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Highly efficient one-pot cascade cyclization of 3-(5-hydroxy-3-methylpyrazol-4-yl)-3-arylpropionitriles into spirocyclopropyl pyrazolones

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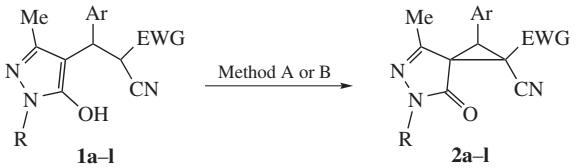
Bromine-assisted one-pot cascade cyclization of 3-(5-hydroxy-3-methylpyrazol-4-yl)-3-arylpropionitriles affords medicinally relevant spirocyclopropyl pyrazolones in 60–97% yields.

The cyclopropane subunit plays a prominent role in organic chemistry[1] due to various biological activities of its derivatives.[2] In particular, fused spirocyclopropane heterocycles have been recognized as α-L-fucosidase,[3] β-lactamase,[3] and HIV-1 non-nucleoside reverse transcriptase[4] inhibitors as well as diagnostic markers for the early detection of colorectal and hepatocellular cancers.[5] Among compounds of this type, spirocyclopropyl pyrazolones are perspective for their pharmacological and physiological activities.[6–8]

In the course of our studies on cascade and multicomponent reactions we suggested a new chemical strategy to construct substituted cyclopropanes from activated olefins and CH-acids[9–11] as well as from carbonyl compounds and CH-acids.[12,13] Taking into consideration these results, we were prompted to design a convenient facile and efficient cascade one-pot method for the cyclization of 3-(5-hydroxy-3-methylpyrazol-4-yl)-3-arylpropionitriles **1a–l** into substituted spirocyclopropyl pyrazolones **2a–l** (Scheme 1).†



1a–l **2a–l**

1a–l, **2a–l**	R	Ar	EWG	Isolated yield of **2** (%) (method, ratio of isomers)
a	H	Ph	CN	83 (A), 70 (B)
b	H	4-MeC_6H_4	CN	80 (A), 71 (B)
c	H	4-Bu^tC_6H_4	CN	72 (A), 70 (B)
d	H	4-MeOC_6H_4	CN	68 (A), 61 (B)
e	H	4-ClC_6H_4	CN	77 (A, 3:1), 72 (B, 3:1)
f	H	3-BrC_6H_4	CN	85 (A, 3:2), 83 (B, 3:2)
g	H	4-FC_6H_4	CN	97 (A, 3:1), 88 (B, 3:1)
h	H	Ph	CO_2Me	69 (A), 63 (B)
i	H	4-ClC_6H_4	CO_2Me	71 (A), 65 (B)
j	Ph	Ph	CN	77 (A, 4:1), 73 (B, 4:1)
k	Ph	3-BrC_6H_4	CN	89 (A, 3:1), 83 (B, 4:1)
l	Ph	4-Bu^tC_6H_4	CN	75 (A), 65 (B)

Scheme 1 *Reagents and conditions*: Method A: 5 mmol of **1**, 5 mmol of Br_2, 6 mmol of EtONa, 20 ml of EtOH, ambient temperature, 3 h; Method B: 5 mmol of **1**, 25 ml of 0.2 M bromine in water, 15 ml of EtOH, 40 °C, 1 h.

† *Method A*. Sodium ethoxide (6 mmol) in ethanol (10 ml) was added to an ethanolic solution (10 ml) of 3-(5-hydroxy-3-methylpyrazol-4-yl)-3-arylpropionitrile **1** (5 mmol) in a 50 ml beaker. Bromine (5 mmol) was added without external cooling. The mixture was magnetically stirred at room temperature for 3 h and then cooled down to 0 °C within 1 h. The solid phase was filtered and dried to isolate pure spirocyclopropyl pyrazolone **2**.

Initially, we studied cyclization **1a** → **2a** by the action of bromine in ethanol in the presence of EtONa as a base (Method A). The best yield of spirocyclopropyl pyrazolone **2a** (78%) was achieved when 1.2 equiv. of EtONa was used. Application of other quantities of EtONa resulted in lowering the yields: 61% with 1.0, 65% with 1.5, and 59% with 2.0 equiv. EtONa within 3 h of processing.

Under the optimal conditions thus found, a series of 3-(5-hydroxy-3-methylpyrazol-4-yl)-3-arylpropionitriles **1a–l** was cyclized into spiro products **2a–l** in 60–97% yields (see Scheme 1). Notably, in the case of compounds **1a–d**,**h**,**i**,**l** only one isomer of **2** was obtained, whereas reactants **1e–g**,**j**,**k** produced diastereomeric pairs. The configuration of the products was readily established based on NOESY experiments which revealed the relevant characteristics correlation (Figure 1).

The NOESY spectrum for the (2*R**,3*S**) isomer (compounds **2a–d** and major isomer of **2e–g**) showed an interaction between

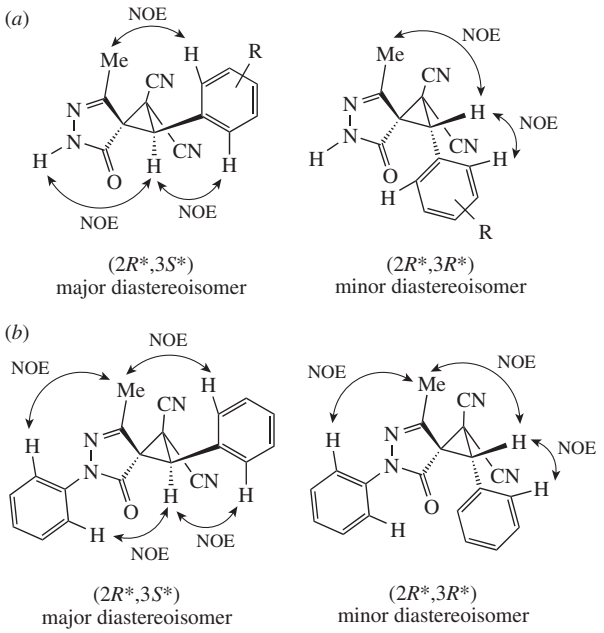


Figure 1 NOESY interactions for (*a*) **2a–g** and (*b*) **2j**.

Method B. 25 ml of 0.2 M bromine in water (5 mmol) was added dropwise to an ethanolic solution (10 ml) of substrate **1** (5 mmol) in a 50 ml three-necked flask for 3 min. The mixture was magnetically stirred at 40 °C for 1 h and then cooled down to 0 °C within 1 h. The solid phase was filtered, washed with water and dried to isolate pure product **2**.

For characteristics of the products, see Online Supplementary Materials.

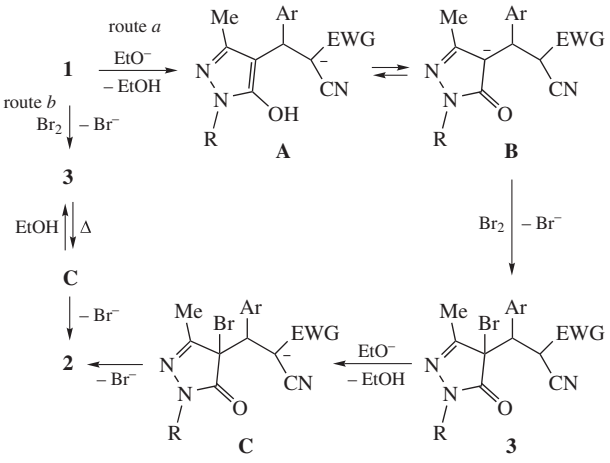
NH group of the pyrazolone ring and the H atom in cyclopropane as well as interactions between Me group and *ortho*-H of phenyl ring. As for minor (2*R**,3*R**) isomer of **2e**–**g**, the interactions between Me group and the H substitute of cyclopropane ring, and interactions between the latter and *ortho*-H of phenyl ring were observed.

The analogous NOESY spectra confirmed (2*R**,3*S**) configuration for the major isomer of **2j**,**k** and cyclopropane **2l**. The (1*S**,2*R**,3*R**) structure of **2h** and **2i** with the phenyl, methyl and cyano substituents lying on the one side of cyclopropane plane was established earlier.[14]

Recently we have found base-free conditions in the cascade synthesis of tetracyanocyclopropanes from benzylidenemalononitriles and malononitrile on the solely bromine action.[10] Herein, we have carried out cyclization of compounds **1** by the direct treatment with bromine (Method B) and obtained spirocyclopropyl pyrazolones **2** in yields of 60–88%. These yields were somewhat lower than those achieved by Method A.

Based on the results discussed above and the mechanistic data on the cascade transformation of alkylidenemalononitriles and malononitrile into tetracyano-substituted cyclopropanes[9] the following mechanistic rationalization for the cyclization **1** → **2** in the presence of EtONa (Method A) is proposed (Scheme 2, route *a*). At the first stage reaction of substrate **1** with ethoxide anion affords anion **A**, which exists in equilibrium with anion **B**. Then, bromination leads to bromo-substituted arylpropionitrile **3**, whose further cyclization under the action of the next ethoxide anion furnishes final product **2**.

In the absence of base (Method B), at first bromination of compound **1** affords bromonitrile **3** (Scheme 2, route *b*). Intermediate **3** is a reasonably strong CH-acid which could under heating provide a sufficient concentration of anion of brominated arylpropionitrile **C** in ethanol to ensure its subsequent cyclization into compound **2**.



Scheme 2

In conclusion, we have developed a new highly efficient bromine-assisted one-pot cascade cyclization of 3-(5-hydroxy-3-methyl-pyrazol-4-yl)-3-arylpropionitriles into medicinally relevant substituted spirocyclopropyl pyrazolones in 60–97% yields. The procedure employs inexpensive reagents, it is easy to perform and the work up is not complicated. The products are crystallized directly from the reaction mixture, consequently, the isolation includes only filtration and washing with water.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.01.008.

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