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One-pot transformation of cyano oxiranes into furo[3,2-*c*]isothiazole derivatives

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ABSTRACT

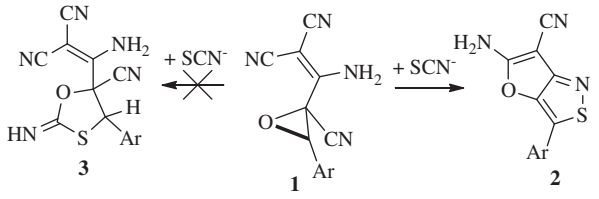
The one-pot reactions of 2-[amino(2-cyano-3-aryloxiran-2-yl)methylene]malononitriles with thiocyanate to afford 5-amino-3-arylfuro[3,2-*c*]isothiazole-6-carbonitriles in good yields.

Cascade-heterocyclization reactions have a special place in modern organic synthesis and achieve complicated chemical transformations in one synthetic operation. Their use in reactions of cyano-containing compounds allows the synthesis of functional mono-, bi-, and polycyclic structures.[1] Prospective substrates for the synthesis of new heterocyclic compounds are 2-[amino(2-cyano-3-aryloxiran-2-yl)methylene]malononitriles **1**,[2] which are obtained by epoxidation of arylmethylidene derivatives of malononitrile dimers.[3] The use of these compounds in organic synthesis has enabled the development of one-pot syntheses of 5-amino-3-arylfuro[3,2-*c*]isothiazole-6-carbonitriles **2**. The presence of enamine-carbonitrile moieties makes them promising for further chemical transformations. Besides some isothiazole derivatives are known to possess cytotoxic, antiproliferative, antiviral, antibacterial, and antipsychotic activity.[4]

Substituted isothiazoles are a poorly-represented class of heterocyclic compounds, however, several general approaches to their synthesis have been developed. One of the main synthetic approaches to fused isothiazoles is based on reactions between imino-containing compounds and thiocyanates.[5]

Herein, we describe a new method for the preparation of isothiazoles **2a–e** (Scheme 1), fused with a furan ring. The method involves the one-pot reaction of 2-[amino(2-cyano-3-aryloxiran-2-yl)methylene]malononitriles **1** and sodium, potassium or ammonium thiocyanates in a 1,4-dioxane-water mixture. A series of intramolecular transformations leads to 5-amino-3-arylfuro[3,2-*c*]isothiazole-6-carbonitriles **2a–e** in 76–89% yields (Table 1).[6]

The structures of compounds **2a–e** were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectra of **2a–e** exhibited singlets at δ 9.02–9.12 ppm for the amino group and expected resonances for the aryl group and other substituents. The ^{13}C NMR spectrum of **2a** displayed resonances in agreement with the structure. The structural assign-



Scheme 1. Synthesis of isothiazoles **2a–e**.

Table 1
Synthesis of 5-amino-3-arylfuro[3,2-*c*]isothiazole-6-carbonitriles **2a–e**

Oxirane	Ar	Product	Yield[a] (%)
1a	C_6H_5	**2a**	82
1b	2-ClC_6H_4	**2b**	86
1c	4-$H_3CC_6H_4$	**2c**	83
1d	4-FC_6H_4	**2d**	76
1e	3-ClC_6H_4	**2e**	89

[a] Yield of isolated product.

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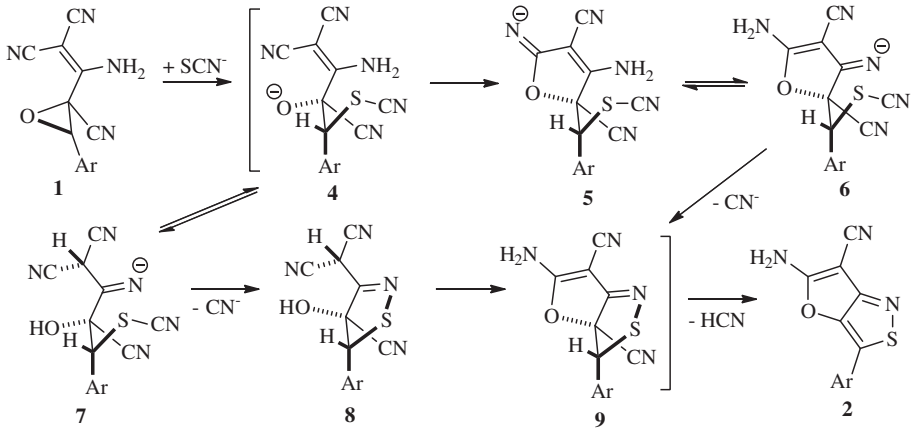

Scheme 2. Proposed mechanism for the synthesis of isothiazoles **2a–e**.

ments made on the basis of the mass spectra of compounds **2** displayed molecular ion peaks and other fragmentations, including peaks due to [Ar–C≡S$^+$] fragments.

According to published data, ring-opening of oxiranes under the action of thiocyanates can lead to the formation of 2-imino-1,3-oxathiolanes **3**.[7] Depending on the structures of the reactants and the reaction conditions, derivatives of various classes of heterocycles, such as thiiranes, 1,3-oxathiolanes and thiazoles can be formed. The structures of the final products **2** and the proposed mechanism for this transformation do not require formation of **3** as an intermediate in the reaction of oxiranes **1** with thiocyanates.

Ring-opening of an oxirane ring can occur stereospecifically via approach of a nucleophile from the rear of the C–O[7] bond by an S_N2 mechanism. Therefore, during the first stage we assume initial formation of intermediate **4** (Scheme 2).

This intermediate undergoes intramolecular heterocyclization with the formation of iminofuran **5**, subsequent tautomerization of which gives intermediate **6**. The proximity of the imine anion and thiocyanate group leads to formation of an isothiazole ring accompanied by the elimination of a cyanide anion and the formation of intermediate **9**.

An alternative reaction course is also possible. This involves the formation of the isothiazole ring **8** after tautomerization of **4** into intermediate **7**. Further, intramolecular cyclization leads to formation of bicycle **9**. Finally, aromatization occurs via elimination of hydrogen cyanide.

In earlier published work the only method for the synthesis furo[3,2-*c*]isothiazoles and benzofuro[3,2-*c*]isothiazoles involved intramolecular nucleophilic replacement with the participation of azido- and thione groups.[8] Thus, the proposed method is the first approach for the synthesis of polyfunctional furo[3,2-*c*]isothiazoles.

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6. *Typical procedure for the preparation of 5-amino-3-arylfuro[3,2-c]isothiazole-6-carbonitriles* **2a–e**. NaSCN (0.81 g, 10 mmol) was dissolved in a solution of 2-[amino(2-cyano-3-phenyloxiran-2-yl)methylene]malononitrile **1a** (2.36 g, 10 mmol) in a mixture of 1,4-dioxane (20 mL) and H_2O (20 mL). The mixture was stirred at 70 °C for 1 h, cooled filtered and washed with 1,4-dioxane (20 mL) and H_2O (20 mL). Compound **2a**: mp 285–286 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 7.48 (1H, t, J = 7.3 Hz, C_6H_5), 7.55 (2H, t, J = 7.5 Hz, C_6H_5), 7.64 (2H, d, J = 7.7 Hz, C_6H_5), 9.04 (2H, s, NH_2). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 59.41 (C^6), 113.65 (CN), 126.32, 127.42, 129.41, 129.52 (C_6H_5), 135.29 (C^3), 138.59 (C^{3a}), 160.36 (C^{6a}), 175.13 (C^5). IR 3334, 3258 (NH_2), 2224 (C≡N). MS (EI, 70 eV): m/z (%) 241 (M^+, 42), 121 ([Ar–C≡S$^+$], 100). Anal. Calcd for $C_{12}H_7N_3OS$: C, 59.74; H, 2.92; N, 17.42. Found C, 59.77; H, 3.03; N, 17.50. Compound **2b**: mp 240–241 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 7.50–7.57 (2H, m, C_6H_4), 7.70 (1H, dd, ^3J = 7.7 Hz, ^4J = 1.6 Hz, C_6H_4), 7.91 (1H, dd, ^3J = 7.5 Hz, ^4J = 2.0 Hz, C_6H_4), 9.05 (2H, s, NH_2). IR 3328, 3267 (NH_2), 2226 (C≡N). MS (EI, 70 eV): m/z (%) 277 (M^+ ^{37}Cl, 24), 275 (M^+ ^{35}Cl, 78), 157 ([Ar–C≡S$^+$], 34), 155 ([Ar–C≡S$^+$], 100). Anal. Calcd for $C_{12}H_6ClN_3OS$: C, 52.27; H, 2.19; N, 15.24. Found C, 52.32; H, 2.22; N, 15.30. Compound **2c**: mp 181–182 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 2.36 (3H, s, CH_3), 7.35 (2H, d, J = 8.1 Hz, C_6H_4), 7.53 (2H, d, J = 8.2 Hz, C_6H_4), 9.02 (2H, s, NH_2). IR 3333, 3262 (NH_2), 2226 (C≡N). MS (EI, 70 eV): m/z (%) 255 (M^+, 68), 135 ([Ar–C≡S$^+$], 100). Anal. Calcd for $C_{13}H_9N_3OS$: C, 61.16; H, 3.55; N, 16.46. Found C, 61.22; H, 3.57; N, 16.51. Compound **2d**: mp 214–215 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 7.39–7.43 (2H, m, C_6H_4), 7.67–7.70 (2H, m, C_6H_4), 9.07 (2H, s, NH_2). IR 3336, 3257 (NH_2), 2224 (C≡N). MS (EI, 70 eV): m/z (%) 259 (M^+, 36), 139 ([Ar–C≡S$^+$], 100). Anal. Calcd for $C_{12}H_6FN_3OS$: C, 55.59; H, 2.33; N, 16.21. Found C, 56.08; H, 2.47; N, 16.02. Compound **2e**: mp 265–266 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 7.53–7.58 (2H, m, C_6H_4), 7.68 (2H, s, C_6H_4), 9.12 (2H, s, NH_2). IR 3326, 3256 (NH_2), 2233 (C≡N). MS (EI, 70 eV): m/z (%) 277 (M^+ ^{37}Cl, 27), 275 (M^+ ^{35}Cl, 80), 157 ([Ar–C≡S$^+$], 37), 155 ([Ar–C≡S$^+$], 100). Anal. Calcd for $C_{12}H_6ClN_3OS$: C, 52.27; H, 2.19; N, 15.24. Found C, 52.39; H, 2.33; N, 15.23.
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