Direct Access to Various 1-Substituted-imidazo[1,5-*a*]pyridine-3(2*H*)-thione Derivatives

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In connection with our medicinal chemistry research program, we were interested in preparing a series of 1-substituted-imidazo[1,5-*a*]pyridine-3(2*H*)-thione derivatives (Figure 1).

Although synthesis of 1-phenyl-imidazo[1,5-*a*]pyridine-3(2*H*)-thione (**1**) has been reported previously by Glover and coworkers,[1] its analogues, compounds possessing diverse R_1 and R_2 groups, have not been known to date.[2] Therefore, we decided to investigate the synthesis of its various derivatives and evaluate them as a novel scaffold for new drug development. However, precedented synthesis of **1** requires many steps (Scheme 1).[1] Thus, phenyl-2-pyridyl ketone (**2**) was first converted to the corresponding oxime, which upon reduction with Zn in acetic acid, provided the amine **3**.[3] The reaction of amine **3** with phenyl isothiocyanate led to the thiourea **4** which was heated to reflux in xylene to afford **1**. In addition, phenyl-2-pyridyl ketone (**2**) itself has to be synthesized.[4]

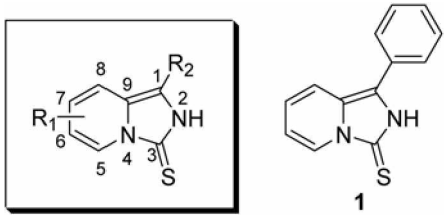
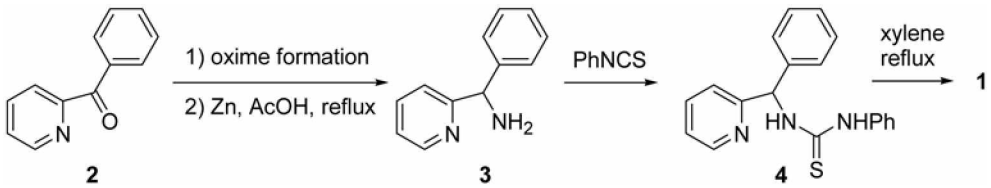


Figure 1

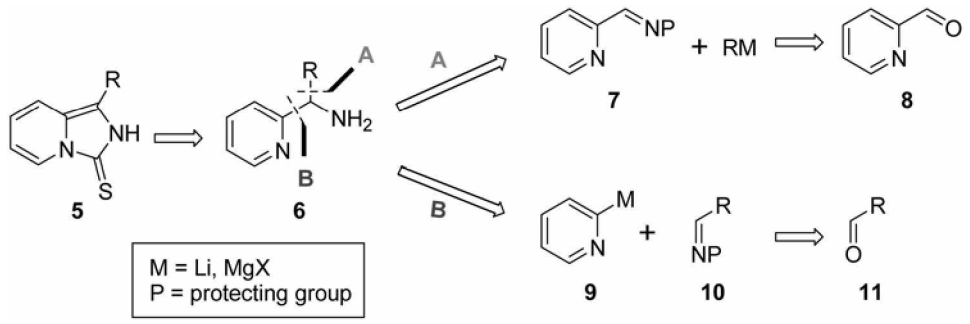
In order to make a wide variety of 1-substituted-imidazo-[1,5-*a*]pyridine-3(2*H*)-thione derivatives efficiently, more direct route was sought. In this communication, we wish to report an expedient synthesis of 1-substituted-imidazo[1,5-*a*]pyridine-3(2*H*)-thione analogues.

As retrosynthetically shown in Scheme 2, it was conceived that cyclic thioureas **5** should be derived from amines **6**, which in turn could be obtained from the commercially available 2-pyridinecarboxaldehyde (**8**) *via* the addition of various organometallic species (RM) to the aldimines **7** (route **A**).[5] Alternatively, amines **6** could be constructed from the addition of **9** to aldimines **10** which should be available from aldehydes **11** (route **B**).

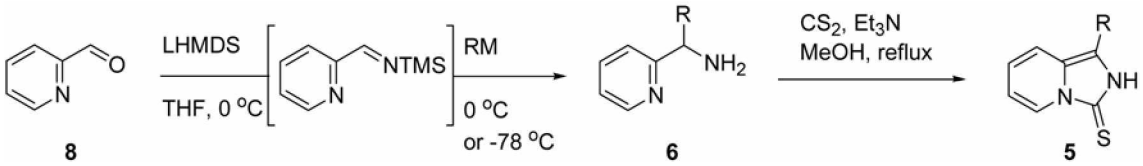
In both routes, *in situ* formation of aldimines would be desirable in order to increase efficiency. Among the methods to make aldimines *in situ* from aldehydes, Hart's procedure[6] was elected since the adduct, *N*-silylated amines, can be easily hydrolyzed to generate primary amines **6** directly during the aqueous work-up. Surprisingly, this protocol has not



Scheme 1



Scheme 2. Retrosynthetic analysis.

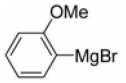
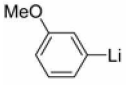
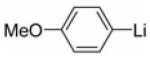
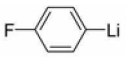
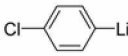
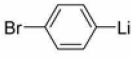
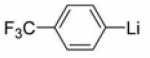
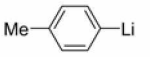
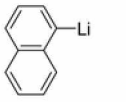
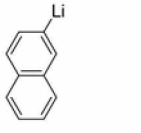
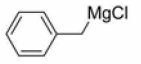
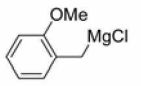
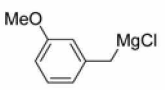
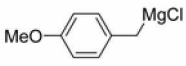
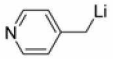
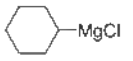
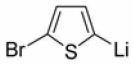
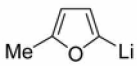
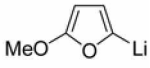
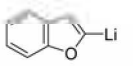
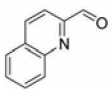
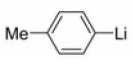


Scheme 3

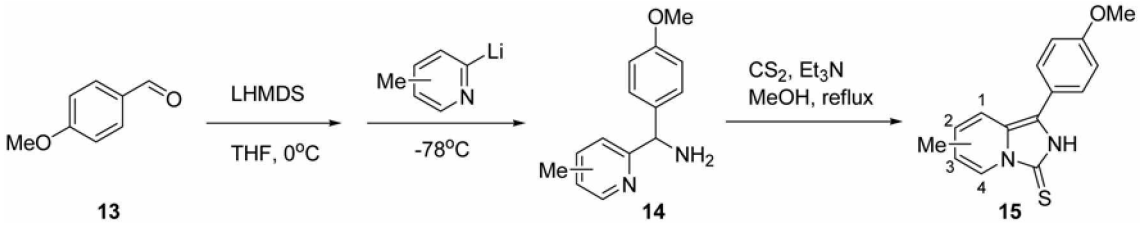
been exploited frequently with nitrogen-containing heteroaromatic aldehydes such as 2-pyridinecarboxaldehyde.[7] Since it is difficult to make *N*-TMS aldimines **10** from aldehydes **11** in some cases,[8] we first opted to use the route **A**.

Thus, a solution of 2-pyridinecarboxaldehyde (**8**) was treated with lithium bis(trimethylsilyl)amide (LHMDS) at 0 °C to afford *N*-trimethylsilylaldimine, which was then

Table 1.

Entry	Aldehydes	RM	Temp[a]	6[b]	5[b]	Work-up[c]
1	 **8**		0	**6a** (89)	**5a** (82)	**A**
2	**8**		0	**6b** (93)	**5b** (85)	**A**
3	**8**		0	**6c** (88)	**5c** (90)	**A**
4	**8**		−78	**6d** (79)	**5d** (92)	**B**
5	**8**		−78	**6e** (75)	**5e** (82)	**B**
6	**8**		0	**6f** (80)	**5f** (81)	**B**
7	**8**		−78	**6g** (83)	**5g** (84)	**B**
8	**8**		−78	**6h** (78)	**5h** (91)	**B**
9	**8**		0	**6i** (81)	**5i** (85)	**B**
10	**8**		−78	**6j** (78)	**5j** (82)	**B**
11	**8**		−78	**6k** (89)	**5k** (81)	**A**
12	**8**		−78	**6l** (88)	**5l** (86)	**B**
13	**8**		−78	**6m** (89)	**5m** (93)	**B**
14	**8**		−78	**6n** (82)	**5n** (91)	**B**
15	**8**		−78	**6o** (69)	**5o** (79)	**A**
16	**8**	MeMgCl	0	**6p** (95)	**5p** (81)	**C**
17	**8**	EtMgBr	−78	**6q** (98)	**5q** (79)	**C**
18	**8**	*i*-PrMgCl	−78	**6r** (93)	**5r** (80)	**C**
19	**8**		0	**6s** (96)	**5s** (75)	**C**
20	**8**	*n*-BuLi	0	**6t** (94)	**5t** (83)	**C**
21	**8**		0	**6u** (92)	**5u** (80)	**A**
22	**8**		−78	**6v** (79)	**5v** (76)	**B**
23	**8**		−78	**6w** (84)	**6w** (72)	**B**
24	**8**		−78	**6x** (75)	**5x** (81)	**B**
25	**8**		0	**6y** (90)	**5y** (83)	**B**
26	**8**		0	**6z** (80)	**5z** (77)	**B**
27	**8**		−78	**6aa** (78)	**5aa** (75)	**B**
28	**8**		−78	**6bb** (70)	**5bb** (76)	**B**
29	**8**		0	**6cc** (84)	**5cc** (82)	**B**
30	 **12**		−78	**6dd** (82)	**5dd** (92)	**A**

[a]Temperature (°C) when *N*-trimethylsilylaldimine was added to organometallic reagents. [b]Isolated yields (%) in parenthesis. [c]Work-up procedure **A**, **B**, or **C**.



Scheme 4

low temperature to provide amines **6** in good to high yields (Scheme 3).[9] Next, two reaction conditions were evaluated to effect cyclization. Amines **6** were treated with 1,1'-thiocarbonyldiimidazole in CH_2Cl_2 to obtain the cyclic thioureas **5**. Alternatively, exposure of **6** to CS_2 and Et_3N in refluxing MeOH[10] led to the same products **5** in good to high yields. This method was superior to the former one with respect to yield and work-up. In most cases, the products **5** were precipitated out as the reaction proceeded. Overall, this two-step procedure enables us to rapidly access to various 1-substituted-imidazo[1,5-*a*]pyridine-3(2*H*)-thione derivatives.

As summarized in Table 1, we were able to incorporate aryl (**5a-5j**), benzyl (**5k-5o**), alkyl (**5p-5u**), heterocyclic (**5v-5cc**) groups at C1 of thioureas **5**, respectively. 2-Quinolinecarboxaldehyde (**12**) (entry 30) was also successfully utilized as aldehyde partner.

By following the route **B**, we also synthesized several derivatives containing one methyl group on the pyridine ring (1, 2, 3, and 4 position of **15**) although yields were poor (not optimized) (Scheme 4).[11]

In conclusion, we have demonstrated a novel, two step approach to 1-substituted-imidazo[1,5-*a*]pyridine-3(2*H*)-thione derivatives[12] starting from aldehydes, employing the nucleophilic addition of organometallic compounds to aldimines prepared *in situ*. This process should be useful for the synthesis of structurally related thioureas given a number of readily available organometallic reagents. Biological evaluation of these new compounds are currently underway and will be reported in due course.

Typical Experimental Procedure

To a solution of 2-pyridinecarboxaldehyde (**8**) in THF was slowly added LHMDS solution (1.0 M in THF, 1.2 equiv) at 0 °C. After 20 min, this solution was transferred to a solution of organometallic reagents (purchased or freshly prepared by appropriate methods, 1.8-2.0 equiv) in THF at either 0 or −78 °C depending on the organometallic species. After the reaction was complete, the reaction mixture was quenched with H_2O. The mixture was diluted with ethyl acetate and washed with water and brine. The water layer was extracted with ethyl acetate one more. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo*.[13] For characterization purposes, the resulting residue was further purified by column chromatography (hexane:ethyl acetate = 1:1 to ethyl acetate only to methylene chloride: methanol = 10:1) to give amines **6**.

Amines **6** were dissolved in MeOH, and CS_2 (7.2 equiv) and Et_3N (2.0 equiv) were added at room temperature. The reaction mixture was heated to reflux overnight. After being cooled to room temperature, the mixture was concentrated under reduced pressure. The following work-up procedures were chosen depending on the product solubility. **Work-up A:** The residue was diluted with methylene chloride and washed with water. The water layer was extracted with methylene chloride one more. The combined organic layer was dried with $MgSO_4$, filtered, and evaporated in vacuo. The crude residue was suspended in small amount of ethyl acetate and filtered. Top solid was washed with small amount of ethyl acetate two or three times to afford cyclic thiourea **5**. **Work-up B:** In case of the product **5** slightly soluble in methylene chloride, the reaction mixture was concentrated *in vacuo*. The resulting residue was suspended in ethyl acetate and water. This mixture was then filtered and washed with water and ethyl acetate, successively. Even in the case where product was isolated by filtration, the filtrate was further purified by silica gel flash column chromatography for higher yields. **Work-up C:** In case of products very soluble in ethyl acetate and/or methylene chloride, the crude residue after aqueous work-up was purified by silica gel flash column chromatography (hexane:ethyl acetate: methylene chloride = 5:1:2 to 3:1:2).

Compound 5c: 300 MHz ^{1}H NMR (DMSO-d_6) δ 13.7 (1H, br s), 8.11 (1H, dt, J = 7.4, 1.0 Hz), 7.62 (2H, d, J = 8.9 Hz), 7.62-7.56 (1H, m), 7.03 (2H, d, J = 8.9 Hz), 6.82 (1H, ddd, J = 9.4, 6.3, 1.0 Hz), 6.67 (1H, ddd, J = 7.3, 6.4, 1.0 Hz), 3.79 (3H, s); 125 MHz ^{13}C NMR (DMSO-d_6) δ 158.7, 152.1, 127.4, 124.1, 122.9, 122.3, 120.9, 118.1, 117.4, 114.7, 113.2, 55.3; MS (EI) m/z $[M]^+$ for $C_{14}H_{12}N_2OS$: calcd 256.07, found 256, 241, 224, 182, 136. **Compound 5d:** 200 MHz ^{1}H NMR (DMSO-d_6) δ 13.8 (1H, br s), 8.17 (1H, dd, J = 7.4, 1.2 Hz), 7.85-7.60 (3H, m), 7.32 (2H, t, J = 9.0 Hz), 6.91 (1H, dd, J = 6.4, 5.2 Hz), 6.72 (1H, t, J = 7.2 Hz); 125 MHz ^{13}C NMR (DMSO-d_6) δ 162.2, 160.3, 128.1, 128.0, 125.0, 124.9, 124.3, 123.7, 123.1, 117.9, 116.3, 116.2, 116.1, 113.3; MS (EI) m/z $[M]^-$ for $C_{13}H_9FN_2S$: calcd 244.05, found 244, 212, 185, 157, 122. **Compound 5e:** 200 MHz ^{1}H NMR (DMSO-d_6) δ 13.9 (1H, br s), 8.19 (1H, dd, J = 7.2, 0.8 Hz), 7.85-7.60 (3H, m), 7.51 (2H, d, J = 9.0 Hz), 6.94 (1H, dd, J = 9.4, 6.6 Hz), 6.74 (1H, dd, J = 7.2, 6.4 Hz); 125 MHz ^{13}C NMR (DMSO-d_6) δ 153.1, 131.6, 129.1, 127.4, 127.2, 124.4, 124.2, 123.6, 117.9, 115.9, 113.4; MS (EI) m/z $[M]^+$ for $C_{13}H_9ClN_2S$: calcd 260.02, found 260, 225, 201, 192, 166. **Compound 5k:** 200 MHz ^{1}H NMR (DMSO-d_6) δ 13.4 (1H,

br s), 7.96 (1H, dt, J = 7.2, 1.2 Hz), 7.42 (1H, dt, J = 9.4, 1.6 Hz), 7.40-7.08 (5H, m), 6.68 (1H, ddd, J = 9.4, 6.6, 1.4 Hz), 6.56 (1H, ddd, J = 7.6, 6.4, 1.6 Hz), 4.10 (2H, s); 125 MHz ^{13}C NMR (DMSO-d_6) δ 140.4, 132.6, 129.3, 128.5, 128.3, 125.9, 125.2, 122.5, 119.3, 117.5, 113.1, 32.9; MS (EI) m/z $[M]^+$ for $C_{14}H_{12}N_2S$: calcd 240.07, found 240, 221, 205, 180, 152. **Compound 5n:** 200 MHz ^{1}H NMR ($CDCl_3$) δ 12.0 (1H, br s), 8.11 (1H, d, J = 7.4 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.00 (1H, d, J = 9.4 Hz), 6.84 (2H, d, J = 8.6 Hz), 6.61 (1H, dd, J = 9.4, 5.6 Hz), 6.49 (1H, t, J = 6.4 Hz), 4.08 (2H, s), 3.78 (3H, s); 125 MHz ^{13}C NMR (DMSO-d_6) δ 158.0, 150.9, 130.7, 129.4, 123.8, 123.5, 120.1, 117.9, 117.7, 114.0, 112.6, 55.1, 28.4; MS (EI) m/z $[M]^+$ for $C_{15}H_{14}N_2OS$: calcd 270.08, found 270, 237, 210, 167, 121. **Compound 5r:** 200 MHz ^{1}H NMR ($CDCl_3$) δ 8.13 (1H, d, J = 7.2 Hz), 7.18 (1H, dd, J = 9.4, 1.2 Hz), 6.60 (1H, t, J = 6.4 Hz), 6.49 (1H, t, J = 6.4 Hz), 3.27 (1H, septet, J = 7.4 Hz), 1.40 (6H, d, J = 7.4 Hz); 125 MHz ^{13}C NMR (DMSO-d_6) δ 150.8, 124.2, 123.4, 122.2, 119.5, 117.9, 112.5, 24.1, 22.2; MS (EI) m/z $[M]^+$ for $C_{10}H_{12}N_2S$: calcd 192.07, found 191.9 (97), 176.9 (100), 131.8 (14), 116.9 (58). **Compound 5z:** 300 MHz ^{1}H NMR (DMSO-d_6) δ 13.8 (1H, br s), 8.06 (1H, d, J = 7.4 Hz), 7.65 (1H, dt, J = 9.4, 1.1 Hz), 6.86 (1H, dd, J = 9.4, 6.0 Hz), 6.76 (1H, d, J = 3.3 Hz), 6.68 (1H, t, J = 7.2 Hz), 6.22 (1H, dd, J = 3.3, 1.0 Hz), 2.35 (3H, s); 125 MHz ^{13}C NMR (DMSO-d_6) δ 152.6, 151.6, 142.6, 124.0, 122.6, 122.5, 118.7, 113.5, 109.9, 107.8, 106.8, 13.4; MS (EI) m/z $[M]^+$ for $C_{12}H_{10}N_2OS$: calcd 230.05, found 230.0 (100), 186.9 (68), 171.8 (14), 127.9 (25). **Compound 5dd:** 200 MHz ^{1}H NMR (DMSO-d_6) δ 13.6 (1H, br s), 10.9 (1H, d, J = 8.6 Hz), 7.66 (1H, dd, J = 7.4, 2.0 Hz), 7.58 (2H, d, J = 8.2 Hz), 7.57-7.34 (3H, m), 7.32 (2H, d, J = 8.0 Hz), 7.13 (1H, d, J = 9.4 Hz), 2.37 (3H, s); 125 MHz ^{13}C NMR (DMSO-d_6) δ 157.0, 137.9, 134.9, 129.7, 127.8, 127.1, 127.0, 126.1, 125.7, 124.7, 124.0, 123.0, 120.4, 117.2, 116.2; MS (EI) m/z $[M]^+$ for $C_{18}H_{14}N_2S$: calcd 290.09, found 290.1 (100), 230.1 (35), 217.1 (13), 144.9 (19).

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References and Notes

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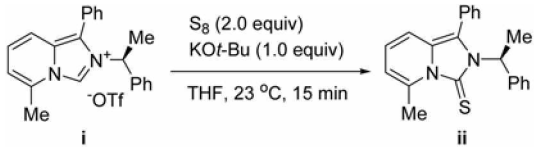

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