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

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ABSTRACT

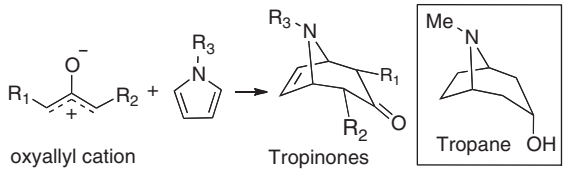
A concise [4+3] cycloaddition reaction of pyrroles with 2-(silyloxy)allyl cations has been developed. The oxyallyl cations stabilized with a methylthio group or geminal methyl groups were generated from the corresponding allylic alcohols under the influence of a Brönsted acid (Tf_2NH), respectively. The use of *N*-nosyl-protected pyrroles as the four-carbon unit was found to give tropinone derivatives in high yield.

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] stemofoline[3] and himandrine[4] 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]

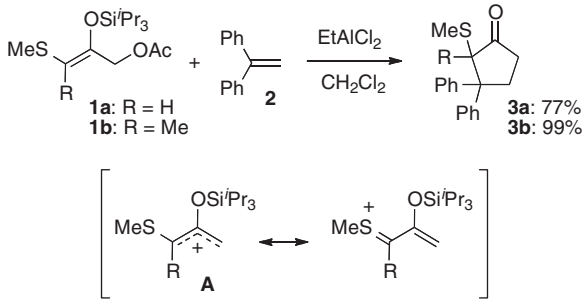
While there are a number of reports concerning the [4+3] cycloaddition reactions of furans or cyclopentadienes,[5] the use of pyrroles as four-carbon units is generally difficult due to competition with the Friedel–Crafts type reaction.[6] The oxyallyl cation species applicable to pyrroles thus far have been confined to those generated from α,α′-dihaloketones[7] or allenamides.[8] On the other hand, one of the authors reported the regio- and stereoselective [3+2] cycloaddition reactions using allyl acetates **1a** and **1b** as a three-carbon unit (Scheme 2).[9] Under the influence of $EtAlCl_2$, 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 cycloadducts.[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.

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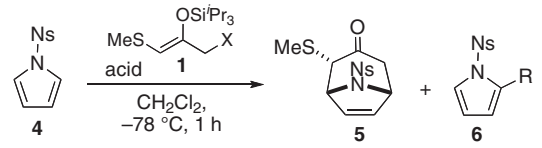
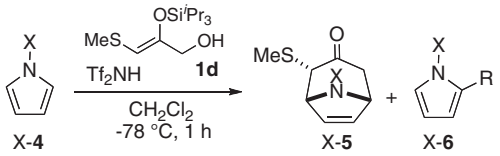
Table 1
The reactions of **4** with three-carbon units **1** promoted by an acid[a]



Entry	**1**:X	Acid	Yield[b] (%)	
			5	**6**
1	**1a**:OAc	$EtAlCl_2$	15	0
2	**1a**:OAc	Tf_2NH	34	27
3	**1c**:OCO_2Me	Tf_2NH	54	0
4	**1d**:OH	Tf_2NH	85	5
5	**1d**:OH	TfOH	41	38

R = $CH_2C(O)CH_2SMe$.
[a] Conditions: *N*-nosyl pyrrole (0.10 mmol), **1** (0.30 mmol), acid (0.60 mmol), CH_2Cl_2 (0.2 M).
[b] Isolated yield.

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

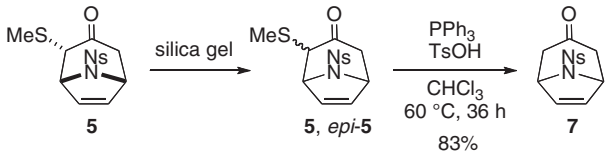
R = $CH_2C(O)CH_2SMe$.
[a] Conditions: pyrrole X-**4** (0.10 mmol), **1d** (0.30 mmol), Tf_2NH (0.60 mmol), CH_2Cl_2 (0.2 M).
[b] Isolated yield.
[c] NMR yield using $CHBr_3$ as an internal standard.

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 $EtAlCl_2$ led to the formation of cycloadduct **5** in 15% yield (entry 1),[12] the use of a Brönsted acid was found to be more effective for the desired transformation. Thus, under the influence of trifluoromethanesulfonimide (Tf_2NH), tropinone **5** was obtained in 34% yield along with 27% of **6** (entry 2). Interestingly, the Tf_2NH-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 Tf_2NH 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 PPh_3 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]



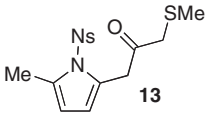
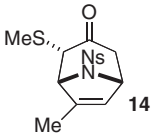
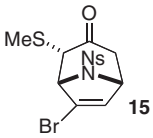
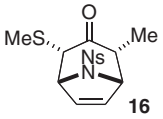
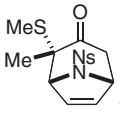
Scheme 3. Desulfurization of cycloadduct **5**.

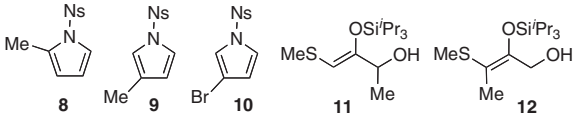
Having established the suitable conditions of the [4+3] cycloaddition reaction, the scope of the tropinone synthesis was examined (Table 3). Although the reaction of *N*-nosyl-2-methylpyrrole (**8**) led to the formation of the Friedel–Crafts product **13** (entry 1), 3-methylpyrrole (**9**) underwent 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 Tf_2NH 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).

Table 3
Substrate scope in the [4+3] cycloaddition reactions

Entry	Pyrrole	Alcohol	Conditions	Product	Yield[a] (%)
1	**8**	**1d**	−78 °C 60 min	 **13**	64
2	**9**	**1d**	−60 °C 120 min	 **14**	71
3	**10**	**1d**	−40 °C 10 min	 **15**	30
4	**4**	**11**	0 °C 3 min	 **16**	55
5	**4**	**12**	0 °C 5 min	 **17**	25



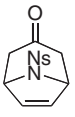
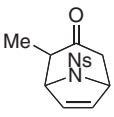
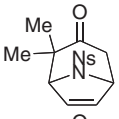
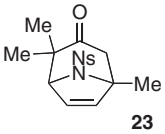
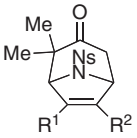
Conditions: *N*-nosyl pyrrole (0.10 mmol), allyl alcohol (0.30 mmol), Tf_2NH (0.60 mmol), CH_2Cl_2 (0.2 M).
[a] Isolated yield.

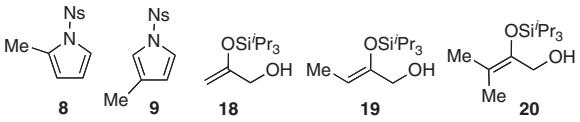
Finally, the utility of the present [4+3] cycloaddition reaction was demonstrated through the synthesis of tricyclic compound **28**, possessing a common framework with biologically active natural products such as *Daphniphyllum* alkaloids.[19] Ketone **26**, which was prepared from pyrrole **25** and alcohol **20** via a [4+3] cycloaddition reaction, was converted to the corresponding enol silyl ether **27**. Treatment of **27** with silver (I) trifluoroacetate[20] effected the intramolecular alkylation reaction to provide the desired tricyclic compound **28** in 46% yield from ketone **26** (Scheme 4).

In conclusion, the [4+3] cycloaddition reaction of pyrroles leading to various tropinones was developed.[20] The use of *N*-nosyl pyrrole derivatives was found to afford the desired cycloadducts in good yields. The 2-(silyloxy)allyl cation was generated by treating the corresponding allyl alcohol with Tf_2NH, while the cation-stabilizing effect of a methylthio group or a *gem*-dimethyl group was essential for generation of the reactive species. The present [4+3] cycloaddition protocol provides a powerful method for constructing substituted tropane skeleton, and the applications to the synthesis of complex natural products are currently underway in our laboratory.[†]

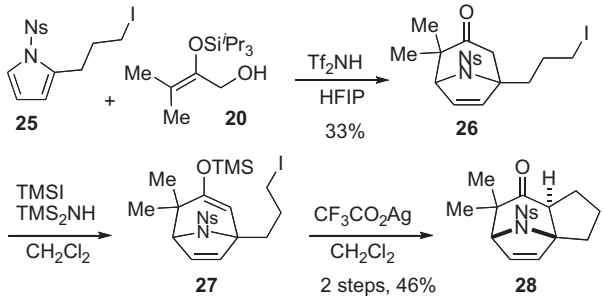
[†] OLE: Object Linking and Embedding; a program-integration technology you can use to share information between programs. All of the Office programs support OLE, so you can share information through linked and embedded objects. For instance you can import an Excel® graph into Word® by using 'Paste special. . ..' on the 'Edit' menu or, essentially the same, using the option on the 'Tables and figures' menu.

Table 4
The [4+3] cycloaddition reactions of *N*-nosyl pyrroles with siloxyallyl alcohol derivatives having no methylthio group

Entry	Pyrrole	Alcohol	Product	Yield[a] (%)
1	**4**	**18**	 **7**	0
2	**4**	**19**	 **21**	0
3	**4**	**20**	 **22**	67 (54)[b]
4	**8**	**20**	 **23**	48(20)[b]
5	**9**	**20**	 **24a**: R^1=Me, R^2=H **24b**: R^1=H, R^2=Me	65 (47)[b]



Reaction conditions: *N*-nosyl pyrrole (0.10 mmol), allyl alcohol (0.30 mmol), Tf_2NH (0.60 mmol), HFIP (0.2 M), 0 °C, 30 min.
[a] Isolated yield.
[b] The reaction was conducted in dichloromethane at 0 °C.



Scheme 4. Synthesis of tricyclic ketone **28** via a [4+3] cycloaddition reaction.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.130.

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11. For review, see: Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359.
12. The yield of 5 was substantially increased up to 66% when the reaction temperature was elevated to −40 °C.
13. The reaction using catalytic amount of Tf_2NH (10 mol %) did not proceeded at −78 °C, and the nosylpyrrole 4 (quant) and three carbon unit 1d (90%) were recovered after 1 h. The similar reaction with increasing temperature induced only decomposition of 1d.
14. Connolly, T. J.; Durst, T. *Synlett* **1996**, 663–664.
15. Typical procedure: To a solution of Tf_2NH (169 mg, 0.60 mmol) in CH_2Cl_2 (0.25 mL) was added a mixture of 1d (83 mg, 0.30 mmol) and 4 (25.2 mg, 0.1 mmol) in CH2Cl2 (0.25 mL) at −78 °C. After the mixture was stirred at −78 °C for 1 h, the reaction was quenched with a 3 M aqueous NaOH solution at −78 °C. The mixture was extracted with CH_2Cl_2 (×2), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column choromatography (elution with hexane/ethyl acetate = 3/1 to 2/1) to give 5 (30 mg, 85%) as a pale brown solid.
16. Decomposition and polymerization of nosyl-protected pyrroles were not observed even in the excess amount of strong acid such as Tf_2NH. The [4+3] cycloadducts were also sufficiently stable until completion of the reaction, although the prolonged period of the reaction induced decomposition of cycloadducts. The strong electron-withdrawing inductive effect of *N*-nosyl group was considered to suppress the retro-Mannich reaction leading to Friedel–Crafts type by-products and decomposition. Decomposition and polymerization of pyrroles were observed when other protecting groups, not involving sulfonamides, were used.
17. After quenching the reaction, 15 was stable enough to be purified by column chromatography and stored for several months in the freezer.
18. The use of HFIP as a solvent for the reaction of methylthio-substituted analog 1d was not effective.
19. For recent review on the *Daphniphyllum* alkaloids, see: Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936–962.
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