



Concise [4+3] cycloaddition reaction of pyrroles leading to tropinone derivatives

Ryuichi Fuchigami^a, Kosuke Namba^{b,*}, Keiji Tanino^{b,*}

^a Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo 060-0810, Japan

^b Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

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ABSTRACT

A concise [4+3] cycloaddition reaction of pyrroles with 2-(silyloxy)allyl cations has been developed. The oxyallyl cations stabilized with a methylthio group or geminal methyl groups were generated from the corresponding allylic alcohols under the influence of a Brønsted acid (Tf₂NH), respectively. The use of *N*-nosyl-protected pyrroles as the four-carbon unit was found to give tropinone derivatives in high yield.

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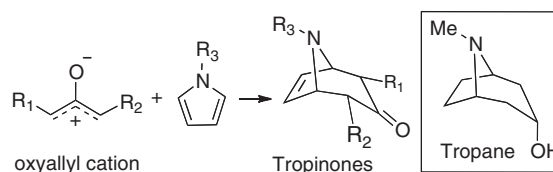
Tropane alkaloids, which comprise a large family of natural products, have received a great deal of attention due to their variety of pharmacological activities and structural diversities.¹ In particular, atropine, cocaine, and scopolamine are famous lead compounds of pharmaceuticals,² stemofoline³ and himandrine⁴ are also known as a class of challenging synthetic targets. One of the most powerful synthetic approaches to tropane scaffold may be a [4+3] cycloaddition reaction of pyrroles with oxyallyl cations, giving rise to tropinones (Scheme 1).⁵

While there are a number of reports concerning the [4+3] cycloaddition reactions of furans or cyclopentadienes,⁵ the use of pyrroles as four-carbon units is generally difficult due to competition with the Friedel–Crafts type reaction.⁶ The oxyallyl cation species applicable to pyrroles thus far have been confined to those generated from α,α' -dihaloketones⁷ or allenamides.⁸ On the other hand, one of the authors reported the regio- and stereo-selective [3+2] cycloaddition reactions using allyl acetates **1a** and **1b** as a three-carbon unit (Scheme 2).⁹ Under the influence of EtAlCl₂, allyl acetate **1** reacted with alkene **2** to afford cyclopentanone **3** in good yield. In this reaction, the methylthio group of **1** plays an important role in stabilizing the allyl cation species **A** as well as controlling the regioselectivity of the cycloadditions.¹⁰

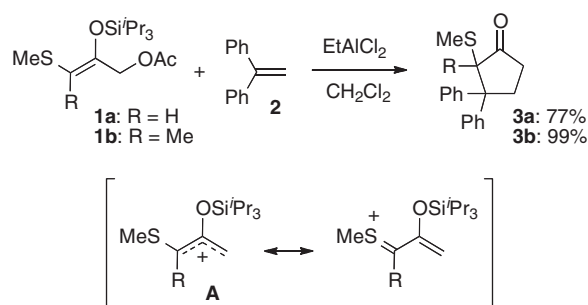
These results led us to examine the [4+3] cycloaddition reaction of **1** with pyrrole derivatives. Herein, we describe concise [4+3] cycloaddition reactions of 2-(silyloxy)allyl cations stabilized by a

methylthio group or *gem*-dialkyl groups with pyrroles having various substituents.

The 2-nitrobenzenesulfonyl (nosyl, Ns) group,¹¹ which can be removed under mild conditions, was chosen for protection of the



Scheme 1. The [4+3] cycloaddition reaction of oxyallyl cation with pyrrole derivative.

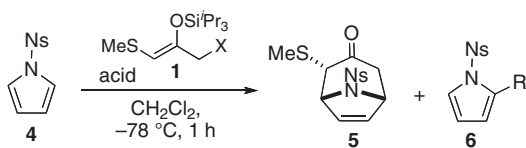


Scheme 2. The [3+2] cycloaddition reaction using sulfur-stabilized siloxyallyl cations.

* Corresponding authors. Tel.: +81 11 706 2703; fax: +81 11 706 4920 (K.N.); tel.: +81 11 706 2705; fax: +81 11 706 4920 (K.T.).

E-mail addresses: namba@mail.sci.hokudai.ac.jp (K. Namba), ktanino@sci.hokudai.ac.jp (K. Tanino).

Table 1
The reactions of **4** with three-carbon units **1** promoted by an acid^a



| Entry | 1:X | Acid | Yield ^b (%) | |
|-------|--------------------------------|---------------------|------------------------|----|
| | | | 5 | 6 |
| 1 | 1a :OAc | EtAlCl ₂ | 15 | 0 |
| 2 | 1a :OAc | Tf ₂ NH | 34 | 27 |
| 3 | 1c :OCO ₂ Me | Tf ₂ NH | 54 | 0 |
| 4 | 1d :OH | Tf ₂ NH | 85 | 5 |
| 5 | 1d :OH | TfOH | 41 | 38 |

R = CH₂C(O)CH₂SMe.

^a Conditions: *N*-nosyl pyrrole (0.10 mmol), **1** (0.30 mmol), acid (0.60 mmol), CH₂Cl₂ (0.2 M).

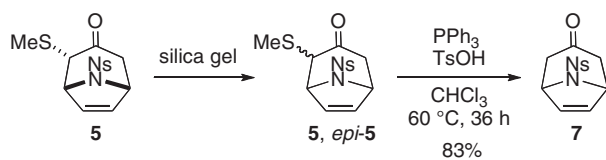
^b Isolated yield.

nitrogen atom. The reactions of *N*-nosyl pyrrole (**4**) with **1a** or its derivatives under acidic conditions are summarized in Table 1.

While the reaction of **4** with **1a** promoted by EtAlCl₂ led to the formation of cycloadduct **5** in 15% yield (entry 1),¹² the use of a Brønsted acid was found to be more effective for the desired transformation. Thus, under the influence of trifluoromethanesulfonamide (Tf₂NH), tropinone **5** was obtained in 34% yield along with 27% of **6** (entry 2). Interestingly, the Tf₂NH-promoted reaction of **4** with carbonate **1c** gave 54% of **5** (entry 3), and the yield increased to 85% with alcohol **1d**⁹ (entry 4).¹³ On the other hand, the use of trifluoromethanesulfonic acid (TfOH) instead of Tf₂NH in the reaction of **4** and **1d** resulted in decrease of **5** (entry 5), probably because of the low solubility of TfOH in dichloromethane.

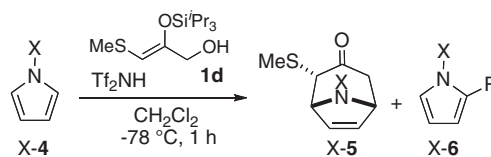
It is noteworthy that tropinone **5** was produced as a single diastereomer which underwent partial isomerization to afford *epi*-**5** by chromatography on silica gel. The stereostructure of these compounds was determined by the NOE experiments, indicating that **5** possesses the methylthio group and the nitrogen atom on the opposite face of the seven-membered ring (endo-type stereochemistry). The methylthio group of **5** was easily removed by treating with PPh₃ and *p*-toluenesulfonic acid (TsOH) to give tropinone **7** in good yield, according to the desulfurization protocol of Durst (Scheme 3).¹⁴ Thus, the [4+3] cycloaddition reaction using sulfur-stabilized 2-(silyloxy)allyl cation is proven to be a concise and effective method for the preparation of tropinone derivatives.¹⁵

Next, the [4+3] cycloaddition reaction of pyrroles possessing various protecting groups (X) with allyl alcohol **1d** was examined (Table 2). While *N*-(*p*-toluenesulfonyl) and *N*-methanesulfonyl pyrroles Ts-**4** and Ms-**4** afforded the corresponding tropinones Ts-**5** and Ms-**5** in low yields, respectively (entries 2 and 3), *N*-benzyloxycarbonyl (Cbz), *N*-acetyl (Ac), *N*-benzyl (Bn), and unsubstituted pyrroles failed to undergo the cycloaddition reaction (entries 4–7). These results suggest that the electron-withdrawing inductive effect of the protecting group (Ns > Ts, Ms > Ac, Cbz) is of more significance than the steric bulkiness.¹⁶



Scheme 3. Desulfurization of cycloadduct **5**.

Table 2
Comparison of the protecting group on pyrrole^a



| Entry | X | Yield ^b (%) | |
|-------|-----|------------------------|----------------|
| | | X-5 | X-6 |
| 1 | Ns | 85 | 5 |
| 2 | Ms | 33 | 30 |
| 3 | Ts | 46 | 23 |
| 4 | Cbz | 0 | 9 ^c |
| 5 | Ac | 0 | 23 |
| 6 | Bn | 0 | 0 |
| 7 | H | 0 | 0 |

R = CH₂C(O)CH₂SMe.

^a Conditions: pyrrole X-**4** (0.10 mmol), **1d** (0.30 mmol), Tf₂NH (0.60 mmol), CH₂Cl₂ (0.2 M).

^b Isolated yield.

^c NMR yield using CHBr₃ as an internal standard.

Having established the suitable conditions of the [4+3] cycloaddition reaction, the scope of the tropinone synthesis was examined (Table 3). Although the reaction of *N*-nosyl-2-methylpyrrole (**8**) led to the formation of the Friedel–Crafts product **13** (entry 1), 3-methylpyrrole (**9**) underwent the desired [4+3] cycloaddition reaction at –60 °C to afford tropinone **14** in 71% yield as a single product (entry 2). The configuration of **14** and the stereochemical relationship between the methyl group and the methylthio group were determined by the ¹H–¹H COSY and the NOE experiments. Similarly, tropinone **15** was obtained from the corresponding pyrrole **10** in a regio- and stereoselective manner, albeit in low yield due to the instability of the vinyl bromide moiety.¹⁷

The reaction of methyl-substituted three-carbon unit **11** with pyrrole **4** at 0 °C afforded the desired cycloadduct **16** in 55% yield. The three-carbon unit **12** having a methyl group at the other side also gave cycloadduct **17** as a single regio- and stereoisomer, while the yield was low.

Next, the stabilizing effect of a methylthio group on the 2-(silyloxy)allyl cation was compared with that of an alkyl group (Table 4). The reaction of allyl alcohol **18** with **4** under the influence of Tf₂NH gave neither cycloadduct **7** nor a Friedel–Crafts type product (entry 1), and allyl alcohol **19** possessing a methyl group instead of the methylthio group of **1d** also failed to undergo the [4+3] cycloaddition reaction (entry 2). On the other hand, the use of *gem*-dimethyl-substituted derivative **20** led to the formation of the desired cycloadduct **22** in 54% yield (entry 3). These results indicate that a *gem*-dimethyl group is as effective as a methylthio group in stabilizing a 2-(silyloxy)allyl cation, while a single methyl group of **19** is not sufficient for this purpose. Furthermore, we later found that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) is a better solvent for the reaction of *gem*-dimethyl-substituted analog **20**, and the yield of **22** was increased to 67% (entry 3).¹⁸ In contrast to the reaction of 2-methylpyrrole **8** with alcohol **1d** which gave only substituted pyrrole **13** (entry 1 in Table 3), cycloadduct **23** was obtained by the use of **20** as the three-carbon unit (entry 4). It is noteworthy that the regiochemical outcome of the reaction of alcohol **20** is also different from that of the sulfur-containing alcohol **1d**. Thus, for the reactions with 3-methylpyrrole **9**, alcohol **20** afforded a 1:1 regioisomeric mixture of cycloadducts **24a** and **24b** in 65% yield (entry 5), while the use of **1d** resulted in the formation of cycloadduct **14** as a single regioisomer (entry 2 in Table 3).

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