Novel Synthesis of Stable Furan and Thiophene o-Amino Thioaldehydes by Reaction of o-Azido Aldehydes with Hexamethyldisilathiane

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A new synthesis of monomeric o-aminothioaldehydes of thiophene, benzof[b]thiophene, furan and benzof[b]furan by reacting the corresponding o-azido aldehydes with hexamethyldisilathiane in neat acetonitrile and/or in methanol in the presence of hydrochloric acid at room temperature is reported.

In recent years considerable attention has been devoted to the chemistry of highly reactive thioaldehydes and thioketones which have been proved to be valuable intermediates in organic synthesis. In particular, simple thioaldehydes have historically been considered to be elusive compounds owing to their especially pronounced tendency to suffer oligo- and polymerization reactions. However, since the first preparation of a stable monomeric pyrrolocarboxialdehyde reported by Woodward et al. in 1960, it has become apparent that the highly reactive thioformyl moiety can be effectively stabilized by the mesomeric effect of an electron-rich heterocyclic ring or carbon-carbon double bond. Indeed, other stable thioaldehydes, often derived from the pyrrole ring or enamino systems, have been reported since, but in a relatively limited number. More recently Becher and co-workers reported several o-aminothioaldehydes in the pyrazole and indole series, which represent additional examples of chemically stable heteroaromatic thioaldehydes due to delocalization of the amino nitrogen lone pair. These o-aminoheteroaromaticthioaldehydes were generally produced by reaction of the corresponding o-azido aldehydes with gaseous hydrogen sulfide.

In previous work we showed that hexamethyldisilathiane (HMST), a known valuable agent for the thionation of carbonyl compounds, reacts with heteroaromatic o-azido aldehydes in MeCN, at room temperature and in the presence of HCl or Lewis acids such as CoCl$_2$, 6H$_2$O or trimethylsilyl trifluoromethanesulfonate, to give o-azido thioaldehydes. According to the reaction conditions these transient compounds can undergo intramolecular cyclization to fused isothiazoles and/or be intermolecularly intercepted by 1,3-dienes to give Diels-Alder cycloadducts. Subsequently, we showed that HMST can also perform selective reduction of heterocyclic aldehydes to amino aldehydes when reacted in methanolic solution in the absence of any acid catalyst. Here we report the additional use of HMST in a convenient one-pot conversion of o-azido aldehydes derived from the furan and thiophene rings into novel, chemically stable amino thioaldehydes.

A solution of 3-azido-2-formylfuran (1a) in MeCN reacted smoothly with a three-fold excess of HMST at room temperature over 4.5 h to give the corresponding amino thioaldehyde 3a through the intermediate amino aldehyde 2a. Column chromatography of the crude product gave the pure thioaldehyde 3a in good yield (Method A).

Method A (Me$_3$Si)$_2$S/MeCN, r.t. 40-67%

Method B (Me$_3$Si)$_2$S/MeOH/HCl, r.t. 45-70%

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Method B (Me$_3$Si)$_2$S/MeOH/HCl, r.t. 45-70%
tory yields of these thioaldehydes 3e–g were successfully isolated by means of an analogous procedure using MeOH as solvent instead of MeCN (Method B). All the new o-aminothioaldehydes 3a–d, f, g are stable orange to red compounds which can be stored in the cold with no significant sign of decomposition, the only exception being the amino thioaldehyde 3e which is rather unstable. Their structures were generally supported by 1H and 13C NMR, and mass spectral data in addition to elemental analyses. In particular, the 1H NMR spectra, measured in CDCl3, showed a thioformyl proton resonance at δ = 10.3 – 11.1, while the 13C NMR spectra showed a thiocarbonyl absorption in the range of δ = 180 – 200.13 The mass spectra generally exhibited the molecular ion peak as the base peak as well as an abundant ion peak corresponding to M+ – 1.

Like the previously reported o-aminothioaldehydes in the pyrazole and indole series,7 the stability of our present thioaldehydes is ascribable to resonance conjugation of the heteroaromatic thioformyl group with the adjacent amino function. In the case of compound 2a, restricted rotation of the thioformyl group was clearly seen from the 1H NMR spectrum obtained in DMSO-d6, which showed the presence of two thioformyl protons in ca. 1:1 ratio at δ = 10.38 and 10.29.

In the present study HMDST was also found to be able to convert 2-azido-1-ethyl-3-formylindole (1h)9 to the isoamino thioaldehyde 3h in good yield. This finding, while providing an additional instance of stable indolecarbothioaldehyde, also suggests that HMDST can generally act as a valid substitute for H3S gas in the transformation of five-membered heteroaromatic o-azido aldehydes to o-aminothioaldehydes.

Similar to its heterocyclic analogs 1a–h, o-azidobenzaldehyde was readily transformed by HMDST, according to method B, into o-aminobenzaldehyde that however proved to be not isolable owing to prompt trimerization (and polymerization) reactions of its thioformyl moiety. As might have been anticipated, in such a case aromatic character of the benzene ring would prevent adequate stabilization of the thioformyl function.

In conclusion, we have shown that the reaction of HMDST with five-membered heterocaryl o-azido aldehydes offers an easy synthetic entry to o-aminothioaldehydes alternative to the previously reported procedure employing H3S gas.7 Moreover, we have shown for the first time that o-aminothioaldehydes derived from thiophene and furan rings are stable compounds like their analogs in the pyrazole and indole series. Present and previous findings thus open the way to an extensive investigation of this attractive class of o-aminosubstituted heteroaromatic thioaldehydes.

**o-Amino Thioaldehydes 3a–h; General Procedures:**

**Method A:** The appropriate azido aldehyde (0.9 mmol) and HMDST (0.38 mL, 1.8 mmol) in MeCN (15 mL) were stirred at r.t. for 1 h, after which further HMDST (0.19 mL, 0.9 mmol) was added and the stirring was continued until disappearance of the starting azide (TLC). Dilution with CH2Cl2, washing with 10% NaHCO3 and evaporation of the solvent afforded the crude amino thioaldehyde which was purified by column chromatography on neutral Al2O3, using CHCl3 as eluent.

**Method B:** The appropriate azido aldehyde (0.9 mmol) and HMDST (0.38 mL, 1.8 mmol) in MeOH (15 mL) were stirred at r.t. until essential conversion to the amino derivative (TLC). Conc. HCl (3 equiv) and HMDST (0.28 mL, 1.35 mmol) were then added and stirring continued until complete disappearance of the intermediate amino aldehyde (TLC). Useful workup (see Method A) and purification by column chromatography on neutral Al2O3, using CHCl3 as eluent, gave the pure amino thioaldehyde.

3-Amino-2-thioformylfuran (3a): Method A; 4.5 h; orange-yellow solid; mp 69 – 70°C; yield: 76.6 mg (67%).

1H NMR (CDCl3, 200 MHz): δ = 6.19 (d, 1 H, J = 2.0 Hz), 7.20 (br s, 2 H), 7.37 (d, 1 H, J = 2.0 Hz), 10.36 (s, 1 H).

13C NMR (CDCl3, 50 MHz): δ = 185.9, 151.0, 149.8, 147.0, 105.0.

MS: m/z (%) = 127 (100, M+), 126 (21), 110 (8), 99 (7).

Anal. Caled for C8H12NO5: 172.2; C, 47.22; H, 3.96; N, 11.01.

Found: C, 47.50; H, 4.05; N, 10.87.

3-Amino-2-thioformylbenzofuran (3b): Method A; 4 h; red-brown solid; yield: 90.8 mg (57%).

1H NMR (CDCl3, 200 MHz): δ = 7.18 – 7.32 (m, 2 H), 7.41 – 7.62 (m, 4 H), 10.56 (s, 1 H).

13C NMR (CDCl3, 50 MHz): δ = 195.2, 167.0, 148.8, 125.5, 124.9, 124.0, 116.8, 111.1, 110.4.

MS: m/z (%) = 177 (100, M+), 176 (34), 133 (31), 104 (12).

Anal. Caled for C9H10NO5: 172.2; C, 60.99; H, 3.98; N, 7.90.

Found: C, 60.75; H, 4.11; N, 7.72.

3-Amino-2-thioformylthiophene (3c): Method A; 7 h; red-brown solid; yield: 57.7 mg (40%).

1H NMR (CDCl3, 300 MHz): δ = 7.35 – 7.55 (m, 4 H), 6.78 – 7.83 (m, 2 H), 10.72 (s, 1 H).

13C NMR (CDCl3, 75 MHz): δ = 199.3, 156.7, 130.2, 125.9, 122.5, 122.6.

MS: m/z (%) = 193 (100, M+), 192 (72), 191 (49), 84 (6).

Anal. Caled for C6H4NS2: 193.3; C, 55.92; H, 3.65; N, 7.25.

Found: C, 55.68; H, 3.77; N, 7.07.

3-Amino-2-thioformylbenzothiophene (3d): Method A; 4 h; red-brown solid; yield: 69.5 mg (40%).

1H NMR (CDCl3, 300 MHz): δ = 6.58 (d, 1 H, J = 4.9 Hz), 7.20 (br s, 2 H), 7.60 (d, 1 H, J = 4.9 Hz), 10.66 (s, 1 H).

MS (30 eV): m/z (%) = 143 (61, M+), 142 (10), 141 (100), 126 (11), 99 (16).

This compound showed a tendency to decompose at r.t. and a satisfactory elemental analysis was not obtained.

3-Amino-3-thioformylfuran (3f): Method B; 4 h; orange-yellow solid; mp 154 – 155°C; yield: 100.4 mg (63%).

1H NMR (CDCl3, 300 MHz): δ = 7.18 – 7.33 (m, 5 H), 7.59 – 7.62 (m, 1 H), 10.75 (s, 1 H).

13C NMR (CDCl3, 50 MHz): δ = 188.3, 155.3, 145.6, 145.4, 132.5, 122.7, 121.0, 120.4, 112.9.

MS (30 eV): m/z (%) = 177 (67, M+), 175 (27), 144 (58), 84 (100), 58 (50).


Found: C, 61.12; H, 3.87; N, 8.00.

3-Amino-3-thioformylbenzothiophene (3g): Method B; 4 h; orange-yellow solid; mp 139 – 140°C; yield: 121.6 mg (70%).
$^1$H NMR (CDCl$_3$, 300 MHz): $\delta = 7.22-7.29$ (m, 1 H), 7.32-7.39 (m, 3 H), 7.47-7.52 (m, 1 H), 7.70-7.74 (m, 1 H), 11.03 (s, 1 H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta = 196.4, 169.6, 136.6, 126.1, 124.6, 124.1, 122.7, 121.8, 118.1$.

MS (30 eV): $m/z$ (%) = 193 (84, M$^+$), 160 (100), 133 (18), 121 (20), 89 (26).

Anal. Calcd for C$_{11}$H$_7$NS$_2$: C, 55.92; H, 3.65; N, 7.25. Found: C, 56.03; H, 3.47; N, 7.33.

2-Amino-1-ethyl-3-thioformylindole (3b): Method B; 2 h; orange-yellow solid; mp 129-130°C; yield = 115.7 mg (63%).

$^1$H NMR (CDCl$_3$, 200 MHz): $\delta = 1.40$ (t, 3 H, $J = 8.8$ Hz), 3.96 (q, 2 H, $J = 8.8$ Hz), 7.02-7.22 (m, 3 H), 5.78-7.65 (m, 1 H), 8.42 (br s, 2 H), 10.42 (s, 1 H).

$^{13}$C NMR (CDCl$_3$, 50 MHz): $\delta = 186.4, 155.2, 133.9, 125.2, 123.5, 122.9, 116.5, 115.6, 108.3, 36.3, 12.9$.

MS: $m/z$ (%) = 204 (100, M$^+$), 203 (31), 176 (36), 175 (34), 155 (10).

Anal. Calcd for C$_{11}$H$_7$N$_2$S (204.3): C, 64.67; H, 5.92; N, 13.69. Found: C, 64.81; H, 6.13; N, 13.49.

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