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INTRAMOLECULAR CYCLIZATION OF 2-(*o*-CARBORAN-1-YL) METHYLTHIO-3-CYANOPYRIDINES IN BASIC CONDITIONS

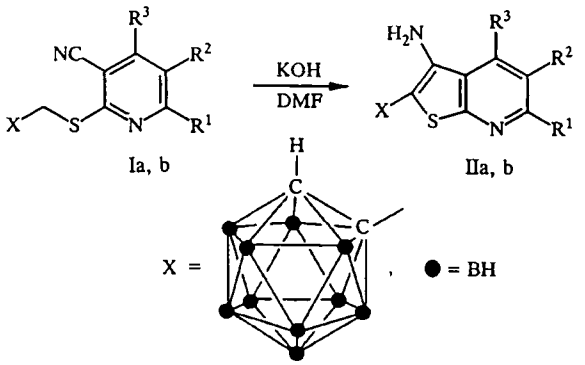
A. A. Semioshkin, V. A. Artemov, V. L. Ivanov, G. M. Ptashits, P. V. Petrovskii, A. M. Shestopalov, V. I. Bregadze, and V. P. Litvinov

Substituted 2-(o-carboran-1-yl)methylthio-3-cyanopyridines and -pyrimidines undergo Thorpe–Ziegler cyclization under the influence of KOH in DMF to give the corresponding thienopyridines and thienopyrimidines. The reaction is complicated by a side reaction in which the closo*-carborane nucleus is converted to a* nido*-system. The yield of thienopyridines containing a* closo*-carborane unit is increased by introduction of an acceptor substituent in the pyridine ring. Destruction of the* closo*-carborane nucleus is not observed with the pyrimidine derivatives. The structures of the series of new carborane-containing thienopyridines and pyrimidines was confirmed by spectroscopic methods.*

We have previously described nucleophilic substitution at the α-methylene group of 1-bromomethyl-*o*-carborane under the influence of 3-cyano-2(1H)-pyridinthiones to give 2-(*o*-carboran-1-yl)methylthio-3-cyanopyridines (I) [1]. It is known that 2-(Z-methylthio)3-cyanopyridines, in which Z is a π-electron acceptor group (COR, CN, COOR, etc.) readily undergo Thorpe–Ziegler cyclization to give thieno[2,3-*b*]pyridines [2]. The *o*-carboran-1-yl substituent has σ-electron acceptor properties [3], readily losing a proton from the methylene group in compound I. Thorpe–Ziegler cyclization with the assistance of a σ-acceptor has not been described in the literature.

The current work is concerned with a study of the behavior of 2-(*o*-carboran-1-yl)methylthio-3-cyanopyridines Ia-c under the conditions of the Thorpe–Ziegler cyclization and the synthesis of carboranyl substituted thienylpyridines by this method. Characteristics of the compounds synthesized are given in Tables 1 and 2.

Treatment of compounds Ia, b with aqueous KOH in DMF solution gave the substituted 3-amino-2-(*o*-carboran-1-yl)thieno[2,3-*b*]pyridines IIa, b:



Ia, b IIa, b

I, II a $R^1 = NH_2$, $R^2 = CN$, $R^3 = H$; b $R^1 = R^3 = Ph$, $R^2 = H$; c $R^1 = R^3 = Me$, $R^2 = H$

A. N. Nesmeyanov Institute of Elementoorganic Chemistry, Russian Academy of Sciences, Moscow 117813. N. D. Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 790-793, June, 1998. Original article submitted September 22, 1997.

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Molecular formula	(Found, %) / (Calculated, %)			mp, °C	Yield, %
		C	H	N		
IIa	$C_{10}H_{16}B_{10}N_4S$	35,48 36,13	4,76 4,85	16,08 16,85	233	78
IIb	$C_{21}H_{24}B_{10}N_2S$	55,75 56,60	5,79 5,65	6,03 6,29	114	24
III	$C_{11}H_{21}B_9N_2S$	40,82 42,53	6,66 6,81	8,56 9,02	270	90
V	$C_9H_{18}B_{10}N_4S_2$	29,16 30,49	4,94 5,12	15,32 15,80	Decomp.	85
VI	$C_9H_{18}B_{10}N_4S_2$	29,47 30,49	5,16 5,12	15,14 15,80	205...213	80

TABLE 2. Spectroscopic Characteristics of the Synthesized Compounds

Compound	^{1}H NMR spectrum, δ, ppm*	^{11}B NMR spectrum, δ, ppm†	IR spectrum, ν, cm^{-1}	Mass spectrum (*m/e*)
IIa	8,57 (1H, s, 4-H); 7,27 (2H, s, 6-NH_2); 5,97 (2H, s, 3-NH_2); 5,43 (1H, br. s, CH-carb.); 3,10...1,60 (10H, br. m, BH)	-3,2 (1B); -2,7 (1B); -10,1 (6B); -12,3 (2B)	3500, 3400, 3240 (NH), 2630 (BH), 2240 (CN), 1670	332
IIb	8,17 (2H, m, *o*-H in 6-Ph); 7,78 (1H, s, 5-H); 7,60...7,40 (8H, m and *p*-H in 6-Ph, 4-Ph); 5,96 (2H, br. s, NH_2); 4,91 (1H, br. s CH-carb.); 3,10...1,00 (10H, m, BH)	-3,6 (2B, J_{BH} = 141,2); -9,9(2B, J_{BH} = 151,7); -13,8 (6B, J_{BH} = 163,9)	3420, 3260 (NH), 2600 (BH), 1670	444
III	7,86 (1H, s, 5-H); 7,16 (2H, br. s, NH_2); 2,65 (3H, s, 4-CH_3); 2,52 (3H, s 6-CH_3); 3,00...1,00 (11H, br. m, BH); -3,00 (1H, br. d, J = 57, BHB)			
V	7,22 (2H, br. s, NH_2); 4,72 (1H, br. s, CH-carb.); 4,16 (2H, s, SCH_2); 2,42 (3H, s, 5-CH_3); 3,00...1,00 (10H, br. m, BH)	-3,5 (1B); -6,0 (1B); -10,1 (4B); -11,4 (2B); -13,3 (2B)	3520, 3320, 3230 (NH), 2610 (BH), 2220 (CN), 1620	354
VI	7,09 (2H, br. s, 6-NH_2); 5,48 (1H, br. s, CH-carb.); 5,38 (2H, br. s, 3-NH_2); 2,62 (3H, s, 5-CH_3); 3,00...1,00 (10H, br. m, BH)	-3,4 (1B); -6,2 (1B); -10,1 (4B); -11,6 (2B); -13,3 (2B)	3510, 3380, 3320, 3200 (NH), 2640 (BH), 1640	354

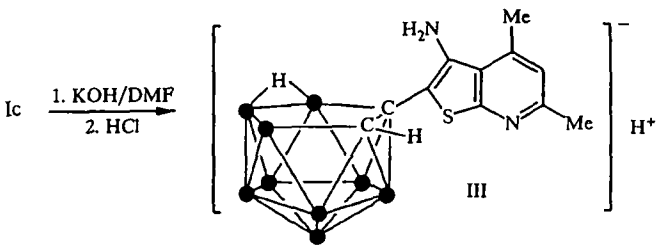
*Spectra of compounds IIa, V, and VI were recorded in DMSO-D_6, those of IIb and III in CD_3CN.

†J_{BH} was not resolved for compounds IIa, V, and VI.

The presence of the thienopyridine system in compounds II was established from ^{1}H NMR and IR spectra. ^{11}B NMR and mass spectroscopy confirmed unambiguously the *closo*-structure of the carborane unit. The yield of *closo*-compounds of type II was inversely related to the reaction time for compound I (TLC) and depended on the substituent on the latter. For example, the amino substituted (carboranyl)methylthiocyanopyridine Ia disappeared from the reaction mixture in 2-3 h (yield of product IIa reached 78%), whereas the diphenyl substituted analog Ib was completely converted in 12 h under the same conditions (yield of the corresponding *closo*-compound IIb was only 24%). Finally the dimethyl substituted analog Ic did not give the expected product IIc on interaction with aqueous KOH in DMF for 15 h, but was almost completely converted into the *nido*-derivative III, the yield of which reached 90%.

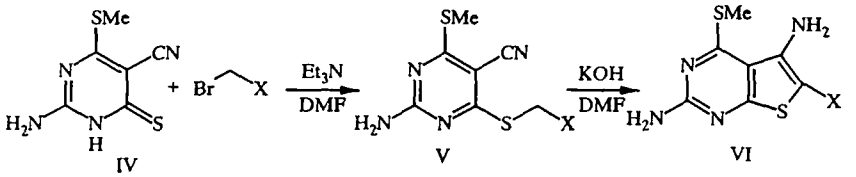
The ^{1}H NMR spectrum of compound III has signals for protons of the methyl groups (2.65 and 2.52 ppm), the pyridine ring (7.86 ppm) and the amino group (7.16 ppm). Signals of the carboranyl CH proton were not resolved, probably because it is hidden by the general multiplet of the BH groups from 3.0-1.0 ppm. The signal of the bridging hydrogen atom (B−H−B)

appears as a characteristic broad doublet at ~3.00 ppm. We suggest that compound has a zwitterion structure, but this suggestion requires proof.



In all probability when the cyclization is slow, as it is in the case of compounds IIb, c, then the basic direction of the reaction becomes the slow decomposition of the *closo*-nucleus to the *nido*-system. When an acceptor substituent is introduced into the pyridine ring the Thorpe–Ziegler cyclization is accelerated and the *closo*-nucleus does not have time to undergo decomposition.

Our proposal was confirmed by the preparation in high yield of the thienopyrimidine (VI) from 2-amino-4-methylthio-6-(*o*-carboran-1-yl)methylthio-3-cyanopyrimidine (V) (which was itself prepared from bromomethyl-*o*-carborane and the pyrimidinthione (IV)) on treatment with alkali:



Thus we have shown that it is possible in principle for the Thorpe–Ziegler cyclization to occur under the influence of such σ-acceptor substituents as *o*-carboran-1-yl.

EXPERIMENTAL

IR Spectra were recorded on KBr disks with a Specord-80 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with a Bruker AMX-400 machine at 400 and 104 MHz respectively. ^{11}B NMR spectra were recorded with a Bruker AC-200 machine ($BF_3 \cdot Et_2O$ standard). Mass spectra were obtained with a Kratos MS-890 (70 eV) instrument. The quoted microanalyses were obtained with Perkin-Elmer C, H, N analyzer. Melting points were determined in a block with open capillaries. TLC analyses were carried out on Kieselgel 60 F_{254} strips with 6:1 hexane–ethyl acetate as eluant and $PdCl_2$ as developer. The starting materials Ia to Ic were prepared by a previously published method.

3,6-Diamino-2-(*o*-carboran-1-yl)-5-cyanothieno[2,3-*b*]pyridine (IIa). KOH (10% aqueous solution, 0.17 ml, 0.3 mmole) was added to a solution of compound Ia (100 mg, 0.3 mmole) in DMF (5 ml). The mixture was kept at room temperature for 2.5 h. The product was precipitated with an excess of water, filtered off, washed successively with water, ethanol, and hexane, and air dried. ^{13}C NMR Spectrum (DMSO-D_6): 161.48 and 159.31 ($C_{(6)}$, $C_{(7a)}$); 139.19 ($C_{(3)}$); 137.41 ($C_{(4)}$); 118.11 and 117.02 ($C_{(2)}$, CN); 91.76 and 88.34 ($C_{(3a)}$, $C_{(5)}$); 75.28 (C-carb); 67.21 (CH-carb).

3-Amino-2-(*o*-carboran-1-yl)-4,6-diphenylthieno[2,3-*b*]pyridine (IIb) was made analogously to product IIa from pyridine Ib (100 mg, 0.23 mmole) and 10% aqueous KOH (0.13 ml). Reaction time 12 h.

***nido*-(3-Amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)carborane (III).** KOH (10% aqueous solution, 0.56 ml, 1 mmole) was added to pyridine Ic (320 mg, 1 mmole) in DMF (10 ml) and the mixture was kept at room temperature for 15 h. Water (5 ml) and concentrated HCl solution were added to the reaction mixture to bring it to pH 1. The precipitate was filtered off, washed successively with water, ethanol, and hexane, and air dried.

2-Amino-6-(*o*-carboran-1-yl)methylthio-4-methylthio-5-cyanopyrimidine (V). Triethylamine (0.2 ml, 1.7 mmole) and bromomethyl-*o*-carborane (270 mg, 1.1 mmole) were added to a solution of pyrimidinthione IV (220 mg, 1.1 mmole) in DMF (5 ml) and the reaction was kept at 180°C for 4 h. After cooling, the product was precipitated with excess water, filtered, washed successively with water, ethanol, and hexane, and air dried.

3,6-Diamino-2-(*o*-carboran-1-yl)-4-methylthiothieno[2,3-*b*]pyrimidine (VI). Compound VI was obtained analogously to product IIa from pyrimidine V (100 mg, 0.3 mmole) and 10% aqueous KOH (0.15 ml). Reaction time 2 h.

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