SYNTHESIS OF 4*H*-PYRROLO[2,1-*c*][1,4]BENZOTHIAZINES AND *N*-METHYL-1,3,4,5-TETRAHYDRO-2*H*-3-BENZAZEPIN-2-ONES

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Abstract —— Pummerer-type reaction was carried out with α-acyl sulfides and phenyliodine(III) bis(trifluoroacetate) instead of α-acyl sulfoxides to prepare 4*H*-pyrrolo[2,1-*c*][1,4]benzothiazines and *N*-methyl-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-ones.

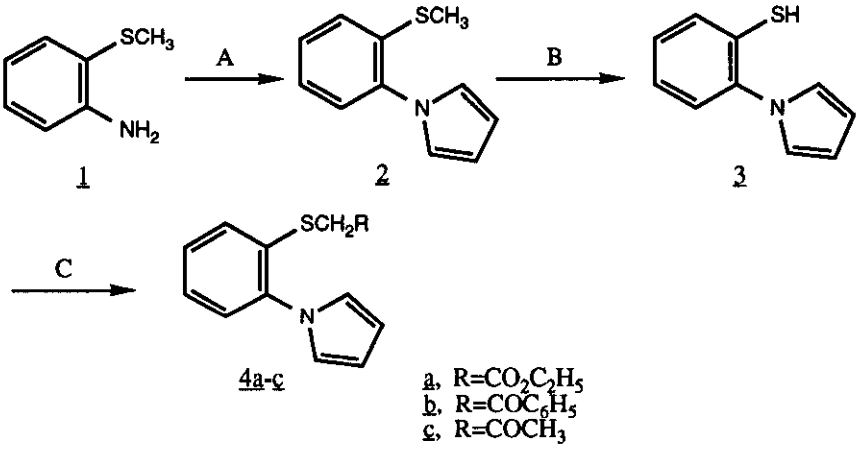
The Pummerer reaction normally proceeds from sulfoxide to product *via* thionium ion ($-\overset{+}{S}=CH-$) that reacts with a nucleophile at carbon, this reaction is useful synthetically.[1]

In recent years, it has been shown that α-acyl sulfoxides under Pummerer reaction conditions undergo carbon-carbon bond forming reactions such as the Friedel-Crafts reaction[2] and olefin cyclization.[3] According to Tamura *et al.*, treatment of α-acyl sulfides with phenyliodine(III) bis(trifluoroacetate) (PIFA)[4] resulted in a Pummerer-type reaction to give the same products as obtained by the Pummerer reaction of the α-acyl sulfoxides.[5] In this work, Pummerer-type reaction of α-acyl sulfides using PIFA was applied to prepare 4*H*-pyrrolo[2,1-*c*][1,4]-benzothiazines[6] and *N*-methyl-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-ones.[7]

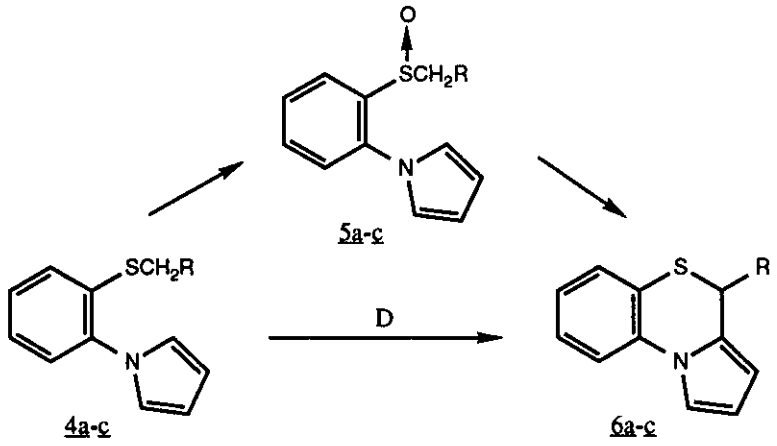
The synthesis of the title compounds according to Scheme I was achieved from 2-(methylthio)aniline (1), which was subsequently converted into 1-(2-methylthiophenyl)pyrrole (2) by treatment with 2,5-dimethoxytetrahydrofuran in boiling glacial acetic acid with yield 82%.[8] Demethylation of 2 with sodium in dimethylacetamide under a nitrogen atmosphere gave 1-(2-mercaptophenyl)pyrrole (3) in yield 76%.[9] Sulfides (4a-c) were readily prepared from 3 and the appropriate alkyl halide in ethanol. Treatment of 4a-c with PIFA caused cyclization to give the

corresponding 4*H*-pyrrolo[2,1-*c*][1,4]benzothiazines (6a-c) in moderate yields. The overall yield is better than the reported method, which involves oxidation of 4a-c to the sulfoxides (5a-c) and cyclization of 5a-c to 6a-c under Pummerer reaction conditions.[6]

Scheme I

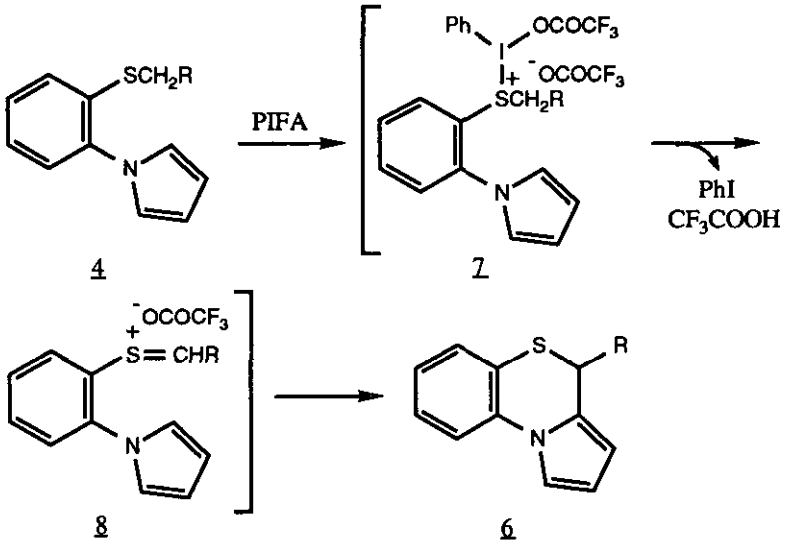


Reagents : A) 2,5-dimethoxytetrahydrofuran / CH_3CO_2H
B) Na / $CH_3CON(CH_3)_2$
C) RCH_2Cl / C_2H_5OH / KOH
D) PIFA / $ClCH_2CH_2Cl$



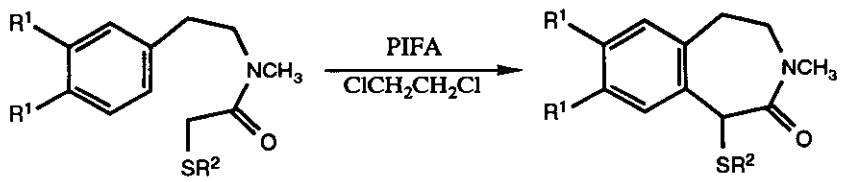
The cyclization from 4 to 6 is assumed to proceed through Pummerer-type reaction intermediate (8) which would be formed by attack of PIFA on the sulfur atom of 4, followed by simultaneous elimination of the α-hydrogen and iodobenzene from the resultant sulfonium salt (7), as shown in Scheme II.

Scheme II



Similarly, treatment of sulfides (9a-c) with PIFA in 1,2-dichloroethane caused cyclization to give the corresponding *N*-methyl-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-ones (10a-c) in moderate yields. (Scheme III)

Scheme III



9a-c 10a-c

a, R_1=OCH_3, R_2=CH_3
b, R_1=OCH_3, R_2=C_6H_5
c, R_1=H, R_2=C_6H_5

In conclusion, our results here demonstrate that PIFA is a useful reagent for Pummerer-type reaction of α-acyl sulfides to prepare 4*H*-pyrrolo[2,1-*c*][1,4]benzothiazines and *N*-methyl-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-ones.

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EXPERIMENTAL

All melting points are uncorrected. The ir absorption spectra were recorded on a Shimadzu IR-27G spectrophotometer, and ^{1}H-nmr spectra on a Varian Gemini-200 spectrometer. Chemical shifts were measured in ppm (δ) with respect to TMS. Ms were obtained JEOL JMS D-300 instrument.

1-(2-Methylthiophenyl)pyrrole (2) : A mixture of 2,5-dimethoxytetrahydrofuran (7.27 g, 0.055 mol) and 2-(methylthio)aniline (7 g, 0.05 mol) in glacial acetic acid (15 ml) was refluxed for 30 min, then poured into crushed ice. The organic solution was washed twice with aqueous sodium bicarbonate (5%), then with water, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oily residue, which was purified by distillation under reduced pressure to afford 2 (8.11 g, 82%), bp 136-138 °C / 5 mmHg (lit.,[6] bp 115-117 °C / 0.8 mmHg).

1-(2-Mercaptophenyl)pyrrole (3) : To a solution of 1-(2-methylthiophenyl)pyrrole 2 (3.02 g, 0.016 mol) in dimethylacetamide (40 ml), small pieces of sodium (1.84 g, 0.08 mol) were added and the mixture was stirred under nitrogen atmosphere at 100 °C for 15 h. After cooling to room temperature the reaction mixture was poured into crushed ice. The aqueous solution was washed with ether once, acidified with hydrochloric acid (4M) to pH 3 and then extracted with ether. The organic solution was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oily residue, which was purified by distillation under reduced pressure to afford 3 (2.13 g, 76%), bp 130-132 °C / 3 mmHg (lit.,[6] bp 90 °C / 0.1 mmHg).

1-(2-Ethoxycarbonylmethylthiophenyl)pyrrole (4a) : To a stirred solution of potassium hydroxide (0.8 g, 14.26

mmol) in absolute ethanol (48 ml), 1-(2-mercaptophenyl)pyrrole 3 (2.4 g, 13.69 mmol) in absolute ethanol (125 ml) was added dropwise. After stirring an additional 20 min, ethyl chloroacetate (1.69 g, 13.75 mmol) in absolute ethanol (125 ml) was added dropwise. After stirring overnight, the reaction mixture was filtered and the filtrate reduced to one half the orginal volume *in vacuo*. An equal volume of water (150 ml) was added and the murky solution extracted with chloroform (2 × 100 ml). The combined organic layers were washed with water then aqueous potassium hydroxide (5%), and dried over sodium sulfate. Evaporation of the solvent gave an oily residue, which was purified by column chromatography on silica gel with chloroform-hexane (1:2) as an eluting solvent to give 4a (2.51 g, 70%) as an oil, bp 172-174 °C / 2 mmHg (lit.,[6] bp 160-163 °C / 0.7 mmHg).

1-(2-Benzoylmethylthiophenyl)pyrrole (4b) : By using a procedure similar to that described for 4a, 3 gave 4b (85%) as an oil (lit.,[6] an oily semisolid). Satifactory combustion analysis could not be obtained for this compound.

1-(2-Acetylmethylthiophenyl)pyrrole (4c) : By using a procedure similar to that described for 4a, 3 gave 4c (82%), mp 66-67 °C (recrystallized from ethyl acetate-hexane). Ir (KBr) υ 1715 cm^{-1}; ^{1}H-nmr ($CDCl_3$) : 2.14 (s, 3H, $COCH_3$), 3.34 (s, 2H, SCH_2), 6.34 (t, *J*=2.2 Hz, 2H, pyrrole β-H), 6.88 (t, *J*=2.2 Hz, pyrrole α-H), 7.24-7.50 (m, 4H, ArH); ms m/z 231 (M^+). Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found : C, 67.54; H, 5.74; N, 6.03.

2-Ethoxycarbonyl-4*H*-pyrrolo[2,1-*c*][1,4]benzothiazine (6a) : A solution of 4a (214 mg, 1 mmol) in anhydrous 1,2-dichloroethane (2 ml) was added slowly to a stirred solution of PIFA (516 mg, 1.2 mmol) in anhydrous 1,2-dichloroethane (8 ml) at room temperature. The mixture was refluxed for 4 h. After cooling, the resultant mixture was quenched with water (20 ml) and extracted with dichloromethane (3 × 25 ml). The organic layer was washed with water (3 × 20 ml) and dried over magnesium sulfate. Evaporation of the solvent gave an oily residue, which was purified by column chromatography on silica gel with chloroform-hexane (1:4) as an eluting solvent to give 6a (166 mg, 64%) as an oil, bp 162-165 °C / 2 mmHg (lit.,[6] bp 140-150 °C / 0.5 mmHg).

2-Benzoyl-4*H*-pyrrolo[2,1-*c*][1,4]benzothiazine (6b) : By using a procedure similar to that described for 6a, 4b gave 6b (60%), mp 105-106 °C (lit.,[6] mp 106-107 °C).

2-Acetyl-4*H*-pyrrolo[2,1-*c*][1,4]benzothiazine (6c) : By using a procedure similar to that described for 6a, 4c gave 6c (57%), mp 102-103 °C (recrystallized from ethyl acetate-hexane). Ir (KBr) υ 1715 cm^{-1}; ^{1}H-nmr ($CDCl_3$) : 2.15 (s, 3H, $COCH_3$), 6.08 (s, 1H, H-2), 6.40-6.61 (m, 2H, H-3 and H-4), 7.15-7.95 (m, 5H, H-5 and ArH); ms m/z 229 (M^+). Anal. Calcd for $C_{13}H_{11}NOS$: C, 68.09; H, 4.84; N, 6.11. Found : C, 67.95; H, 4.85; N, 6.11.

N-Methyl-2-phenylthio-*N*-(2-phenylethyl)acetamide (9c) : A solution of (phenylthio)acetyl chloride (4.85 g, 26 mmol) in ether (30 ml) was added dropwise to a solution of the *N*-methyl-2-phenylethylamine (3.51 g, 26 mmol) in triethylamine (3.9 g, 38 mmol) in ether (70 ml) at 0 °C. The mixture was stirred at 0 °C for 30 min and diluted with water (10 ml). The organic layer was washed with brine, dried over magnesium sulphate, and concentrated in vacuo to give a residue which was purified by column chromatography on silica gel with ethyl acetate-benzene (1:8) as an eluting solvent to give 5.78 g (78%) of 9c, mp 50-51 °C (recrystallized from chloroform). Ir (KBr) υ 1635 cm^{-1}; ^{1}H-nmr ($CDCl_3$) : 2.77-2.95 (m, 2H), 2.92 and 2.98 (both s, total 3H, NCH_3),[10] 3.42-3.73 (m, 4H), 7.10-7.50 (m, 10H, ArH); ms m/z 285 (M^+). Anal. Calcd for $C_{17}H_{19}NOS$: C, 71.54; H, 6.71; N, 4.91. Found : C, 71.53; H, 6.72; N, 4.92.

1,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-1-methylthio-2*H*-3-benzazepin-2-one (10a) : A solution of 9a (283 mg, 1 mmol) in anhydrous 1,2-dichloroethane (2 ml) was added slowly to a stirred solution of PIFA (516 mg, 1.2 mmol) in anhydrous 1,2-dichloroethane (8 ml) at room temperature. The reaction mixture was stirred for 5 min at room temperature, and then heated at 60 °C for 7 h. After cooling, the resultant mixture was quenched with water (20 ml) and extracted with dichloromethane (3 × 25 ml). The organic layer was washed with water (3 × 20 ml) and dried over magnesium sulfate. Evaporation of the solvent gave an oily residue, which was purified by column chromatography on silica gel with ethyl acetate-benzene (2:1) as an eluting solvent to give 169 mg (60%) of 10a, mp 81-82 °C (lit.,[7] mp 81-82 °C).

1,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-1-phenylthio-2*H*-3-benzazepin-2-one (10b) : By using a procedure similar to that described for 10a, 9b gave 10b (56%); mp 109-110 °C (lit.,[7] mp 110-111 °C).

1,3,4,5-Tetrahydro-3-methyl-1-phenylthio-2*H*-3-benzazepin-2-one (10c) : By using a procedure similar to that described for 10a, 9c gave 10c (61%) as an oil. Ir (neat) υ 1635 cm^{-1}; ^{1}H-nmr ($CDCl_3$) : 3.06 (s, 3H, NCH_3), 3.12-3.44 (m, 3H, H-5 and one of H-4), 4.81 (m, 1H, one of H-4), 5.13 (s, 1H, H-1), 7.05-7.60 (m, 9H, ArH); Exact ms m/z Calcd for $C_{17}H_{17}NOS$: 283.1031, found : 283.1031.

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10. The splitting of *N*-methyl signal may be attributable to the partial double bond character of the amide bond.

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