Synthesis of 3-phenylbenzo[*c*]isoxazoles by thermocyclization of 2-azidobenzophenones

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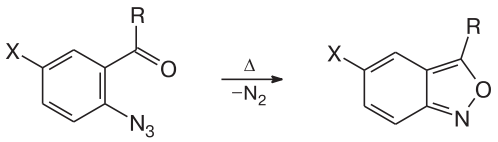
3-Phenylbenzo[*c*]isoxazoles were synthesized by non-catalytic thermolysis of 2-azidobenzophenones in dry xylene with quantitative yields. The trace content of water in solvents reduces the yields of the reaction products. 2-Azidobenzoic acid esters are stable under the indicated conditions.

Key words: 3-phenylbenzo[*c*]isoxazole, 2-azidobenzophenone, cyclization, thermolysis.

The interest in searching for new and optimizing known methods for synthesizing benzo[*c*]isoxazoles is determined by their high biological activity[1—5] and the possibility of using 1,4-benzodiazepines, quinolines, quinazolines and other heterocyclic compounds[6—10] as the starting material.

To access benzo[*c*]isoxazoles, three main strategies were implemented, aimed at the annulation of the isoxazole cycle at the benzene ring with the closure of C—O and N—O bonds separately or simultaneously.[11—17] Synthesis of 3-substituted benzo[*c*]isoxazoles with the formation of the N—O bond was first realized during the thermolysis of 2-azidobenzophenone **1a** and other 2-azidoaryl ketones in decalin with yields of about 50% (Scheme 1).[18] Later, catalysis with iron(II) bromide made it possible to increase the yields of benzo[*c*]isoxazoles to 99%, while the duration of the synthesis increased to 16 hours.[19] Therefore, optimizing the heterocyclization of 2-azidoaryl ketones over time while maintaining the yield and cost of the process is an important task.

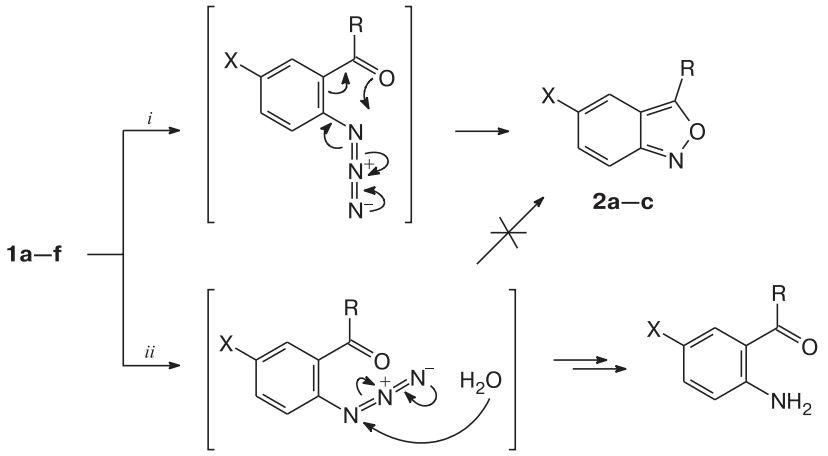
Scheme 1



1a—f **2a—c**

1, **2**	X	R	**1**	X	R
a	H	Ph	**d**	H	H
b	Br	Ph	**e**	H	OMe
c	I	Ph	**f**	H	OPr^i

Scheme 2



Reagents and conditions: *i*. 135 °C, 1 h, *o*-xylene, 98—99%; *ii*. 135 °C, 1 h, *o*-xylene—H_2O.

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Benzo[*c*]isoxazoles were obtained in a series of solvents with a change in temperature and duration of heterocyclization in the absence of catalysts. We have found that during thermolysis of 2-azidobenzophenones **1a—c**, benzo[*c*]isoxazoles **2a—c** are formed with quantitative yields in *o*-, *m*-, *p*-xylenes (Scheme 2). A decrease in the product yield was observed when changing the solvent: toluene (70%), benzene (50%), DMF (30%). The yields of compounds **2a—c** were significantly lower when the flask was overheated above 140 °C, or in moist solvents.

During the thermolysis of azidobenzaldehyde **1d**, benzo[*c*]isoxazole was formed in trace amounts, while 2-azidobenzoic acid esters **1e**,**f** remained intact under these conditions. In the presence of water, esters **1e**,**f** underwent thermolysis with the formation of a number of products with low yields, the main of which were the corresponding amines.

As discussed earlier,[20—22] the formation of the N—O bond of the isoxazole cycle occurs during 6π-electrocyclization with the nucleophilic attack of the carbonyl oxygen atom on the nitrene atom and the simultaneous elimination of the nitrogen molecule. An indirect evidence of this assumption is the thermal stability of esters **1e**,**f**, which is explained by the low nucleophilicity of the ester oxygen atom. In wet solvents, a competitive nucleophilic attack of water on the nitrene nitrogen atom of the azide group changes the reaction path and causes decrease in the yield of benzo[*c*]isoxazoles.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MR spectrometer (400 and 100 MHz, respectively) in $CDCl_3$. The chemical shifts are given relative to the solvent peak ($CDCl_3$: 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). Mass spectra were recorded on the Thermo Electron DSQ II device, EI ionization (70 eV), direct input. A control of azide conversion and accumulation of the reaction products was carried out by HPLC on a Shimadzu LC-20AD instrument with an SPD-M20A detector, 20 μL loop (Discovery C-18 column, 5 μm, d = 3 mm, l = 25 cm, gradient elution of the ethanol (10%)—water (90%) system with a linear decrease in 25 minutes to 0% water and continuing elution with ethanol for 60 minutes. The flow rate was 0.15 mL min^{-1}). Elemental analysis was performed on a Vario Micro cube Elementar CHNS analyzer. Aromatic azides were synthesized according to the procedure described in[19].

Synthesis of 3-phenylbenzo[*c*]isoxazoles 2a—c (general procedure). In dry *o*-xylene (2 mL), azide **1a—c** (0.4 mmol) was stirred in an oil bath at 135 °C for 1 h without air moisture access. The solvent was removed under reduced pressure, the product was recrystallized from hexane.

3-Phenylbenzo[*c*]isoxazole (2a). Yield 77 mg (99%), yellow crystals. M.p. 52 °C. ^{1}H NMR, δ: 7.06 (dd, 1 H, H (5), J = 8.9 Hz, J = 6.4 Hz); 7.33 (dd, 1 H, H (6), J = 9.0 Hz, J = 6.4 Hz); 7.53—7.46 (m, 1 H); 7.59—7.53 (m, 2 H); 7.62 (d, 1 H_{arom}, J = 9.1 Hz); 7.84 (d, 1 H_{arom}, J = 8.8 Hz); 8.03 (dd, 2 H_{arom}, J = 7.1 Hz, J = 1.4 Hz). ^{13}C NMR, δ: 114.5 (—CH=), 115.7 (C_{arom}), 120.7 (C_{arom}), 124.7 (—CH=), 126.8 (—CH=), 128.6 (C_{arom}), 129.4 (C_{arom}), 130.4 (C_{arom}), 130.8 (C_{arom}), 158.0 (=C—O), 164.6 (C=N). MS, m/z (I_{rel} (%)): 196 (13), 195 (71) $[M]^+$, 168 (12), 167 (90), 166 (44), 140 (24), 139 (37), 105 (20), 92 (16), 77 (100), 64 (14), 63 (22), 51 (36), 50 (17). Found (%): C, 80.12; H, 4.73; N, 7.05. $C_{13}H_9NO$. Calculated (%): C, 79.98; H, 4.65; N, 7.17.

5-Bromo-3-phenylbenzo[*c*]isoxazole (2b). Yield 107 mg (99%), yellow crystals. M.p. 114 °C. ^{1}H NMR, δ: 7.37 (dd, 1 H, H(6), J = 9.4 Hz, J = 1.6 Hz); 7.61—7.49 (m, 4 H); 8.00—7.95 (m, 2 H); 8.03 (dd, 1 H_{arom}, J = 1.7 Hz, J = 0.9 Hz). ^{13}C NMR, δ: 115.5 (—CH=), 117.3 (C_{arom}), 118.4 (C_{arom}), 122.7 (—CBr=), 126.7 (—CH=), 128.0 (C_{arom}), 129.5 (C_{arom}), 130.8 (C_{arom}), 134.7 (C_{arom}), 156.4 (=C—O), 164.3 (C=N). MS, m/z (I_{rel} (%)): 275 (29) $[M(^{81}Br)]^+$, 273 (29) $[M(^{79}Br)]^+$, 194 (22), 166 (54), 165 (9), 164 (8), 140 (17), 139 (23), 105 (14), 89 (9), 88 (15), 87 (9), 77 (100), 76 (13), 75 (10), 74 (11), 63 (15), 62 (16), 51 (43), 50 (12). Found (%): C, 57.23; H, 3.01; N, 4.93. $C_{13}H_8BrNO$. Calculated (%): C, 56.96; H, 2.94; N, 5.11.

5-Iodo-3-phenylbenzo[*c*]isoxazole (2c). Yield 126 mg (98%), light pink crystals. M.p. 120 °C. ^{1}H NMR, δ: 7.40 (dd, 1 H, H (6), J = 9.4 Hz, J = 1.0 Hz); 7.61—7.48 (m, 4 H); 7.98 (dt, 2 H, J = 8.1 Hz, J = 1.2 Hz); 8.29 (d, 1 H_{arom}, J = 1.2 Hz). ^{13}C NMR, δ: 89.2 (—CI=), 116.6 (C_{arom}), 117.2 (—CH=), 126.8 (—CH=), 128.0 (C_{arom}), 129.5 (C_{arom}), 129.7 (C_{arom}), 130.8 (C_{arom}), 139.3 (C_{arom}), 156.3 (=C—O), 163.9 (C=N). MS, m/z (I_{rel} (%)): 322 (10), 321 (100) $[M]^+$, 194 (24), 167 (10), 166 (72), 165 (8), 164 (7), 140 (20), 139 (27), 105 (8), 89 (7), 88 (6), 83 (9), 77 (61), 76 (6), 74 (5), 70 (6), 63 (8), 62 (9), 51 (22). Found (%): C, 48.73; H, 2.63; N, 4.23. $C_{13}H_8INO$. Calculated (%): C, 48.62; H, 2.51; N, 4.36.

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