Improved Syntheses of Thieno[2,3-*b*]- and [3,2-*b*]-fused Naphthyridines

Patrick Björk, Torunn Aakermann, Anna-Britta Hörnfeldt and Salo Gronowitz*

Organic Chemistry 1, Chemical Center, Lund University,
Box 124, 221 00 Lund, Sweden

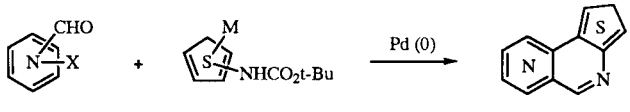
Recieved August 17, 1994
Revised January 20, 1995

The preparation of eight isomeric thieno[2,3-*b*]- and [3,2-*b*]-fused naphthyridines [1] was improved through the Pd(0) catalyzed cross-coupling of 3-formyl-4-iodopyridine, 2-formyl-3-iodopyridine, 3-bromo-4-formylpyridine and 2-bromo-3-formylpyridine with *t*-butyl *N*-(2-trimethylstannyl-3-thienyl)carbamate and *t*-butyl *N*-(3-trimethylstanny-2-thienyl)carbamate.

J. Heterocyclic Chem., **32**, 751 (1995).

In previous work we discovered that the cross-coupling between *o*-formyl(trialkylstannyl)pyridines and *o*-aminohalothiophenes generally resulted in low yields of [3,2-*b*]- and [2,3-*b*]-fused naphthyridines. The yields were in an interval 9-57% and most of the time below 20% [2].

The reason for this is most probably the low reactivity of *o*-aminohalothiophene derivatives in the oxidative insertion of palladium, the rate of which parallels nucleophilic aromatic substitution. Switching the positions of the trialkyltin group and the halide thus reacting *o*-halopyridine aldehydes with *o*-trimethylstannylthienylcarbamates should lead to fast oxidative insertion, as the *o*-halopyridine aldehydes are very reactive in nucleophilic substitution. Good yields have previously been obtained in the preparation of the twelve thieno[*c*]naphthyridines from *o*-haloaminopyridines, which should be somewhat less reactive than the corresponding *o*-halopyridine aldehydes, and *o*-formylthiophene boronic acids or *o*-trialkylstannylthiophene aldehydes [3,4].

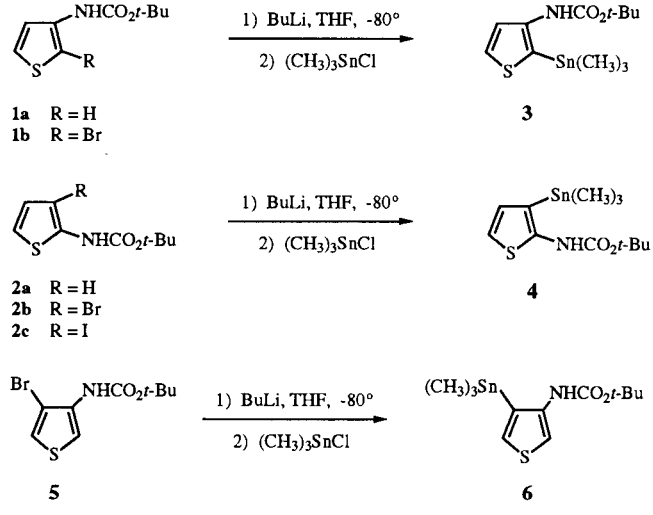


M = $Sn(CH_3)_3$, X = Br or I

Therefore in the present paper an improved synthesis of eight isomeric thieno[2,3-*b*]- and [3,2-*b*]fused naphthyridines will be described.

Results and Discussion.

For the preparation of the *o*-trialkylstannylthienylcarbamates, we first tried metallation of *t*-butyl *N*-(3-thienyl)carbamate (**1a**), following the procedure described by Rocca *et al.* [5]. This reaction resulted in a mixture of the desired compound **3** and an unidentified component in a ratio of 3:2. We therefore decided to use the halogen-metal exchange reaction, starting from *t*-butyl *N*-(2-bromo-3-thienyl)carbamate (**1b**) and *t*-butyl *N*-(3-bromo-2-thienyl)carbamate (**2b**). Treatment with butyllithium at -70 - -80° followed by addition of trimethylstannyl chloride at the same temperature resulted in *t*-butyl *N*-(2-trimethylstannyl-3-thienyl)carbamate (**3**) and *t*-butyl *N*-(3-trimethylstannyl-2-thienyl)carbamate (**4**). When the temperature was kept lower than -78° and the reaction was quenched with sodium chloride, excellent yields of **3** and **4** were obtained. Attempts to purify the crude products were not successful. The tin-carbon bond was cleaved upon column chromatography on silica gel (100%), during distillation under reduced pressure (0.06 mm Hg, 50%) and during purification by hplc on a RP-18 column (40-50%) or on a neutral alumina column (10-15%). The crude products had a deep brown colour, but the ^1H nmr spectra indicated no other impurity than 5-20% of *t*-butyl *N*-(3-thienyl)carbamate (**1a**) and *t*-butyl *N*-(2-thienyl)carbamate (**2a**), respectively. In spite of the impurities the ^1H nmr spectra of the desired compounds were unambigously interpreted. Less strict temperature control (-70 - -75°) and/or quenching with aqueous ammonium chloride resulted in increased cleavage of the tin-carbon bond. The crude compounds **3** and **4** could be

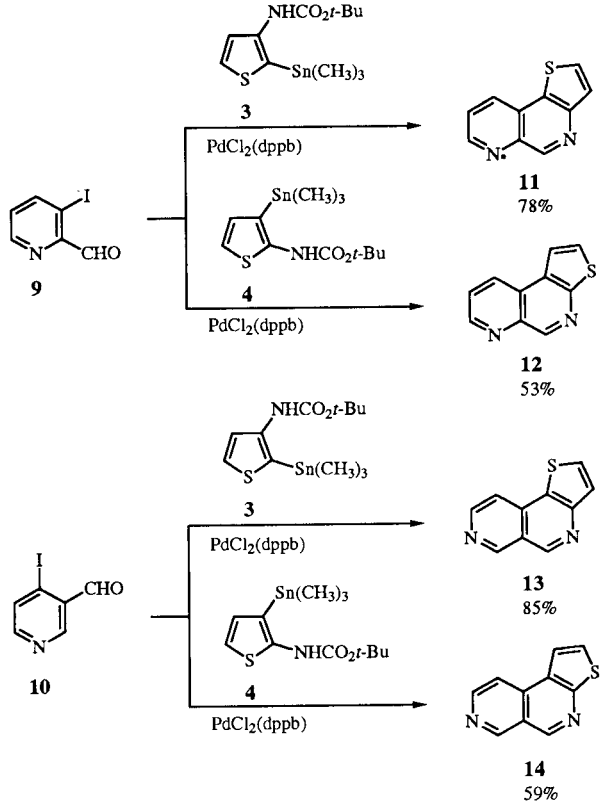


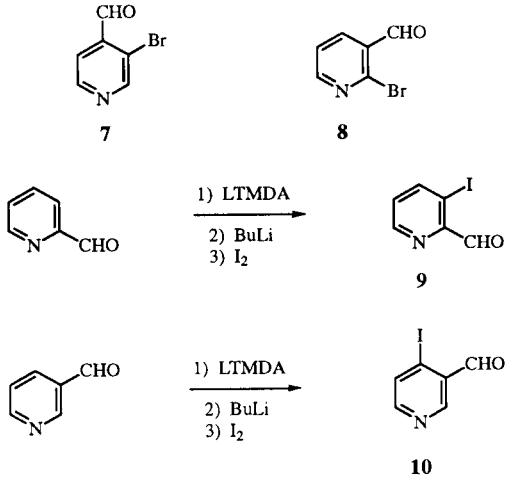
used directly in the palladium-catalyzed coupling reactions. When *t*-butyl *N*-(3-iodo-2-thienyl)carbamate (**2c**) was used as starting material the product contained only the destannylated compound **2a**.

Addition of butyllithium to cooled solutions of the carbamates **1b** and **2b** or *vice versa,* did not influence the product distribution. Concerning *t*-butyl *N*-(4-bromo-3-thienyl)carbamate (**5**) the number of components in the product was lower when **5** was added to a cooled solution of butyllithium than when the addition was the opposite. *t*-Butyl *N*-(4-trimethylstannyl-3-thienyl)carbamate (**6**) was more stable than **3** and **4**. When the temperature was strictly controlled (-78 - -80°) and the reaction quenched with sodium chloride solution, **6** was obtained in 42% yield after column chromatography.

Two of the four isomeric *o*-haloformylpyridines, 3-bromo-4-formylpyridine (**7**) and 2-bromo-3-formylpyridine (**8**) were prepared according to known literature methods [6-8]. The remaining two *o*-haloformylpyridines we decided to prepare *via* the convenient directed *o*-metalation technique introduced by Comins and Killpack [9]. They *o*-metalated formylpyridines with butyllithium after protecting the carbonyl function with *N'*-lithio-*N,N,N'*-trimethylethylenediamine. This technique has previously been employed by us in the preparation of three of the four *o*-formyl(trialkylstannyl)pyridines [2]. When iodine was used as electrophile the yields were poor. 3-Iodo-2-formylpyridine (**9**) and 4-iodo-3-formylpyridine (**10**) were obtained in 20% and 18% yields, respectively. These yields could not be improved, neither by using a variety of conditions for adding the electrophile, nor when quenching the reaction mixture. Difficulties in using iodine as electrophile have also been encountered by other researchers [10,11]. Attempts to prepare 3-bromo-2-formylpyridine by using bromine or 1,2-dibromoethane as electrophile gave only trace amounts of the desired compound. We also tried iododestannylation according to Yamamoto [12] on the previously prepared 3-trimethylstannyl-4-formylpyridine and 4-trimethylstannyl-3-formylpyridine [2] but without success.

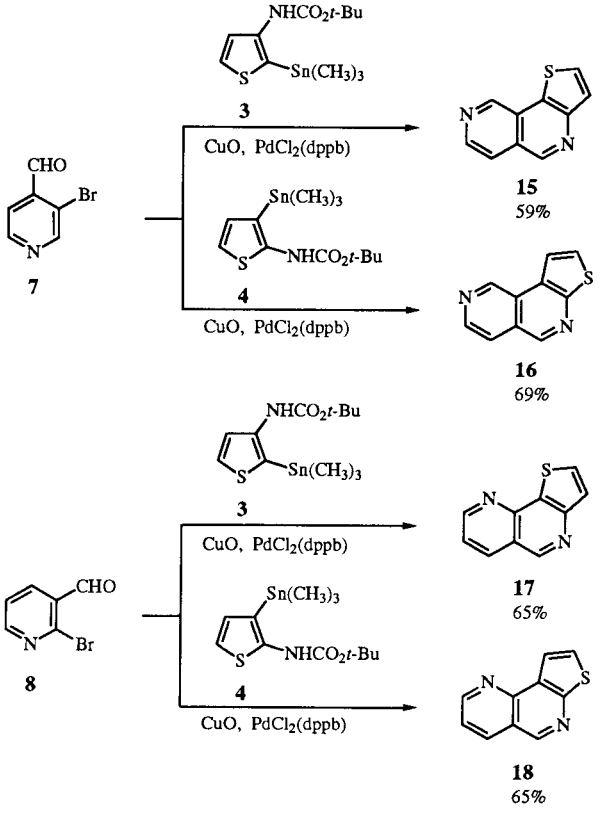
With the carbamates **3** and **4** and the *o*-haloformylpyridines **7-10** cross-couplings were successfully carried out. The *o*-iodoformyl derivatives gave thieno[3,2-*b*][2,8]naphthyridine (**11**), thieno[2,3-*b*]-[2,8]naphthyridine (**12**), thieno[3,2-*b*][2,7]naphthyridine (**13**) and thieno[2,3-*b*][2,7]naphthyridine (**14**) in 53-85% yield using dichloro(diphenylphosphinebutane)palladium(II) [13] as catalyst and without employing any co-reagent.





In the cross-coupling between the *o*-bromoformylpyridines and the carbamates **3** and **4**, thieno-[3,2 *b*][2,6]naphthyridine (**15**), thieno[2,3-*b*][2,6]naphthyridine (**16**), thieno[3,2-*b*][2,5]naphthyridine (**17**) and thieno[2,3-*b*][2,5]naphthyridine (**18**) were obtained in 59-69% yield. Copper(II) oxide had to be used as co-reagent [14].

The reaction times for the cross-coupling reactions were less than two hours and the yields between 59 and 85%. All yields were improved compared with those in our previous investigation. The largest increase in yield was for **16** from 9% to 69%. Our results clearly demonstrate the importance of a fast oxidative insertion for successful cross-couplings.



EXPERIMENTAL

The ^{1}H nmr spectra were recorded on a Varian XL-300 Spectrometer. Mass spectra and high resolution mass spectra were recorded on a JEOL JMS-SX 102 spectrometer. All melting points are uncorrected. 2-Formyl- and 3-formylpyridine, sodium hydride (80%) and *N,N,N'*-trimethylethylenediamine were purchased from Janssen. Trimethyltin chloride was purchased from Aldrich. *N,N*-Dimethylformamide, petroleum ether (40-60°) and ethyl acetate were distilled and kept over molecular sieves prior to use. Tetrahydrofuran and diethyl ether were distilled over sodium. All other solvents were purchased from the manufacturer in analytical grade and used without further purification.

t-Butyl *N*-(2-Trimethylstannyl-3-thienyl)carbamate (**3**).

In 50 ml of anhydrous tetrahydrofuran 5.85 g (0.021 mole) of *t*-butyl *N*-(2-bromo-3-thienyl)carbamate [15] was dissolved and the solution was cooled to -80°. At -78 - -72°, 23 ml of 2.03 *M* butyllithium in cyclohexane was added dropwise, when the addition was complete the reaction mixture was stirred at -74° for 45 minutes, after which 4.58 g (0.023 mole) of trimethyltin chloride in 10 ml of anhydrous tetrahydrofuran was added dropwise. The reaction mixture was allowed to reach room temperature and sodium chloride was added. The product was extracted with ethyl acetate, the combined organic phases were washed with water, dried over sodium sulfate and evaporated. The title compound was obtained in a yield of 8.24 g (>100%) as a brown oil; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 9.44 (broad s, 1H, NH), 7.62 (d, 1H, H5, J = 4.8 Hz), 6.94 (d, 1H, H4, J = 4.8 Hz), 1.46 (s, 9H, *t*-Bu), 0.24 (s, 9H, $Sn(CH_3)_3$); ms: m/z 363 + 361 + 359 (M, 1.5 + 1.0 + 0.8), 292 (100), 165 + 163 + 161 ($Sn(CH_3)_3^+$, 9 + 7 + 14), 57 ($(CH_3)_3^+$, 38); hrms: Calcd. for $C_{12}H_{21}NO_2SSn$: 363.0315. Found: 363.0316.

t-Butyl *N*-(3-Trimethylstannyl-2-thienyl)carbamate (**4**).

This compound was prepared as described for **3** from 5.85 g (0.021 mole) of *t*-butyl *N*-(3-bromo-2-thienyl) carbamate [15]. The title compound was obtained in a yield of 8.29 g (>100%) as a brown oil; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 9.28 (broad s, 1H, NH), 7.20 (d, 1H, H5, J = 5.4 Hz), 6.84 (d, 1H, H4, J = 5.4 Hz), 1.44 (s, 9H, *t*-Bu), 0.23 (s, 9H, $Sn(CH_3)_3$); ms: m/z 363 + 361 + 359 (M, 1.0 + 0.8 + 0.5), 292 (100, 165 + 163 + 161) ($Sn(CH_3)_3^+$, 10 + 8 + 15), 57 ($(CH_3)_3^+$, 35); hrms: Calcd. for $C_{12}H_{21}NO_2SSn$: 363.0315. Found: 363.0313.

t-Butyl *N*-(4-Trimethylstannyl-3-thienyl)carbamate (**6**).

This compound was prepared as described for **3** from 11.1 g (0.04 mole) of *t*-butyl *N*-(4-bromo-3-thienyl)carbamate [15] with the modification that the substrate was added dropwise to a cooled (-80°) solution of butyllithium diluted with anhydrous tetrahydrofuran. After the addition of trimethyltin chloride the reaction mixture was stirred for 1 hour at room temperature. The crude product was purified by column chromatography on silica, using ethyl acetate/petroleum ether (9:91) as eluent. The title compound was obtained in a yield of 6.12 g (42%); ^{1}H nmr (deuterated dimethyl sulfoxide): δ 9.10 (broad s, 1H, NH), 7.36 (d, 1H, H5, J = 3.1 Hz), 7.01 (d, 1H, H2, J = 3.1 Hz), 1.45 (s, 9H, *t*-Bu), 0.22 (s, 9H, $Sn(CH_3)_3$); ms: m/z 363 + 361 + 359 (M, 5 + 4.5 + 4), 290 (100), 165 + 163 + 161 ($Sn(CH_3)_3^+$, 6 + 4 + 12), 57 ($(CH_3)_3^+$, 78); hrms: Calcd. for $C_{12}H_{21}NO_2SSn$ 363.0315. Found: 363.0306.

3-Iodo-2-formylpyridine (**9**).

To a stirred solution of 3.06 ml (24 mmoles) of *N,N,N'*-trimethylethylenediamine in 75 ml of anhydrous tetrahydrofuran, 10.9 ml of 2.03 *M* butyllithium was added at -78°. After 15 minutes 2.15 g (0.02 mole) of 2-formylpyridine was added; and the mixture was stirred at -78° for 15 minutes, after which 19.7 ml of 2.03 *M* butyllithium was added. The stirring was continued for five hours at -78° followed by five hours at -42°. After cooling to -78°, 10.6 g (0.042 mole) of iodine in 50 ml of anhydrous tetrahydrofuran was added over a couple of minutes. The reaction was allowed to reach room temperature for two hours. It was quenched with 200 ml of cold sodium chloride solution and extracted three times with 300 ml of diethyl ether. The combined organic phases were dried over potassium carbonate and evaporated. The crude products were purified by column chromatography on silica, using petroleum ether/ethyl acetate (4:1) as eluent. After purification by hplc on a silica column using heptane/ethyl acetate/2-propanol (15:4:1) as eluent, 0.93 g (20%) of the title compound was obtained as white crystals, mp 58-60°; ^{1}H nmr (deuteriochloroform): δ 10.05 (s, 1H, CHO), 8.79 (dd, 1H, H6, J = 1.4, 4.5 Hz), 8.35 (dd, 1H, H4, J = 1.4, 8.0 Hz), 7.21 (dd, 1H, J = 4.5, 8.0 Hz); ms: m/z 233 (M, 100), 205 (M-CHO, 90), 127 (15), 78 (M-CHO-I, 80) 51 (35); hrms: Calcd. for C_6H_4INO: 232.9337. Found 232.9335.

4-Iodo-3-formylpyridine (**10**).

This compound was prepared as described for **9**, with the difference that the temperature was kept at -42° for three hours.

After purification by hplc 0.84 g (18%) was obtained as white crystals, mp 91-92°; ^{1}H nmr (deuteriochloroform): δ 10.08 (s, 1H, CHO), 8.89 (s, 1H, H1), 8.32 (d, 1H, H6, J = 5.3 Hz), 7.91 (s, 1H, H5, J = 5.3 Hz); ms: m/z 233 (M, 100), 204 (M-CHO, 10), 179 (15), 105 (40), 77 (M-CHO-I, 15); hrms: Calcd. for C_6H_4INO: 232.9337. Found 232.9333.

General Procedure for the Preparation of the Thieno[*b*]naphthyridines **11-18**.

A mixture of 230 mg (1.0 mmole) of the appropriate *o*-iodoformylpyridine or 190 mg (1.0 mmole) of the appropriate *o*-bromoformylpyridine, 30 mg (0.05 mmole) of dichloro (diphenylphosphinebutane)palladium(II) [13] and 80 mg (1.0 mmole) of copper(II)oxide, if using the bromo compounds, in 4.0 ml of *N,N*-dimethylformamide was stirred at 100° under nitrogen. After 5 minutes, 540 mg (1.50 mmoles) of the appropriate trimethylstannyl thienylcarbamate in 1.0 ml of *N,N*-dimethylformamide was added all at once to the reaction mixture. After the starting materials were consumed (2 hours), the reaction mixture was allowed to reach room temperature. The precipitate was filtered off and the filtrate was evaporated. The residue was subjected to column chromatography using ethyl acetate/petroleum ether (1:1) as eluent and then sublimated at 30° below the mp at 2 mm Hg. Spectroscopical data, for the isolated compounds were identical with those given in our previous works [2,16].

Thieno[3,2-*b*][2,8]naphthyridine (**11**) was obtained in a yield of 145 mg (78%), mp 125-126° (lit [2] 128-131°).

Thieno[2,3-*b*][2,8]naphthyridine (**12**) was obtained in a yield of 99 mg (53%), mp 107-109° (lit [2] 110-111°).

Thieno[3,2-*b*][2,7]naphthyridine (**13**) was obtained in a yield of 158 mg (85%), mp 138-139° (lit [2] 140-141°).

Thieno[2,3-*b*][2,7]naphthyridine (**14**) was obtained in a yield of 110 mg (59%), mp 112-114° (lit [2] 112-116°).

Thieno[3,2-*b*][2,6]naphthyridine (**15**) was obtained in a yield of 110 mg (59%), mp 129-130° (lit [2] 131-132°).

Thieno[2,3-*b*][2,6]naphthyridine (**16**) was obtained in a yield of 128 mg (69%), mp 129-131° (lit [2] 130-131°).

Thieno[3,2-*b*][2,5]naphthyridine (**17**) was obtained in a yield of 121 mg (65%), mp 115-116° (lit [2] 120-122°).

Thieno[2,3-*b*][2,5]naphthyridine (**18**) was obtained in a yield of 121 mg (65%), mp 116-117° (lit [2] 117-119°).

Acknowledgement.

A grant from the Swedish Natural Science Research Council to S. G. and A.-B. H. are gratefully acknowledged. Dr Torunn Aakerman was supported by a post-doctoral grant from the Norwegian Research Council for scientific and Industrial Research. This work was completed during a stay of S. G. as a Schönbrunn Visiting Professor at the Hebrew University of Jerusalem.

REFERENCES AND NOTES

[1] For convenient comparison with the *c*-fused systems we consider all systems as *b*-fused. The nomenclature does **not** agree with IUPAC rules.

[2] P. Björk, A.-B. Hörnfeldt and S. Gronowitz, *J. Heterocyclic Chem.*, **31**, 1161 (1994).

[3] S. Gronowitz, J. Malm and A.-B. Hörnfeldt, *Collect. Czech. Chem. Commun.*, **56**, 2340 (1991).

[4] J. Malm, B. Rehn, A.-B. Hörnfeldt and S. Gronowitz, *J. Heterocyclic Chem.*, **31**, 11 (1994).

[5] P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron*, **49**, 49 (1993).

[6] F. Lotz, U. Kraatz and F. Korte, *Z. Naturforsch.*, **34b**, 306 (1979).

[7] X. Wang and V. Snieckus, *Tetrahedron Letters*, **32**, 4883 (1991).

[8] E. J. Corey and S. G. Pyne, *Tetrahedron Letters*, **24**, 3291 (1983).

[9] D. L. Comins and M. O. Killpack, *J. Org. Chem.*, **55**, 69 (1990).

[10] A. Godard, J.-M. Jacquelin and G. Quéguiner, *J. Organomet. Chem.*, 273 (1988).

[11] R. Raap, *Can. J. Chem.*, **49**, 2139 (1971).

[12] Y. Yamamoto and A. Yanagi, *Chem. Pharm. Bull.*, **30**, 1731 (1982).

[13] J. M. Jenkins and J. G. Verkade, *Inorg. Synth.*, **11**, 108 (1968).

[14] S. Gronowitz, P. Björk, J. Malm and A.-B. Hörnfeldt, *J. Organomet. Chem.*, 127 (1993).

[15] S. Gronowitz, A.-B. Hörnfeldt and Y. Yang, *Chem. Scripta*, **28**, 281 (1988).

[16] J. Malm, P. Björk, S. Gronowitz and A.-B. Hörnfeldt, *Tetrahedron Letters*, **33**, 2199 (1992).