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Reaction of Heteroaromatic *o*-Aminothioaldehydes with Alkynes: a Novel Entry to *b*-Fused Pyridines.

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Abstract: o-Aminothioaldehydes derived from benzo[*b*]furan, benzo[*b*]thiophene, indole and furan rings smoothly react with mono- and disubstituted electron deficient alkynes to give *b*-fused dihydropyridines which can be converted to corresponding pyridines upon heating under vacuum.

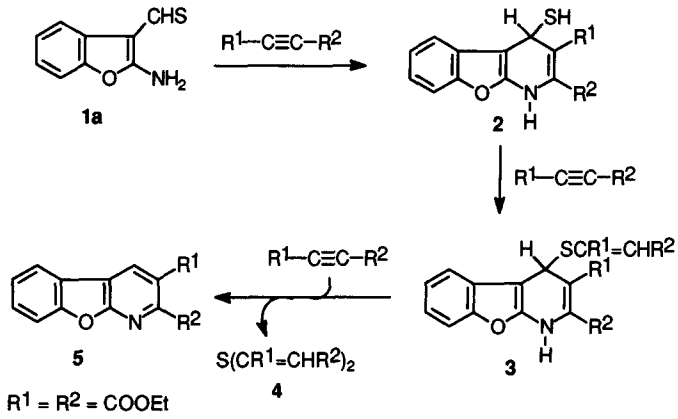
Highly reactive thioaldehydes (and thioketones) have been recently proved to be valuable intermediates in organic synthesis.[1,2] Simple thioaldehydes normally show a pronounced tendency to afford oligo- and polimerization products, but the thioformyl moiety can be effectively stabilized by the mesomeric effect of an electron-rich heterocyclic ring or carbon-carbon double bond.[3]

In very recent years it has been shown that the thioformyl group can be especially stabilized when it is attached to the *ortho* position of five- and six-membered aminoheteroarenes. In fact a variety of chemically stable monomeric *o*-aminothioaldehydes have been readily prepared in the indole,[4] pyrazole,[4] furan,[5] thiophene,[5] benzo[*b*]furan[5] and benzo[*b*]thiophene[5] series from corresponding *o*-azidoaldehydes as well as in the uracil series using Vilsmeier reaction products of the 6-amino derivatives.[6] However, despite the fact that these types of heterocyclic thioaldehydes are now easily accessible, their chemical and synthetic potential still remains virtually unknown.

In this paper we report a useful application of five-membered heteroaromatic *o*-aminothioaldehydes in the construction of *b*-fused pyridine ring systems.

Reaction of 2-amino-3-thioformylbenzo[*b*]furan **1a** (0.1 mmol) with a three-fold excess of diethyl acetylenedicarboxylate in benzene (3 mL) at room temperature for 2h (until disappearance of the starting thioaldehyde **1a**) led to a rather complex reaction mixture, from which column chromatography separated the dihydropyridine adduct **3** (50%), the pyridine **5** (25%) as well as the bis-vinyl sulfide **4** (25%). The observed

formation of the compounds **3-5** can be conceivably explained on the basis of the mechanism outlined in the Scheme. This would involve initial occurrence of the thiol intermediate **2** through nucleophilic addition of the thioaldehyde **1a** amino moiety to the alkyne and subsequent intramolecular cyclization of the resulting enamine onto the thioformyl function. Further reaction of **2** with the alkyne would give the vinyl sulfide **3** which could then afford the aromatized *b*-fused pyridine **5** by formal elimination of a HSC(COOEt)=CHCOOEt unit, in turn being trapped by the alkyne to give the isolated sulfide **4**.[7]



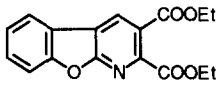
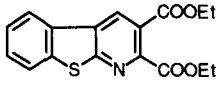
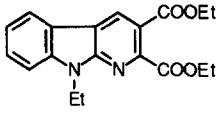
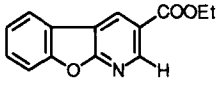
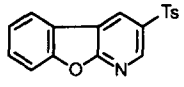
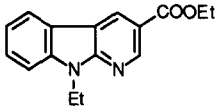
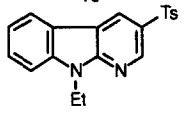
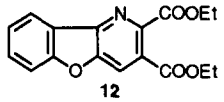
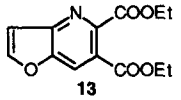
Scheme

In a repeated experiment the crude reaction mixture, after removal of the benzene solvent, was heated at 110 °C under vacuum (15 mmHg) for ca. 5h and then chromatographed to directly afford, besides the sulfide **4**, the desired benzofuro[2,3:*b*]pyridine **5** in 70% yield, (Table, entry 1).

By means of an analogous one-pot procedure 2-amino-3-thioformylbenzo[*b*]thiophene **1b** and 2-amino-1-ethyl-3-thioformylindole **1c** also led with diethyl acetylenedicarboxylate to the corresponding disubstituted pyridines **6** and **7** in moderate yields (Table, entries 2 and 3). Additionally, with ethyl propiolate and *p*-toluenesulfonylacetylene, the thioaldehydes **1a** and **1c** could be similarly converted into the 3-functionalized benzofuro[2,3:*b*]pyridines **8**, **9** and indolo[2,3:*b*]pyridines **10**, **11**, but using longer reaction times (Table, entries 4-7). Like the aminothioaldehydes **1a-c**, in a similar way 3-amino-2-thioformylbenzo[*b*]furan **1d** and 3-amino-2-thioformylfuran **1e** with diethyl acetylenedicarboxylate could furnish the respective furopyridines **12** and **13** in comparable yields (Table, entries 8 and 9).

Instead the aminothioaldehyde **1a** was found to be unreactive towards poorly electrophilic alkynes (trimethylsilylacetylene and hex-1-yne) or electron-deficient alkenes (dimethyl fumarate and maleate) even in boiling benzene

Table. Synthesis of *b*-fused pyridines from reaction of *o*-aminothioaldehydes with alkynes.

Entry	Thioaldehyde	R^1—C≡C—R^2	Reaction time, h[a]	Pyridine[b]	Yield (%)[c]
1	**1a**	$R^1 = R^2 =$ COOEt	2	 **5**	70
2	**1b**	$R^1 = R^2 =$ COOEt	3	 **6**	40
3	**1c**	$R^1 = R^2 =$ COOEt	5	 **7**	60
4	**1a**	R^1 = COOEt, R^2 = H	3	 **8**	37
5	**1a**	R^1 = Ts, R^2 = H	14	 **9**	35
6	**1c**	R^1 = COOEt, R^2 = H	48	 **10**	60
7	**1c**	R^1 = Ts, R^2 = H	24	 **11**	41
8	**1d**	$R^1 = R^2 =$ COOEt	2	 **12**	67
9	**1e**	$R^1 = R^2 =$ COOEt	4	 **13**	40

[a]Time required for complete reaction of the starting thioaldehyde and alkyne at room temperature. [b]Pyridine produced after heating of the crude at 110 °C under vacuum for 2-5 hrs (see text). Structural assignments of all new pyridines were based on ^{1}H, and ^{13}C NMR and MS spectral data in addition to elemental analyses. [c]Yield isolated by column chromatography on silica gel.

In conclusion, we have shown that *b*-fusion of a pyridine ring onto five-membered heteroarenes can be usefully accomplished through mild reaction of the *o*-aminothioaldehyde derivatives with alkynes, provided that the alkyne reactants be properly activated by strongly electron-withdrawing substituent(s). It is worth noting that we have presently ascertained that an analogous method cannot be applied to corresponding aminoaldehydes[5] as a presumable consequence of comparatively lesser nucleophilic power of their amino nitrogen. Construction of pyridines *b*-fused to five-membered heteroarenes is of significant chemical and pharmacological interest, but unfortunately the available methods are normally rather difficult and/or give low yields.[8]

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References.

(1) McGregor,W.M.; Sherrington, D.C. *Chem. Soc. Rev.* **1993**, 199. Metzner, P. *Synthesis* **1992**, 1185. Metzner, P.; Thuillier, A. *Sulfur reagents in Organic Synthesis* ; Academic Press: London, 1994.

(2) Capperucci, A.; Degl'Innocenti, A.; Ricci, A.; Mordini, A.; Reginato, G. *J. Org. Chem.* **1991**, *56*, 7323. Degl'Innocenti, A.; Capperucci, A.; Mordini, A.; Reginato, G.; Ricci, A.; Cerreta, F. *Tetrahedron Lett.* **1993**, *34*, 873.

(3) Woodward, R.B.; Ayer, W.A.; Beaton, J.M.; Bickelhaupt, P.; Bonnet, R.; Buchschacher, P.; Closs, G.L.; Dutler, H.; Hannah, J.; Hauck, F.P.; Ito, S.; Langeman, A.; LeGroff, E.; Leimgruber, W.; Lwowski, W.; Sauer, J.; Volz, H. *J. Am. Chem. Soc.* **1960**, *82*, 3800. Mackie, R.K.; McKenzie, S.; Reid, D.H.; Webster, R.G. *J. Chem. Soc. Perkin Trans. I* **1973**, 657 and refs. cited therein. Tang, S.C.; Weinstein, G.N.; Holm, R.M. *J. Am. Chem. Soc.* **1973**, *95*, 613. McKinnon, D,M.; Buchschriber, J.M. *Can. J. Chem.* **1971**, *49*, 3299. Davy, H.; Vialle, J. *Bull. Chem. Soc. Fr.* **1975**, 1435. Muraoka, M.; Yamamoto, T.; Takeshima, T. *Chem. Lett.* **1982**, 101. For thioaldehydes stabilized by steric hindrance see: Okazaki, R.; Ishii, A.; Inamoto, N. *J. Am. Chem. Soc.* **1987**, *109*, 279 and references cited therein. Muraoka, M.; Yamamoto, T.; Enomoto, K.; Takeshima, T. *J. Chem. Soc. Perkin Trans. I* **1989**, 1241.

4. Becher, J.; Jorgensen, P.L.; Frydendahl, H.; Falt-Hansen, B. *Synthesis* **1991**, 609.
5. Capperucci, A.; Degl'Innocenti, A.; Funicello, M.; Scafato, P.; Spagnolo, P. *Synthesis* **1996**, 1185.
6. Hirota, K.; Sajiki, H.; Kubo, K.; Kido, M.; Nakagawa, K. *Tetrahedron* **1996**, *52*, 9971.
7. Dallas, G.; Lown, J.W.; Ma, J.C.N. *J. Chem. Soc. (C)* **1968**, 2510.
8. Degl'Innocenti, A.;Funicello, M.; Scafato, P.;Spagnolo, P.; Zanirato, P. *J. Chem. Soc. Perkin Trans. I* **1996**, 2561 and references cited therein. Gronowitz, S.; Westerlund, C.; Hornfeldt, A. -B. *Acta Chem. Scand. Ser. B* **1975**, *29*, 224. Levancher, V.; Boussad, N.; Dupas, G.; Bourguignon,J.; Queguiner, G. *Tetrahedron* **1992**, *48*, 831. Benoit,R; Dupas, G.; Bourguignon,J.; Queguiner, *Synthesis* **1987**, 1124.

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