Synthetic Applications of Bis(trimethylsilyl)sulfide: Part II.[1] Synthesis of Aromatic and Heteroaromatic *o*-Azido-Thioaldehydes

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Treatment of aromatic and heteroaromatic *o*-azidoaldehydes with bis(trimethyl-silyl)sulfide and a suitable catalyst affords an easy access to the corresponding *o*-azidothioaldehydes as their Diels-Alder cycloadducts with dienes.

Increasing interest has recently been shown in the synthesis and the reactivity of thiocarbonyl compounds.[2] The generally high reactivity of thioxo derivatives, that renders such compounds versatile as intermediates in the synthesis of complex natural products,[3] has hampered their investigation, though substantial work has recently been devoted to the development of novel synthetic methodologies for their preparation and synthetic applications.[2,4]

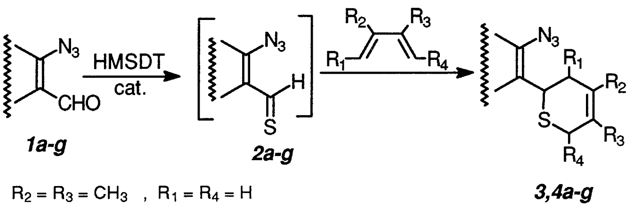
In this context, thioaldehydes[4] appear to be particularly attracting, but had been considered until recently as elusive compounds, owing to their great tendency to give cyclic or linear polymers by further reaction of the C=S bond. Numerous attempts to prepare monomeric thioaldehydes have revealed that simple thioaldehydes can only be detected spectroscopically[5] or by chemical trapping.[4c-d,6] Only a relatively limited number of stable thioaldehydes are known,[6] their fair stability commonly arising from mesomeric stabilization by a heterocyclic ring.[7a,c]

Our joint interest in the chemistry of thiocarbonyl[8] and azido compounds[9] very recently led us to undertake a chemical investigation of previously unknown aromatic and heteroaromatic *o*-azidocarbo-thioaldehydes.

In a previous report[1] we showed that we had probably succeeded in producing a number of (undetected) thiophene, furan and indole *o*-azidocarbothioaldehydes by reacting corresponding oxo-compounds with bis(trimethylsilyl)sulfide (HMDST) in acetonitrile, at room temperature and in the presence of hydrochloric acid. Under these circumstances our presumably formed heteroaromatic thioaldehydes were found to suffer intramolecular trapping by the adjacent azido function to give fused isothiazoles. *o*-Azidobenzothioaldehyde was also similarly produced but was instead isolated as trimeric species which, upon pyrolysis at 200° C, afforded 2,1-benzisothiazole in modest yield. Consequently our generated *o*-azidothioaldehydes proved to be useful precursors of fused isothiazole ring systems, but seemingly useless for any alternative synthetic exploitation of their chemistry.

In the light of these findings we were therefore prompted to investigate the above reaction of *o*-azidobenzaldehyde ***1a*** and several heteroaromatic *o*-azidocarbaldehydes ***1b-g*** in the presence of 2,3-dimethyl-1,3-butadiene and 1,3-cyclohexadiene. Our aim was to uncover whether these dienes might be capable of trapping the thioformyl moiety of the possible transient *o*-azidothioaldehydes ***2a-g*** as their Diels-Alder adducts ***3, 4*** (Scheme).

If this should be the case, conclusive evidence in favour of the actual generation of the thioaldehydes ***2a-g*** would be obtained. Moreover, concrete evidence would also be gained that the synthetic potential of their thioformyl and azido functions might be suitably exploited.



$R_2 = R_3 = CH_3$, $R_1 = R_4 = H$

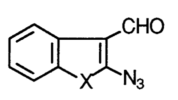
R_1 , $R_4 = -[CH_2]_2-$, $R_2 = R_3 = H$

Scheme

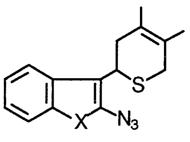
We now report that, in the presence of the appropriate diene, the reaction of the azidoaldehydes ***1a-e*** with HMDST can actually lead to the desired cycloadducts ***3a-e*** and ***4a*** in reasonable yields, provided that $CoCl_2.6H_2O$[8] be used as a catalyst rather than hydrochloric acid[10] (Table).

As can be seen in the Table, the reaction of *o*-azidobenzaldehyde ***1a*** in the presence of a five-fold excess of 2,3-dimethyl-1,3-butadiene or 1,3-cyclohexadiene gave the corresponding thioaldehyde-diene cycloadducts ***3a*** and ***4a*** in fairly high yields. Under similar conditions the heteroaromatic azidoaldehydes ***1b-d*** also reacted in the presence of 2,3-dimethyl-1,3-butadiene to afford the Diels-Alder adducts ***3b-d,*** but in lower yields, owing to the competing occurrence of isothiazole product.[1] However, the mild catalyst $CoCl_2.6H_2O$ was found to be rather ineffective to promote the thionation of the azide ***1e.*** In such case a satisfactory yield of the thioaldehyde-dimethylbutadiene adduct ***3e*** could only be obtained by using a stronger Lewis acid such as $CF_3SO_3SiMe_3$[8] as well as performing the reaction in the neat diene.

On the other hand 2-azido-3-formyl-benzothiophene ***1f*** and -benzofuran ***1g*** can give none of the corresponding cycloadducts ***3f-g***, when reacted in the presence of 2,3-dimethyl-1,3-butadiene. In such cases only unidentified products were formed, probably resulting from ring-cleavage fragmentation of the azido adducts ***3f-g*** initially formed. Indeed, both 2-azido-benzothiophene and -benzofuran are known to be unstable compounds affording ring-cleavage products upon spontaneous decomposition at room temperature.[11]



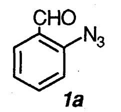
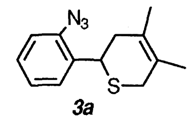
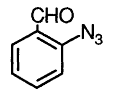
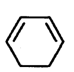
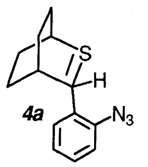
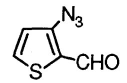
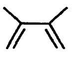
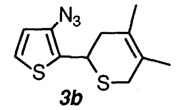
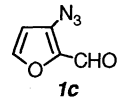
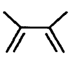
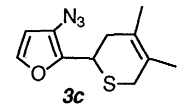
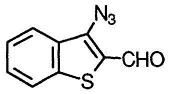
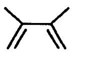
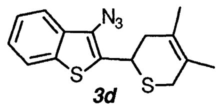
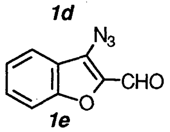
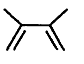
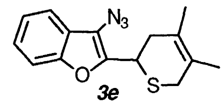
1f : X = S
1g : X = O



3f : X = S
3g : X = O

In conclusion, we have now shown that aromatic and heteroaromatic *o*-azidocarbothioaldehydes can conveniently be produced from fairly readily available *o*-azidocarboaldehydes[1]

Table. Synthesis of o-azidothioaldehydes

Reagent	Diene	Product	Yield (%) [a]
 1a		 3a	76
 1a		 4a	71
 1b		 3b	59 [b]
 1c		 3c	55 [c]
 1d		 3d	45 [d]
 1e		 3e	41 [e]

[a]Yield refer to isolated products. Reactions generally run in the presence of $CoCl_2 \cdot 6H_2O$. [b]Thienoisothiazole[1] was also isolated in 20% yield. [c]Furoisothiazole[1] was also obtained in 45% yield. [d]Benzothienoisothiazole[1] was also isolated in 12% yield. [e]Reaction run in the presence of TfOTMS.

through our simple procedure which uses very mild conditions and in principle should be of wide applicability. It is worth noting that our present conditions allow selective thionation of the formyl function, in contrast to those recently employed by Becher et al. which resulted in the formation of heteroaromatic o-aminothioaldehydes *via* preliminary reduction of the azido moiety.[7a] o-Azidocarbothioaldehydes, which represent a new class of thioaldehydes, appear of considerable potential utility in view of the numerous and attractive synthetic applications available to their azido and thioformyl moieties. Further study of the reactivity of o-azidocarboaldehydes with bis(trimethylsilyl)sulfide is still in progress in our laboratory.

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References and Notes

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10 ***Typical procedure:*** To a solution of 50 mg (0.34 mmol) of o-azidobenzaldehyde and 140 mg (1.70 mmol) of 2,3-dimethylbutadiene in 0.2 mL of CH_3CN were added, at room temperature and under nitrogen, 80 mg (0.34 mmol) of $CoCl_2 \cdot 6H_2O$ dissolved in 1.2 mL of CH_3CN. To the resulting stirred mixture were then added very slowly 121 mg (0.68 mmol) of bis(trimethylsilyl)sulfide. The progress of the reaction was monitored by tlc. Quenching with saturated aqueous solution of $NaHCO_3$ and extraction with diethyl ether allowed to isolate a yellowish oil which, after purification by TLC (petroleum ether/diethyl ether 10 : 1), gave 64 mg of the cycloadduct *3a* (76%). ^1H NMR (200 MHz; $CDCl_3$) δ (ppm): 7.08-7.37 (m, 4H, CH arom.), 4.32 (d, 1H, J=5.4 Hz), 4.28 (d, 1H, J=5.4 Hz), 3.45 (bd, 1H), 2.90 (bd, 1H), 2.28-2.41 (m, 1H), 1.77 (bs, 3H, CH_3), 1.71 (bs, 3H, CH_3). IR (Nujol): 2193 cm^{-1} (N_3).

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