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SYNTHESIS OF SUBSTITUTED DIBENZOXAZEPINES AND DIBENZTHIAZEPINE USING OF 4-BROMO-5-NITROPHTHALONITRILE

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Abstract - Proposed a method of synthesis of new cyano containing compounds of oxazepine and thiazepine series based on activated aromatic nucleophilic substitution reaction of bromine atom and nitro group in 4-bromo-5-nitrophthalonitrile by various bifunctional *O-, N-, S*-nucleophiles.

There is an obvious interest to compounds of oxazepine series. But synthetic methods of these heterocyclic systems have certain limitations that do not permit to expand area of theirs derivatives. In this article we discuss new applications of known reactions of activated aromatic nucleophilic substitution which can lead to seven-atom cycle formation.

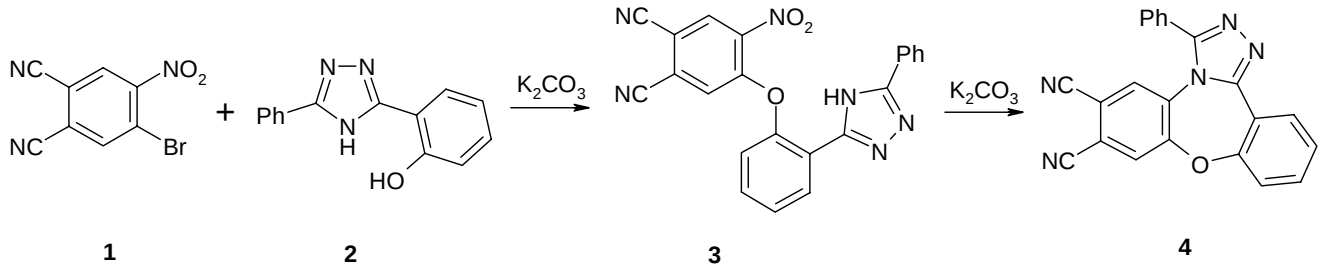
Interaction of activated halogenonitrobenzenes with secondary aliphatic amines and triazoles, phenols and thiophenols in the presence of various bases was widely discussed in literature and used in practice.[1-5]

4-Bromo-5-nitrophthalonitrile (**1**) is special case among high activated nitroaromatic substrates. It has carbon atom connected with bromine atom activated by *orto*-nitro group. Both cyano groups increases acceptor influence of nitro group, simultaneously activating atom connected with nitro group. As a result, firstly the active bromine atom is being substituted in S_NAr reactions with various *O-, N-, S*-nucleophiles at room temperature.[2-5] As was shown in cited works in the most monosubstituted products the nitro group can be also substituted by nucleophils though it requires more hard conditions. Such reaction of **1** with bifunctional nucleophils with reactive centers in proximity which permits formation of cyclic fragments, enabled us to synthesize wide range of 6-, 7-, 8-member heterocyclic compounds of various classes:[5-7] dioxine, oxazine, quinoxaline, phenoxathiine, thianthrene, dioxocine and dioxepine which can be used, after corresponding functionalization, to synthesize hexazocyclanes,[8] phthalocyanines[9] and a number of other compounds with anhydride, imide and isoindole fragments.

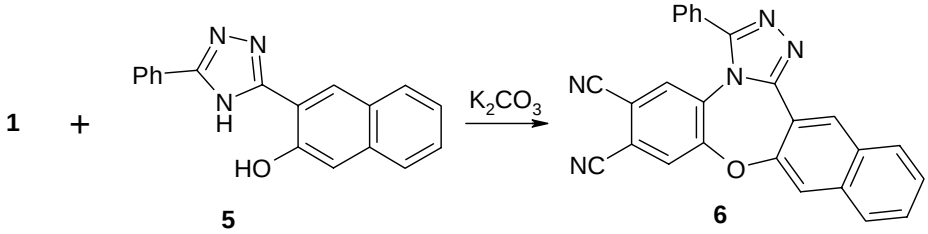
For the purpose of synthesis of new cyanic compounds of oxazepine series we worked out several simple methods of synthesis of bifunctional nucleophils. The basis of the first is reaction of condensation of different benzonitriles with hydrazides of salicylic acids.[10] Another one is based on reduction of corresponding azomethines. The main characteristic of newly synthesized compounds is that they have two active nucleophilic centers (*O*- and *N*-), capable (after deprotonization) to undergo reaction of nucleophilic substitution with formation of oxazepine cyclic system.

Taking into account results of our previous investigations[4] we believe that 2-(5-phenyl-4*H*-1,2,4-triazol-3-yl)phenol (**2**) in the presence of potassium carbonate undergoes deprotonization yielding *in situ* corresponding phenoxide. This intermediate reacting in heterophase conditions with **1**, gives intermediate (**3**) with active enough *N*-nucleophilic center (Scheme 1). The last endues intramolecular substitution of nitro group in the presence of K_2CO_3 which leads to the cycle closing and formation of 3-phenyldibenzo[*b,f*][1,2,4]triazolo[4,3-*d*][1,4]oxazepine-6,7-dicarbonitrile (**4**).

Analogous reaction (Scheme 2), which takes place under same conditions between **1** and 3-(5-phenyl-4*H*-1,2,4-triazol-3-yl)-2-naphthol (**5**), gives 3-phenylnaphtho[2,3-*b*][1,2,4]triazolo[3,4-*d*][1,5]benzoxazepine-6,7-dicarbonitrile (**6**).

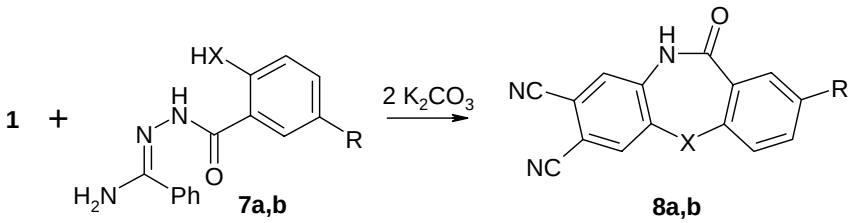


Scheme 1



Scheme 2

High reactivity of **1** in reactions of nucleophilic substitution enabled us to synthesize oxazepine and thiazepine derivatives having free (nonsubstituted) *N* atom. Using hydrazonamide of salicylic and thiosalicylic acids as reactants we get products with atoms *O* and *S* in heterocycls. And in both cases the final stage of 7-membered ring formation was accompanied by benzamidine fragment elimination. So the heating of equimolecular quantities of **1** and **7a,b** in DMF in the presence of potassium carbonate (Scheme 3) gave with a good yield 11-oxo-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-7,8-dicarbonitrile (**8a**) and corresponding bromine derivative (**8b**):



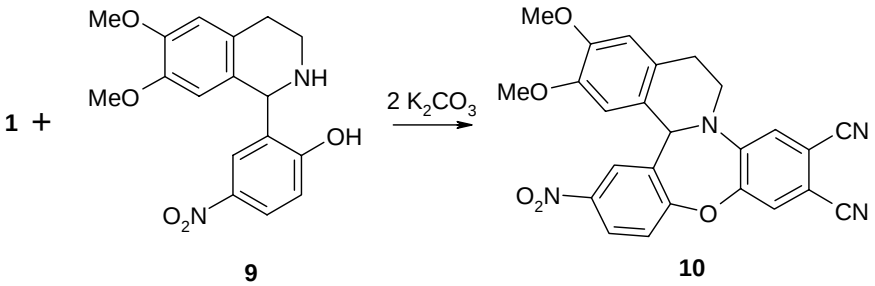
a: X = S, R = H; **b:** X = O, R = Br

Scheme 3

Oxazepine cycle can be easily formed under the same conditions with bifunctional nucleophiles of another type, e.g. 2-(6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolinyl)-4-nitrophenol (**9**). Unlike compound (**2**) with aromatic properties, the cycloaliphatic secondary amine (**9**) does not require deprotonic agent.[4] Any acceptor of HBr is good enough, in our case potassium carbonate was used. Besides, being taken in double quantity, K_2CO_3 deprotonizes phenol and creates another, *O*-nucleophilic center – phenoxide. Mechanism of formation of oxazepine cycle is analogous to that specified above. The only difference is that in the first one the bromine atom is substituted by more active *N*-nucleophile. The following intramolecular substitution of nitro group ends formation of oxazepine cycle (Scheme 4) that gives 2,3-dimethoxy-15,16-dihydro-4b*H*-dibenzo[2,3:6,7][1,4]oxazepino[5,4-*a*]isoquinoline-11,12-dicarbonitrile (**10**).

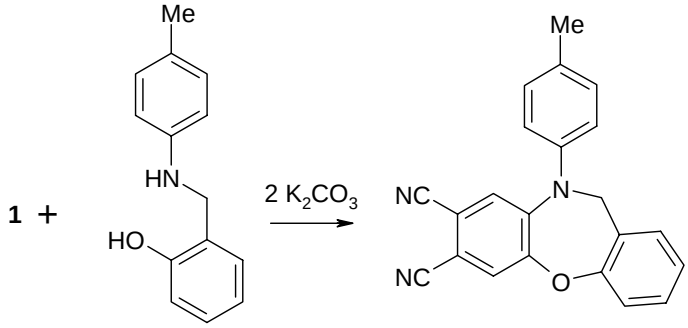
Similar but simpler oxazepin heterocyclic system is formed under the same conditions as a result of interaction of **1** with 2-(4-toluidinomethyl)phenol (**11**) which has less reactive *N*-nucleophilic center. In this case (scheme 5) the bromine atom of **1** is substituted by phenoxy ion formed *in situ*, following

intramolecular substitution finishing formation of 7-ring of 10-phenyl-10,11-dihydrodibenzo[*b*,*f*][1,4]-oxazepine-7,8-dicarbonitrile (**12**).



9 **10**

Scheme 4



11 **12**

Scheme 5

EXPERIMENTAL

Elemental and ^{1}H NMR analyses were measured by Organic Chemistry Institute of Russian Academy of Science. The ^{1}H NMR spectra were recorded at 300 MHz in DMSO-d_6 containing Me_4Si as an internal standard. Melting points are uncorrected.

Typical procedure for the preparation of compounds (4, 6, 8a, 8b, 10, 12)
To 30 mL of DMF 2.37 g (0.01 mol) of **2**, 2.80 g (0.02 mol) of K_2CO_3 and 2.52 g (0.01 mol) of 4-bromo-5-nitrophthalonitrile (**1**) were added. The resulting mixture was intensively stirred at 90 ^{0}C for 2 h. After cooling to rt, the reaction mixture was added to 100 mL of water; the precipitate formed was filtered off, washed with 50 mL of water and crystallised from DMF.

4: Yield 79%, mp>300 ^{0}C, Anal. Calcd for $C_{22}H_{11}N_5O$: C, 73.12; H, 3.07; N, 19.38; Found C, 72.90; H, 3.06; N, 19.42. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.57 (s, 1H), 8.45 (s, 1H), 8.21 (m, 2H), 8.11 (d, 1H, J=8.3 Hz), 7.70 (t, 1H, J=8.1 Hz), 7.52 (m, 5H).
6: Yield 69%, mp>300 ^{0}C, Anal. Calcd for $C_{26}H_{13}N_5O$: C, 75.90; H, 3.19; N, 17.02; Found C, 75.70; H, 3.20; N, 16.97; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.75 (s, 1H), 8.60 (d, 1H, J=8 Hz), 7.49 (d, 1H, J=8.1 Hz), 7.27 (s, 1H), 8.15 (d,1H, J=8 Hz), 8.08 (d, 1H, J=8.2 Hz), 8.00 (d, 1H, J=8.2 Hz), 7.60 (m, 5H).
8a: Yield 61%, mp>300 ^{0}C, Anal. Calcd for $C_{15}H_6N_3O_2Br$: C, 52.97; H, 1.78; N, 12.35; Found C, 52.83; H, 1.78; N, 12.40. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.20 (s, 1H), 8.20 (s, 1H), 7.91 (s, 1H), 7.84 (d, 1H, J=7.9 Hz), 7.71 (s, 1H), 7.35 (d, 1H, J=8 Hz).

8b: Yield 56%, mp>300 ^{0}C, Anal. Calcd for $C_{15}H_7N_3OS$: C, 64.97; H, 2.54; N, 15.15; S, 11.56; Found C, 64.81; H, 2.55; N, 15.11; S, 11.58. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.15 (s, 1H), 8.30 (s, 1H), 7.78 (s, 1H), 7.70 (d, 1H, J=8.2 Hz), 7.50 (m, 3H).
10: Yield 84%, mp 253-255 ^{0}C, Anal. Calcd for $C_{25}H_{18}N_4O_5$: C, 66.07; H, 3.99; N, 12.33; Found C, 65.93; H, 4.00; N, 12.38. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.20 (d, 1H, J=8.1 Hz), 7.80 (s, 1H), 7.62 (s, 1H), 7.50 (d, 1H, J=8.0 Hz), 7.25 (s, 1H), 6.90 (s, 1H), 6.70 (s, 1H), 6.62 (s, 1H), 3.90 (s, 3H), 3.73 (s, 3H), 3.49 (m, 1H), 3.40 (m,1H), 3.05 (m,1H), 2.85 (m, 1H).
12: Yield 72%, mp 218-221 ^{0}C, Anal. Calcd for $C_{22}H_{15}N_3O$: C, 78.32; H, 4.48; N, 12.45; Found C, 78.14; H, 4.49; N, 12.48. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.65 (s, 1H), 7.35 (t, 1H, J=7.9 Hz), 7.25 (d, 3H, J=8.3 Hz), 7.15 (m, 2H), 7.03 (d, 2H, J=8.1 Hz), 6.55 (s, 1H), 4.95 (s, 2H), 2.40 (s, 3H).

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