Hexamethyldisilathiane: Its Use in the Conversion of Aromatic and Heteroaromatic Azides to Amines

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Introduction

Several recent reports in the literature have demonstrated that hexamethyldisilathiane (HMDST) may be efficiently employed in the formation of thiocarbonyl compounds, including *inter alia* thioaldehydes, thioketones, thioamides and thiolactams.[1] Very recently, this thionating agent has been utilized in our laboratory to effect the conversion of aromatic and heteroaromatic *o*-azidoaldehydes to *o*-azidothioaldehydes, a new class of reactive thioaldehydes. Azidothioaldehydes were produced by reacting the corresponding oxo compounds with HMDST in acetonitrile at room temperature and in the presence of hydrochloric acid or Lewis acids such as $CoCl_2 \cdot 6H_2O$ and TMSOTf. According to the reaction conditions transient azidothioaldehydes underwent intramolecular cyclization to fused isothiazoles[2] and/or intermolecular Diels–Alder reaction with 1,3-dienes to give thioaldehyde–diene cycloadducts.[3] Now we wish to report that HMDST can also act as an efficient agent in the transformation of aromatic and heteroaromatic azides to amines.

Results and Discussion

Brief reaction of the azidohetarenecarbaldehydes **1a–i** (all previously known, except **1c** and **d**) with a 2-fold excess of HMDST in methanol, at room temperature, led to isolation of the corresponding aminoaldehydes **2a–i** in good to fairly good yields (Table 1, entries 1–9). 2-Amino-3-formyl- (**2h**) and 3-amino-2-formylbenzo[*b*]thiophene (**2g**) were previously obtained (but in moderate yields) by reduction of the nitro derivatives with iron powder and ammonium chloride.[4] 3-Amino-2-formylthiophene (**2b**),[5] 3-amino-2-formylfuran (**2a**),[5] and 2-amino-3-formylbenzo[*b*]furan (**2f**)[6] were previously prepared by related reduction of the appropriate azide **1b,a,f** with hydrogen sulfide gas in the presence of base. On the other hand, the compounds **2c–e** and **2i** represent new examples of somewhat rare aminohetarenecarbaldehydes which are chemically stable due to delocalization of the amino-nitrogen lone pair.[6] It is worth noting that hitherto known *o*-aminoaldehydes derived from five-membered heteroaryl systems are normally prepared by hydrogen sulfide reduction[5,6] of *o*-azidoaldehydes, which in turn can be obtained from *o*-halocarbaldehydes through nucleophilic aromatic substitution reaction with sodium azide in DMSO.[2,5,6] The scope of this nucleophilic substitution reaction is, however, not general since it may especially fail in the preparation of the α-azides owing to their tendency to suffer decomposition under (very) mild thermal conditions to give ring cleavage products.[6,7] Very recently we uncovered that 2-formyl-3-nitro- and 3-formyl-2-nitrobenzo[*b*]thiophene readily react with sodium azide in HMPA or DMSO, respectively, to give the azides **1g,h** in very satisfactory yield.[2]

In the present work a similar procedure proved to be effective to produce the previously unknown 2-azidothiophenes **1c** and **d**. These unstable azides **1c,d** could in fact be obtained in 40 and 60% isolated yield through brief reaction of the corresponding nitro derivatives with sodium azide in HMPA at 0 °C. Prolonged reaction times and/or higher reaction temperatures resulted in essential decomposition of the produced azides. Previous attempts to prepare the azidothiophene **1c**, either through reaction of 2-bromo-3-formylthiophene with NaN_3[5] or through azido transfer reaction of tosyl azide with 2-lithiated 3-formylthiophene ethylene acetal,[8] proved to be totally unsuccessful.

Similar to its heterocyclic analogs **1a–i**, *o*-azidobenzaldehyde (**1k**)[9–12] was converted, under comparable conditions, into *o*-aminobenzaldehyde (**2k**) in good yield (Table 1, entry 11). This unprecedented reduction of *o*-azidobenzaldehyde (**1k**) is of interest especially since we succeeded in obtaining this azide, in virtually quantitative yield, by direct reaction of *o*-nitrobenzaldehyde with sodium azide in HMPA. Consequently, we concomitantly disclosed a new clean method for the formation of *o*-aminobenzaldehyde from the nitro derivative. It is known that the reductions of *o*-nitrobenzaldehydes to aminoaldehydes are complicated by competing inter- and intramolecular condensation reactions of the intermediate hydroxylamines, which often requires a critical choice of reducing agent.[13]

3-Azido-2-nitrobenzo[*b*]thiophene (**1j**) newly prepared by nucleophilic substitution of 3-bromo-2-nitrobenzo[*b*]thiophene by azide ion, as well as the nitro- and cyanophenyl azides **1l–o** were also found to undergo smooth reaction with HMDST to give the amines **2j,l–o** in fairly high yields (Table 1, entries 12–15). Additionally, parent 2-azidobenzo[*b*]thiophene **1p** was similarly converted into the amine **2p** (Table 1, entry 16), but

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(9) *o*-Azidobenzaldehyde has been prepared by diazotization of *o*-aminobenzaldehyde oxime,[10] by hydrolysis of *o*-azidobenzaldehyde azine,[11] or more recently, by oxidation of *o*-azidobenzyl alcohol with pyridinium chlorochromate.[12]
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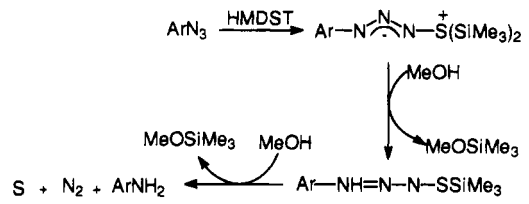
Table 1. Synthesis of Aromatic and Heteroaromatic Amines from Azides and HMDST

entry	azide	amine	time	yield,[a] %
1	**1a**	3-amino-2-formylfuran (**2a**)	30 min	45
2	**1b**	3-amino-2-formylthiophene (**2b**)	1h	70
3	**1c**	2-amino-3-formylthiophene (**2c**)	30 min	50
4	**1d**	2-amino-5-formylthiophene (**2d**)	30 min	68
5	**1e**	3-amino-2-formylbenzo[*b*]furan (**2e**)	1h	60
6	**1f**	2-amino-3-formylbenzo[*b*]furan (**2f**)	30 min	81
7	**1g**	3-amino-2-formylbenzo[*b*]thiophene (**2g**)	1h	90
8	**1h**	2-amino-3-formylbenzo[*b*]thiophene (**2h**)	30 min	87
9	**1i**	2-amino-1-ethyl-3-formylindole (**2i**)	1h	75
10	**1j**	3-amino-2-nitrobenzo[*b*]thiophene (**2j**)	1h	65
11	**1k**	*o*-aminobenzaldehyde (**2k**)	3h	78
12	**1l**	*o*-nitroaniline (**2l**)	3h	86
13	**1m**	*p*-nitroaniline (**2m**)	3h	92
14	**1n**	*m*-nitroaniline (**2n**)	6h	60
15	**1o**	*o*-aminobenzonitrile (**2o**)	1.5h	90
16	**1p**	2-aminobenzo[*b*]thiophene (**2p**)	1h	55

[a] Yields isolated by column chromatography.

Scheme 1



phenyl azide proved to be totally unreactive with HMDST even upon prolonged heating at 60–80 °C.

It therefore appears that HMDST can generally effect straightforward reduction of aryl and heteroaryl azides, provided that the azido function be properly activated by the attached ring.

A likely mechanism of such azide reductions would involve initial nucleophilic attack of the HMDST sulfur atom at the terminal azido nitrogen, followed by methanol desilylation of the ensuing azide-HMDST complex (Scheme 1).

Conclusions

The reaction of HMDST with electrophilic aromatic and heteroaromatic azides provides a novel simple and high-yielding procedure for the formation of amines.

This method is especially useful for selective reduction of *o*-azido to *o*-amino aldehydes, which are important starting material for the construction of annulated heterocyclic systems,[6,13] and therefore adds to the one so far employed for such conversions using hydrogen sulfide gas.[5,6]

Moreover, the easy reduction of *o*-azidoaldehydes, coupled with their observed availability from *o*-nitroaldehydes, furnishes a new convenient entry to *o*-aminoaldehydes from *o*-nitroaldehydes.

Experimental Section

The starting *o*-azidoaldehydes **1a,b**,[5] **1e,g,h,i**,[2,4] and **1f**[6] and the azidobenzothiophene **1n**[14] were prepared according to literature methods. The aryl azides **1l–o** were prepared by diazotization of the corresponding anilines followed by treatment with NaN_3 according to a standard procedure.[15]

***o*-Azidobenzaldehyde (1k).**[10–12] A solution of *o*-nitrobenzaldehyde (1.0 g, 6.8 mmol) and sodium azide (910 mg, 14 mmol) in HMPA (40 mL) (*Caution*: HMPA is highly toxic and suspected of being a carcinogen) was stirred at rt for 8 h. The reaction mixture was poured onto water and then extracted several times with ether. Evaporation of the combined ether extracts gave the crude azide, mp 30–34 °C (lit.[12] mp 34 °C), in ca. 100% yield, and sufficiently pure for direct use.

2-Azido-3-formylthiophene (1c). This compound was similarly prepared by reacting 3-formyl-2-nitrothiophene[16] (153 mg, 1 mmol) with NaN_3 (260 mg, 4 mmol) in HMPA (3 mL) for 30 min at 0 °C. The resulting mixture was poured into ice–water and rapidly extracted with cold ether. TLC (SiO_2, 70:30 hexanes/ether) furnished the title azide (40%): mp 80–81 °C dec; IR (neat) 2120, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.90 (d, 1H, J = 6 Hz), 7.25 (d, 1H, J = 6 Hz), 9.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.3, 152.6, 135.2, 125.6, 118.4.

This azide showed a tendency to decompose even in the solid state at rt and was used immediately.

2-Azido-5-formylthiophene (1d). This compound was similarly prepared by reacting commercially available 2-formyl-5-nitrothiophene (350 mg, 2.2 mmol) with NaN_3 (595 mg, 9.1 mmol) in HMPA (5 mL) at 0 °C for 2 h. Workup of the reaction mixture and subsequent flash chromatography (SiO_2, 70:30 hexanes/ether) afforded the title azide (60%) as a white solid: mp 63–65 °C; IR (neat) 2130, 1655; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.73 (d, 1H, J = 4 Hz), 7.57 (d, 1H, J = 4 Hz), 9.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 182.0, 153.1, 137.0, 136.8, 116.4. Anal. Calcd for $C_5H_3N_3OS$: C, 39.21; H, 1.97; N, 27.44. Found: C, 39.30; H, 1.79; N, 27.18.

3-Azido-2-nitrobenzo[*b*]thiophene (1j). This compound was prepared by reacting 3-bromo-2-nitrobenzothiophene[17] (700 mg, 2.75 mmol) and sodium azide (715 mg, 11 mmol) in 14 mL of DMSO for 20 h at rt: yield 60%; mp 103–105 °C dec; IR (neat) 2140, 1360, 1310 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.44–7.52 (m, 1H), 7.58–7.66 (m, 1H), 7.55–7.88 (m, 1H), 7.93–7.98 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 135.9, 132.9, 132.6, 130.7, 127.0, 126.0, 124.6, 122.6. Anal. Calcd for $C_8H_4N_4O_2S$: C, 43.63; H, 1.83; N, 25.44. Found: C, 43.60; H, 1.64; N, 25.21.

Reduction of Azides with HMDST. Standard Procedure. A solution of azide (1 mmol) in methanol (10 mL) was treated with 2 equiv of HMDST and then stirred at rt for the appropriate time until TLC showed the absence of the starting azide. The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, dried, and evaporated. Purification of the crude by column chromatography on silica using a 70:30 hexanes/ether mixture as the eluant gave the pure amine. The physical and/or spectroscopic properties of all known amines **2a,b,f–h,j–p** were consistent with those of authentic specimens (**2g,h**,[4] **2j**,[17] **2k**,[18] and **2l-o**) or with published data (**2a,b**,[5] **2f**,[6] and **2p**[19,20]).

2-Amino-3-formylthiophene (2c): IR (neat) 3360, 3250, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.18 (d, 1H, J = 6 Hz),

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6.74 (bs, 2H), 6.92 (d, 1H, J = 6 Hz), 9.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.1, 164.4, 126.3, 117.5, 107.8; MS (m/z) 127 (100, M^+), 126 (21), 110 (18) 99 (21). Anal. Calcd for C_5H_5NOS: C, 47.22; H, 3.96; N, 11.01. Found: C, 47.00; H, 4.08; N, 10.83.

2-Amino-5-formylthiophene (2d): IR (neat) 3380, 3300 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.8 (bs, 2H), 6.19 (d, 1H, J = 5.5 Hz), 7.42 (d, 1H, J = 5.5 Hz), 9.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.2, 163.0, 139.9, 129.1, 107.9; MS (m/z) 127 (100, M^+), 126 (75), 71 (20). Anal. Calcd for C_5H_5NOS: C, 47.22; H, 3.96; N, 11.01. Found: C, 46.97; H, 4.16; N, 11.16.

3-Amino-2-formylbenzo[*b*]furan (2e): IR (neat) 3440, 3290, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.69 (bs, 2H), 7.21–7.30 (m, 1H), 7.40–7.46 (m, 1H), 7.48–7.56 (m, 1H), 7.59–7.65 (m, 1H), 9.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.7, 155.4, 139.7, 136.3, 130.1, 122.4, 120.7, 120.5, 112.8; MS (m/z) 161 (100, M^+), 160 (12), 104 (86). Anal. Calcd for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.23; H, 4.15; N, 8.55.

2-Amino-1-ethyl-3-formylindole (2i): IR (neat) 3360, 3290, 3180, 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37 (t, 3H, J = 7.5 Hz), 3.98 (q, 2H, J = 7.5 Hz), 6.76 (bs, 2H), 7.07–7.20 (m, 3H), 7.60–7.69 (m, 1H), 9.9 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.0, 152.2, 133.5, 126.4, 122.0, 121.0, 115.1, 108.3, 98.3, 36.0, 13.4; MS (m/z) 188 (100, M^+), 187 (34), 160 (18), 159 (22), 143 (16). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.31; H, 6.27; N, 15.00.

(20) Preparation of 2-aminobenzo[*b*]thiophene **2p** by reduction of the azide **1p** is so far unreported, but a number of related bithienyl azides have been transformed into amines through H_2S or $LiAlH_4$ reduction (cf. Spagnolo, P.; Zanirato, P.; Gronowitz, S. *J. Org. Chem.* **1982**, *47*, 3177).

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