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Reaction of *ortho*-Azidohetarenecarbaldehydes with bis(Trimethylsilyl)sulfide. A Novel Route to Fused Isothiazoles

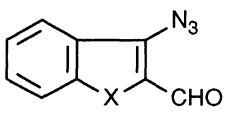
Alessandro DEGL'INNOCENTI,* Maria FUNICELLO, Patrizia SCAFATO, and Piero SPAGNOLO*†
Dipartimento di Chimica, Università della Basilicata, Via N. Sauro 85, I-85100 Potenza, Italy
† Dipartimento di Chimica Organica "A. Mangini", viale Risorgimento 4, I-40136 Bologna, Italy

o-Azidohetarenecarbaldehydes react with bis(trimethylsilyl)sulfide and hydrochloric acid to give fused isothiazoles in yields strongly dependent upon the nature of the heteroaromatic ring through intramolecular cyclization reaction of presumable intermediate o-azidocarbothialdehydes.

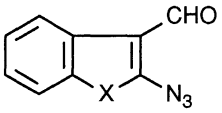
The thermolysis of aryl and heteroaryl azides bearing α,β-unsaturated *ortho*-substituents provides a convenient route for the synthesis of various fused azoles.[1] These intramolecular azide cyclizations, which normally occur under fairly mild conditions, avoid the intermediacy of discrete nitrenes and rather proceed through processes involving concerted ring closure and nitrogen loss.[1]

An impressive example of aryl azide cyclizations of this sort has been reported by Ashby and Suschitzky as early as 1971.[2] These authors in fact uncovered that o-azidothiobenzophenone, available by treatment of the corresponding ketone with hydrogen chloride and hydrogen sulfide gases, undergoes spontaneous decomposition at room temperature to give 3-phenyl-2,1-benzisothiazole in good yield. However, an extension of the same type of reaction to *ortho*-thiocarbonyl substituted heteroaromatic azides does not appear to have been attempted so far.

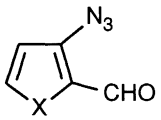
ortho-Azidocarbaldehydes derived from five-membered heteroaromatic systems including, *inter alia*, furan, benzofuran, thiophene, benzothiophene, and indole are readily available. These heterocyclic derivatives



1a, X=S
b, X=O



2a, X=S
b, X=O
c, X=N-Et

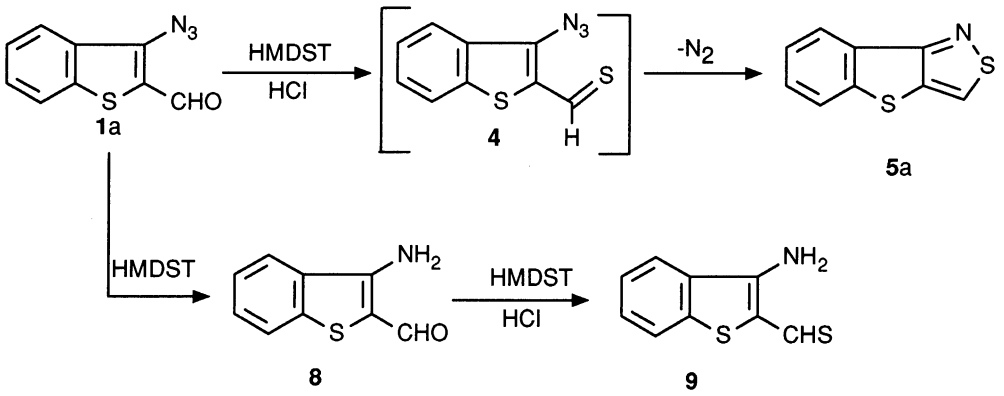


3a, X=S
b, X=O

can be easily prepared from o-halocarbaldehydes through nucleophilic displacement of halo group by azide ion,[3] or from o-aminoaldehydes by diazotization followed by treatment with sodium azide as in the case of 3-azido-2-formyl- **1a** and 2-azido-3-formyl-benzo[*b*]thiophene **2a**.[4] Consequently, the ready access to

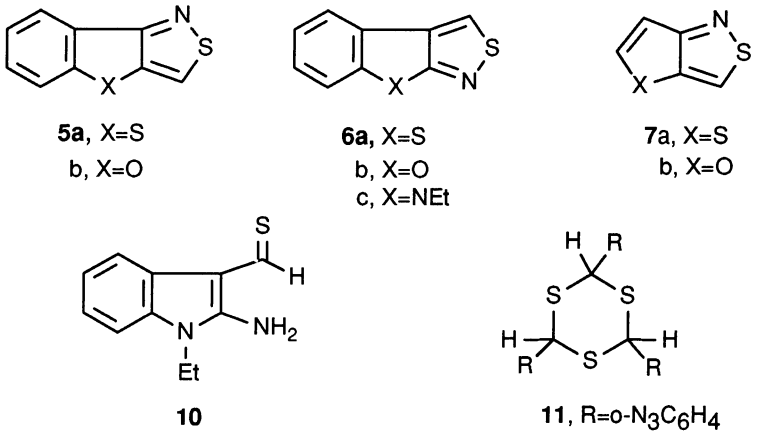
o-azidoheteroarenecarbaldehydes, coupled with our interest in the reactivity of bis(trimethylsilyl)sulfide (HMDST) as a thionating agent,[5] prompted us to investigate the reaction of a number of such heterocyclic derivatives with HMDST as a route to corresponding thioformyl derivatives, which were in principle attractive precursors of fused isothiazole ring systems.

3-Azido-2-formylbenzo[*b*]thiophene **1a**[4,6] in acetonitrile, upon treatment with a slight excess of HMDST and hydrochloric acid, underwent total decomposition at room temperature within 24 h to give, after column chromatography, hitherto unknown benzothieno[3,2-*c*]isothiazole **5a**[7] in ca. 50% yield. The satisfactory occurrence of the isothiazole **5a**, conceivably ascribable to decomposition of the intermediate o-azidothioaldehyde **4** (Scheme 1), is noteworthy since it would emphasize the great effectiveness of an heteroaryl azido group to interact with an adjacent thioaldehyde function, whose very high propensity to undergo oligomerization reaction is well documented.[8]



Scheme. 1.

Incidentally, the azide **1a** was found to react with HMDST in the absence of hydrochloric acid to give the o-aminocarbaldehyde **8**.[4] This compound, upon subsequent reaction with HMDST in the presence of hydrochloric acid, afforded the o-aminothioaldehyde **9** representing an additional instance of the rare monomeric heterocyclic thioaldehydes[9] (Scheme 1).



Under similar conditions isomeric 2-azido-3-formylbenzo[*b*]thiophene **2a**[4,6] as well as

3-azido-2-formylthiophene **3a**[3b] reacted with HMDST and HCl to lead to the previously unknown benzothienoisothiazole **6a**[10] (50%) and the already reported thienoisothiazole **7a**[11] (80%), respectively.

Similarly to their thiophene analogues, 3-azido-2-formyl-furan **3b**[3b] and -benzo[*b*]furan **1b**[12] afforded under comparable conditions the new fused isothiazoles **7b**[13] and **5b**,[14] although in lower yields (27 and 40%). On the other hand 2-azido-3-formylbenzo[*b*]furan **2b**[3a] failed to afford any isolable isothiazole **6b**. The different trend observed in our reactions of thiophene and furan azidocarbaldehydes is likely attributable to a greater instability of resulting furoisothiazoles than thienoisothiazoles under the acidic conditions employed. We observed in fact that the isolable yields of the produced furoisothiazoles **5b** and **7b** were strongly decreased with increasing reaction times.

A peculiar behaviour was encountered with the azido indole **2c**, which was newly prepared by ethylation of 2-chloro-3-formylindole[3a] and subsequent treatment with sodium azide. This azide **2c**, upon reaction with HMDST and HCl in CH_3CN, afforded a 60 : 40 mixture of the aminothioaldehyde **10** and the isothiazole **6c**[15] in good overall yield. This finding suggests that with the compound **2c** reduction of the azido function should favourably compete with thionation of the formyl moiety.

Differently from the above heteroaromatic azides, under our present conditions o-azidobenzaldehyde exclusively led to the o-azidothiobenzaldehyde trimer **11** as a mixture of geometrical isomers, thereby indicating that in such case the intermediate azidothiobenzaldehyde preferred to undergo trimerization reaction rather than intramolecular cyclization to isothiazole. The greater aromatic character of the benzene with respect to the heterocyclic rings would totally discourage the azide cyclization process in favour of the thioformyl oligomerization reaction. However, the trimer **11** could eventually afford 2,1-benzisothiazole in 35% yield upon direct pyrolysis at 200 °C.

In conclusion we have shown that bis(trimethylsilyl)sulfide and hydrochloridric acid would effect selective thionation of the formyl function of aryl and heteroaryl o-azidocarbaldehydes. The resulting transient heteroaromatic thioaldehydes would exhibit a strong propensity to be intercepted by the adjacent azido function, which would result in the preferred formation of cyclized isothiazoles even in the case of the α-heteroaryl azides which are known to undergo smooth ring opening upon decomposition.[1]

As a typical procedure, a solution of azidoformyl derivative (1 mmol), in 10 mL of CH_3CN was treated at room temperature with conc. HCl (3 equiv.), followed by bis(trimethylsilyl)sulfide (3 equiv.). Progress of the reaction was monitored by tlc (5-24 h). The resulting reaction mixture was diluted with ether and washed with 10% $NaHCO_3$. The crude was purified by column chromatography (neutral alumina, petroleum ether/diethyl ether 4:1)

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6) The azide **1a** was presently prepared by reacting 2-formyl-3-nitrobenzo[*b*]thiophene with excess sodium azide in HMPA or DMSO at room temperature. Similarly the azide **2a** was prepared from 3-formyl-2-nitrobenzo[*b*]thiophene by reaction with sodium azide in DMSO at room temperature.

7) ^{1}H NMR ($CDCl_3$): δ (ppm) 7.40-7.54 (2H, m), 7.69-7.78 (1H, m), 8.21-8.29 (1H,m) 8.59 (1H, s); ^{13}C NMR ($CDCl_3$): δ (ppm) 123.3, 124.2, 125.2, 127.8 128.8, 133.1, 135.8, 147.1, 168.5; MS (m/z) (%): 191 (100, M^+), 159 (7), 146 (39). Anal. Calcd for $C_9H_5NS_2$: C, 56.51, H, 2.63, N, 7.32. Found: C, 56.66, H, 2.78, N, 7.15.

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10) ^{1}H NMR ($CDCl_3$): δ (ppm) 7.34-7.46 (2H, m), 7.64-7.74 (1H, m), 7.86-7.92 (1H,m), 8.90 (1H, s); ^{13}C NMR ($CDCl_3$): δ (ppm) 123.1, 124.2, 125.3, 127.6 128.8, 136.9, 138.5, 144.1, 167.7; MS (m/z) (%): 191 (100, M^+), 159 (19), 146(8). Anal. Calcd for $C_9H_5NS_2$: C, 56.51, H, 2.63, N, 7.32. Found: C, 56.37, H, 2.75, N, 7.06.

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12) 3-Azido-2-formylbenzo[*b*]furan **1b** was newly prepared by reacting 3-bromo-2-formylbenzo[*b*]furan with excess sodium azide in DMSO at room temperature.

13) ^{1}H NMR ($CDCl_3$): δ (ppm) 7.23-7.25 (1H, d, J=2.7 Hz), 7.34-7.36 (1H, d, J=2.7 Hz), 8.42 (1H, s).^{13}C NMR ($CDCl_3$): δ (ppm) 103.6, 130.9, 147.5, 159.0, 176.2, 166.2; MS (m/z) (%): 125 (100, M^+), 97 (5), 70 (7), 45 (28). Anal. Calcd for C_5H_3NOS: C, 47.98, H, 2.42, N, 11.20. Found: C, 48.23, H, 2.30, N, 11.0.

14) ^{1}H NMR ($CDCl_3$): δ (ppm) 7.30-7.39 (1H, m), 7.46-7.6 (2H, m), 7.95-8.05 (1H,m), 8.12 (1H, s);^{13}C NMR ($CDCl_3$): δ (ppm) 113.0, 119.5, 120.2, 121.7, 123.5, 128.8, 129.6,130.9, 166.2; MS (m/z) (%): 175 (100, M^+), 146 (12), 103 (13). Anal. Calcd for C_9H_5NOS: C, 61.70, H, 2.88, N, 7.99. Found: C, 61.53, H, 2.95, N, 7.82.

15) ^{1}H NMR ($CDCl_3$): δ (ppm) 1.47 (3H, t), 4.29 (2H, q), 7.12-7.25 (2H, m), 7.38-7.48 (1H, m), 7.8-7.86 (1H, m), 8,68 (1H, s); ^{13}C NMR ($CDCl_3$): δ (ppm) 13.68, 37.75, 109.2, 117.4, 119.6, 122.1, 125.0, 126.9, 134.9, 147.6, 157.0; MS (m/z) (%): 202 (58, M^+), 187 (100), 174 (12). Anal. Calcd for $C_{11}H_{10}N_2S$: C, 65.31, H, 4.98, N, 13.85. Found: C, 65.58, H, 5.14, N, 13.6.

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