SYNTHESIS A NEW 5-HYDROXYSUBSTITUTED TRIAZOLO[1,4]DIAZEPINES

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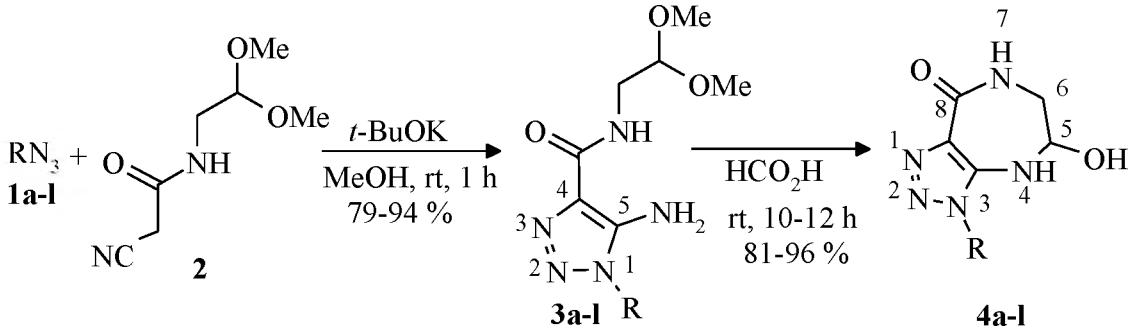
Azoloannelized [1,4]diazepines are synthetically and biologically interesting condensed heterocyclic systems [1,2]. The pharmacological significance of pyrazolo[1,4]diazepines is demonstrated by their use as active substances of the anxiolytic drug zolasepam [3–5] and the antidepressant zomethapine [6,7]. In addition, a number of pyrazolo[1,4]diazepines revealed selective phosphodiasterase inhibitors [8] and oxytocin receptor antagonists [9].

The method proposed earlier by us [10] and other authors [11] for the formation of the hydroxydiazepine cycle based on 5-amino-N-(2,2-dialkoxyethyl)-1H-pyrazole(imidazole)-4-carboxamides turned out to be acceptable for the production of new derivatives triazolo[1,4]diazepines. The key substrates for this reaction were the anionic cyclization of azides**1a–l** synthesized by us with N–(2,2-dimethoxyethyl)-2-cyanacetamide (**2**) 5-amino-N-(2,2-dimethoxyethyl)-1H-1,2,3-triazole-4-carboxamides **3a–l** (Scheme 1).

Scheme 1



The method is general in nature and allows involving alkyl-, aryl- and heterylazides in the process of formation of the triazole cycle and under mild conditions in the presence of t-BuOK as a base leads to 3a-l compounds with yields of 79-94% (Table 1). The N-functionally substituted aminotriazolcarboxamides 3a–l in formic acid at room temperature undergo light intramolecular cyclization at room temperature to form 5-hydroxy substituted triazolo[4,5-e][1,4]diazepines 4a–l with close to quantitative yields (Scheme 1, Table 1).

The IR spectra of 4a–l compounds are characterized by a set of absorption bands corresponding to the valence oscillations of the bonds C =O (1627–1636 cm^{-1}), N–H (3247–3312 cm^{-1}) and OH (3247–3312 cm^{-1}). In the spectra of NMR 1H, along with typical signals of R substituents, there are multiplants of protons 6-CH_2 at 2.98–3.38 m. d., protons of 5-CH at 4.86–5.18 m. d., as well as signals of protons NH: doublets at 7.26–8.01 m. d. and multiplelets at 7.13–7.66 m. d.

Table

Product yields **3, 4 a–l**

Azide	R	Product (yield, %)	Product (yield, %)
1a	Me_2CHCH_2	3a (79)	4a (81)
1b	$PhCH_2$	3b (85)	4b (89)
1c	4-$MeOC_6H_5CH_2$	3c (89)	4c (87)
1d	3-$ClC_6H_4CH_2$	3d (84)	4d (88)
1e	Ph	3e (81)	4e (92)
1f	4-ClC_6H_4	3f (93)	4f (95)
1g	4-MeC_6H_4	3g (88)	4g (91)
1h	4-$MeOC_6H_4$	3h (86)	4h (93)
1i	4-$O_2NC_6H_4$	3i (91)	4i (96)
1j	2,4-$F_2C_6H_3$	3j (91)	4j (90)
1k	2,4-$Me_2C_6H_3$	3k (81)	4k (89)
1l	1-Methylpyrazole-3-yl	3l (92)	4l (94)

Thus, we show that intramolecular cyclization of 5-amino-N-(2,2-dimethoxyethyl)-1H-1,2,3-triazole-4-carboxamides in formic acid is a convenient way to synthesize 5-hydroxy[1,2,3] triazolo[4,5-e][1,4] diazepines, which are promising objects for synthetic and medicinal chemistry.

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