Tetrahedron 71 (2015) 4495–4499

Contents lists available at ScienceDirect

Tetrahedron

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

Acid-catalyzed [4+3] cycloaddition reaction of *N*-nosyl pyrroles

Miki Shibata [a], Ryuichi Fuchigami [b], Ryota Kotaka [a], Kosuke Namba [a,*], Keiji Tanino [c,*]

[a] *Pharmaceutical Science, Tokushima University, 1-78 Shomachi, Tokushima 770-8505, Japan*
[b] *Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo 060-0810, Japan*
[c] *Department of Chemistry, Faculty of Science, Hokkaido University, Kita-ku, Sapporo 060-0810, Japan*

ARTICLE INFO

Article history:
Received 20 January 2015
Received in revised form 18 February 2015
Accepted 19 February 2015
Available online 25 February 2015

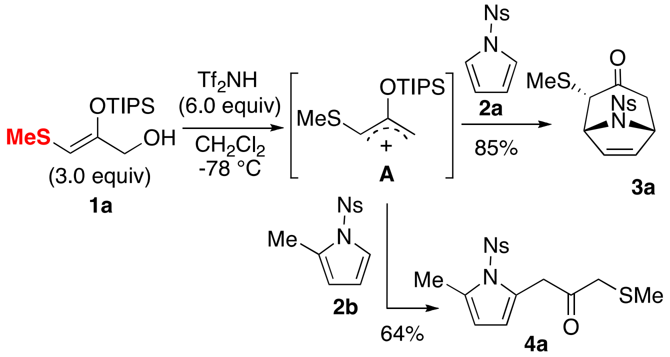
Keywords:
Tropane alkaloid
Tropinone
[4+3] Cycloaddition reaction
N-Nosyl pyrroles

ABSTRACT

An acid-catalyzed [4+3] cycloaddition reaction of *N*-nosyl pyrroles with 2-(*tert*-butyldimethylsilyloxy)acrolein has been developed. The reaction of 2-(silyloxy)acrolein with *N*-nosyl pyrrole was catalyzed by Tf_2NH, and a regio- and stereoselective reaction with 2-substituted *N*-nosyl pyrroles leading to tropinone derivatives possessing tetra-substituted carbon centers was also achieved. High regioselectivities were obtained by using $Cu(OTf)_2$ or $Sc(OTf)_3$ as a catalyst in nitromethane, and the reaction was applicable to various 2-substituted *N*-nosyl pyrroles in good yields and with high regioselectivities.

1. Introduction

Tropane alkaloids comprise a large family of natural products, and they have received a great deal of attention due to the variety of their pharmacological activities and to their structural diversity.[1] A [4+3] cycloaddition reaction of pyrroles with oxyallyl cations leading to tropinones is considered to be one of the most powerful synthetic approaches to the tropane scaffold.[2] However, while there are a number of reports concerning the [4+3] cycloaddition reactions of furans or cyclopentadienes,[2] the use of pyrroles as four-carbon units is generally difficult due to competition with the Friedel–Crafts-type reaction.[3] The oxyallyl cation species applicable to pyrroles have been confined to those generated from α,α′-dihaloketones[4] or allenamides.[5] Recently, we found that oxyallyl cations stabilized by sulfur atoms were also useful three-carbon units for [4+3] cycloaddition reactions with *N*-nosyl pyrroles.[6,7] For example, the sulfur-stabilized oxyallyl cation A, which was generated by the treatment of allyl alcohol **1a** with trifluoromethanesulfonimide (Tf_2NH) at −78 °C, reacted with *N*-nosyl pyrrole **2a** to afford tropinone **3a** in 85% yield (Scheme 1). The reaction was applicable to several *N*-nosyl pyrroles and oxyallyl cations to afford various tropinone derivatives. However, two key improvements have still been needed for the practical synthesis: (i) a large excess amount (6.0 equiv) of strong acid such as Tf_2NH was needed for the completion of the reaction, and (ii) the reaction was not applicable to the 2-substituted pyrrole derivatives. For example, the reaction of oxyallyl cation **A** with 2-methyl-*N*-nosyl pyrrole **2b** afforded only Friedel–Crafts-type analog **4a**, and the desired tropinone, possessing a tetra-substituted carbon center, was not obtained. Therefore, we tried to establish the highly reactive catalytic condition of the [4+3] cycloaddition reaction of oxyallyl cation with *N*-nosyl pyrroles.



Scheme 1. Previous [4+3] cycloaddition reaction of sulfur-stabilized oxyallyl cation with pyrroles.

2. Results/discussion

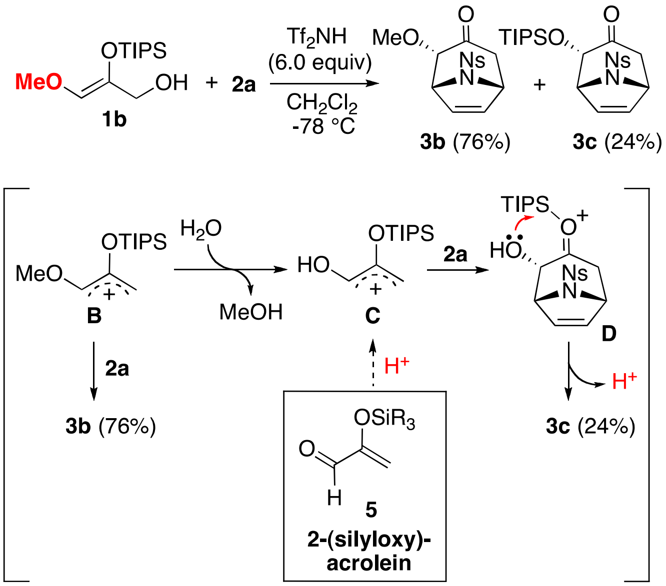
Since the sulfur atom was found to play a significant role in the stabilization of the oxyallyl cation, we were intrigued by oxygen's

---

* Corresponding authors. Tel.: +81 88 633 7293; fax: +81 88 633 8505 (K.N.); tel.: +81 11 706 2705; fax: +81 11 706 4920 (K.T.); e-mail addresses: namba@tokushima-u.ac.jp (K. Namba), ktanino@sci.hokudai.ac.jp (K. Tanino).

http://dx.doi.org/10.1016/j.tet.2015.02.071

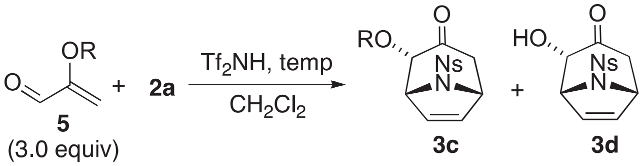
stabilizing effect. Thus, the similar [4+3] cycloaddition reaction of allyl alcohol **1b**, which possesses a methoxy group instead of the methylthio group of **1a**, was examined. Treatment of the mixture of **1b** and **2a** in dichloromethane with 6 equiv of Tf_2NH at −78 °C afforded the desired cycloadduct **3b** in 76% yield, along with TIPS analog **3c** in 24% yield (Scheme 2). The stereostructure of each of these compounds has determined by the NOE experiments, indicating that **3b** possesses the methoxy group and the nitrogen atom on the opposite face of the seven-membered ring (*endo*-type stereochemistry). Although the by-product **3c** was obtained, the conversion into tropinones proceeded quantitatively. Therefore, the oxygen atom was expected to be a better stabilizer of oxyallyl cation. The formation of **3c** was suggested that the oxyallyl cation **B**, which was generated by the dehydration of **1b** under acidic conditions, was converted into hydroxyl analog **C** by the addition of water and the elimination of methanol, although most of the oxyallyl cation **B** directly reacted with **2a** to give **3b**. The reaction of oxyallyl cation **C** with **2a** afforded cycloadduct **D**, which was converted into **3c** by the migration of the TIPS group from a carbonyl oxygen to a hydroxyl group, simultaneously regenerating protons (Scheme 2). On the basis of the side reaction leading to **3c**, we newly planned the reaction of *N*-nosyl pyrroles with the oxyallyl cation **C**, which would also be generated from 2-(silyloxy)acrolein **5**. The pioneering [4+3] cycloaddition reaction using 2-(trimethylsilyloxy)acrolein as a three-carbon unit was reported by Sasaki, and the reaction with cyclopentadiene proceeded in the presence of 1.0 equiv of $SnCl_4$.[8] Recently, Harmata established an efficient method for the preparation of 2-(silyloxy)acroleins and developed stereoselective catalytic conditions for various dienes and furanes.[9–11] Furthermore, Funk also established a method for preparing 3-substituted-2-(silyloxy)acroleins on the basis of their synthesis of 2-(acyloxy)acroleins,[12] and they demonstrated that their [4+3] cycloaddition reaction was applicable to the total synthesis of complex natural product cortistatin J.[13] Although there has not been an example of the application of 2-(silyloxy)acrolein to pyrroles as four-carbon units,[14] *N*-nosyl pyrroles were considered to be applicable based on the result of **3c**. Furthermore, the use of 2-(silyloxy)acrolein has the potential to translate the previous [4+3] cycloaddition reaction from an excess amount of strong acid to catalytic amount.



Scheme 2. Application to oxygen-stabilized oxyallyl cation.

We first investigated the reaction of 2-(triisopropylsilyl(TIPS)oxy)acrolein **5a** with *N*-nosyl pyrrole **2a** under the previous stoichiometric conditions. As we expected, treatment of the mixture of **2a** and **5a** in dichloromethane with 6 equiv of Tf_2NH at −78 °C afforded the desired cycloadduct **3c** in 85% yield (entry 1). The desired result of the stoichiometric reaction using 2-(silyloxy)acrolein **2a** encouraged us to develop the catalytic condition. However, a similar reaction using 20 mol % of Tf_2NH did not proceed, and only starting material **2a** was recovered (entry 2). On the other hand, when the reaction was conducted at room temperature, **3c** was obtained in 89% yield (entry 3). Although the amount of Tf_2NH could be reduced to 10 mol % without a significant loss of yield (entry 4), the use of 5 mol % of catalyst showed a decline in yield because the three-carbon unit **5a** decomposed faster than the consumption of pyrrole **2a** (entry 5). On the other hand, when more reactive 2-(*tert*-butyldimethylsilyl(TBS)oxy)acrolein **5b** was used as a three-carbon unit, the yield of cycloadducts was reduced to 69% as a 1:1 mixture of **3c** and desilylated **3d** (entry 6). As the reactivity of **5b** seemed to be too high, the reaction was conducted at 0 °C to afford cycloadducts **3c** and **3d** in 94% yield as a 5:1 mixture. The mixture of cycloadducts was quantitatively converged on either **3c** or **3d** by treatment with TBSCl or TBAF, respectively. Therefore, we successfully established an efficient catalytic condition for the [4+3] cycloaddition reaction of oxyallyl cation with pyrroles (Table 1).

Table 1
Catalytic [4+3] cycloaddition reaction of 2-(silyloxy)acrolein with **2a**



Entry	3-carbon Unit	Acid (mol %)	Temp (°C)	Time (h)	Yield (%)[a]	
					3c	3d
1	**5a**:R=TIPS	600	−78	1.0	85	0
2	**5a**	20	−78	3.0	0	0
3	**5a**	20	rt	3.0	89	0
4	**5a**	10	rt	3.0	85	0
5	**5a**	5	rt	4.5	60	0
6	**5b**: R=TBS	10	rt	2.5	35	34
7	**5b**	10	0	3.0	78	16

[a] Isolated yield.

Having established the catalytic condition, we next examined the catalytic reaction with 2-substituted pyrroles (Table 2). As the reaction of previous sulfur-stabilized allyloxy cation **A** with 2-methyl pyrrole **2b** did not give the cycloadduct, the [4+3] cycloaddition reaction of 2-substituted pyrroles has been generally difficult. Therefore, although this reaction is an attractive method of constructing tetra-substituted carbon centers, there have been very few examples of the cycloaddition reaction with 2-substituted pyrroles.[2,3a] Furthermore, the catalytic condition has so far not been achieved. Thus, we first tried to apply the established catalytic condition for *N*-nosyl pyrrole **2a** to *N*-nosyl-2-methyl pyrrole **2b**. Since the cycloadducts from **2a** were obtained as a mixture of silylated **3c** and desilylated **3d**, the mixture of cycloadducts was decided to converge on the silylated product by subsequent treatment with TBSCl, $AgNO_3$, and pyridine in DMF.[15] Treatment of the mixture of **2b** and 2.0 equiv of **5b** in dichloromethane with 10 mol % of Tf_2NH followed by silylation afforded cycloadduct **3e** and regioisomer **6** in 29% yield as a 3:2 mixture (entry 1). Although the yield and regioselectivity were not high, the first example of the catalytic cycloaddition reaction of 2-substituted pyrrole