A Comparative Study on the Synthesis of the 1*H*[1]Benzothieno[2,3-*d*]-imidazole and 1*H*[1]Benzothieno[2,3-*d*]-*v*-triazole

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Alternate routes for the synthesis of the new title compounds are described. The experimental procedure for the isolation of the unstable 2,3-diaminobenzo[*b*]thiophene as the dichloride salt is presented.

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The synthesis of unsubstituted 1*H*[1]benzothieno[2,3-*d*]-imidazole **4** has been attempted in some of laboratories [1,2,3], but with discouraging results.

However, the preparation of its 2-methyl- [1,2] and 2-phenyl substituted derivatives [2,3] as well as that of the corresponding imidazol-2(3*H*-)-one [3] have been achieved. To our best knowledge the synthesis of 1*H*[1]benzothieno-[2,3-*d*]triazole **9** has not been reported and the only known heterocyclic compound which contains the tricyclic system of **9** is a coumarin derivative [4]. In view of our recent interest in imidazole nuclei condensed with thiophene moieties [5], we wish to report here the results of our investigations directed towards the synthesis of the title compounds.

The first synthetic approach to **4** was initiated starting from 2-nitro-3-aminobenzo[*b*]thiophene **1**, with the aim to obtain the intermediate 2,3-diaminobenzo[*b*]thiophene, from which structure **4** would normally be derived [6,7].

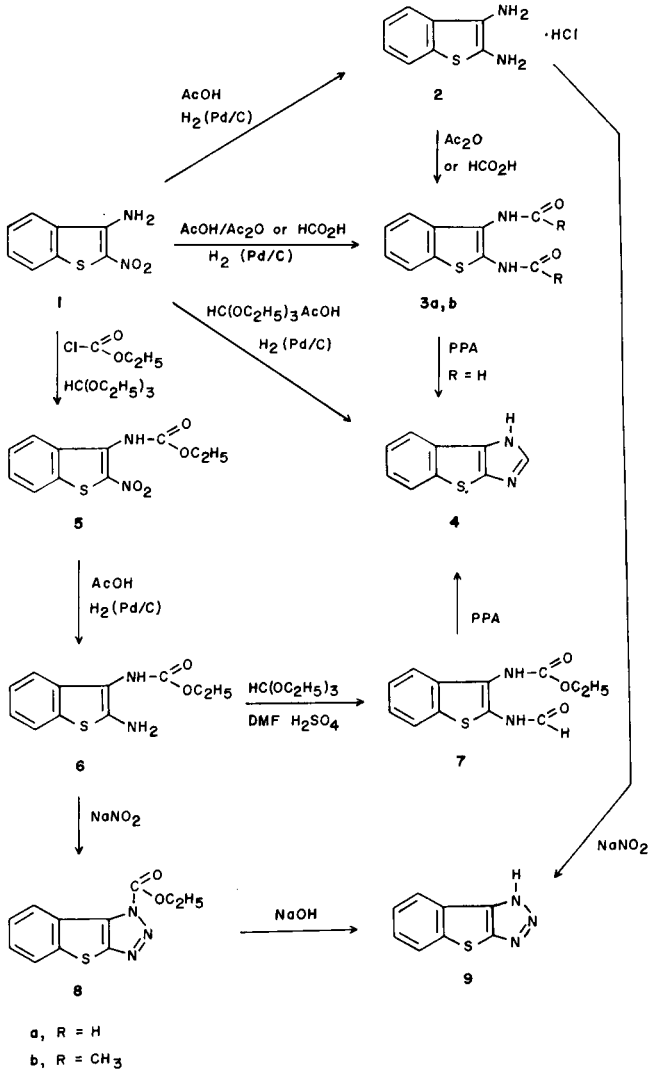
Compound **1** was subjected to catalytic hydrogenation (Pd/C) in acetic acid solution and then to a slow current of dry hydrochloride acid (gas). Upon dilution with ether 2,3-diaminobenzo[*b*]thiophene dihydrochloride precipitated in a 40% yield and in a good state of purity. This compound was stable for a long period of time and was used without further purification for the preparation of 2,3-diacetamidobenzo[*b*]thiophene **3b**, which was obtained however with an unsatisfactory yield (~ 50%).

Compound **3b** as well as the diformamido **3a** were isolated with higher yields (~ 95%) by direct catalytic hydrogenation of **1** performed in the presence of a mixture of acetic acid/acetic anhydride and of formic acid respectively. The synthesis of **4** was finally achieved by cyclization of **3a** with PPA under heating at 150° for 4 hours with a 60% yield.

In a second approach based on direct catalytic reduction of **1**, in a mixture of triethyl orthoformate and acetic acid, compound **4** was isolated in a 50% yield.

Unfortunately, the attempt to obtain the known 2-methyl derivative [1] by catalytic hydrogenation of **1** in the presence of triethyl orthoacetate was unsuccessful.

The above two approaches gave modest yields of compound **4** accompanied by numerous by-products. In order to achieve better yields and easier condition of purification a third approach was followed based on the 2-amino-



3-ethylcarbamate **6** which was considered by us more suitable in the light of its higher stability and presumable reactivity. Compound **6** was readily obtained by catalytic hydrogenation of the 2-nitro-3-ethylcarbamate **5**. Contrary to our expectation, however, the reaction of **6**, performed following the experimental condition described for the cyclization of the benzo analogues, into benzoimidazole by treatment with ethyl orthoformate and sulfuric acid in DMF [8], gave principally the 2-formamido-3-ethylcarbamate **7** which on the other hand was obtained more conveniently by catalytic reduction of **5** in formic acid solution. The final cyclization of **7** either in PPA or in refluxing boiling toluene containing aluminium oxide afforded compound **4** with yields lower than those isolated from the two other approaches.

Compound **6**, however was particularly useful for the synthesis of the triazole derivative **9**.

The diazotation of derivative **6** yield **8** which upon alkaline hydrolysis afforded **9** with satisfactory yield (~ 80%). The triazole derivative **9** was also obtained in one-pot procedure by treating the reduction acetic solution of **1** with sodium nitrite but the yield was much lower.

Analytical and spectroscopic data (ir, ^{1}H-nmr and ms) of all products are in agreement with the described structures.

The results of this study clearly show that the most advantageous methods for the construction of the imidazole nucleus condensed with a benzothiophene moiety remain those which involve either the one-step hydrogenation of **1** in the presence of orthoformate and the cyclization of the diformamido derivative **3a** with PPA.

EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. Elemental analysis were performed on a C. Erba, elemental analyzer Model 1106. The ir spectra were determined using a Perkin-Elmer Spectrophotometer 281. The ^{1}H-nmr spectra were recorded in TFA on a Perkin-Elmer R32 spectrometer operating at 90 MHz. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Mass spectra are run on a Jeol JMS 015G-2 double focusing mass spectrometer with a 10KV accelerating voltage and 75 eV electronic beam energy.

The identification of samples from different experiments was secured by mixed mps and super imposable ir spectra.

2-Nitro-3-aminobenzo[*b*]thiophene (**1**).

This compound was prepared according to the procedure described in literature [9].

2,3-Diaminobenzo(*b*)thiophene Dihydrochloride Salt (**2**).

A solution of **1** (5 mmoles) in glacial acetic acid (50 ml) was hydrogenated over 10% palladinized charcoal (200 mg) for 8 hours. The charcoal was filtered, and the solution was saturated with dry hydrogen chloride followed by the addition of ether. The solid which precipitated was filtered and dried, yield = 40%, m p 285-290° dec.

Anal. Calcd. for $C_8H_{10}Cl_2N_2S$: C, 40.52; H, 4.25; N, 11.81. Found: C, 41.00; H, 4.52; N, 11.37.

2,3-Diacetamidobenzo[*b*]thiophene (**3b**).

From 2,3-Diaminobenzo[*b*]thiophene (**2**).

Five mmoles of **2** were refluxed with 5 ml of acetic anhydride for ten minutes. Upon cooling, the product was precipitated with water, filtered off and crystallized, yield = 40%, mp 272-274° dec lit [1].

From 3-Amino-2-nitrobenzo[*b*]thiophene (**1**).

A solution of **1** (5 mmoles) in a mixture of glacial acetic acid (50 ml) and acetic anhydride (10 ml) was hydrogenated over 10% palladinized charcoal for 12 hours. The charcoal was filtered, and the filtrate was evaporated under reduced pressure, giving a residue which was poured in water. The resulting solid was filtered off and crystallized from ethanol to give **3b**, yield = 90%.

2,3-Diformamidobenzo[*b*]thiophene (**3a**).

A degassed mixture of **1** and 10% palladinized charcoal (250 mg) in 97% formic acid (50 ml) was hydrogenated at 60° for 12 hours. The mixture was then filtered off and the filtrate evaporated under reduced pressure to give a residue which was poured into water. The resulting solid was filtered off and crystallized from ethanol to give **3a**, yield = 95%, mp 240-242° dec; ir (potassium bromide): 1675 and 1640 cm^{-1} (2 × C=O); nmr: δ 7.40-7.80 (m, 4H, arom), 8.45-8.55 (2s, each 1H, 2 × H-C=O), 8.85 and 9.45 (2s, each 1H, 2 × NH).

Anal. Calcd. for $C_{10}H_8N_2O_2S$: C, 54.54; H, 4.36; N, 12.72. Found: C, 54.42; H, 3.50; N, 12.65.

1*H*[1]Benzothieno[2,3-*d*]imidazole (**4**).

From 2,3-diformamidobenzo[*b*]thiophene (**3a**).

A mixture of **3a** (5 mmoles) with PPA was kept at 140° for 3 hours under stirring. After cooling the mixture was poured into ice-water, and then neutralized with sodium hydrogen carbonate. The resulting precipitate was filtered off and crystallized from water to give **4**, yield = 60%, mp 193-195°; nmr: δ 7.40-7.80 (m, 4H, arom), 8.75 (s, 1H, C(2)-H); ms: m/e 174 (M^+, 100), 146 (30).

Anal. Calcd. for $C_9H_6N_2S$: C, 62.04; H, 3.47; N, 16.07. Found: C, 61.98; H, 3.45; N, 16.00.

From 3-Amino-2-nitrobenzo[*b*]thiophene (**1**).

A solution of **1** (5 mmoles) in glacial acetic acid (50 ml) containing ethyl orthoformate (15 ml) was hydrogenated with shaking in the presence of 10% palladinized charcoal (200 mg) at room temperature for 20 hours. The catalyst was then removed by filtration and the filtrate was evaporated under reduced pressure. The residue was poured into water, filtered off and crystallized to give **4**, yield = 50%.

3-Ethylcarbamate-2-nitrobenzo[*b*]thiophene (**5**).

A solution of **1** (5 mmoles) in an equimolecular mixture of ethyl orthoformate and ethyl chloroformate was refluxed for 3 hours. Evaporation of the solvent under reduced pressure gave an oil which crystallized from ethanol to give **5**, yield = 90%, mp 160-162°; ir (potassium bromide): 3240 cm^{-1} (NH), 1715 cm^{-1} (C=O), 1540, 1370 cm^{-1} (NO_2); nmr: δ 1.4 (s, 3H, CH_3), 4.4 (2H, CH_2), 7.60-8.00 (m, 4H, arom), 8.9 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_{10}N_2O_4S$: C, 49.62; H, 3.78; N, 10.52. Found: C, 49.57; H, 3.76; N, 10.45.

2-Amino-3-ethylcarbamatebenzo[*b*]thiophene (**6**).

A solution of **5** in glacial acetic acid (60 ml) was hydrogenated, over 10% palladinized charcoal (200 mg) for 8 hours. The catalyst was removed by filtration and the solution was poured into ice-water and neutralized with sodium hydrogen carbonate. The resulting precipitate was filtered off and crystallized from ethanol/water (1:1) to give **6**, yield = 70%, mp 166-168°; ir (potassium bromide) 3370, 3260 cm^{-1} (NH_2); 3180 cm^{-1} (NH) (broad); 1700 cm^{-1} (C=O); nmr: δ 1.5 (s, 3H, CH_3), 4.5 (s, 2H, CH_2), 7.70-7.90 (m, 4H, arom).

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 56.17; H, 5.14; N, 11.91. Found: C, 56.05; H, 5.03; N, 11.80.

3-Ethylcarbamate-2-formamidobenzo[*b*]thiophene (**7**).

A solution of **5** (5 mmoles) in 97% formic acid (80 ml) was hydrogenated over 10% palladinized charcoal (250 mg) at the temperature of 60° for 18 hours. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The resulting residue was poured into water and the solid was filtered off and crystallized from benzene to give **7**, yield = 80% mp 199-200°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54.55; H, 4.58; N, 10.60. Found: C, 54.48; H, 4.57; N, 10.52.

1-Ethylcarbonate[1]benzothieno[2,3-*d*]triazole (**8**).

A solution of **5** (5 mmoles) was hydrogenated according to the procedure reported for **6**. After the catalyst was removed, the solution was cooled at the temperature of 5° and a solution of sodium nitrite (5 mmoles) was added. The mixture was stirring at this temperature for one hour. The solution was diluted with ice-water and the product which separated was filtered. Crystallization from ethanol give **8**, yield = 80%, mp 80-81°; ir (potassium bromide): 1760 cm^{-1} (C=O); nmr: δ 1.7 (s, 3H, CH_3), 4.9 (s, 2H, CH_2), 7.60-7.80 (m, 4H, arom), ms: m/e 247 (M^+, 100), 177 (80), 146 (95), 120 (85).

Anal. Calcd. for $C_{11}H_9N_3O_2S$: C, 53.44; H, 3.66; N, 17.00. Found: C, 53.59; H, 3.54; N, 16.89.

1*H*[1]Benzothieno[2,3-*d*]triazole (**9**).

From 1-Ethylcarbonate[1]benzothieno[2,3-*d*]triazole (**8**).

A mixture of **8** (5 mmoles) in 20 ml ethanol was added of 5% aqueous potassium hydroxide (20 ml). The solution was stirred for 30 minutes, and then was acidified with hydrochloride acid. The product which separated was filtered and crystallized from water to give **9**, yield = 80%, mp 180-187°; nmr: δ 7.70-8.00 (m, 4H, arom); ms: m/e 175 (M^+, 100), 146 (80), 120 (88).

Anal. Calcd. for $C_8H_5N_3S$: C, 54.84; H, 2.87; N, 23.98. Found: C, 54.78; H, 2.77; N, 23.89.

From 3-Amino-2-nitrobenzo[*b*]thiophene (**1**).

A solution of **1** (5 mmoles) in glacial acetic acid (60 ml) was hydrogenated over 10% palladinized charcoal (200 mg) for 8 hours. After the catalyst was removed by filtration and the solution was cooled at the temperature of 5° and a solution of sodium nitrite (5 mmoles) was added, the mixture was stirred for one hour. The mixture was diluted with water filtered off and crystallized to give **9**, yield = 25%.

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