Chemistry of Heterocyclic Compounds, Vol. 38, No. 5, 2002

SYNTHESIS OF N,N'-ALKYLATED TETRAHYDROQUINOXALINES BY THE REACTION OF 4-BROMO-5-NITROPHTHALO-NITRILE WITH SECONDARY DIAMINES

I. G. Abramov, A. V. Smirnov, M. B. Abramova, S. A. Ivanovskii, and M. S. Belysheva

The reaction of 4-bromo-5-nitrophthalonitrile with aliphatic secondary diamines to give dicyano tetrahydroquinoxalines alkylated on the nitrogen atoms has been investigated for the first time. The latter can be used to prepare imides, phthalocyanines, hexazocyclanes, and other compounds containing isoindoline fragments.

Keywords: bifunctional nucleophiles, 4-bromo-5-nitrophthalonitrile, tetrahydroquinoxaline, nucleophilic substitution.

The reaction of haloalkanes and activated nitrohalobenzenes with secondary aliphatic amines has been described in the literature and is widely used practically. At the same time, the reaction with secondary amines leading to sequential nucleophilic substitution of the halo and nitro groups in a single benzene ring is almost unknown. Similar reactions, taking place under rather mild conditions as discussed in this work, become possible with the use of strongly activated nitroaromatic substrates.

Such a substance is 4-bromo-5-nitrophthalonitrile (BNPN), in which the carbon bearing the bromine atom is activated by an *ortho*-nitro group. Two cyano groups add to the accepting effect of the nitro group on the indicated carbon atom and simultaneously activate the carbon atom bearing the nitro group. As a result, the S_NAr reactions with various O-, N-, and S-nucleophiles primarily substitute the highly mobile bromine atom [1-3]. When the reaction is carried out with bifunctional nucleophiles which have *ortho*-placed reaction centers there are formed the corresponding dicyano containing dibenzo[*b,e*][1,4]dioxin, 10H-phenoxazine etc. [2].

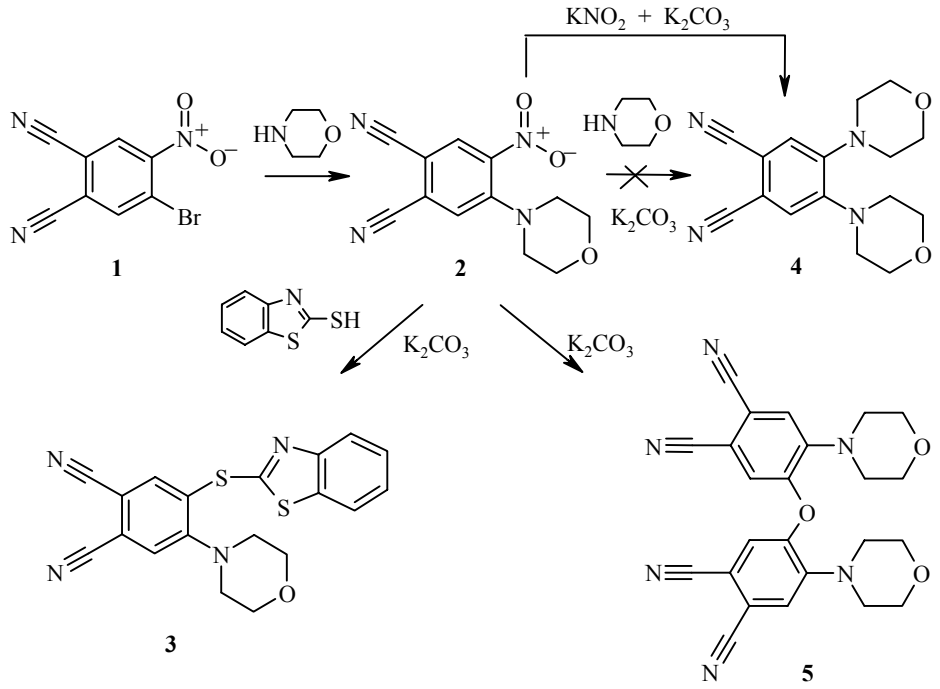
When refluxed in ethanol in the presence of triethylamine, compound **1** reacts equally readily with primary aromatic, aliphatic and secondary aliphatic amines to give the corresponding arylamines, e.g. product **2** (Scheme 1). Triethylamine acts as acceptor of the hydrogen bromide evolved. In its absence, the reaction uses up half of the starting reagent and the remainder is left as the corresponding amine hydrobromide.

The remaining nitro group can be substituted only by reactive nucleophiles under more rigid conditions. Thus heating compound **2** with 1,3-benzothiazole-2-thiol in DMF in the presence of K_2CO_3 gives 4-(1,3-benzothiazol-2-ylthio)-5-morpholinophthalonitrile (**3**). Primary and secondary amines are not active under these conditions due to the strongly deactivating effect of the morpholine fragment in compound **2**.

Yaroslavl State Technical University, Yaroslavl 150023, Russia; e-mail: abramov.orgchem@staff.ystu.yar.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 660-664, May, 2002. Original article submitted February 21, 2001.

 0009-3122/02/3805-0576$27.00

Scheme 1



Heating the phthalonitrile **1** in DMF with a twofold molar amount of secondary aliphatic or cycloaliphatic amine with the aim of sequential substitution of the bromine atom and the nitro group in the presence of potassium carbonate only bromine atom substitution occurred to give compound **2**. Other substitution products, e.g. the phthalonitrile **4**, were not fixed.

The disubstitution product **4** (in 12% yield) was unexpectedly obtained during attempts to substitute the remaining nitro group in compound **2** by a hydroxy group *via* the participation of nitrite ion [4]. As of now we have not been able to explain how, in the presence of a mixture of KNO_2 and K_2CO_3, there occurs the substitution of the nitro group for the morpholine fragment. In the absence of morpholine, and when carrying out the indicated reaction with potassium carbonate alone, the symmetrically substituted diphenyloxide **5** is formed and, in the presence of just potassium nitrite, a tarry product is formed which has not been identified.

The given examples clearly illustrate the difference in mobility of the bromine and nitro group in the 4-bromo-5-nitrophthalonitrile molecule when reacting with N-nucleophiles. At the same time, heating equimolar amounts of BNPN and secondary aliphatic diamines (alkylated N,N'-ethylenediamines) **6a-d** in DMF in the presence of K_2CO_3 gives the previously unreported 1,4-dibenzyl-1,2,3,4-tetrahydro-6,7-quinoxalinedicarbonitriles (**8a-d**) (Scheme 2).

The intermolecular nucleophilic substitution reaction of the halogen atom starts with attack by one of the amino groups of the nucleophile **6a-d** on the carbon atom of compound **1** which directly bears the bromine atom. The intermediate formed **7a-d** contains simultaneously a nitro group and a nucleophilic center quite active towards further substitution. This second nucleophile then takes part in an intramolecular substitution reaction of the nitro group situated in the same molecule and this leads to the ring substitution and to the products **8a-d**.

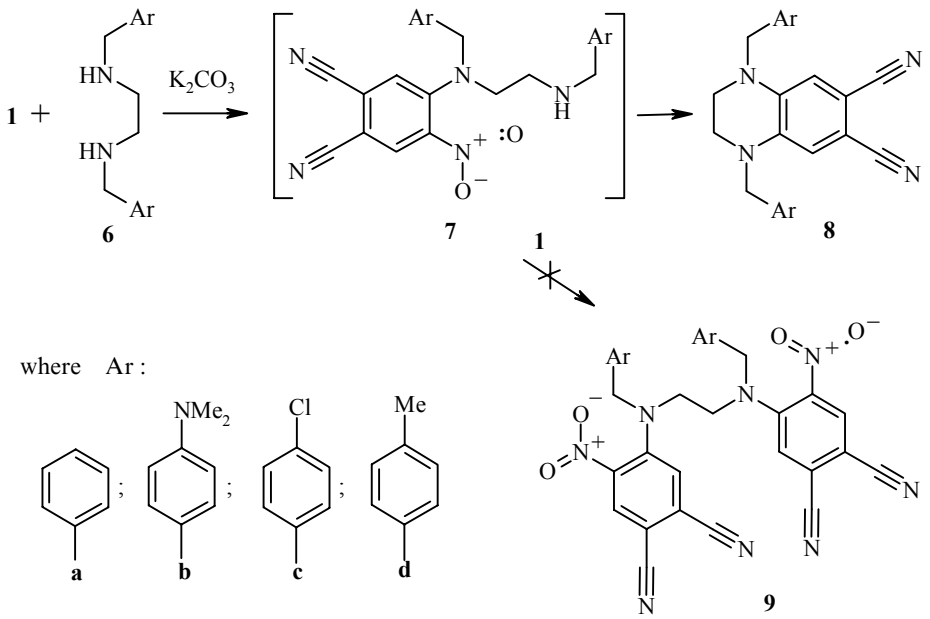
It did not prove possible to prepare the tetracarbonitrile **9a** by carrying out the indicated reaction with a twofold molar excess of the BNPN **1**. In this case compound **8a** was obtained from the reaction mixture in 8% yield.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)	Yield, %
		C	H	N				
2	$C_{12}H_{10}N_4O_3$	55.79 / 55.81	3.79 / 3.90	21.61 / 21.70	188-190	2220 (–CN), 1350 (NO_2), 1115 (C–O–C)	8.45 (1H, s); 8.10 (1H, s); 3.75-3.66 (4H, m); 3.32-3.24 (4H, m)	94.1
3	$C_{19}H_{14}N_4OS_2$*	60.13 / 60.30	3.74 / 3.73	14.81 / 14.80	> 300	2230 (–CN), 1115 (C–O–C)	8.30 (1H, s); 8.00 (1H, dd, *J* = 8.09, 2.10); 7.92 (1H, dd, *J* = 8.00, 1.27); 7.85 (1H, s); 7.55 (td, *J* = 8.00, 7.37, 1.20); 7.40 (td, *J* = 8.09, 7.37, 1.27); 3.62-3.55 (4H, m); 3.27-3.20 (4H, m)	68.4
4	$C_{16}H_{18}N_4O_2$	64.22 / 64.41	6.09 / 6.08	18.70 / 18.78	184-186	2235 (–CN), 1120 (C–O–C)	7.45 (2H, s); 3.76-3.66 (8H, m); 3.25-3.16 (8H, m)	28.7
5	$C_{24}H_{20}N_6O_3$	65.30 / 65.45	4.59 / 4.58	19.17 / 19.08	275-277	2235 (–CN), 1260 (C–O–C), 1120 (C–O–C)	7.75 (2H, s); 7.70 (2H, s); 3.60-3.52 (8H, m); 3.26-3.18 (8H, m)	82.3
8a	$C_{24}H_{20}N_4$	78.85 / 79.09	5.54 / 5.53	15.36 / 15.37	172-174	2230 (–CN)	7.40-7.35 (4H, m); 7.30-7.25 (6H, m); 6.90 (2H, s); 4.65 (4H, s); 3.55 (4H, s)	79.7
8b	$C_{28}H_{30}N_6$	74.43 / 74.64	6.72 / 6.71	18.59 / 18.65	222-224	2230 (–CN)	7.10 (4H, dd, *J* = 8.43, 2.11); 6.90 (2H, s); 6.70 (4H, dd, *J* = 8.43, 2.30); 4.50 (4H, s); 3.50 (4H, s); 2.90 (12H, s)	86.2
8c	$C_{24}H_{18}Cl_2N_4$	66.34 / 66.52	4.20 / 4.19	12.99 / 12.93	198-200	2230 (–CN)	7.30 (4H, dd, *J* = 8.40, 2.44); 7.10 (4H, dd, *J* = 8.40, 2.11); 6.90 (2H, s); 4.68 (4H, s); 3.60 (4H, s)	81.5
8d	$C_{26}H_{24}N_4$	79.33 / 79.56	6.16 / 6.16	14.29 / 14.27	189-191	2230 (–CN)	7.20 (4H, dd, *J* = 8.05, 2.21); 6.90 (2H, s); 6.78 (4H, dd, *J* = 8.05, 2.11); 4.55 (4H, s); 3.53 (4H, s); 2.25 (6H, s)	78.8

* Found: S 16.97%; calculated: S 16.94%.

Scheme 2



In the reaction under discussion, the use of the less active 4,5-dichlorophthalonitrile in place of the phthalonitrile **1** gave a mixture of oily products which could also not be identified. The basicity of the starting diamine must be quite high since the use of phenyl, furyl, or pyridyl substituents in place of the benzyl substituent in the nucleophiles **6** gave a negative result.

The synthesized dicyano tetrahydroquinoxalines, alkylated at the nitrogen atoms, were put through further functionalization using known methods and were used for the synthesis of phthalocyanines, hexazocyclanes, and other compounds which contained imide, isoindoline, and tetrazole fragments. The prepared nitrile derivatives **2-5** and **8a-d** are crystalline materials, the structure of which was confirmed from their spectroscopic parameters (see Table 1).

Thus, in the IR spectra of these compounds, there are characteristic absorption bands for the stretching vibrations of the C≡N bond at 2230, ether at 1260, and thioether at 650 cm^{-1} and the bands typical of NO_2 (1560 and 1340 cm^{-1}) and NH (3130-3300 cm^{-1}) were absent [5]. The ^1H NMR spectra showed the presence of signals for the aromatic and the aliphatic protons.

EXPERIMENTAL

^1H NMR spectra were obtained on a Bruker AM-300 instrument for 5% solutions of the samples in DMSO-d_6 with TMS as internal standard. IR spectra were recorded on an IR-75 instrument (Czechoslovak Socialist Republic) for suspensions in vaseline oil.

4-Bromo-5-nitrophthalonitrile (1) was prepared according to the method reported in [1].

4-Morpholino-5-nitrophthalonitrile (2). BNPN (2.52 g, 0.01 mol), morpholine (0.87 g, 0.01 mol), triethylamine (1.01 g, 0.01 mol), and 2-propanol (50 ml) were placed in a flask fitted with a reflux condenser. The reaction mixture was refluxed for 2 h, cooled, and the precipitated, orange colored precipitate was filtered off. Yield 2.43 g.

4-(1,3-Benzothiazol-2-ylthio)-5-morpholinophthalonitrile (3). Compound **2** (2.58 g. 0.01 mol), anhydrous K_2CO_3 (1.38 g, 0.01 mol), and 2-mercaptobenzothiazole (1.67 g, 0.01 mol) were added successively, with stirring, to DMF (30 ml). The mixture obtained was stirred vigorously at 130-140°C for 2 h. After cooling to room temperature, the reaction mass was poured into water (100 ml) and the precipitate formed was filtered off, washed with water (50 ml), and crystallized from DMF to give compound **3** as a yellow, crystalline powder (2.59 g).

1,4-Dibenzyl-1,2,3,4-tetrahydro-6,7-quinoxalinedicarbonitrile (8a). N,N'-Dibenyzyl-1,2-ethanediamine (2.41 g, 0.01 mol), anhydrous K_2CO_3 (2.8 g, 0.02 mol), and compound **1** (2.52 g, 0.01 mol) were added successively, with stirring, to DMF (30 ml). The mixture obtained was stirred vigorously at 90-100°C for 2 h. After cooling to room temperature, the reaction mass was poured into water (100 ml) and the precipitate formed was filtered off, washed with water (50 ml), and crystallized from DMF to give compound **8a** as a light brown, crystalline powder (2.87 g).

The tetrahydroquinoxalines **8b-d** were prepared similarly.

REFERENCES

1. I. G. Abramov, M. V. Dorogov, S. A. Ivanovskii, A. V. Smirnov, and M. B. Abramova, *Mendeleev Commun.*, 78 (2000).
2. I. G. Abramov, A. V. Smirnov, M. B. Abramova, S. A. Ivanonskii, and V. V. Plakhtinskii, *Khim. Geterotsikl. Soedin.*, 1219 (2000).
3. I. G. Abramov, V. V. Plakhtinskii, M. B. Abramova, and A. V. Smirnov, *Izv. vuzov. Ser. khim. i khim. tekhnol.*, 120 (2000).
4. V. V. Plakhtinskii, V. A. Ustinov, and G. S. Mironov, *Izv. vuzov. Ser. khim. i khim. tekhnol.*, 4 (1985).
5. A. Gordon and R. Ford, *Sputnik Khimika* [Russian translation], Mir, Moscow (1976), 541 p.