The First Synthesis of Thieno[c]isoquinolines and an Improved Synthesis of Phenanthridine and Thieno[c]quinolines through Pd(0) Catalyzed Coupling of *ortho*-Formylarylboronic Acids with Functionalized Aryl Halides

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All three isomeric hitherto unknown thieno[c]isoquinolines have been synthesized in high yields by the Pd(0)-catalyzed coupling of 2-formylbenzeneboronic acid with *t*-butyl-*N*-(*ortho*-halothienyl)carbamates. When 2-bromoacetanilide, instead of 2-bromoaniline, was coupled with *orth*-formylarylboronic acids under Pd-catalysis, phenanthridine and thieno[c]quinolines were obtained in improved yields.

Total assignments of ^{1}H nmr spectra of thieno[c]isoquinolines and thieno[c]quinolines are reported. Assignments are based on high resolution 300 MHz ^{1}H nmr spectra, two-dimentional ^{1}H-^{13}C chemical shift correlation spectra and one-dimentional INADEQUATE ^{13}C nmr spectroscopy.

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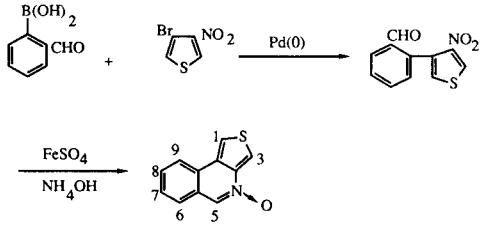
Introduction.

In a previous paper, we described the synthesis of thieno[c]isoquinoline *N*-oxides, which are analogues of phenanthridine *N*-oxide [1]. These compounds were prepared by the coupling of 2-formylbenzeneboronic acid with *ortho*-bromonitrothiophenes, catalyzed by tetrakis-(triphenylphosphine)palladium(0), to give the *o*-formyl-*o'*-nitrophenylthiophenes. Upon treatment with ferrous sulfate in aqueous ammonia, these phenylthiophenes gave somewhat unexpectedly and in high yields the thieno[c]isoquinoline *N*-oxides, as illustrated for one of the isomers in Scheme 1. However, only two of the three possible thieno-[c]isoquinoline *N*-oxides could be obtained, due to the failure of the coupling between 2-formylbenzeneboronic acid and 2-bromo-3-nitrothiophene [1].

In connection with our interest in the effect of the mode of annelation on the physical and chemical properties of thieno-fused tricyclic systems, we wanted to develop a practical approach to synthesize their parent compounds. Even if the reduction of the *N*-oxides could give the parent compounds, the multi-step approach could only afford poor yields of the end products. In order to find a practical approach with high yields, we have investigated the coupling of 2-formylbenzeneboronic acid with *t*-butyl-*N*-(*ortho*-

Scheme 1

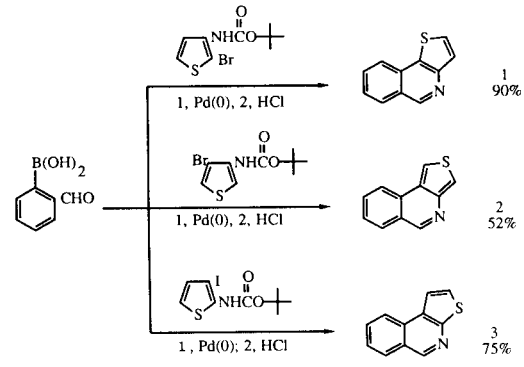


halothienyl)carbamates, and also the coupling of 2-bromoacetanilide with 2-formylbenzeneboronic acid and the three isomeric *ortho*-formylthiopheneboronic acids.

Results and Discussion.

In this work we found that 2-formylbenzeneboronic acid could be coupled with *t*-butyl-*N*-(*ortho*-halothienyl)carbamates in ethylene glycol dimethyl ether, using sodium bicarbonate as base and tetrakis(triphenylphosphine)palladium(0) as catalyst, to give thieno[3,2-c]isoquinoline (**1**), thieno[3,4-c]isoquinoline (**2**) and thieno[2,3-c]isoquinoline (**3**) in high yields and in one pot (Scheme 2).

Scheme 2



The advantage of this approach is a one-pot synthesis with high yields. Furthermore, in comparison with *ortho*-bromonitrothiophenes, the starting materials *t*-butyl-*N*-(*ortho*-halothienyl)carbamates are easier to prepare by one-pot conversion of carboxylic acids to urethanes [2]. In the case of 3-bromo-4-nitrothiophene, the only known synthetic method is the reaction of thienyllithium derivatives with *trans*-chlorovinyliododichloride at $-70°$ to yield dithienyliodonium salt, and subsequent treatment with sodium nitrite [3]. This multi-step procedure is time-consuming and the yields often fluctuate due to the air-sensitivity of the *trans*-chlorovinyliododichloride.

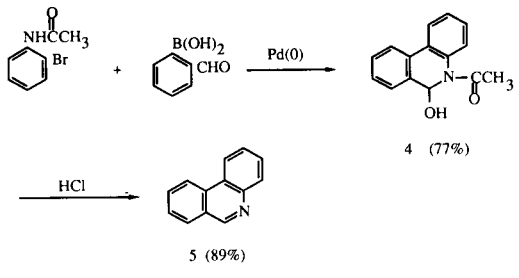
The chemistry of thieno[c]isoquinolines has been explored to a very limited degree, and only few derivatives

have been reported [4a-c]. The preparative route to the parent compounds presented in this paper opens the possibility for extensive studies of the chemistry of these almost completely unknown tricyclic heteroaromatics.

Although many routes to phenanthridine are now available, alternative processes are still of interest. When 2-bromoaniline was converted to 2-bromoacetanilide by acetylation, the product should be more active than the amino derivative, since the oxidative insertion of palladium follows reactivity in nucleophilic aromatic substitution [5].

As illustrated in Scheme 3, the less electron-donating acetamido group enhanced the reactivity. However, the coupling product was the partly aromatized dihydro compound. The formation of the dihydro compound was evident from its ir spectrum, which showed absorption at 3350 cm^{-1} (C-OH) and at 1640 cm^{-1} (C=O). The transformation of the dihydro compound to the corresponding fully aromatized phenanthridine can be effected by refluxing with hydrochloric acid (2*N*) in an isolated yield of 89%.

Scheme 3



The two-step transformation can be conveniently conducted in one-pot without isolation of the dihydro compound, and the separated yield of phenanthridine is 87%. When these reaction conditions were used in the coupling with the three isomeric *ortho*-formylthiopheneboronic acids, all three thieno[*c*]quinolines **6**, **7** and **8** were obtained (Scheme 4). Thus, by converting 2-bromoaniline into 2-bromoacetanilide, the coupling yields in Scheme 4 were increased from 29% for **8**, 34% for **6**, and 38% for **7** to 38% for **8**, 44% for **6**, and 71% for **7** [6].

Yields, melting points and elemental analyses for the tricyclic heteroaromatic compounds are given in Schemes 2 and 4 and in Table 2.

In connection with our interest in the effect of the mode of annelation on the physical and chemical properties of thieno-fused tricyclic systems, we have determined the ^{13}C-^{13}C coupling constants of these heteroaromatics by one-dimensional INADEQUATE ^{13}C nmr spectroscopy [8], in order to obtain insight into the bonding situation in these compounds. In addition, evaluation of these ^{13}C-^{13}C couplings can also remove uncertainties which are often encountered due to ambiguous assignments of the ^{1}H and ^{13}C nmr signals of complex structures. Thus, with the help of INADEQUATE ^{13}C nmr spectroscopy and two-dimensional ^{1}H-^{13}C chemical shift correlation spectra, we were able to achieve the total, unambiguous assignment of the ^{1}H and ^{13}C nmr spectra of all nine dithienopyridines, all three possible thieno[*c*]isoquinolines and all three possible thieno[*c*]quinolines. These results will be discussed in

Scheme 4

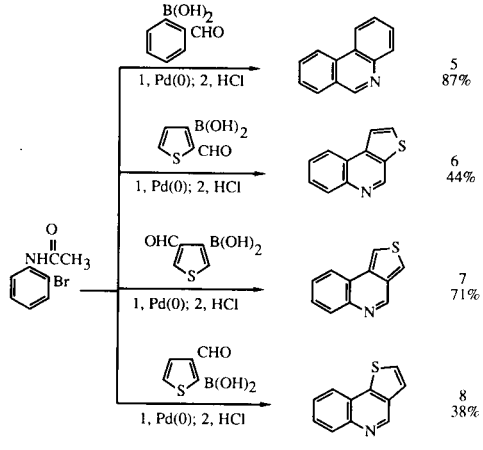


Table 1

Yields, Melting Points and Elemental Analyses of the Tricyclic Heteroaromatics

Compound	Yield (%)	Mp (°C)	Mol. wt [a]	C	H	N
1	90	62-64	185	71.3	3.84	7.49
2	52	35-37	185	71.3	3.78	7.53
3	75	83-85	185	71.6	3.83	7.58
4	77	84-87	239			
5	87	104-105 [b]	179			
6	44	87-89 [c]	185			
7	71	49-51 [c]	185			
8	38	75-76 [c]	185			

[a] Elemental analyses calculated for $C_{11}H_7NS$ (185.25) are C, 71.32; H, 3.81; N, 7.56. [b] lit 104-105° [7]. [c] Identical with lit values [6].

Table 2

^{1}H NMR Chemical Shifts (δ, ppm) of the Thieno[*c*]isoquinolines and Thieno[*c*]quinolines [a-b]

Compound	1H	2H	3H	4H	5H	6H	7H	8H	9H
1		7.73	8.08		9.30	8.28	7.73	7.90	8.18
2	8.18		8.61		8.96	8.04	6.91	7.84	8.44
3	8.18	8.00			9.24	8.27	7.74	7.92	8.52
6	8.00	7.87		9.33		8.31	7.73	7.66	8.24
7	8.08		8.10	9.08		8.21	7.62	7.57	8.04
8		7.60	7.57	9.29		8.23	7.72	7.63	8.14

[a] Spectra recorded in deuteriodimethyl sulfoxide for **1-3**, in deuteriochloroform for **6-7**. [b] The numbering is analogous to the one given in Scheme 1.

Table 3

^{1}H NMR Coupling Constants (J, Hz) for the Thieno[c]isoquinolines and Thieno[c]quinolines [a-b]

Compound	$J_{1,2}$	$J_{2,3}$	$J_{1,3}$	$J_{1,4}$	$J_{5,9}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$	$J_{7,9}$	$J_{8,9}$
1		5.37			0.64	8.16	1.29	7.04	0.99	8.18
2			3.28			8.03	1.37	7.28	1.16	8.03
3	5.80					8.11	1.03	7.00	0.86	8.29
6	5.37			0.86		8.30	1.46	6.90	1.47	8.06
7			2.93	0.98		7.33	1.71	7.33	1.59	7.57
8		5.25				8.30	1.23	6.97	1.47	8.05

[a] Spectra recorded in deuteriodimethyl sulfoxide for **1-3**, in deuteriochloroform for **6-7**. [b] The numbering is analogous to the one given in Scheme 1.

more detail in a forthcoming paper. Table 2 and Table 3 give the total assignment of the ^{1}H nmr chemical shifts and coupling constants of thieno[*c*]isoquinolines and thieno[*c*]quinolines. The numbering is analogous to that given in Scheme 1. These assignments were supported by the two-dimensional ^{1}H-^{13}C chemical shift correlation spectra and one-dimensional INADEQUATE ^{13}C nmr spectroscopy. The coupling constants of the thiophene parts are $J_{1,2} = J_{2,3} = 5.25\text{-}5.80$ Hz and $J_{1,3} = 2.93\text{-}3.28$ Hz, which are in the intervals characteristic for $J_{2,3}$ and $J_{2,5}$ in thiophene [9]. The coupling constants of the benzene parts are in the intervals of 6.90-8.30 Hz and 0.86-1.71 Hz, which is characteristic for J_{ortho} and J_{meta} in benzene [10]. As in other polycyclic aromatics [10], the coupling constants $J_{7,8}$ is about 1 Hz smaller than $J_{6,7}$ or $J_{8,9}$.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H nmr spectra were recorded with a Varian XL-300 spectrometer. The ms were recorded on a Finnigan 4021 spectrometer. The glc analyses were carried out on a Varrian 3700 gas chromatograph using a OV-17, 3%, 2 m column. The elementary analyses were made at the Analytical Department of the Chemical Center, Lund.

General Procedure for the Coupling Reaction to Prepare **1-3** and **5-8**.

A 100 ml three-necked flask equipped with condenser, nitrogen inlet and stirrer was charged with 0.01 mole of aryl halide, 0.35 g (0.0003 mole) of tetrakis(triphenylphorsphine)palladium(0) [11] and 30 ml of ethylene glycol dimethyl ether. After stirring for 10 minutes 0.011 mole of the appropriate *ortho*-formylaryboronic acid was added (2-formylbenzeneboronic acid [6], 2- and 4-formyl-3-thiopheneboronic acids [12] and 3-formyl-2-thiopheneboronic acid [13]), followed by the addition of 0.03 mole of sodium bicarbonate in 20 ml of water. The reaction mixture was refluxed with vigorous stirring and monitored by thin-layer chromatography and gas chromatography until starting material was consumed (between 20 minutes and 4 hours). Subsequently, 30 ml of hydrochloric acid (2*N*) was added and the reaction mixture was refluxed for an additional hour. When cooled to room temperature, the reaction mixture was neutralized with sodium hydroxide solution and the mixture was stirred for 5 minutes. After the organic solvent was removed at reduced pressure, the residue was extracted three times with ether. The combined organic phases were washed with water and dried over magnesium sulfate. After the removal of the drying agent and the solvent, the residue was chromatographed on silica gel 60, eluting with ethyl acetate-hexane (1:3) for **1**, **2** and **3**, heptane-ethyl acetate (1:1) for **5**, **6**, **7** and **8**. Yields, melting points and elemental analyses are given in Table 1 and the assignments of ^{1}H nmr signals in Table 2 and Table 3.

5-Acetamido-6-hydroxyldihydrophenanthridine (**4**).

This compound was prepared from 2.14 g (0.01 mole) of 2-bromoacetanilide [14] and 1.65 g (0.011 mole) of 2-formylbenzeneboronic acid [6], according to the general coupling procedure without the addition of 2*N* hydrochloric acid and the consequent neutralization, to give 1.83 g of the title compound (77%), mp 84-87°; ir (potassium bromide): 3350, 1640, 1320 and 750 cm^{-1}.

Aromatization of **4**.

A 100 ml round-bottomed flask equipped with condenser and magnetic stirrer was charged with 1.20 g (0.005 mole) of 5-acetamido-6-hydroxyldihydrophenanthridine, 10 ml of 2*N* hydrochloric acid and 30 ml of acetone. The mixture was refluxed for 45 minutes. After the acetone was removed, the residue was extracted three times with ether. The combined ether phases were washed with water and dried over magnesium sulfate. After the removal of the ether, the residue was chromatographed on silica gel 60, using heptane-ethyl acetate (1:1) as an eluent to give 0.80 g (89%) of phenanthridine, mp 104-106°. Spectra were identical to previously prepared sample [1].

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REFERENCES AND NOTES

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