Supporting Information.

General Procedure for Hydrolysis of Thio Compounds Using $PhI(OCOCF_3)_2$. Solid [bis(trifluoroacetoxy)-iodo]benzene (0.5 mmol) was added to a room-temperature CH_3CN/H_2O solution (1:1, 2.5 mL) of the thio compound (0.5 mmol) and TFA (5 mmol). After 30 min, additional solid [bis(trifluoroacetoxy)-iodo] benzene (1 mmol) was added, with the reaction being terminated after 2.5 h. A saturated, aqueous solution of Na_2CO_3 was added carrefully and the product was extracted with CH_2Cl_2. The

organic phase was dried over $MgSO_4$ and concentrated in vacuo. Pure compounds were obtained after chromatography on silica gel.

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Supporting Information Available: Spectroscopic data of compounds **7**, **9**, **10**, **12**, **13**, **15**, **16**, **18**, **19**, **22**−**27**, **29**, **30**, **32**, **33**, **36**−**41**, **43**, **45**−**57, 59, 60**; Table S1 describing the metalation study of 2-picoline **1**, NMR spectra of all compounds, crystallographic data and cif files of compounds **13** and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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