Tetrahedron 74 (2018) 5665–5673

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The (3+2)- and formal (3+3)-cycloadditions of *N*-vinylpyrroles with cyclic nitrones and *C,N*-cyclic azomethine imines

Kseniia K. Afanaseva [a], Mariia M. Efremova [a, **], Svetlana V. Kuznetsova [b], Andrey V. Ivanov [b], Galina L. Starova [a], Alexander P. Molchanov [a, *]

[a] *Saint Petersburg State University, Universitetskaya Nab. 7/9, St. Petersburg 199034, Russian Federation*
[b] *A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation*

ARTICLE INFO

Article history:
Received 30 May 2018
Received in revised form
18 July 2018
Accepted 19 July 2018
Available online 30 July 2018

Keywords:
Cycloaddition
N-Vinylpyrroles
Lewis acids
Nitrones
Azomethine imines

ABSTRACT

The addition of Lewis acids changes the path of the reaction of *N*-vinylpyrroles with 3,4-dihydroisoquinoline-*N*-oxides: formal (3 + 3)-cycloaddition proceeds instead of (3 + 2)-cycloaddition. In the case of benzoyl(3,4-dihydroisoquinolin-2-ium-2-yl)amides, reaction path does not change in the same conditions, but changing of the diastereoselectivity occurs and other diastereomer of (3 + 2)-cycloaddition became predominant.

1. Introduction

The 1,3-dipolar cycloaddition is a powerful tool for the synthesis of complex heterocyclic structures, including biologically active substances and analogues of natural compounds [1]. Lewis acids are widely used as catalysts in the 1,3-dipolar cycloaddition, in particular, in the reactions of nitrones and azomethine imines [2]. Using the acid catalysts allows reducing the reaction time, increasing the yields of cycloadducts and the selectivity of the process, the use of complexes with chiral ligands allows the enantioselective reactions [2]. Moreover, the use of Lewis acids opens up new ways of using 1,3-dipoles in organic synthesis [3]. One of the most promising ways is catalytic formal (3 + 3)-cycloadditions, which involve the reactions of donor-acceptor cyclopropanes with nitrones [4] and azomethine imines [5], oxiranes, aziridines, and thiiranes with nitrones [6], azomethine ylides with azomethine imines [7] and others. Such reactions are highly effective and selective methods for the synthesis of otherwise difficult to access six-membered heterocycles containing two or more heteroatoms.

At the same time, compounds containing pyrrole and indole fragments are of a great interest due to their high reactivity as substrates for reactions with 1,3-dipoles [8,9]. The pyrroles and indoles are able to react with 1,3-dipoles with loss of aromaticity and the formation of adducts directly by the double bond of a five-membered heterocycle [8]. In an acidic medium pyrroles and indoles react with nitrones to form products of nucleophilic addition of the heterocycle to the dipole [9]. *N*-Vinylpyrroles are a promising class of highly reactive pyrrole fragment carriers and the study of new ways of using them for the design of complex pyrrolic assemblies is of great interest [10]. These compounds have become widely available due to the discovery and systematic study of the Trofimov reaction: the reaction of ketoximes with acetylene in superbasic catalytic media [11]. The reactions of *N*-vinylpyrroles and indoles with various 1,3-dipoles (nitrones, nitrile oxides, azomethine imines) has been investigated previously [12]. It has been shown, that depending on the structure of starting dipole, dipolarofile and the reaction conditions, two different types of heterocyclic products can be obtained: five-membered pyrrolyl-substituted adducts of 1,3-dipolar cycloaddition[12a-f] or six-membered condensed products of a formal (3 + 3)-cycloaddition [12g]. The formal (3 + 3)-cycloaddition of *N*-vinylpyrroles with 1,3-

---

[*] Corresponding author.
[**] Corresponding author.

E-mail addresses: m.efremova@2012.spbu.ru (M.M. Efremova), a.molchanov@spbu.ru (A.P. Molchanov).

https://doi.org/10.1016/j.tet.2018.07.040

dipoles in the presence of a Lewis acids [12g] represents a prospectively new way for the synthesis of polycyclic systems containing condensed pyrrole fragment. Earlier, the effect of the addition of Lewis acids on the reaction path has been shown for only one type nitrones (acyclic *C*-arylaldonitrones, *Z*-nitrones) and only one type azomethine imines (*N,N*-cyclic azomethine imines derived from pyrazolidin-3-ones). At the same time, it is known that dipoles with different geometry have diverse reactivity and also can give different stereochemical results when they interact with dipolarophiles [2].

In this work, we first investigated the reactions of *N*-vinylpyrroles with bicyclic 1,3-dipoles derived from 3,4-dihydroisoquinoline: 3,4-dihydroisoquinoline-*N*-oxides (cyclic, *E*-nitrones) and (3,4-dihydroisoquinolin-2-ium-2-yl)amides (*C,N*-cyclic azomethine imines) and demonstrated the effect of Lewis acids on the direction and selectivity of processes.

2. Results and discussion

At first, we investigated the reaction of *N*-vinylpyrroles with 3,4-dihydroisoquinoline-*N*-oxides without catalysts. Cycloaddition of these nitrones was carried out at 110 °C in toluene for 22–50 h (Table 1). The reaction proceeds regio- and diastereoselectively giving high yields of pyrrolyl-substituted tetrahydro-1*H*-isoxazolo[3,2-*a*]isoquinolines **3a**–**h** – the products of 1,3-dipolar cycloaddition with the vinyl double bond. The carrying out of the reaction at a lower temperature (80 °C, entry 9) does not lead to changes in the selectivity of the process. The relative configuration of cycloadduct **3b** was confirmed using X-ray diffraction analysis data (Fig. 1) [13]. The relative configuration of all adducts **3a-h** was assigned by analogy using the similarity of the ^{1}H NMR spectra: the spectra of the adducts contain signals of two methine protons of the isoxazolidine ring in the regions 4.81–5.01 ppm (m) and 6.02–6.59 ppm (dd, $J = 7.7$–8.01, 2.5–3.3 Hz). The signals of two methylene protons are in the region 2.54–3.53 ppm, but in most cases they overlap with the signals of other aliphatic protons.

It should be noted, that the products of 1,3-dipolar cycloaddition of 3,4-dihydroisoquinoline-*N*-oxides (*E*-nitrones) are only *trans*-isomers, while cycloaddition of acyclic *Z*-nitrones to *N*-vinylpyrroles gives *cis*-isomers predominantly [12a-c].

Earlier, we established that optimal yields and selectivity for catalytic (3 + 3)-cycloaddition of nitrones can be achieved using $Ni(ClO_4)_2 \cdot 6H_2O$ (20 mol%) in toluene at 80 °C [12f]. However, taking into account the differences in the structure and reactivity of nitrones we additionally optimize the reaction conditions for the interaction of *N*-vinylpyrrole **1a** with nitrone **2a** (Table 2). We used various Lewis acids, amount of catalysts and solvents.

We have tried to use nickel (II) perchlorate and three silver salts as a catalyst for the reaction. In all cases except for entry 11, the formal (3 + 3)-cycloaddition was observed instead of (3 + 2)-cycloaddition. Signals of the other products, including isoxazolidine **3a**, were not observed in appreciable amounts in ^{1}H NMR spectra of the crude reaction mixtures. Then silver acetate was used (entry 11), the reaction mixture did not contain any cycloadducts in appreciable amounts. In the case of using silver trifluoroacetate, the reaction proceeds with good diastereoselectivity (91:9), but only with a moderate yield (entry 9). For the reactions with nickel perchlorate we also varied solvent and amount of catalysts. The best results were obtained for the using of $Ni(ClO_4)_2 \cdot 6H_2O$, 10 mol% in toluene (entry 3), therefore these conditions have been used further. A further decrease in the amount of the catalyst leads to a decreasing of the yield of the cycloadducts (entry 4). The carrying out of the reaction at a higher temperature (110 °C, entry 9) are also results in a decreasing of the yield.

As can be seen from Table 3, in the case of *N*-vinylpyrroles **1a**, **d** the reaction with nitrones **2a, b** proceeds to form a mixture of diastereomeric tetrahydropyrrolo[2′,1':4,5][1,2,5]oxadiazino[3,2-*a*]isoquinolines **4a**–**d** and **4a'**–**d'**. (Table 3). In the case of pyrroles **1b** and **1c** the complex mixtures containing starting *N*-vinylpyrrole predominantly were obtained. The ^{1}H NMR spectrum of the reaction mixture of **1b** with **2a** contained less than 10% of the (3 + 2)-cycloadduct besides starting pyrrole and did not contain the characteristic signals of (3 + 3)-adducts. For reaction of **1c** with **2a** the signals of the (3 + 2)-cycloadducts (less than 20%) and presumably one (3 + 3)-adduct (less than 10%) were observed besides signals of starting **1c**. The reaction products were not separated.

Previously, the following mechanism was proposed for formal (3 + 3)-cycloaddition: it can be assumed that the reaction proceeds through the formation of the complex of Lewis acid with oxygen atom of nitrone which leads to an increase in the electrophilicity of the carbon atom of the dipole and also creates steric hindrances for the concerted process of 1,3-dipolar cycloaddition, subsequent electrophilic attack on C2-atom of the pyrrole ring, 1,7*H*-migration, and intramolecular cyclization lead to the final products [12g]. Instead of 1,7*H*-migration, the stepwise variant can be proposed: the rearomatisation of the pyrrole ring and ensuing enamine protonation to give the iminium form. Nitrone **2b** was less reactive than nitrone **2a** in the catalytic cycloaddition with pyrroles **1a** and **1c**. It can be rationalized due to it lower electrophilicity because of the presence of two electron-donating methoxy groups. The isomers were separated by column chromatography on silica gel. The ^{1}H NMR spectra of adducts **4a**–**d** contain signals of two methine protons of the oxadiazinane ring in the regions 5.15–5.21 ppm (s) and 5.55–5.72 ppm (m). The characteristic feature of both ^{1}H and ^{13}C NMR spectra of *trans*-isomers **4a**–**d** is the broadening of signals, which can be explained by inversion of isoquinoline nitrogen atom. For isomers **4a'**–**d'** the corresponding signals are shifted to the upfield (5.11–5.16 ppm, s) and downfield (5.71–5.72 ppm, q, $J = 5.5$–5.6 Hz) respectively. The relative configuration of the cycloadduct **4a** was confirmed using X-ray diffraction analysis data (Fig. 2) [14]. The relative configuration of the diastereomers **4a-d** and **4a'-4d'** was assigned by analogy using the similarity of the ^{1}H NMR spectra.

To evaluate the possibility of isomerization of the reaction products and the contribution of thermodynamic factors to stereoselectivity, pure isomers **4a** and **4a'** were heated at 80 °C in toluene with 10 mol% of $Ni(ClO_4)_2 \cdot 6H_2O$ during 3 h. In both cases, the mixtures of diastereomers were obtained. From pure **4a** a mixture was obtained with ratio **4a**:**4a'** 3.8:1, from **4a'** – mixture with ratio **4a**:**4a'** – 1:2. At the same time, product **3a** is not isomerized under the same condition, which indicates that it is not an intermediate in the formation of products **4**, and the presence of nickel perchlorate modifies the course of the reaction.

In order to study the dependence of diastereoselectivity on conversion the reaction process of **1a** with **2a** was monitored by ^{1}H NMR. Samples were taken every half hour for three hours (time required for complete conversion of nitrone). However, significant change in the ratio of isomers **4a** and **4a'** was not observed. Thus, it can be assumed that the product ratios reflect the thermodynamics of the various systems.

Next, we have investigated the influence of the addition of nickel perchlorate on the reaction path for the interaction of *N*-vinylpyrroles **1a**, **d** with *C,N*-cyclic azomethine imines **5a**, **b** also containing 3,4-dihydroisoquinoline framework. It has been established that the reactions proceeds only as (3 + 2)-cycloaddition by vinyl double bond giving hexahydropyrazolo[5,1-*a*]isoquinolines (Table 4).

The separation and purification of the reaction products were carried out using column chromatography on silica gel. In the absence of the catalyst *trans*-isomers are formed predominantly. ^{1}H