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Efficient synthesis of tetrazole derivatives of cytisine using the azido-Ugi reaction

Danil P. Zarezin [a], Adil M. Kabylda [a], Valentina I. Vinogradova [b], Pavel V. Dorovatovskii [c], Victor N. Khrustalev [d, e], Valentine G. Nenajdenko [a, *]

[a] Department of Chemistry, Lomonosov Moscow State University, Moscow 119991, Russia
[b] Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic Uzbekistan, Uzbekistan
[c] National Research Center "Kurchatov Institute", Moscow, Russia
[d] Peoples' Friendship University of Russia (RUDN), Moscow, Russia
[e] Nesmeyanov Institute of Organoelement Compounds of RAS, Moscow, Russia

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ABSTRACT

The azido-Ugi reaction with natural alkaloid cytisine was investigated. It was demonstrated that the reaction could be performed with various carbonyls (both aldehydes and ketones) and isocyanides. The transformation proceeded under mild conditions in methanol using TMSN3 as a source of hydrazoic acid to give target tetrazole derivatives of cytisine in up to 98% yield. The diastereoselectivity of this reaction was studied using both aliphatic and aromatic aldehydes. A family of tetrazole derived cytisine compounds was prepared. Selective deprotection of tetrazoles was elaborated to synthesize the corresponding NH-tetrazoles.

1. Introduction

The chemistry of tetrazoles and their derivatives has garnered considerable interest over the past decades [1]. These heterocyclic compounds play an important role in modern medicinal chemistry, organometallic and coordination chemistry, organocatalysis and chemistry of materials (e.g., as highly energetic compounds) [2]. Many current drugs such as valsartan, losartan, candesartan, azosemide, siloxithil, irbesartan, tazanolast, pentetrazole and a series of the cephalosporin β-lactam antibiotics contain the tetrazole moiety in the structure (Fig. 1).

It is known that NH-tetrazoles are bioisosteres of carboxylic acids, and 1,5-disubstituted tetrazoles mimic *cis*-amide bonds in peptides [3]. An important factor is also the ability of nitrogen atoms of tetrazole to form hydrogen bonds involved in the formation of complexes with enzymes [4]. This approach is widely used in modern drug design to create new biologically active molecules [5]. One of the most efficient methods of synthesis of tetrazole derivatives is the azido-Ugi reaction, which is a variation of the classical Ugi-reaction where HN_3 is employed as an acid component. This approach can be used for the synthesis of various molecules having 1,5-disubstituted tetrazole fragments [6].

On the other hand, another trend in drug design is modification and improvement of properties of natural compounds [7]. For example, such parameters as lipophilicity, solubility, bioavailability, and toxicity can be modulated by such approach. Cytisine, [(1*R*,5*S*)-1,2,3,4,5,6-hexahydro-1,5-methano-8*H*-pyrido [1,2a] [1,5] diazocin-8-one] also known as baptitoxine and sophorine, is a natural quinolizidine alkaloid that occurs in several plants, such as *Laburnum* and *Cytisus* belonging to the family Fabaceae (Fig. 2) [8]. It was demonstrated that (−)-cytisine has a high affinity at nicotinic acetylcholine receptors (nAChRs), which are related to a growing list of diseases [9]. For example, autoimmune myasthenia gravis is a syndrome characterized with the direct involvement of AChRs, in which an antibody-mediated autoimmune response to muscle AChRs [10].

This alkaloid is the lead molecule to find new selective ligands for the nAChRs, however cytisine itself has significant side effect. Moreover, it is quite toxic compound (LD_{50} in mice 2 mg/kg). At the

* Corresponding author.
E-mail address: nenajdenko@org.chem.msu.ru (V.G. Nenajdenko).

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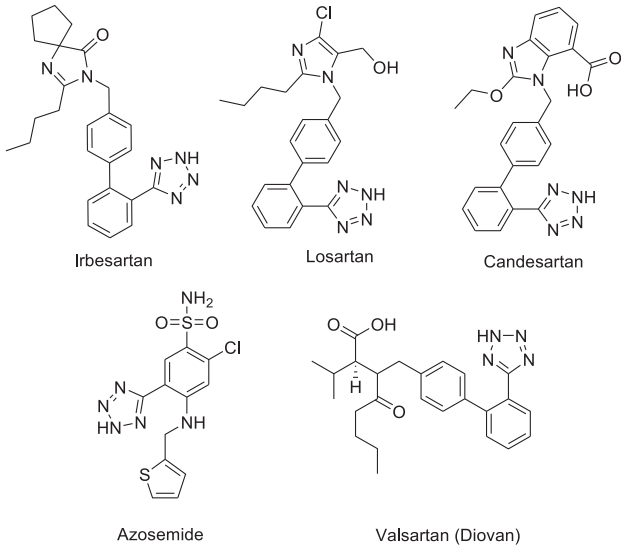


Fig. 1. Drugs containing the tetrazole moiety.

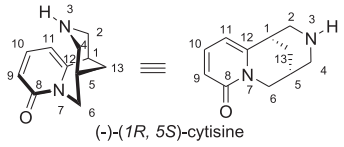


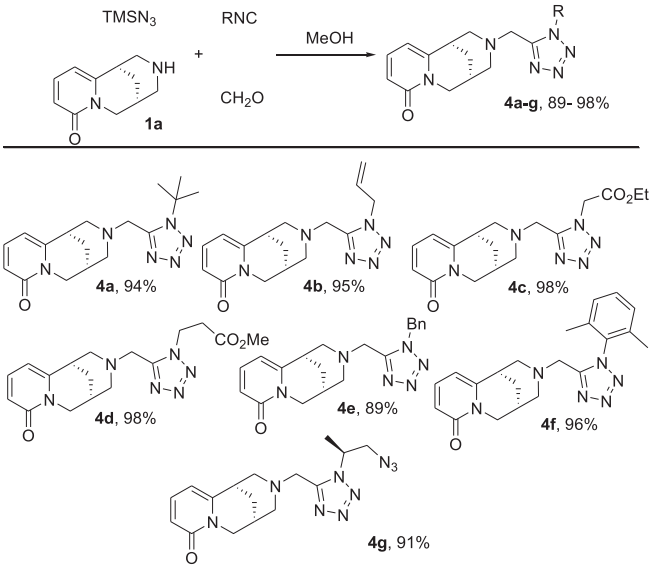
Fig. 2. Two and three dimensional structure and absolute configuration of (−)-cytisine with IUPAC numbering of the atoms.

moment the main interest in this alkaloid relates to its application as an aid to quit tobacco smoking, but cytisine activity is quite low and its molecular scaffold requires improvement to develop more effective drugs [11]. During the last few years a number of cytisine derivatives were investigated in order to obtain compounds with enhanced therapeutic potential [12].

Previously we investigated the azido-Ugi reaction with some cyclic imines to show the possibility to synthesize tetrazole derived 5–7 membered cyclic amines [13]. Recently we also studied the azido-Ugi reaction with α-substituted cyclic amines and demonstrated that the reaction proceeds efficiently with high control of diastereoselectivity (up to 100% de) [14]. Natural cytisine is a chiral cyclic secondary amine, which is very attractive for preparation of small molecules for subsequent biological study. Preparation of NH-tetrazoles bearing cytisine moiety is of special interest due to its ability to act as a bioisostere carboxylic group and possibility of its incorporation into a number of drug-candidate structures. We expected also that the azido-Ugi reaction with this alkaloid could be diastereoselective. This article is devoted to the study of the azido-Ugi with cytisine.

2. Results and discussion

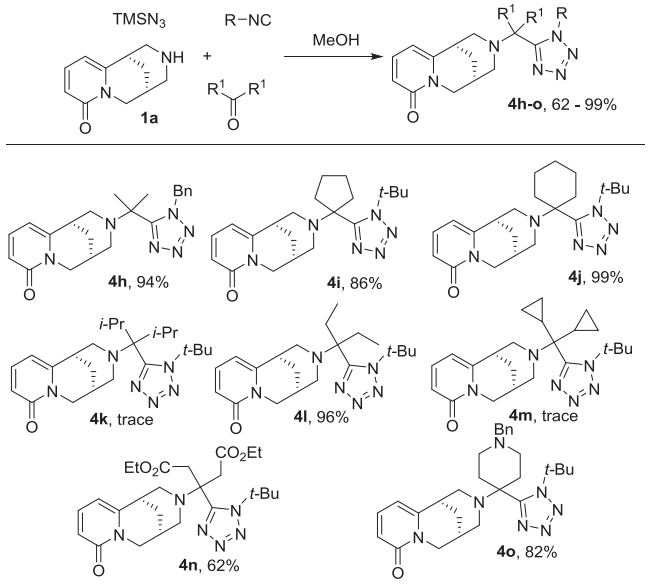
We started our investigation with the study of the azido-Ugi reaction with formaldehyde as the simplest but quite reactive carbonyl compound. Trimethylsilyl azide was used as safe and efficient precursor of hydrazoic acid. Our first experiments have shown that the reaction of cytisine with various isocyanides and $TMSN_3$ proceeded very smoothly in methanol for 24 h to give target products 4a-g in almost quantitative isolated yield (up to 98%) (Scheme 1). It should be noted that no limitation of isocyanides was found. Aliphatic, aromatic, functionalized and sterically hindered



Scheme 1. The azido-Ugi reactions with formaldehyde.

isocyanides can be used for this purpose. Application of azidoisocyanides [15] opens access to subsequent modification of prepared tetrazoles via click chemistry.

Next, the reaction with various ketones was investigated. It was found, that the reaction has broad scope in terms of ketones. The corresponding products were obtained in high yields (up to 99%) using both linear and cyclic ketones as inputs for azido-Ugi reaction (Scheme 2). For instance, acetone, diethyl ketone, cyclopentanone, and cyclohexanone gave the corresponding products very efficiently. However, the reaction has some limitations. In the case of sterically hindered ketones such as diisopropyl ketone and dicyclopropyl ketone the desired products were detected in trace amounts and the major product was *t*-butyl-1H-tetrazole that resulted from the addition of hydrazoic acid to *t*-butyl isocyanide. Nevertheless, the reaction is compatible with other functional groups. For example, the reaction with *N*-benzylpiperidone-4 and the diethyl ester of acetonedicarboxylic acid gave efficiently the



Scheme 2. The azido-Ugi reactions with ketones.