INTRAMOLECULAR SULFENYLATION USING SULFOXIDES. PREPARATION OF *N*-ALKYL PYRROLO[2,1-*b*]- [1,3,4]BENZOTHIADIAZINES

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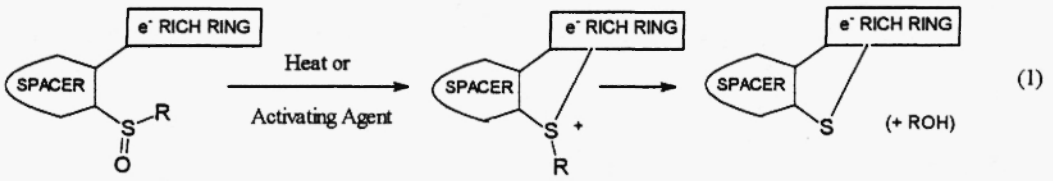
Abstract Refluxing sulfoxides **5a,b**, prepared in four steps from 2-(ethylthio)aniline, in *p*-xylene solution promotes electrophilic ring closure to produce **6a,b** by loss of ethanol.

A wide variety of dibenzo-sulfur bridged heterocyclic compounds (*e.g.* phenothiazines, *etc.*) are prepared by intramolecular aromatic nucleophilic substitution on a haloaromatic by a thiophenol derivative (1). However, the traditional synthetic routes often are not applicable due to the different reactivity patterns of pi-excessive heteroaromatics such as thiophene and pyrrole. An umpoled approach, involving electrophilic sulfenylation, could prove useful in cases where nucleophilic aromatic substitution is not a viable approach. A complication of electrophilic sulfenylation is the electrophilic halogen species generally used to activate the sulfur atom for sulfenylation may competitively or preferentially react with the pi-excessive heteroaromatic (2).

We have developed (3) a mild procedure for C-S bond formation using intramolecular electrophilic sulfoxide sulfenylation (SES) of pyrroles (eq 1). The procedure uses either mildly electrophilic (4) sulfoxides alone (3b,5) or sulfoxides activated by an electrophilic reagent such as trifluoroacetic anhydride, TFAA (3a,c), in which case the active species is presumably a trifluoroacetoxysulfonium trifluoroacetate. We report synthesis of *N*-alkyl pyrrolo-[2,1-*b*][1,3,4]benzothiadiazines, novel pyrrole analogues of the pharmaceutically important phenothiazine nucleus.



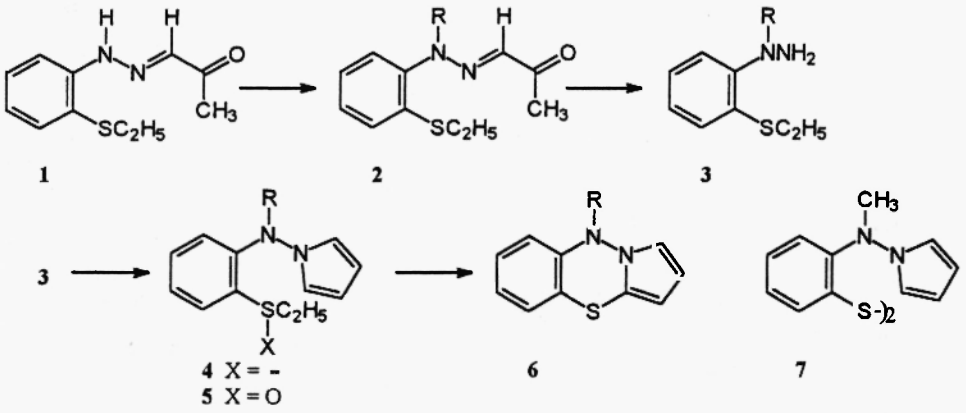
(1)

The requisite sulfoxides, **5**, were readily prepared as shown in Scheme 1. Thus, 2-(ethylthio)aniline (6) was converted to hydrazine derivatives **3** (7). This procedure is an excellent source of alkylated phenylhydrazine derivatives, prepared by phase-transfer alkylation of the intermediate hydrazone **1** (8). Hydrazines **3a-c** were capped to the pyrrole **4** (9) and oxidized to **5** with either *m*-CPBA or $NaIO_4$ (10).

Refluxing sulfoxide **5a** in *p*-xylene (11) for 6.5 h gave the desired **6a** (12) in 42% unoptimized yield after chromatography along with a small amount (7%) of the disulfide **7**. Compound **5b** cyclized similarly to **6b** (13) (94%), however, the benzyl derivative **5c** decomposed upon heating in *p*-xylene solution. We had also hoped to use **5d** to prepare a derivative of **6** that could be deblocked to the parent heterocycle. Unfortunately, **2d** could not be isolated from the reaction of **1** with phenylsulfonyl chloride.

Molecular mechanics calculations (and common sense) indicate the most stable conformation of **5**, places the sulfoxide sulfur and a pyrrole α-carbon far from each other. The *N*-substituent clearly impacts the relative energies of the two predominate conformers. We are currently studying the effect of size of the *N*- substituent on both the yield of cyclized product and the calculated conformational behavior of **5**.

Scheme 1



a $R = CH_3$ b $R = C_3H_7$ c $R = CH_2Ph$ d $R = SO_2Ph$

References and Notes

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(8) Alternatively, diazotization/reduction, with or without isolation of the intermediate *N*-nitroso derivative, worked very poorly. We were unable to overcome overreduction (N-N bond cleavage in the hydrazine) using either Na_2SO_3 or $SnCl_2$.

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(11) Some sulfoxides undergo intramolecular sulfenylation in the presence of added bases such as triethylamine and *p*-dimethylaminopyridine (D.K. Bates, K.A. Tafel *J. Org. Chem.* **1994**, *59*, 8076). Therefore, the basic site in **5** was not considered to be an impediment to cyclization.

(12) 6a: mp 78-80 °C; ^1H nmr ($CDCl_3$): δ 7.31-7.10 (s, 4H), 6.91 (dd, J = 3.0, 1.9 Hz, 1H), 6.11 (dd, J = 4.0, 3.0 Hz, 1H), 6.02 (dd, J =4.0, 1.9 Hz, 1H), 3.25 (s, 3H)

(13) **6b**: oil; ^1H nmr ($CDCl_3$): δ 7.30-7.15 (m, 4H), 6.85 (dd, J = 2.9, 1.9 Hz, 1H), 6.08 (dd, J = 3.9, 2.9 Hz, 1H), 6.02 (dd, J = 3.9, 1.9 Hz, 1H), 3.34 (t, J = 7.4 Hz, 2H), 1.55 (sextet, J = 7.4 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H)

Received April 27, 1995