SYNTHESIS OF TRICYCLIC SYSTEMS OF BIOLOGICAL INTEREST

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Abstract: Methods for the preparation of 4-halo-5-imidazolecarboxaldehydes have been studied. They can be used in Pd(0)-catalyzed Stille couplings with-butyl-*N*-(2-trimethylstannyl-3-thienyl)-carbamate or *t*-butyl-*N*-(3-trimethylstannyl-2-thienyl)carbamate to give the new tricyclic compounds 3-benzyloxymethylimidazo[4,5-*d*]thieno[3,2-*b*]pyridine (13a), 3-benzyloxymethylimidazo[4,5-*d*]thieno-[2,3-*b*]-pyridine (14) and 3-methylimidazo[4,5-*d*]thieno[3,2-*b*]pyridine (13c).

Introduction

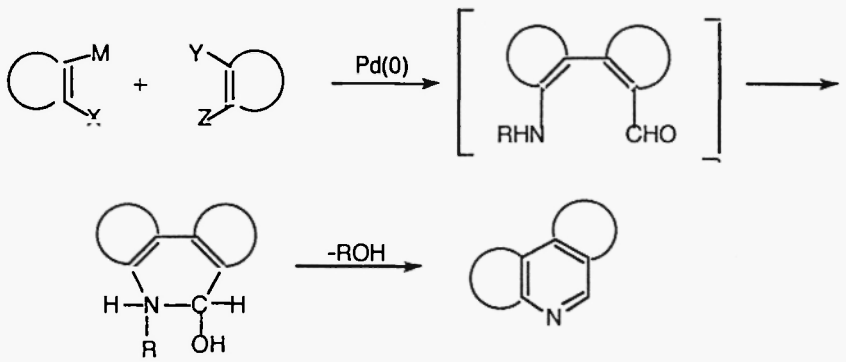
During recent years we developed convenient methods for the synthesis of tricyclic heterocyclic aromatic systems with angular annelation pattern. Pd(0)-catalyzed reactions between *o*-formylthiopheneboronic and amino-protected *o*-aminohalothiophenes (Suzuki-reaction) were used for the preparation of most of the nine isomeric dithienopyridines [1]. As an alternative route the Pd(0)-catalyzed Stille reaction using *o*-formylstannylthiophenes as the organometallic reagent has also been employed [2].

Detailed experimental and theoretical studies of electrophilic substitution, metalation and halogen-metal exchange of several of these systems has been carried out (for review cf ref [3]). Detailed studies of NMR-parameters including ^{13}C-^{13}C-coupling constants [4] as well as HeI photoelectron spectra were also carried out on all isomers and crystal and molecular structure were determined by X-ray diffraction for some representative cases [5].

The Pd(0)-catalyzed methodology has also been demonstrated to be very useful for the preparation of phenanthridine itself and thieno[*c*]quinolines and thieno[*c*]isoquinolines [6,7], furo-annelated compounds [8] and especially in connection with the synthesis of the twelve isomeric thieno[*c*]naphtyridines from *o*-amino-halopyridine derivatives and *o*-formylthiopheneboronic acids or *o*-trialkylstannylthiophenealdehydes [9,10]. The twelve isomeric thieno[*b*]naphtyridines were first prepared through the coupling of *o*-trialkystannylpyridine aldehyde derivatives with *t*-butyl-*N*-(*o*-halothienylcarbamates [11]. However, it was found that in most cases it was more convenient to switch components and react *o*-halopyridine aldehydes with *t*-butyl *N*-(*o*-tralkylstannyl-thienyl)carbamates in

order to obtain better yields and shorter reaction times [12]. Although the thieno[*c*]- and thieno [*b*]-naphthyridines are much more deactivated towards electrophilic substitution, it was possible to achieve bromination under forced conditions [13]. The photoelectron spectra of the thienonaphthyridines have also been studied in detail [14,15].

The reaction path of this one-pot method for the preparation of tricyclic heterocyclic systems with angular annelation consists of Pd(0)-catalyzed carbon-carbon bond formation followed by ring-closure through reaction of the formyl group with the amino function. In some cases spontaneous aromatization occurs by elimination of water. In other cases this is achieved by reaction with dilute hydrochloric acid (scheme 1) [1].



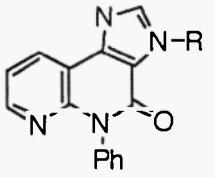
M=$B(OH)_2$, SnR_3; Y=I, Br; R=Me, Bu; X=CHO, Z=NHR; R=H, $COCH_3$, CO_2tBu

Scheme 1 The circles symbolyze phenyl, thienyl or pyridine rings

Many derivatives of the above-mentioned tricyclic heterocyclic systems are of interest as starting materials for natural products or for the preparation of potential pharmacologically active compounds. Thus benzo[*c*]-2,7-naphthyridines has been used for the synthesis of perolidine an alkaloid present in perennial rye grass and also as starting material for an attempted synthesis of meridine[16, 17]. 4-Substituted 1-(2-methylphenyl)thieno[2,3-c]-1.5-naphthyridines have been prepared as potential reversible inhibitors of gastric $H^+.K^+$-ATPase [18].

We were therefore interested in expanding our investigations to imidazo[4,5-*d*]thieno[*b*]pyridines to study reactivity and spectral properties and especially, as imidazole is an important building block for several biologically active compounds [19]. Suzuki and co-workers have reported anti-inflammatory [20] and bronchodilating [21,22] effects for some heterocyclic tricycles containing imidazole (**1** and **2**). It should therefore be of interest to prepare and study the properties of compounds in which the pyridino and benzo moiety of **1** and **2** is changed to thiopheno as in compounds of type **3**.

As in the preparation of the thieno [*b*]napthyridines, two strategies can be used for the preparation of



1

2

R=simple alkyl

3a : R_2=H

3b : R_2=CH_3

3c : R_2=CH_2Ph

the parent imidazo-fused compounds. Either *o*-formylhaloimidazoles could be coupled with *o*-amino(trialkylstannyl)thiophenes or *o*-formyltrialkylstannyl)imidazoles are coupled with protected *o*-aminohalothiophenes. In this paper the results of the first-mentioned approach will be described.

Experimental

The reactions were carried out in dried glassware. Reagents and solvents were handled by using standard syringe techniques. The starting materials 2,4,5-tribromoimidazole [23], 2,4,5- triiodoimidazole (**6**) [24,25], 4-iodoimidazole (**7a**) [24,26], *t*-butyl *N*--(2-trimethylstannyl-3-thienyl)carbamate (**10**) [12], *t*-butyl *N*-3-trimethylstannyl-3-thienyl)carbamate (**11**) [12], and *t*-butyl *N*-(4-trimethylstannyl-3-thienyl)-carbamate (**12**) [12] were prepared according to literature procedures. Uncorrected melting points were determined using a Wetzlar microscope. The ^{1}H NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts are reported in parts per million downfield from TMS. The mass spectra were recorded on a Jeol JMS-SX 102 spectrometer. Flash column chromatography was carried out using Merck silica gel 60. Heptane, pentane, ethyl acetate, dichloromethane and tetrachloromethane were freshly distilled over molecular sieves, chloroform over phosphorous pentoxide, diethyl ether and tetrahydrofuran from sodium dispersion prior to use. For HPLC a preparative polygosil/silica column (250x20 mm) was used.

1-Benzyloxymethyl-2,4,5-tribromoimidazole (4b) [27].

To 0.96g (0.04 mol) of sodium hydride in 5.0 ml of anhydrous tetrahydrofuran, 12.2 g (0.04 mol) of 2,4,5-tribromoimidazole [23] in 200 ml of anhydrous tetrahydrofuran was added dropwise with stirring. The suspension was stirred for 30 minutes before 5.6 ml (0.04 mole) of benzyl chloromethyl ether was added dropwise. When the addition was complete, saturated sodium chloride solution was added, the product was extracted with ether and the combined organic phases were washed with aqueous sodium chloride solution. The crude product was purified by column chromatography on silica with ethyl acetate/hexane (3:7)as eluent. The title compound was obtained in a yield of 14.1 g (84%). ^{1}H NMR (deuteriochloroform): δ 7.39 - 7.29 (m, 5H, Ph-H), 5.42 (s, 2H, N-CH_2), 4.60 (s, 2H,

Ph-CH_2). MS: m/z 426 (M, 8), 424 (M, 9), 345 (M-Br), 91 ($PhCH_2^{+\cdot}$,100).

1-Benzyloxymethyl-4-bromoimidazole-5-carboxaldehyde (5b).

To a solution of 10 ml 2.03 M butyllithium in cyclohexane diluted with 80 ml of anhydrous tetrahydrofuran cooled to -80 °C 8.50 g (0.02 mol) of 1-benzyloxymethyl-2,4,5-tribromoimidazole (**4b**) in 50 ml of anhydrous tetrahydrofuran was added dropwise at -78 - -82 °C. After stirring for 20 minutes at -77 °C, 2.6 ml (0.02 mol) of freshly distilled chloro trimethylsilane was added dropwise at such a rate that the temperature did not exceed -75 °C. The reaction mixture was allowed to reach room temperature and was stirred for an additional 1.5 h before cooling to -80 °C. 10 ml of 2.03 M butyllithium in cyclohexane diluted with 5.0 ml of anhydrous tetrahydrofuran was added dropwise at -78 - -80 °C. After stirring for 30 minutes 2.0 ml of anhydrous *N,N*-dimethylformamide was added and the reaction mixture was allowed to reach room temperature. Saturated aqueous ammonium chloride was added, the product was extracted with ethyl acetate and the combined organic phases were washed with aqueous sodium chloride solution. The crude product was purified by column chromatography on silica, using ethyl acetate/heptane (1:1) as eluent. The title compound was obtained in a yield of 1.63 g (28 %). ^{1}H NMR (deuteriochloroform): δ 9.79 (s, 1H, CHO), 7.73 (s, 1H, H2), 7.37-7.27 (m, 5H, Ph-H), 5.74 (s, 2H, N-CH_2), 4.61 (s, 2H, Ph-CH_2). ^{13}C NMR (deuteriochloroform): δ 179.5 (CHO), 142.4 (C2), 136.1 (PhC) 130.9 (C5), 128.7, 128.4, 127.9 (PhC), 126.4 (C4), 75.5 (N-CH_2), 71.6 ($PhCH_2$). MS: m/z 295 (M). HRMS calcd. for $C_{12}H_{12}O_2N_2Br$ $(M+H)^+$: 295.0082. Found: 295.0090.

4-Iodo-1-methylimidazole (7d).

A suspension of 250 mg (10.3 mmol) of sodium hydride in 5.0 ml of anhydrous tetrahydrofuran was treated dropwise with 2.00 g (10.3 mmol) of 4-iodoimidazole (**7a**) [24,26] in 20 ml of anhydrous tetrahydrofuran. After stirring for 15 minutes 1.92 ml (10.3 mmol) of methyl *p*-toluenesulphonate in 10.0 ml of anhydrous tetrahydrofuran was added dropwise. After 45 minutes the starting materials were consumed and water was added. The product was extracted with ether. The combined organic phases were washed with aqueous sodium chloride solution and purified by column chromatography on silica, using methanol/dichloromethane (1:9) as eluent. The yield after purification was 1.53 g (71 %). ^{1}H NMR (deuterated methanol): δ 7.32 (d,1H, H2, J = 1.2 Hz), 6.96 (d, 1H, H5, J = 1.2 Hz), 3.68 (s, 3H, N-CH_3). MS: m/z 208 (M, 100), 81 (M-127, 23). **5-Iodo-1-methylimidazole** was obtained as a minor component in a yield of 22% in the same procedure. ^{1}H NMR (deuterated methanol): δ 7.62 (s, 1H, H2), 7.12 (s, 1H, H4), 3.61 (s, 3H, CH_3).

5-Hydroxymethyl-4-iodoimidazole (8a).

A mixture of 8.00 g (41 mmol) of 4-iodoimidazole (**7a**), 5.74 g (70 mmol) of sodium acetate, 3.50 ml (62 mmol) of acetic acid and 29 ml of 37% formaldehyde was refluxed for 28 h. The reaction mixture was cooled and mixed with 325 ml of water The resulting mixture was made weakly alkaline

(pH 7.5-8) with aqueous sodium bicarbonate solution and extracted first with ethyl acetate, then with dichloromethane. The water phase was evaporated to dryness and the residue extracted with dichloromethane. The combined extracts were purified by column chromatography on silica, using methanol/dichloromethane (1:9) as eluent. The isolated yield was 1.78 g (19 %). ^{1}H NMR (deuterated methanol): δ 7.67 (s, 1H, H2), 4.52 (s, 2H, CH_2OH). ^{13}C NMR (deuterated methanol): δ 141.6 (C2), 136.8 (C5), 85.6 (C4), 59.0 (CH_2OH). MS m/z: 224 (M, 100), 207 (M-17, 20), 195 (15), 97 (M-127, 25). HRMS calcd. for. $C_4H_5IN_2O$: 223.9447. Found: 223.9446.

5-Hydroxymethyl-4-iodo-1- methylimidazole (8b).

As described above for **14a**, 4.20 g (20 mmol) of **1**-methyl-4-iodoimidazole (**7d**) was hydroxymethylated. After purification 2.25 g (47%) of the title compound was obtained. ^{1}H NMR (deuteriochloroform): δ 7.65 (s, 1H, H2), 4.57 (s, 2H, CH_2OH), 3.77 (s, 3H, N-CH_3). ^{13}C NMR (deuterated methanol): δ 144.3 (C2), 137.5 (C5), 87.2 (C4), 57.7 (CH_2OH),36.1 (CH_3). MS: m/z 238 (M, 100), 221 (M-17, 80), 111 (M-127, 40).

4-Iodo-5-imidazolecarboxaldehyde (9a).

To 100 mg (0.45 mmol) of 5-hydroxymethyl-4-iodolimidazole (**8a**) in 4.5 ml of 1,4-dioxane 390 mg (4.5 mmol) of activated manganese(IV)oxide was added. The mixture was heated to 85 °C and stirred for 1.5 h. The solid material was filtered off and washed repeatedly with ethyl acetate. The filtrate was evaporated to dryness. The isolated yield of the title compound was 0.07 g (73 %). ^{1}H NMR (deute-rated methanol): δ 9.61 (s, 1H, CHO), 7.96 (s, 1H, H2). ^{13}C NMR (deuterated dimethylsulfoxide): δ 185.9 (CHO); 148.1(C2), 138.4 (C5), 98.2 (C4). MS: m/z 222 (M, 100), 193 (M-29), 94 (M-128) HRMS calcd. for $C_4H_3IN_2O$: 221.9290. Found: 221.9291.

4-Iodo-1-methyl-5-imidazolecarboxaldehyde (9b).

To 100 mg (0.42 mmol) of 4-iodo-1-methyl-5-hydroxymethylimidazole (**8b**) in 7.5 ml of chloroform 420 mg (4.2 mmol) of activated manganese(IV)oxide was added. The mixture was refluxed for 1.5 h and worked up as described for **9a**. The title compound was obtained in a yield of 850 mg (85%). ^{1}H NMR (deuterated dimethylsulfoxide): δ 9.63 (s, 1H, CHO), 7.55 (s, 1H, H2), 3.92 (s, 3H, N-CH_3). ^{13}C NMR (deuterated dimethylsulfoxide): δ 185.8 (CHO), 151.5 (C2), 134.9 (C5), 106.6 (C4), 39.0 (CH_3). MS: m/z 236 (M, 100), 207 (M-29 (CHO), 5), 109 (M-127 (I), 16). HRMS calcd. for. $C_5H_5IN_2O$: 235.9447. Found: 235.9449.

3-Benzyloxymethylimidazo[4,5-*d*]thieno[3,2-*b*]pyridine (13a).

To 4.0 ml of anhydrous *N,N*-dimethylformamide 370 mg (1,25 mmol) of 1-benzyloxymethyl-4-bromo-5-formylimidazole (**5b**), 70 mg (0.06 mmol) of *tetrakis*(triphenylphosphine)palladium(0) [28] and 100 mg (1.25 mmol) of cupric oxide were added. The reaction mixture was heated to 100 °C and after 5 minutes 650 mg (1.80 mmol) of *t*-butyl-*N*-(2-trimethylstannyl-3-thienyl)carbamate (**10**) [12] in

2.0 ml of anhydrous *N,N*-dimethylformamide was added. When the aldehyde was consumed (after approximately 1 **h**) the reaction mixture was cooled to room temperature. After evaporation, the residue was dissolved in ether and the black precipitate filtered off. The crude product was purified by column chromatography on silica, using acetone/heptane (6:4) as eluent. The title compound was obtained in a yield of 0.31 g (84 %).^{1}H NMR (deuteriochloroform): δ 9.02 (s, 1H, H-C=N), 8.11 (s, 1H, H2- im), 7.70 (d, 1H, H5-th, J = 5.6 Hz), 7.67 (d, 1H, H4-th, J = 5.6 Hz), 7.36-7.28 (m, 5H, Ph-H), 5.73 (s, 2H, N-CH_2), 4,51 (s, 2H, Ph-CH_2). ^{13}C NMR (deuteriochloroform): δ 151.3 (C2-thieno), 144.9 (C2-im), 144.2 (C3-th), 135.4 (quart. C-Ph) 132.2 (C=N), 128.5 (2C-Ph), 128.3 (C-Ph), 127.7 (C-Ph), 127.3 (C5-th), 126.7 (quart.) 124.6 (C4-th), 124.0 (quart.), 74.3 (N-CH_2) 70.7 (Ph-CH_2). MS: m/z 295 (M, 88), 265 (34), 251 (3), 91 ($PhCH_2^{+\cdot}$, 100). HRMS calcd. for $C_{16}H_{13}N_3OS$: 295.0779. Found 295.0778.

3-Methylimidazo[4,5-*d*]thieno[3,2-*b*]pyridine (13c).

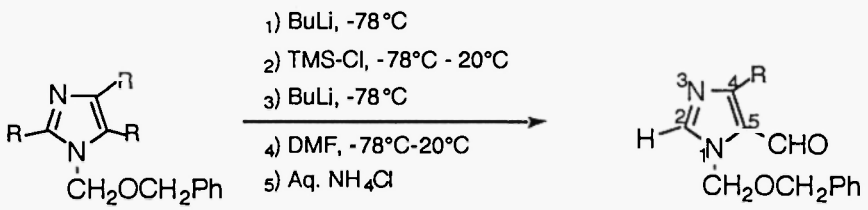
To 5.0 ml of anhydrous *N,N*-dimethylformamide 320 mg (1.36 mmol) of 4-iodo-1-methyl-5-imidazolecarboxaldehyde (**9b**) [29], 79 mg (0.068 mmol) of *tetrakis*(triphenylphosphine)palladium(0) [28] and 110 mg (1.35 mmol) of cupric oxide were added. The reaction mixture was heated to 100 °C and after 5 minutes 740 mg (2,03 mmol) of *t*-butyl-*N*-(2-trimethylstannyl-3-thienyl)carbamate (**10**) [12] in 2.0 ml of anhydrous *N,N*--dimethylformamide was added. When the aldehyde was consumed (after app-roximately 3 h) the reaction mixture was cooled to room temperature. After evaporation, the residue was dissolved in ether and the black precipitate filtered off. The crude product was purified by column chromatography on silica, using methanol/dichloromethane (1:9) as eluent. The title compound was obtained in a yield of 0.21 g (82%). ^{1}H NMR (deuteriochloroform): δ 8.80 (s, 1H, H-C=N), 7.97 (s, 1H, H2-im), 7.63 (d, 1H, H5-th, J = 5.6 Hz), 7.60 (d, 1H, H4-th, J = 5.6 Hz,), 3.98 (s, 3H, N-CH_3). ^{13}C NMR (deuteriochloroform): δ 151.0 (C2-th), 145.3 (C2-im), 143.7 (C3-th), 131.7 (C=N), 126.4 (C5-th), 125.2 (C4-th), 123.8 (quart.), 31.9 (N-CH_3). MS m/z: 189 (M, 100), 188 (22), 147 (12). HRMS calcd. for $C_9H_7N_3S$: 189.0359. Found 189.0361.

3-Benzyloxymethylimidazo[4,5-*d*]thieno[2,3-*b*]pyridine (14).

This compound was prepared from 370 mg (1.25 mmol) of 1-benzyloxymethyl-4-bromoimidazole-5-carboxaldehyde (**5b**) and 650 mg (1.80 mmol) of *t*-butyl-*N*-(2-trimethylstannyl-3-thienyl)carbamate (**11**) [12] as described for (**13**). The isolated yield was 0.20 g (54 %). ^{1}H NMR (deuteriochloroform): δ 8.94 (s, 1H, H-C=N), 8.09 (s, 1H, H2-im), 7.84 (d,1H, H5-th, J = 5.9 Hz), 7.67 (d, 1H, H4-th, J = 5.9 Hz), 7.37-7.28 (m, 5H, Ph), 5.73 (s, 2H, N-CH_2), 4,50 (s, 2H, $PhCH_2$) ^{13}C NMR (deuteriochloroform): δ 155.6 (C2-th), 144.5 (C3-th), 144.2 (C2-im), 135.5 (C-Ph, quart.), 131.5 (C=N), 128.6 (C-Ph), 128.4 (quart.), 128.3 (C-Ph), 127.1 (C5-th), 124.8 (quart.), 118.5 (C4-th), 74.0 (N-CH_2) 70.4 (Ph-CH_2). MS: m/z 295 (M, 38), 265 (12), 91 ($PhCH_2^{+\cdot}$, 100). HRMS calcd. for $C_{16}H_{13}ON_3S$: 295.0779. Found: 295.0779.

Results and Discussion

1-Benzyloxymethyl-2,4,5-tribromoimidazole (**4b**) was prepared according to Lipshutz and Hagen [27] in 84 % yield. Using the one-pot reaction sequence described by Groziak and Wei [30] gave in our hands 1-benzyloxymethyl-4-bromo-5-imidazolecarboxaldehyde (**5b**) in only 28 % yield. We then attempted the preparation of 1-benzyloxymethyl-4-iodo-5-imidazolecarboxaldehyde (**5a**) from 1-benzyloxymethyl-2,4,5-triiodoimidazole (**4a**). However, inspite of using freshly distilled anhydrous solvents and reagents together with strict temperature control (-78 - -80 °C) did not in our hands give yields of **5a** anywhere near the reported 62 % [30] .



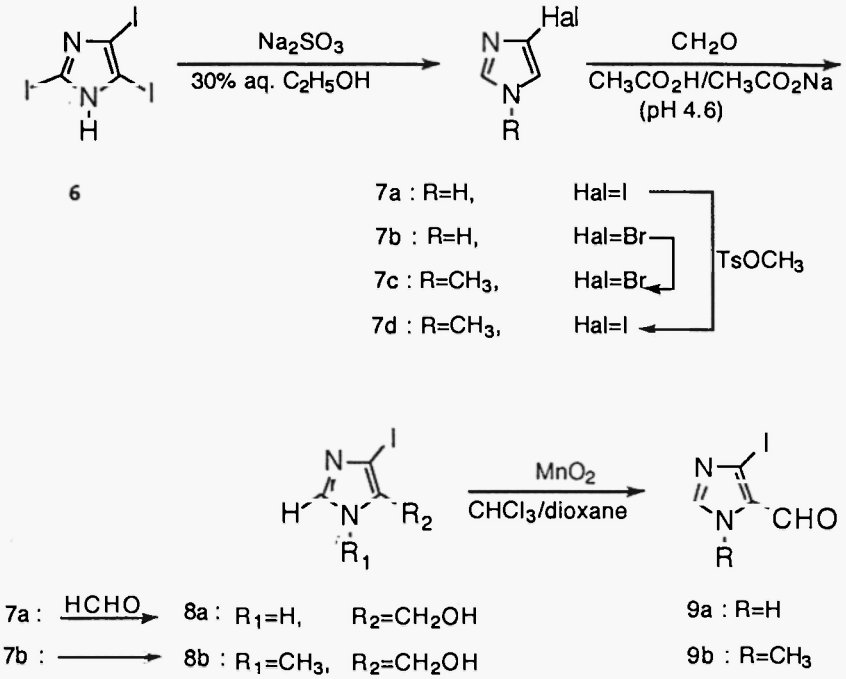
4a R=I
4b R=Br

5a R=I
5b R=Br

The attention was therefore turned towards a different strategy for obtaining the *o*-haloimidazolecarboxaldehydes involving deiodination of 2,4,5-triiodoimidazole (**6**) to monoiodoimidazole (**7a**) with excess sodium sulfite in 30 % aqueous ethanol [24,26,31], followed by hydroxymethylation to **8** with formaldehyde in an acetic acid/sodium acetate buffer (pH = 4.6) [29,32,33] and a final oxidation to the aldehyde, **9**, using activated manganese(IV)-oxide [29,34-36]. According to the literature [32,33,37] *N*-protected imidazoles provide 2-hydroxymethylimidazoles while 2-alkylated and/or imidazoles with an free NH group give the 5-hydroxymethyl derivative.

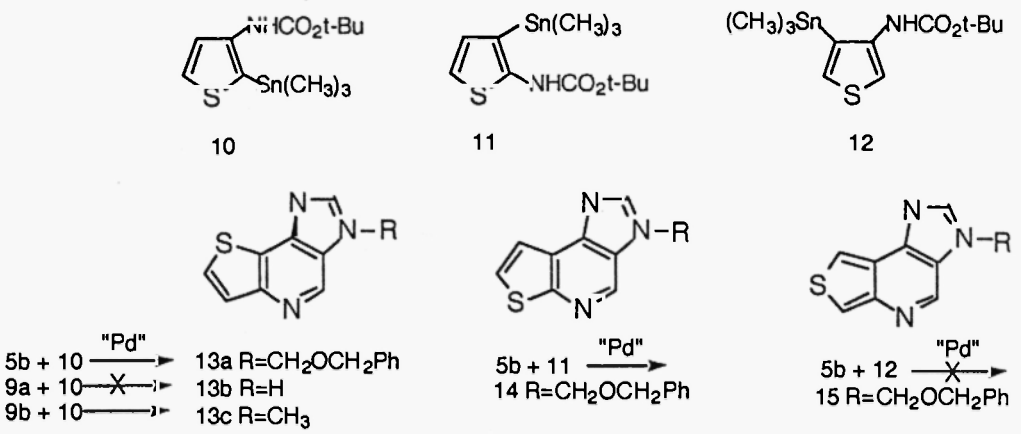
Ohba *et al.* [29] claimed that hydroxymethylation of 4-bromo-1-methylimidazole (**7c**) resulted in the 5-hydroxymethyl isomer in 76 % yield. Masui *et al.* [33] hydroxymethylated 2,4-dialkylated imidazole derivatives with a free NH group, achieving 5-hydroxymethylated compounds with yields varying between 11 and 27 %. We obtained a yield of only 13 % of 5-hydroxymethyl-4-iodoimidazole (**8a**), when the procedure described by Masui and co-workers [33] was employed. This low yield was not surprising, in the light of the fact that varying yields in the hydroxymethylation of imidazoles, with especially low yield for 4-bromoimidazole (**7b**) has been reported previously [38]. Hydroxymethylation is facilitated by electron-releasing groups, such as the methyl group. In order to increase the yield, 4-iodo-1-methylimidazole (**7d**) was therefore prepared and subsequently hydroxymethylated under the same conditions as used for 4-iodoimidazole (**7a**). This led to complete conversion as judged by thin layer chromatography, however only 13 % of 5-hydroxymethyl-4-iodo-1-methylimidazole (**8b**) could be isolated after work-up and purification according to Masui *et al.* [33]. Modification of the work-up procedure, avoiding distillation of the combined organic extracts and instead evaporating off the

solvent over night resulted in an increased yield of **8b** of 47 %. This procedure combined with exrac-



tion with dichloromethane of the evaporated water phase from **7a**, raised the yield of 5-hydroxymethyl-4-iodoimidazole (**9a**) to a modest 19%. Oxidation with activated manganese(IV)oxide in refluxing chloroform [29] resulted in 85 % yield of 4-iodo-1-methyl-5-imidazolecarboxaldehyde (**9b**) after 1.5 hours. As **8a** was not soluble in chloroform it was heated with activated manganese(IV) oxide in dioxane at 80 °C for two hours [34,35,36] giving **9a** in a yield of 66%.

Coupling of the imidazoles **5a** and **5b** with the three isomeric *t*-butyl *N*-(*o*-trimethylstannyl-thienyl)-carbamates **10**, **11** and **12** [12] using *tetrakis*(triphenyphosphine)palladium(0) as catalyst and cupric oxide as co-reagent [39,40] gave different results for the different trimethylstannyl-thiophene-carbamates. Starting from *t*-butyl-*N*-(2-trimethylstannyl-3-thienyl)carbamate (**10**) and 1-benzyloxymethyl-4-bromo-5-imidazolecarboxaldehyde (**5b**) the tricyclic compound 1-benzyloxymethylimidazo[4,5-d]thieno[3,2-b]pyridine (**13a**) was obtained in 84 % yield. With (**11**) a 54 % yield of 1-benzyloxymethyl[4,5-*d*]thieno[2,3-*b*]pyridine (**14**) was achieved under identical reaction conditions. Coupling of the bromoaldehyde **5b** with *t*-butyl-*N*-(4-trimethylstannyl-3-thienyl)carbamate (**12**) did not result in the tricyclic compound **15**. ^{1}H NMR of the isolated product showed signals due to the aldehyde and the carbamate groups. Attempts to cyclize and aromatize the isolated product or the reaction mixture in the usual way [1] by refluxing with 2 M hydrochloric acid did not lead to aromatization.



The two aldehydes **9a** and **9b** were reacted with (**10**) under the same conditions as described above gave the best results yielding 1-methylimidazo[4,5-d]thieno[3,2-b]pyridine (**13c**) in a yield of 82 %. However, **9a** did not give the desired compound **13b**.

Conclusions.

Our preliminary results show that the biologically interesting imidazo[4,5-d]thieno[b]pyridines can be obtained by Stille reaction between 1-protected 4-iodo-5-imidazolecarboxaldehydes and t-butyl (o-trimethylstannylthienyl)carbamates. However better methods for the preparation of the imidazoles have to be developed

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