Synthesis of 3-Hetaryl-4,5,6,7-tetrahydrobenzo[*b*]thiophenes

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A novel efficient synthesis of 3-hetaryl-4,5,6,7-tetrahydrobenzo[*b*]thiophenes was achieved by the cyclocondensation of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate with selected *o*-substituted aromatic amines or with alifatic, aromatic and heterocyclic acid hydrazides in the presence of polyphosphoric acid.

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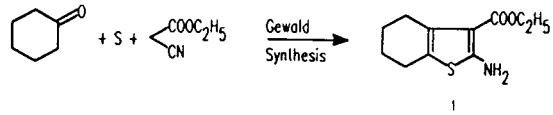
Many novel heterocyclic compounds have been synthesized and reported as fluorescent brighteners and dyes in the recent past. The fluorophoric heterocycles such as benzoxazoles [1], benzimidazoles [2] pendent to another heterocycle in a suitable position finds an exceeding important place in some commercial fluorescent whiteners illustrated in the patent literature. Benzimidazoles [3] are established inhibitors of cytochrome P-450 mediated enzyme activity of various species. Compounds with 1,3,4-oxadiazole ring system [4] attract special attention on account of their strong fluorescence. We have recently reported the synthesis of novel heterocyclic dyes and fluorescent brighterers such as thiophenes [5-6], coumarins [7], quinoxalines [8-9] and study of their biomedical and textile applications. The versatility of benzo[*b*]thiophenes [10-12] in the dyestuff field was also demonstrated by us. The results of this study have encouraged us to explore the utility of benzo[*b*]thiophenes in developing a variety of fluorescent heterocyclic compounds. Several patents [13-14] describe the synthesis and technical importance of benzo[*b*]thiophene dyes. Benzo[*b*]thiophenes have been found to possess good medicinal activity [15].

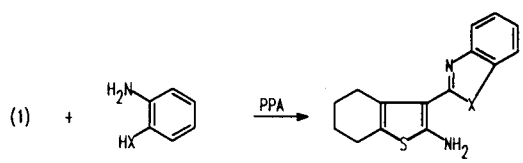
In this communication, we wish to report a facile synthesis of few hitherto unknown 3-hetaryl-4,5,6,7-tetrahydrobenzo[*b*]thiophenes by a novel method. Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **1** is a versatile intermediate in the synthesis of heterocyclic systems. It is interesting to study various characteristics reactions of **1** in developing novel, fluorescent heterocycles. The key compound **1** has been synthesized by the cyclocondensation of cyclohexanone, sulfur and ethyl cyanoacetate following the Gewald Synthesis [16].

The principle advantage of the key compound used here are that the yield is high, the time of reaction is short, the procedure involved only one facile step, the work-up is convenient and the starting material can be very easily prepared. The presence of a diazotisable amino group adjacent to electro withdrawing group such as carbethoxy results in the deepening of hues of the dyes on polyester fibres and the hydrophobic nature of the tetrahydrobenzo structure is useful for better dispersability and dyeability.

The object of this present study was the synthesis of novel, fluorescent heterocycles. It was therefore planned to develop a variety of fluorophores such as benzimidazole, benzoxazole, benzothiazole, 1,3,4-oxadiazole pendant to tetrahydrobenzo[*b*]thiophene at 3-position by a one pot method in excellent yield and study of the fluorescent properties of various 3-hetaryl-4,5,6,7-tetrahydrobenzo[*b*]thiophenes. The sequence involved in the present synthesis consists of the condensation of **1** with selected *o*-substituted aromatic amines **2** such as *o*-aminothiophenol, *o*-aminophenol, *o*-phenylenediamine in the presence of polyphosphoric acid afforded 3-hetaryl-4,5,6,7-tetrahydrobenzo[*b*]thiophenes **3** in high yield.



1

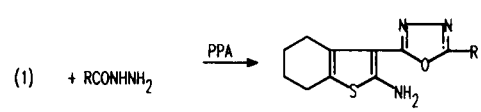


2

a X = S
b X = O
c X = NH

3

a X = S
b X = O
c X = NH



4

a R = CH_3
b R = C_6H_5
c R =

5

a R = CH_3
b R = C_6H_5
c R =

In connection with our interest to study the fluorescent properties of **5**, we have devised the route for the efficient synthesis of **5**. We have now made an observation that a smooth reaction of **1** with alifatic, aromatic and heterocyclic acid hydrazides **4** such as acetic hydrazide, benzoic hydrazide, isonicotinic hydrazide in the presence of polyphosphoric acid afforded 3-hetaryl-4,5,6,7-tetrahydrobenzo[*b*]thiophenes **5** in excellent yield.

The promising fluorescent properties of **3** and **5** have been studied and the wavelength of absorption maxima, fluorescence emission maxima and the values of the logarithms of the extinction coefficients are recorded. The application to synthetic fibres (polyester) resulted in moderate whitening of the fibres. The compounds **3** and **5** possessed bluish-green fluorescence in daylight in most of the organic solvents.

EXPERIMENTAL

All melting points are uncorrected and are in °C. The infrared spectra were recorded on Perkin-Elmer Model 397 spectrophotometer in Nujol mull. The ^{1}H nmr spectra were recorded on Varian-60 MHz instrument EM-360-L using TMS as internal standard and the chemical shifts are given in δ (ppm) scale. Mass spectra were recorded on a Varian Mat-311 instrument (70 eV). Absorption and fluorescence emission spectra in DMF solution were recorded on Beckman Model-25 spectrophotometer and Aminco Spectrophotofluorometer, respectively.

2-Amino-3-(benzothiazol-2-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**3a**).

A mixture of 2.25 g (0.01 mole) of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **1** and 1.25 g (0.01 mole) of *o*-aminothiophenol **2a** in polyphosphoric acid (10 ml) was stirred and heated at 160° for 3 hours. The reaction mixture was cooled, slowly added to ice-water mixture and neutralised with aqueous ammonia when the product precipitated. The product was filtered, washed with water, dried and recrystallised from ethanol to yield 2.25 g (79%) of **3a** as a yellow crystalline solid, mp 134-136°; ir (nujol): 3330, 3420 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.7-2.03 (m, 4H, 2H-5, 2H-6), 2.27-2.81 (m, 4H, 2H-4, 2H-7), 6.81 (s, 2H, NH_2), 7.7-8.16 (m, 4H, aromatic); ms: m/z 286 (M^+); λ max absorption 374 nm, λ max emission 421 nm, log ϵ 4.16.

Anal. Calcd. for $C_{15}H_{14}N_2S_2$: C, 62.93; H, 4.89; N, 9.79; S, 22.37. Found: C, 62.97; H, 4.87; N, 9.72; S, 22.34.

2-Amino-3-(benzoxazol-2-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**3b**).

The same procedure as described for **3a** was applied except *o*-aminophenol **2b** was used in place of **2a** yielding 2-amino-3-(benzoxazol-2-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene **3b**, recrystallised from DMF to yield 2.26 g (84%) of **3b**, mp 348-351°; ir (nujol): 3340, 3430 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.83-2.00 (m, 4H, 2H-5, 2H-6), 2.33-2.86 (m, 4H, 2H-4, 2H-7), 6.79 (s, 2H, NH_2), 7.62-8.01 (m, 4H, aromatic); ms: m/z 270 (M^+); λ max absorption 386 nm, λ max emission 442 nm, log ϵ 4.28.

Anal. Calcd. for $C_{15}H_{14}N_2OS$: C, 66.66; H, 5.18; N, 10.37; S, 11.85. Found: C, 66.63; H, 5.21; N, 10.33; S, 11.83.

2-Amino-3-(benzimidazol-2-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**3c**).

The same procedure as described for **3a** was applied except *o*-phenylenediamine **2c** was used in place of **2a** yielding 2-amino-3-(benzimidazol-2-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene **3c**, recrystallised from DMF to yield 2.17 g (81%) of **3c**, mp 266-267°; ir (nujol): 3320, 3450, 3280 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.79-2.01 (m, 4H, 2H-5, 2H-6), 2.29-2.84 (m, 4H, 2H-4, 2H-7), 6.80 (s, 2H, NH_2), 7.68-8.11 (m, 4H, aromatic); ms: m/z 269 (M^+): λ max absorption 389, λ max emission 439 nm, log ϵ 4.31.

Anal. Calcd. for $C_{15}H_{15}N_3S$: C, 66.91; H, 5.57; N, 15.61; S, 11.89. Found: C, 66.93; H, 5.52; N, 15.64; S, 11.83.

2-Amino-3-(2-methyloxadiazol-5-yl)-4,5,6,7-tetrahydrobenzo[*b*]-thiophene (**5a**).

A mixture of 2.25 g (0.01 mole) of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **1** and 0.74 g (0.01 mole) of acetic hydrazide **4a** in polyphosphoric acid (10 ml) was stirred and heated at 180° for 5 hours. The reaction mixture was cooled, slowly added to an ice-water mixture and neutralised with aqueous ammonia when the product precipitated. The product was filtered, washed with water, dried and recrystallised from ethyl acetate to yield 2.04 g (87%) of **5a**, mp 192-193°; ir (nujol): 3350, 3420 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.86-2.12 (m, 4H, 2H-5, 2H-6), 2.59-2.84 (m, 4H, 2H-4, 2H-7), 6.72 (s, 2H, NH_2), 2.9 (s, 3H, CH_3); ms: m/z 235 (M^+); λ max absorption 382 nm, λ max emission 446 nm, log ϵ 4.26.

Anal. Calcd. for $C_{11}H_{13}N_3OS$: C, 56.17; H; 5.53; N, 17.87; S, 13.61. Found: C, 56.16; H, 5.55; N, 17.89; S, 13.65.

2-Amino-3-(2-phenyloxadiazol-5-yl)-4,5,6,7-tetrahydrobenzo[*b*]-thiophene (**5b**).

The same procedure as described for **5a** was applied except benzoic hydrazide **4b** was used in place of **4a** yielding 2-amino-3-(2-phenyloxadiazol-5-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene **5b**, recrystallised from ethyl acetate to yield 2.43 g (82%) of **5b**, mp 138°; ir (nujol): 3330, 3460 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.75-2.04 (m, 4H, 2H-5, 2H-6), 2.67-2.91 (m, 4H, 2H-4, 2H-7), 6.89 (s, 2H, NH_2), 7.75-8.01 (m, 5H, aromatic); ms: m/z 297 (M^+); λ max absorption 392 nm, λ max emission 453 nm, log ϵ 4.35.

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.64; H, 5.05; N, 14.14; S, 10.77. Found: C, 64.61; H, 5.02; N, 14.11; S, 10.72.

2-Amino-3-(2-[4′-pyridyl]oxadiazol-5-yl)-4,5,6,7-tetrahydrobenzo-[*b*]thiophene (**5c**).

The same procedure as described for **5a** was applied except isonicotinic hydrazide **4c** was used in place of **4a** yielding 2-amino-3-(2-[4′-pyridyl]oxadiazol-5-yl)-4,5,6,7-tetrahydrobenzo[*b*]-thiophene **5c**, recrystallised from DMF to yield 2.56 g (86%) of **5c**, mp 312-314°; ir (nujol): 3350, 3510 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.82-2.04 (m, 4H, 2H-5, 2H-6), 2.8-3.1 (m, 4H, 2H-4, 2H-7), 6.92 (s, 2H, NH_2), 8.3 (d, 2H, pyridine), 8.75 (d, 2H, pyridine); ms: m/z 298 (M^+); λ max absorption 394 nm, λ max emission 465 nm, log ϵ 4.41.

Anal. Calcd. for $C_{15}H_{14}N_4OS$: C, 60.40; H, 4.69; N, 18.79; S, 10.73. Found: C, 60.46; H, 4.63; N, 18.77; S, 10.71.

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