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Heteroaromatic Boron Compounds. XIV. Halogen—Lithium Interconversion of Some Bromo- and Iodo-substituted 3,2-Borazaropyridines

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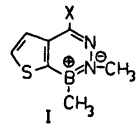
Halogen-metal exchange has successfully been carried out between some iodo- and bromo-substituted 3,2-borazaropyridines and butyllithium, which opens the route to many substituted derivatives of this heteroaromatic boron heterocycle. In 4,6-dibromo-2,3-dimethyl-5-ethyl-3,2-borazaropyridine, it is the 6-bromine which undergoes halogen-metal exchange.

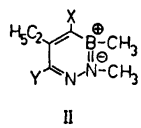
It has been found[1] that 6,7-dimethyl-7,6-borazarothieno[3,2-*c*]pyridine can be iodinated to the 4-iodo derivative (Ia), and that 2,3-dimethyl-5-ethyl-3,2-borazaropyridine can be iodinated to the 4-iodo derivative (IIa) and brominated to the 4,6-dibromo derivative (IIb).

We were interested in finding out if such halogen derivatives undergo halogen-metal exchange with alkyllithium derivatives, which would open the possibility to introduce various substituents into the borazaropyridine system.

It is known from the classical work of Gilman and Spatz[2,3] that 2-bromopyridine, 3-bromo- and 3-iodopyridine give halogen-metal exchange with butyllithium at −35 °C, and Wibaut *et al.*[4] found that this could also be achieved with 4-bromopyridine at −75 °C. Under these conditions, complications due to addition over the azomethine bond were not serious. Gronowitz and Röe[5] found that such addition was the preferred reaction with 5-bromopyrimidine at −70 °C, and halogen-metal exchange could only be obtained as the preferred reaction when the temperature was decreased to −100 °C. It was therefore not *a priori* possible to predict how the 3,2-borazaropyridine system would react even though it is isoelectronic with pyridine.



I



II

a X=I
b X=CHO
c X=Br
d X=OCH_3

a X=I, Y=H
b X=Y=Br
c X=CHO, Y=H
d X=Br, Y=H
e X=Br, Y=CHO

We found that both Ia and IIa rapidly give halogen-metal exchange at −70 °C with butyllithium, yielding upon reaction with *N,N*-dimethylformamide, 6,7-dimethyl-4-formyl-7,6-borazarothieno[3,2-*c*]pyridine (Ib) and 2,3-dimethyl-5-ethyl-4-formyl-3,2-borazaropyridine (IIc) in good yields. Reaction of IIb with one equivalent of butyllithium at −70 °C showed that the 6-bromine was the most reactive. Hydrolysis of the lithium derivative with methanol gave only one product according to GLC. Its NMR spectrum proved it to be 4-bromo-2,3-dimethyl-5-ethyl-3,2-borazaropyridine (IId). As mentioned earlier,[1] bromination of 2,3-dimethyl-5-ethyl-3,2-borazaropyridine gave a mixture of the 4- and 6-bromo derivatives, which could not be separated. The preparation of pure IId in the above-mentioned way was of importance

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for the analyses of the bromination products.[1] Reaction of the 4-bromo-6-lithio derivative with *N,N*-dimethylformamide gave 4-bromo-2,3-dimethyl-5-ethyl-6-formyl-3,2-borazaropyridine (IIe) in good yield.

Attempts to obtain a dilithium derivative by the use of excess butyllithium failed. The reason for this became evident when the reaction between IIb and butyllithium was studied. After 45 min at −70 °C, no reaction had occurred. At −30 °C the starting material disappeared, and several new compounds were formed after hydrolysis, according to GLC analysis. However, none was the expected 2,3-dimethyl-5-ethyl-3,2-borazaropyridine. It is thus evident that with the 4-bromo derivative (in contrast to the 4-iodo derivative) halogen-metal exchange is so slow that other reactions compete. However, it is evident from our results that 6-bromo and 4-iodo derivatives of 3,2-borazaropyridines behave similarly to the isoelectronic pyridines, and the halogen-metal exchange reaction opens the route to many derivatives.

We have also made some preliminary attempts to carry out nucleophilic aromatic substitution with some halo derivatives of 3,2-borazaropyridines, a well-known reaction of pyridines. Reacting 4-bromo-6,7-dimethyl-7,6-borazarothieno[3,2-*c*]pyridine [1] (Ic) with sodium methoxide at room temperature gave 4-methoxy-6,7-dimethyl-7,6-borazarothieno-[3,2-*c*]pyridine (Id) in only 19 % yield. The reason for this was, as found by GLC analysis of the reaction mixture, ring-opening reactions of Id.

In contrast to the pyridines, all attempts to carry out the Tschitchibabin reaction with 6,7-dimethyl-7,6-borazarothieno[3,2-*c*]pyridine or 2,3-dimethyl-4-ethyl-3,2-borazaropyridine failed. Only starting material was recovered.

EXPERIMENTAL

6,7-Dimethyl-4-formyl-6,7-borazarothieno[3,2-c]-pyridine (Ib). To a solution of 1.17 g (0.0041 mol) of 6,7-dimethyl-4-iodo-7,6-borazarothieno-[3,2-*c*]pyridine [1] in 150 ml of anhydrous ether cooled to −70 °C, 5.0 ml of 1.50 N (0.0075 mol) butyllithium in hexane diluted with 20 ml of anhydrous ether was added dropwise with stirring under nitrogen. After the addition was complete (10 min), the mixture was stirred for 10 min, and 0.68 g of *N,N*-dimethylformamide in 15 ml of anhydrous ether was added. The cooling bath was removed, and when the temperature had risen to −20 °C, the mixture was poured onto ice-water and acidified with 5 N hydrochloric acid. The ether phase was separated and the aqueous phase neutralized with solid sodium bicarbonate and extracted three times with ether. The combined ether phases were washed with water, dried over magnesium sulfate and evaporated. The solid residue was recrystallized from 60 % aqueous ethanol, yielding 0.59 g (76 %) of the title compound, m.p. 96.5–97.5 °C. NMR (CD_3COCD_3)$_2$: δ 9.82 (CHO), 8.35 and 8.13 (thioph.), 3.95 (NCH_3), 1.05 (BCH_3); J_{23} 4.8 Hz. [Found: C 49.91; H 4.72; B 5.61; N 14.53. Calc. for $C_8H_8BN_2OS$ (192.1): C 50.03; H 4.72; B 5.63; N 14.59.]

2,3-Dimethyl-5-ethyl-4-formyl-3,2-borazaro-pyridine (IIc). From 0.20 g (0.765 mmol) of 2,3-dimethyl-5-ethyl-4-iodo-3,2-borazaropyridine,[1] 2.0 ml of 1.42 N butyllithium and 2.5 g of *N,N*-dimethylformamide in the appropriate amounts of anhydrous ether, following the description given above, 73 mg (58 %) of the title compound was obtained as a liquid after distillation *in vacuo*. NMR ($CDCl_3$): δ 10.57 (CHO), 7.83 (H-6), 3.77 (NCH_3), 2.82 (CH_3), 1.22 (CH_3), 0.87 (BCH_3). [Found: C 58.49; H 7.88; B 6.47. Calc. for $C_8H_{13}BN_2O$ (164.0): C 58.59; H 7.99; B 6.59.]

4-Bromo-2,3-dimethyl-5-ethyl-6-formyl-3,2-bor-azaropyridine (IIe). From 1.20 g (0.0041 mol) of 4,6-dibromo-2,3-dimethyl-5-ethyl-3,2-borazaropyridine [1] in 60 ml of anhydrous ether, 7.0 ml of 1.50 N of butyllithium in hexane, diluted with 50 ml of dry ether and 3.0 g of anhydrous *N,N*-dimethylformamide in 50 ml of ether, 0.51 g (51 %) of the title compound, b.p. 75–76 °C/0.25 mmHg, was obtained following the procedure given above. Recrystallization from 60 % aqueous ethanol gave white needles, m.p. 68.5–69.5 °C. NMR ($CDCl_3$): δ 9.73 (CHO), 3.90 (NCH_3), 3.22 (CH_2), 1.13 (CH_3), 0.98 (BCH_3). [Found: C 39.71; H 5.05; B 4.57; Br 33.05; N 11.41. Calc. for $C_8H_{12}BBrN_2O$ (242.9): C 39.56; H 4.98; B 4.45; Br 32.89; N 11.53.]

4-Bromo-2,3-dimethyl-5-ethyl-3,2-borazaropyri-dine (IId). To a solution of 0.80 g (2.73 mmol) of 4,6-dibromo-2,3-dimethyl-5-ethyl-3,2-borazaropyridine [1] in 50 ml of anhydrous ether, cooled to −70 °C, 5.2 ml of 1.50 N butyllithium in hexane diluted with ether was added dropwise under nitrogen. After 10 min, 5 ml of methanol was added to the reaction mixture and the cooling-bath removed. When the temperature had risen to −20 °C, the reaction mixture was worked up as described above. Distillation *in vacuo* gave 175 mg (59 %) of the title compound, b.p. 104–106 °C/10 mmHg. NMR ($CDCl_3$): δ 7.70 (H-6), 3.73 (NCH_3), 2.68 (CH_2), 1.18 (CH_3), 0.85 (BCH_3). [Found: C 39.19; H 5.65; B 4.99; Br 37.23; N 13.00. Calc. for $C_7H_{12}BBrN_2$ (214.9): C 39.12; H 5.63; B 5.03; Br 37.18; N 13.04.]

6,7-Dimethyl-4-methoxy-7,6-borazarothieno-[3,2-c]pyridine (Id). A solution of 4.86 g (0.020 mol) of 4-bromo-6,7-dimethyl-7,6-borazarothieno[3,2-c]pyridine in 200 ml of 0.2 N sodium methoxide in methanol was stirred for 10 h. The solution was neutralized with dilute hydrochloric acid and extracted with ether. The solvent was evaporated and the residual oil purified by preparative TLC on silica gel using hexane-ether (4:1) as eluent. The band corresponding to the title compound was identified by GLC. In order to obtain good separation, the plate was dried and re-eluated twice. After recrystallization from 50 % aqueous ethanol, 0.58 g (15 %) of the title compound, m.p. 38.0–39.5 °C, was obtained. NMR ($CDCl_3$): δ 7.73 and 7.75 (thioph.), 3.97 (OCH_3), 3.67 (NCH_3), 0.88 (BCH_3); J_{23} 4.8 Hz. [Found: C 49.93; H 5.58; B 5.66; N 14.68. Calc. for $C_8H_{11}BN_2OS$ (194.0): C 49.51; H 5.71; B 5.57; N 14.43.]

GLC analyses were carried out on a Varian model 1400 gas chromatograph, NMR spectra were recorded on a Varian A-60 NMR spectrometer and mass spectra were recorded on an LKB A-9000 mass spectrometer. Elemental analyses were carried out by Dornis und Kolbe, Mikroanalytisches Laboratorium, Mülheim/Ruhr.

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