The First Synthesis of Pyrido[2,1-*a*]phthalazinium System and its Three Thieno-fused Analogues

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Substituted biaryl compounds **9, 14-16** were synthesized through Pd(0)-catalyzed cross coupling reactions between boronic acids or tin derivatives and aryl halides. *N*-Amination, and subsequent ring closure resulted in the new angularly-fused pyrido[1,2-*b*]pyridazinium systems **1-4**. The use of silver oxide as a cocatalyst in the couplings of tin derivatives was essential in order to obtain rapid reaction and better yields. Structures were determined by ^{1}H nmr and ^{13}C nmr spectra.

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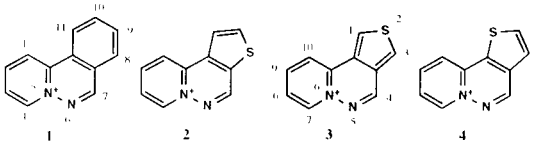
Introduction.

We have recently been interested in studying the effect of the annelation of thiophene rings in tricyclic heterocyclic systems, with angular annelation pattern, on chemical and spectroscopic properties. Recently, we developed convenient procedures involving Pd(0)-catalyzed cross-coupling of boronic acids or organotin derivatives with heteroaryl halides for the synthesis of benzo- and thieno[*c*]-fused quinoline and isoquinoline *N*-oxides [1,2], thieno-[*c*]-fused 1,8-naphthyridines [3], as well as all nine isomeric dithienopyridines [4]. The ^{1}H-nmr and ^{13}C-nmr spectra of these compounds have been analyzed [5] and a study of their substitution reactions including *ab initio* calculation of the nitration [6] is in progress.

As a continuation of these studies we decided to apply a similar strategy to the synthesis of bridge-head-nitrogen containing fused azinium compounds. The reaction of such positively charged salts with nucleophiles has proven to be a suitable tool for the preparation of heteroaryl dienes [7,8] which have been shown to be excellent intermediates for several ring closure reactions [9,10,11].

In the present paper we report the synthesis of pyrido-[2,1-*a*]phthalazin-5-ium perchlorate (**1**) and its three thieno-fused analogues **2-4** (Scheme I). Compound **1** is a benzo[*c*] derivative of the fully aromatic pyrido[1,2-*b*]pyridazinium salt which has quite recently been prepared for the first time by condensation of 2-alkyl-1-aminopyridinum salts with 1,2-dicarbonyl compounds [12]. However, the synthesis and reactivity of the olates related to this system have previously been extensively studied [13].

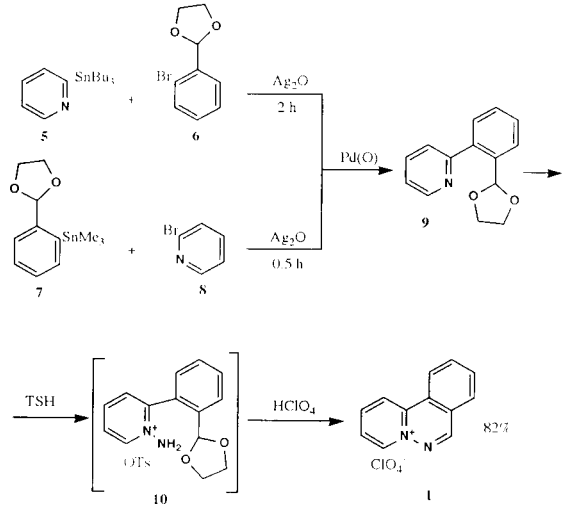
Scheme I



Synthesis.

We considered *o*-(2-pyridyl)benzaldehyde to be the key compound for the preparation of **1**. However, somewhat surprisingly our attempts to couple *o*-formylbenzeneboronic acid with 2-bromopyridine according to our modification of the Suzuki reaction failed, as did Stille coupling of *o*-tributylstannylbenzaldehyde with 2-bromopyridine. Reversing the functionalities, using 2-tributylstannylpyridine (**5**) and *o*-bromobenzaldehyde also failed, probably due to rapid decomposition of the product. We have recently found that the use of one equivalent of silver oxide in the Stille reaction increased the rates and yields [15]. However in the above mentioned reactions no effect of silver oxide was observed. Similarly no coupling was observed using **5** and the acetal protected *o*-bromobenzaldehyde (**6**) or 2-bromopyridine (**8**) and acetal protected *o*-trimethylstannylbenzaldehyde (**7**). However in these cases the addition of silver oxide had a marked effect and the desired biaryl compound **9** was obtained by coupling of **5**

Scheme II



[16] with 2-(2-bromopheny)-1,3-dioxolane (**6**) [17] in moderate yield (Scheme II). In order to increase the yield, we prepared the less sterically crowded 2-(2-trimethylstannylphenyl)-1,3-dioxolane (**7**) by metalation of **6** with *n*-butyllithium, followed by reaction with trimethyltin chloride at −70°. We found that **7** can indeed be coupled with **8** in the presence of silver oxide to give the same biaryl compound **9**. In addition to the higher yield, shorter reaction time was achieved. Another advantage of this method is that the by-product trimethyltin bromide can be easily removed from the reaction mixture by washing with water. When **9** was *N*-aminated by *O*-tosylhydroxylamine (TSH) [18], a spontaneous ring closure of the *N*-amino derivative **10** took place, and the desired compound **1** was isolated in 82% yield.

For the synthesis of the thieno-fused systems we followed the same strategy. The cross-coupling reaction of **8** and 2-formyl-3-thiopheneboronic acid (**11**) and 4-formyl-3-thiopheneboronic acid (**12**) under modified Suzuki conditions [19] were, in contrast to the corresponding attempts with *o*-formylphenylboronic acid, successful and afforded 2-formyl-3-(2′-pyridyl)thiophene (**14**) and 4-formyl-3-(2′-pyridyl)thiophene (**15**) in good yields. Due to the easy deboronation of 3-formyl-2-thiopheneboronic acid, the coupling in this case was carried out under anhydrous conditions (triethylamine in DMF) [20], however the third biaryl **16** was only formed in trace amounts. We therefore turned our attention to the tin methodology. Tributylstannyl-3-thiophene aldehyde (**13**) gave 3-formyl-2-(2′-pyridyl)thiophene (**16**) in only 15% yield, a large amount of the homocoupled product, 3,3′-diformyl-2,2′-bithienyl (**17**) (mp 155-156°, lit [21] 155-157°) was also formed. Compound **16** could be obtained in 60% yield by the reaction of **13** with **8** in the presence of silver oxide, in this case the reaction time was only five minutes (Scheme III). *N*-amination and subsequent ring closure of these biaryls **14-16** afforded the desired thieno-fused pyrido[1,2-*b*]pyridazinium salts **2-4** in satisfactory yields. We believe that this route is a convenient approach to the hitherto unknown angularly fused pyridopyridazinium derivatives. Yields, melting points and elemental analyses for all new compounds are given in the experimental section. The ^{1}H-nmr chemical shift of the tricyclic systems studied in this paper are given in Tables I and II. The ^{1}H-nmr spectra of the four azinium salts were in accordance with their structures. The characteristic feature of these spectra is that the azomethine protons (H_7 and H_4) and the α-protons of the positively charged pyridine moieties (H_4 and H_7) are more deshielded than other protons, owing to the adjacent nitrogen atoms and the positive charge. The thiophene hydrogens appear as an AB quartet with normal thiophenic 2,3-coupling constants (5-5.5 Hz) and 2,5-coupling constants (2.8-3.5 Hz) [22]. In the case of compounds **2** and **3** characteristic long-range coupling (zig-zag) between the H_1 and H_4 ($J_{1,4}$ = 0.5 Hz) also confirmed the structure. The ^{13}C-nmr spectra of these compounds have also been determined. Protonated carbons were assigned by 2D heteronuclear shift correlation experiments (HETCOR spectra) are given in Table III. Comparison between the ^{13}C-nmr chemical shifts of the thiophene moieties of **2-4**, (which are aza-analoques of thieno[*c*]quinolines) and thieno-[*c*]quinolines shows that the conjugation with the thiophene ring in these positively charged systems results in

Scheme III

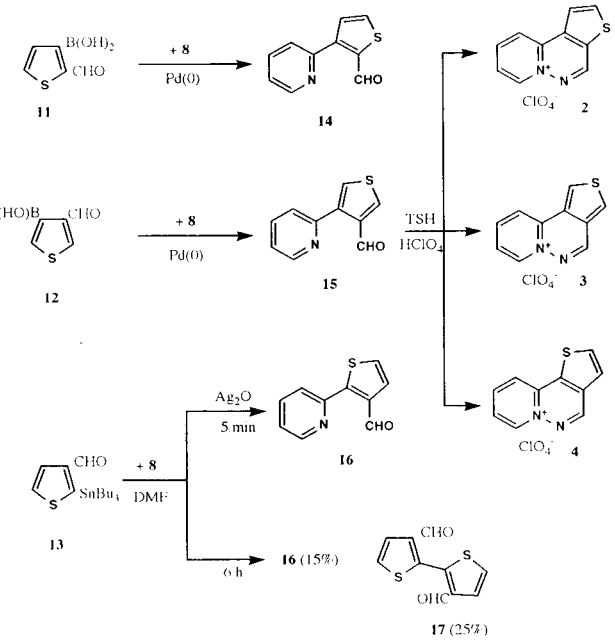


Table I. ^{1}H nmr Chemical schifts (δ, ppm) of compounds **1-4** [a]

Compound	1H	2H	3H	4H	7H	8H	9H	10H	11H
1	9.51	8.83	8.33	9.70	9.93	8.49	[b]	[b]	9.17
2	8.70	8.83		10.11	9.70	8.28	8.76	9.23	
3	9.47		9.03	9.65	9.49	8.17	8.74	9.13	
4		8.70	8.07	9.92	9.68	8.23	8.68	9.01	

[a] The numbering is analogues to that given in Scheme I.
[b] 8.30-8.37 ppm overlaping signals

Table II ^{1}H nmr coupling constants (J, Hz) for compounds **1-4**

Compound	J_{12}	J_{23}	J_{13}	J_{34}	J_{78}	J_{79}	J_{89}	J_{810}	J_{910}	J_{1011}
1	9.0		1.1				8.1	1.1		8.9
2	5.2				7.0	1.1	8.1	1.6	8.4	
3			3.0		6.8	1.2	7.5	1.6	8.0	
4		5.1			6.8	0.8	7.5	1.6	8.4	

downfield shift ranging 3.0-10.0 ppm for all carbons in the thiophene ring, relative to thieno[*c*]quinolines [23].

Table III. The chemical schift (δ ^{13}C, ppm) of compounds **1-4** [a]

Compound	C1	C2	C3	C4	C7	C8	C9	C10	C11
1	123.2	142.0	125.8	142.8	154.2	129.5	[b]	[b]	125.0
2	123.5	141.2		147.5	141.4	124.8	141.3	124.0	
3	129.0		133.1	149.7	142.3	125.0	143.5	123.7	
4		139.4	125.3	147.9	141.6	124.8	141.1	123.8	

[a] Containing only the CH carbons.
[b] 134.9 and 135.1 ppm overlaping signals.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr and ^{13}C-nmr spectra were recorded with a Varian XL-300 spectrometer in DMSO-d_6 solution. The glc analysis were carried out on a Varian 3700 gas chromatograph using an OV-17, 3%, 2 m column.

General Procedure for the Preparation of Azinium Salts **1-4**.

Equivalent amounts (10 mmoles) of the biaryl compounds **9**, **14-16** in 10 ml of dichloromethane were stirred at 0° with a solution of 1.87 g (10 mmoles) of *O*-tosylhydroxylamine (TSH) in 40 ml of dichloromethane for 15 minutes, and at 25° for two hours. The reaction mixture was evaporated to 15 ml mixed with 1 ml of 70% perchloric acid. Ethyl acetate (15 ml) was then added to precipitate the crude azinium salts **1-4** which were recrystallized from acetonitrile-ether to give pure compounds.

Pyrido[2,1-*a*]phthalazin-5-ium Perchlorate (**1**).

This compound was obtained as white needles, yield 82%, mp 214-215°.

Anal. Calcd. for $C_{12}H_9N_2 \cdot ClO_4$: C, 51.30; H, 3.20; N, 9.98. Found: C, 51.03; H, 3.24; N, 9.96.

Pyrido[1,2-*b*]thieno[3,2-*d*]pyridazin-6-ium Perchlorate (**2**).

This compound was obtained as white plates, yield 60%, mp 202-204°.

Anal. Calcd. for $C_{10}H_7N_2S \cdot ClO_4$: C, 41.88; H, 2.44; N, 9.77. Found: C, 41.46; H, 2.48; N, 9.85.

Pyrido[1,2-*b*]thieno[3,4-*d*]pyridazin-6-ium Perchlorate (**3**).

This compound was obtained as white needles, yield 75%, mp 249-250°.

Anal. Calcd. for $C_{10}H_7N_2S \cdot ClO_4$: C, 41.88; H, 2.44; N, 9.77. Found: C, 41.53; H, 2.50; N, 9.78.

Pyrido[1,2-*b*]thieno[3,4-*d*]pyridazin-6-ium Perchlorate (**4**).

This compound was obtained as white needles, yield 73%, mp 189-190°.

Anal. Calcd. for $C_{10}H_7N_2S \cdot ClO_4$: C, 41.88; H, 2.44; N, 9.77. Found: C, 41.49; H, 2.47; N, 9.79.

2-(2-Trimethylstannylphenyl)-1,3-dioxolane (**7**).

To a stirred solution of 2-(2-bromophenyl)-1,3-dioxolane (**6**) (4.6 g, 20 mmoles) in 30 ml of anhydrous ether, 10 ml of 2.1 *N* *n*-butyllithium in cyclohexane was added dropwise at −70° under nitrogen. After stirring for 30 minutes, trimethyltin chloride (4.0 g, 20 mmoles) in 10 ml of ether was added dropwise. After the addition was complete the mixture was stirred at −70° for an additional 4 hours and then allowed to warm to 0°. With ice-cooling 10 ml of water was added and the organic phase was separated. The organic phase was washed twice with brine, and after drying (magnesium sulfate) it was evaporated. The oily residue became solid after standing at room temperature for a few hours, yield 78%, mp 36-37°; ^{1}H-nmr (deuteriochloroform): δ 7.8-7.4 (m, 4H, Ar), 5.85 (s, 1H, CH), 4.2 (m, 4H, CH_2CH_2), 0.4 (m, 9H, CH_3).

Anal. Calcd. for $C_{12}H_{18}O_2Sn$: C, 46.05; H, 5.75. Found: C, 46.35; H, 5.75.

2-Formyl-3-(2′-pyridyl)thiophene (**14**).

To a solution of tetrakis(triphenylphosphine)palladium(0) (1.049 g, 0.910 mmole) in ethylene glycol dimethyl ether (DME) (20 ml) a solution of 2-bromopyridine (4.8 g, 30 mmoles) in DME (60 ml) was added. After stirring the mixture for ten minutes under nitrogen, 2-formyl-3-thiopheneboronic acid (5.1 g, 33 mmoles) was quantitatively transferred to the flask with help of another 10 ml of DME, immediately followed by 7.5 g of sodium bicarbonate dissolved in 80 ml of water. The reaction mixture was refluxed for 4 hours with vigorous stirring under nitrogen. After cooling to room temperature, the organic solvent was evaporated and the residue extracted with three 50 ml portions of ether. After drying the combined ethereal phases were evaporated, and the residue was recrystallized from cyclohexane to give 4.38 g (73%) of product as white needles, mp 72-73° (cyclohexane); ^{1}H-nmr (deuteriochloroform): δ 10.46 (1H, d, J = 1.1 Hz, CHO), 8.71 (1H, dd, J = 5.1, 1.1 Hz, 6′-H), 7.81 (1H, m, 4′-H), 7.71 (1H, dd, J = 5.1, 1.1 Hz, 4-H), 7.62 (1H, dd, J = 7.8, 1.1 Hz, 3′-H), 7.44 (1H, d, J = 5.1 Hz, 5-H), 7.33 (1H, m, 5′-H).

Anal. Calcd. for $C_{10}H_7NOS$: C, 63.47; H, 3.73; N, 7.40. Found: C, 63.55; H, 3.82; N, 7.45.

4-Formyl-3-(2′-pyridyl)thiophene (**15**).

Using the above procedure from 4-formyl-3-thiopheneboronic acid (5.1 g, 33 mmoles), 2-bromopyridine (4.8 g, 30 mmoles) and Pd(0) (1.049 g, 0.910 mmole) to give 5.1 g (85%) of product, mp 76-77° (cyclohexane); ^{1}H-nmr (deuteriochloroform): δ 10.26 (1H, s, CHO), 8.65 (1H, dd, J = 5.1, 1.1 Hz, 6′-H), 8.23 (1H, d, J = 3.2 Hz, 5-H), 7.76 (1H, m, 4′-H), 7.62 (1H, d, J = 3.2 Hz, 2-H), 7.60 (1H, dd, J = 7.8, 1.1 Hz, 3′-H), 7.26 (1H, m, 5′-H).

Anal. Calcd. for $C_{10}H_7NOS$: C, 63.47; H, 3.73; N, 7.40. Found: C, 63.59; H, 3.87; N, 7.42.

3-Formyl-2-(2′-pyridyl)thiophene (**16**).

To a solution of tetrakis(triphenyphosphine)palladium(0) (0.35 g, 0.3 mmole) and 2-bromopyridine (1.6 g, 10 mmoles) in dimethylformamide (100 ml) 10 mmoles of silver oxide was added. After the reaction mixture had been stirred at 100° for 5 minutes under nitrogen, 2-tri-*n*-butylstannyl-3-thiophenecarboxaldehyde (6 g, 15 mmoles) in 10 ml of DMF was added. After stirring at 100° for 5 minutes the reaction was complete and the mixture was cooled to room temperature and evaporated. The residue was filtered through a pad of neutral alumina using ethyl acetate as eluent. The filtrate was evaporated and the residue was chromatographed over silica gel 60 using chloroform as eluent. After evaporation the oily residue was triturated with cyclohexane and the resulting precipitate was filtered to give 1.2 g (60%) of product, mp 54-56°; ^{1}H-nmr (deuteriochloroform): δ 10.40 (1H, s, CHO), 8.71 (1H, d, J = 5.0 Hz, 5-H), 7.80 (1H, m, 4′-H), 7.66 (1H, dd, J = 7.6, 1.0 Hz, 6′-H), 7.61 (1H, d, J = 5.0 Hz, 4-H), 7.33 (1H, m, 5′-H).

Anal. Calcd. for $C_{10}H_7NOS$: C, 63.47; H, 3.73; N, 7.40. Found: C, 63.52; H, 3.79; N, 7.46.

2-(2-pyridylphenyl)-1,3-dioxolane (**9**).

a). Using the above procedure with a reaction time of 2 hours, 2-(2-bromophenyl)-1,3-dioxolane (**6**) (1.15 g, 5 mmoles), 2-tri-*n*-butylstannylpyridine (**5**) (2.75 g, 7.5 mmoles), silver oxide (5 mmoles) and Pd(0) (0.18 g, 0.15 mmole) gave 0.48 g (42%) of product, mp 65-66°; ^{1}H-nmr (deuteriochloroform): δ 8.72 (1H, dd, J = 5.3, 1.1 Hz, 6'-H), 7.70 (2H, m, Ar), 7.58 (1H, dd, J = 7.8, 1.2 Hz, 3'-H), 7.47 (3H, m, Ar), 7.27 (1H, m, Ar), 5.96 (1H, s, 1-H), 3.95-4.15 (4H, m, $-CH_2-CH_2-$).

b). 2-(2-Trimethylstannylphenyl)-1,3-dioxolane (**7**) (2.0 g, 6.3 mmoles), 2-bromopyridine (**8**) (0.8 g, 5 mmoles), silver oxide (5 mmoles) and Pd(0) (0.18 g, 0.15 mmoles) gave by the same procedure with a reaction time of 30 minutes, 0.66 g (58%) of product, mp 65-66°.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 74.00; H, 5.72; N, 6.16. Found: C, 73.85; H, 5.83; N, 5.92.

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