

# One-pot synthesis of tropinone by tandem (domino) ene-type reactions of acetone silyl enol ethers

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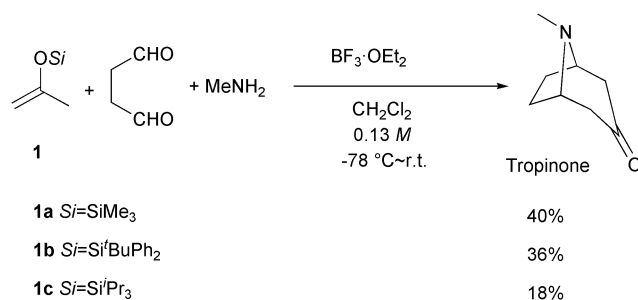
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A synthetic approach for tropane alkaloids on the basis of tandem (domino) ene-type reactions of acetone silyl enol ethers with iminium ions is shown to be triggered by intermolecular ene-type reactions followed by 6-(2,5) silatropic ene-type cyclizations.

Tropane alkaloids<sup>1</sup> have received much attention as synthetic target molecules, because many of them reveal remarkable biological activity and their unique structural feature, the so-called tropane skeleton. Willstätter achieved the first synthesis of a tropane alkaloid, tropinone through a long sequence of reactions.<sup>2</sup> A number of synthetic studies have since been reported, which can be classified principally into five categories: iminium cyclization,<sup>3,4</sup> cycloaddition reaction,<sup>5</sup> conjugate addition,<sup>6</sup> transition metal mediated reaction,<sup>7</sup> and rearrangement.<sup>8</sup>

Among them, Robinson's pioneering synthesis using acetonedicarboxylic acid, methylamine and succinaldehyde is noteworthy but requires the further operations of acidification and thermal decarboxylation to obtain the final product, tropinone. Herein, we report the one-pot synthesis of the tropane alkaloid based on tandem (domino)<sup>9</sup> ene-type reactions of acetone silyl enol ethers **1** without acidification and decarboxylation. In the tandem (domino) reaction sequence, the first carbon-carbon bond formation would proceed *via* intermolecular ene-type reactions<sup>10</sup> accompanied by 6-(2,5) silatropic ene cyclizations, following [1,5]-hydrogen shift systems (*vide infra*).<sup>13</sup>

As expected, tropinone was found to be synthesized in one-pot with succinaldehyde and methylamine in CH<sub>2</sub>Cl<sub>2</sub> followed by the addition of acetone silyl enol ether **1** and BF<sub>3</sub>·OEt<sub>2</sub> at -78 °C (Scheme 1).



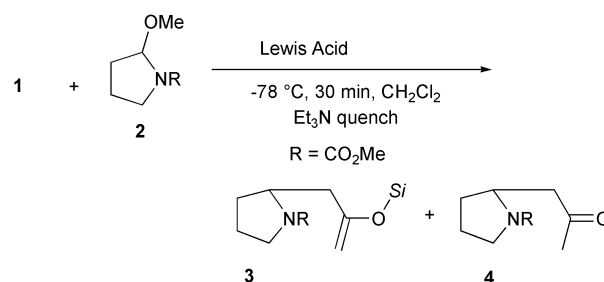
Scheme 1

The sterically less demanding trimethylsilyl enol ether gave a better yield presumably because of the higher silyl-migratory aptitude.

In order to clarify the first carbon-carbon bond formation process, the reaction of silyl enol ether **1a-c** and monomethoxy pyrrolidine **2**<sup>4d</sup> was examined in the presence of Lewis acids such as BF<sub>3</sub>·OEt<sub>2</sub> and TMSOTf (Scheme 2).

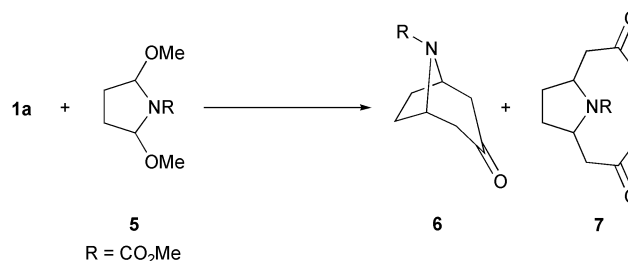
Significantly, silyl enol ether **3** was indeed obtained *via* a prototropic ene-type reaction with only a trace amount of ketone **4**.

When the reaction of dimethoxypyrrolidine **5**<sup>14</sup> with **1a** was carried out, tropinone derivative **6** was obtained albeit in low yields (9%) with bis-adduct **7** (22%) (Scheme 3).



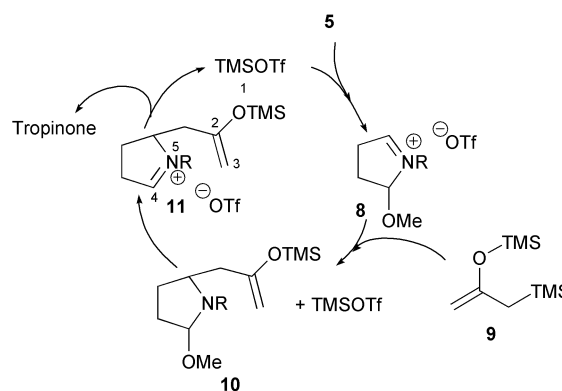
Entry	1	Lewis Acid	3 (%Yield)	4 (%Yield)
1	1a	TMSOTf	73	0
2	1b	TMSOTf	75	trace
3	1c	BF <sub>3</sub> ·OEt <sub>2</sub>	40	trace

Scheme 2



Scheme 3

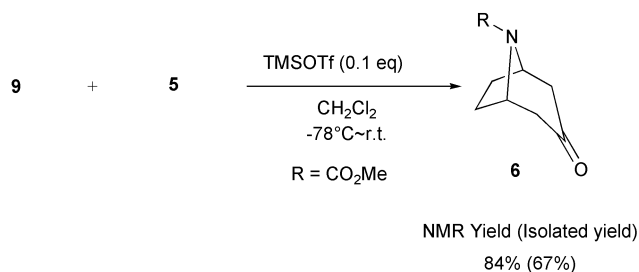
A catalytic use of TMSOTf with siloxyallylsilane **9**<sup>15</sup> should afford tropinone in higher yields *via* the sequential generation of iminium ions (**8** and then **11**) (Scheme 4). Iminium ion **8** generated by TMSOTf (cat.) would react with **9** to give silyl enol ether **10** accompanied by the reproduction of TMSOTf. Subsequently, the regioisomeric iminium ion **11** would be generated from **10** to give tropinone by six-membered ring formation *via* the (2,5) silyl-migratory ene-type reaction. Indeed, a model reaction of **9** with monomethoxypyrrolidine **2** in the presence of a catalytic amount of TMSOTf at -78 °C



Scheme 4

gave silyl enol ether **3**, which has a similar structure to **10**, in 68% yield (not shown).

Gratifyingly, the TMSOTf catalysed reaction between **9** and **5** afforded tropinone analogue **6** in a significantly higher yield than that obtained with silyl enol ether **1** (Scheme 5).



Scheme 5

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