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A new method of synthesis of substituted 1-(1*H*-imidazole-4-yl)-1*H*-1,2,3-triazoles and their fungicidal activity

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ABSTRACT

Based on the deoxygenation reaction of 1-(1-*tert*-butyl-3-nitroazetidine-3-yl)-1*H*-1,2,3-triazoles a new method for the synthesis of substituted 1-(1*H*-imidazole-4-yl)-1*H*-1,2,3-triazoles has been developed. Fungicidal activity of these compounds has been investigated at a range of phytopathogenic fungi.

1. Introduction

Imidazoles are an important class of heterocycles. Their chemical and biological importance has been well investigated.[1] Many bioactive heterocyclic compounds and natural products containing this cycle show a wide spectrum of pharmacological activities such as anticancer, antiviral, antibacterial, antitubercular, anti-inflammatory and antidiabetic.[2] The imidazole ring is a frequent structural unit found innumerous natural products and biologically active compounds.[3]

The 1,2,3-triazole moiety is not present in nature although synthetic molecules containing 1,2,3-triazole unit show diverse biological activities including antibacterial, herbicidal, fungicidal, antiallergic and anti-HIV.[4]

Antifungal agents including imidazole and triazole rings such as bifonazole, clotrimazole, ketoconazole and fluconazole are widely used in clinical practice for fungal infection treatment (Fig. 1).[5] It is commonly considered that the imidazole ring could efficiently coordinate with the iron(II) ion of heme to restrain the biosynthesis of ergosterol thus inhibiting the growth of fungi.[6]

We studied the structures of different antifungal drugs both in combinations with halogen-substituted aromatic residues and with each other and found out that most of the combinations contain 1*H*-imidazole as well as 1*H*-1,2,4-triazole. However there is no information about the system that contains 1,2,3-triazole in the fourth position of the imidazole ring. In this work we focused our attention on the creation of new molecules which contain 1*H*-imidazole and monosubstituted or 1,4-disubstituted 1*H*-1,2,3-triazole rings. 1,2,3-Triazole moieties are interesting molecules for this purpose. They are stable to metabolic degradation and are capable of hydrogen bonding which can be favorable in binding biomolecular targets and for solubility.[6,7]

The number of methods and reagents that allow the direct introduction of 1*H*-1,2,3-triazole ring in the fourth position of the 1*H*-imidazole are limited by only 2- and 5- substituted imidazoles.[8] The preparation method of these molecules involves using *n*-butyllithium or diazonium ion which is impossible in our conditions.

In the current work we developed a new and original way to synthesize 1-(1*H*-imidazole-4-yl)-1*H*-1,2,3-triazoles (**1a-k**) (Fig. 2).

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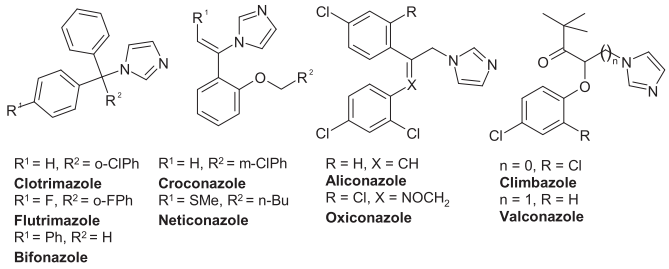
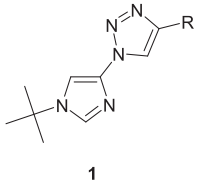


Fig. 1. Some imidazole-based antifungal compounds.



1

R = H (**1a**); $SiMe_3$ (**1b**); cyclo-Pr (**1c**), C_6H_5 (**1d**), 2-FC_6H_4 (**1e**), 2-ClC_6H_4 (**1f**), 3-ClC_6H_4 (**1g**), 2,4-$Cl_2C_6H_3$ (**1h**), 4-$CF_3C_6H_4$ (**1i**), 3-$CF_3C_6H_4$ (**1j**), 3-$CH_3OC_6H_4$ (**1k**)

Fig. 2. Substituted1-(1*H*-imidazole-4-yl)-1*H*-1,2,3-triazoles.

2. Results and discussion

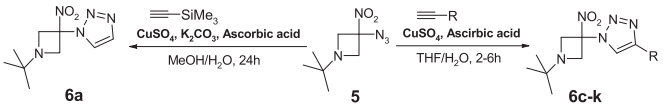
Several methods are currently known for deoxygenation of primary and secondary nitroalkanes with trivalent phosphorus compounds, leading to the formation of nitriles,[9] amines,[10] and derivatives of oximes.[11] Recently we have shown that substituted 1-(5-nitro-1,3-dioxan-5-yl)-1*H*-1,2,3-triazoles easily transform into a new 4,7-dihydro-1,3,5-dioxazepine heterocyclic system by heating with triethyl phosphite.[12] The positive results of this investigation did allow us to use 1-(1-*tert*-butyl-3-nitroazetidine-3-yl)-1*H*-1,2,3-triazoles **6a-k** as starting materials for the 1-(1*H*-imidazole-4-yl)-1*H*-1,2,3-triazoles **1a-k** synthesis.

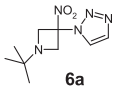
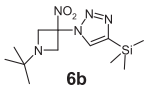
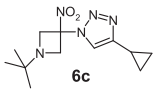
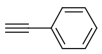
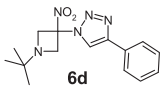
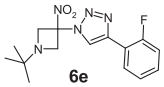
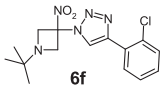
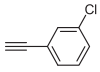
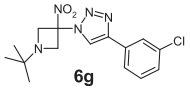
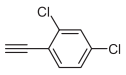
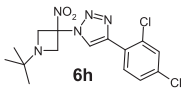
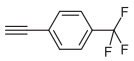
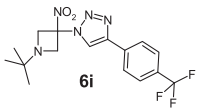
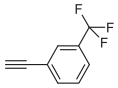
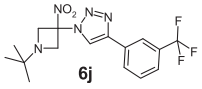
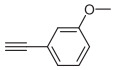
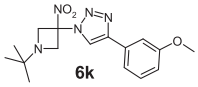
3-Azido-3-nitro-azetidine **5** was used as a key intermediate for the synthesis of 1-(1-*tert*-butyl-3-nitroazetidine-3-yl)-1*H*-1,2,3-triazoles **6a-k**. The heminal nitroazide **5** was obtained by a previously developed scheme with nitromethane, formaldehyde and *tert*-butyl amine.[13] The main method of the preparation of α-nitroazides consists of oxidative coupling of the azide anion with nitroalkane salts. The reaction is performed in an alkaline medium in the excess of azide under the conditions of electrochemical and chemical oxidation.[14] In the latter case, ammonium persulfate or potassium ferricyanide are most widely used as oxidants. In the current work the nitroazetidine salt was obtained in situ using retro-Henry reaction from **4** (Sheme 1). Potassium ferricyanide was used as an oxidant.

As it was shown in our previous work[15] heterocyclic α-nitroazides are highly reactive in 1,3-dipolar cycloaddition to terminal acetylenes under thermal cyclization conditions giving a mixture of 1,4- and 1,5-triazoles regardless of the structure of the aliphatic heterocycle. Performing the cyclization in the presence of copper(I) salts resulted in a selective formation of 1,4- disubstituted triazoles.

In the current work we used both 1-substituted and 1,4-disubstituted 1,2,3-triazoles. The monosubstituted triazole **6a** was synthesized from the 3-azido-3-nitro-azetidine **5** and trimethylsilyl acetylene (TMS-acetylene). The reaction was performed at room temperature in aqueous methanolic medium in the presence of copper(II) sulfate, ascorbic acid, and potassium carbonate.[16] The process was found to be selective without formation of trimethylsilyl-substituted triazole according to NMR spectroscopy and LC-MS. The 1,4-disubstituted triazoles **6c-k** were obtained by addition of 3-azido-3-nitro-azetidine **5** to substitute acetylenes in the presence of ascorbic acid and copper(II) sulfate. 1-(1-*tert*-Butyl-3-nitroazetidine-3-yl)-4-trimethyl-silyl-1*H*-1,2,3-triazole **6b** was synthesized from 3-azido-3-nitro-azetidine **5** and TMS-acetylene without a catalyst[15] (Table 1):

Table 1
Synthesis of substituted azetidines.



Entry	Acetylene	Time, [h]	Product	Yield, [%][a]
1		24	 **6a**	86[b]
2		48	 **6b**	78[c]
3		3	 **6c**	50[d]
4		2	 **6d**	74[d]
5		2	 **6e**	75[d]
6		4	 **6f**	77[d]
7		4	 **6g**	93[d]
8		3	 **6h**	58[d]
9		4	 **6i**	87[d]
10		4	 **6j**	81[d]
11		6	 **6k**	81[d]

[a] Isolated yield.
[b] Reaction conditions: K_2CO_3 (1.25 mmol), ascorbic acid (0.2 mmol), TMSA (1.2 mmol), $CuSO_4 \cdot 5H_2O$ (0.1 mmol), 3-azido-1-*tert*-butyl-3-nitro-azetidine **5** (1 mmol), MeOH (10 mL), H_2O (5 mL), 24 h, rt.
[c] Reaction conditions: 3-azido-1-*tert*-butyl-3-nitro-azetidine **5** (1 mmol), TMSA (10 mmol), CH_2Cl_2 (10 mL), reflux 48 h.
[d] Reaction conditions: Ascorbic acid (0.5 mmol), acetylene (1.05 mmol), $CuSO_4 \cdot 5H_2O$ (0.15 mmol), 3-azido-1-*tert*-butyl-3-nitro-azetidine **5** (1 mmol), THF (10 mL), H_2O (5 mL), 2–6 h, rt.