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An intramolecular hetero Diels–Alder reaction of α-(alkynylsiloxy)aldimine derivatives

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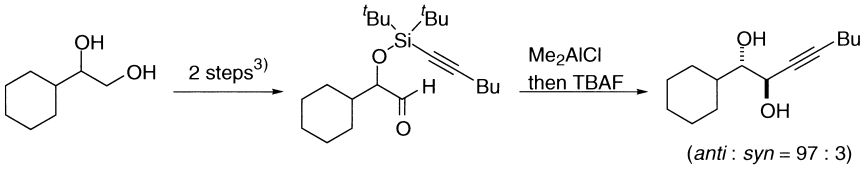
Abstract

Intramolecular hetero Diels–Alder reactions of α-(alkynylsiloxy)aldimine derivatives were developed. α-(Alkynylsiloxy)aldehydes, which were prepared from 1,2-alkanediols in two steps, were converted into the corresponding biscarbamates or *N*-arylimines. In the presence of $BF_3{\cdot}OEt_2$, the biscarbamates afforded oxazine derivatives in high diastereoselectivity. On the other hand, quinoline derivatives were obtained in good yields by treating the *N*-arylimines with trifluoromethanesulfonic acid.

Keywords: Diels–Alder reactions; imines; carbamates; alkynes; oxazines; quinolines.

Hetero Diels–Alder reactions of aldimine derivatives with various dienes provide a powerful methodology for the synthesis of nitrogen-containing compounds.[1] From a synthetic viewpoint, the intramolecular version of the cycloaddition reaction is particularly useful because of the high regio- and stereoselectivity.[2] On the other hand, we have recently reported a convenient method for the synthesis of α-(alkynylsiloxy)aldehydes from 1,2-alkanediols in two steps.[3] Under the influence of Me_2AlCl, the aldehyde underwent an intramolecular alkynylation reaction to yield an *anti* diol predominantly (Scheme 1).



Scheme 1.

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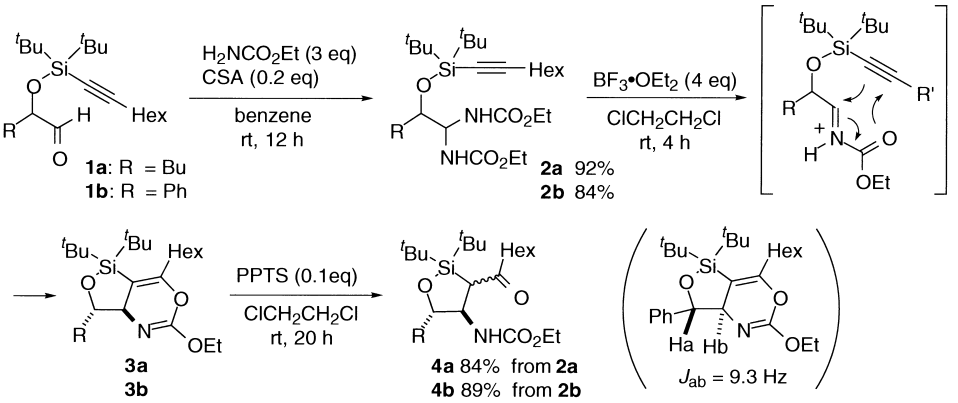
The high stereoselectivity of the above reaction led us to examine a similar transformation using the corresponding aldimine derivatives; the method was found, however, to afford bicyclic products through an intramolecular hetero Diels–Alder reaction.

At first, biscarbamates **2a** and **2b**, which were chosen as a precursor of an *N*-acyliminium intermediate,[4] were prepared in high yield by treating α-(alkynylsiloxy)aldehydes **1a** and **1b** with urethane and a catalytic amount of 10-camphorsulfonic acid (Scheme 2).[5] Treatment of the biscarbamates with $BF_3{\cdot}OEt_2$ induced an intramolecular hetero Diels–Alder reaction to give bicyclic oxazines **3a** and **3b** as a single isomer, respectively. The *trans* relationship between the phenyl group and the nitrogen atom of **3b** was determined by ^1H NMR spectra, in which the coupling constant between Ha and Hb has a fairly large (9.3 Hz) value. Since these oxazines proved to easily undergo hydrolysis by silica gel column chromatography, the cycloadducts were isolated as the corresponding ketocarbamates **4** after being treated with pridinium *p*-toluenesulfonate (PPTS).[6]



Scheme 2.

The stereochemistry of the intramolecular hetero Diels–Alder reaction can be rationalized by assuming transition state models **TS-1** and **TS-2**, both of which have the substituent R on the quasi equatorial position. Since **TS-2** suffers from gauche repulsion between the substituent R and the iminium ion moiety, the reaction would proceed mainly through **TS-1** to give the *anti*-product (Fig. 1).

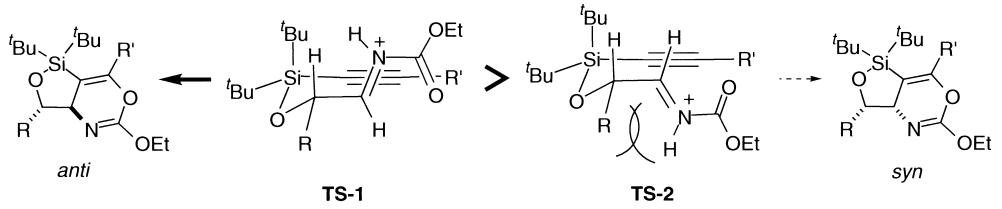
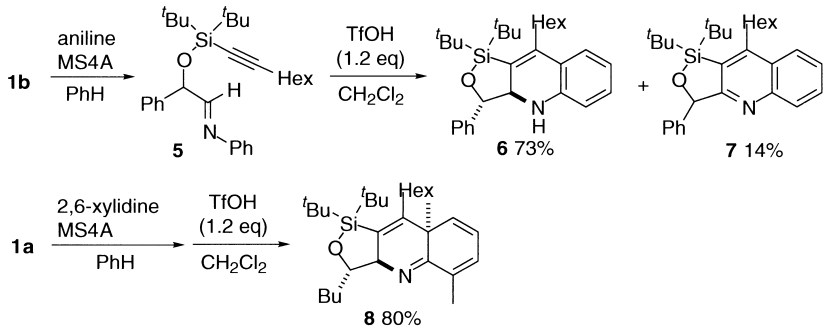


Figure 1.

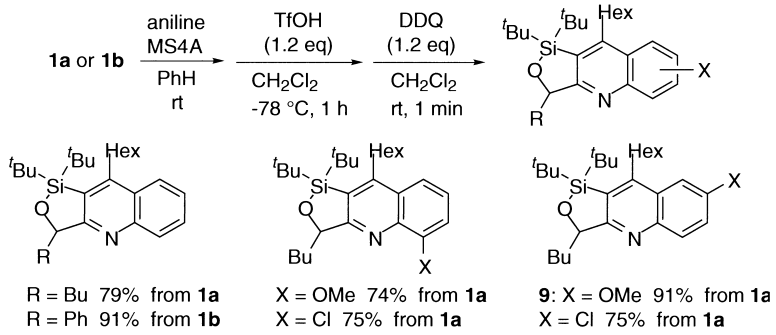
Next, α-(alkynylsiloxy)aldehyde **1b** was subjected to a condensation reaction with aniline in the presence of MS4A to afford *N*-arylimine **5**. Under the influence of trifluoromethanesulfonic acid, imine **5** gave dihydroquinoline derivative **6** along with a small amount of quinoline **7** via an

intramolecular hetero Diels–Alder reaction (Scheme 3).[7] In a similar manner, dihydroquinoline derivative **8**, having an angular methyl group was obtained from **1a** and 2,6-xylidine as a single diastereomer. The ^{1}H NMR spectra of **6** and **8** indicated the *anti*-stereochemistry at the five-membered ring, which would be explained by a transition state model similar to **TS-1** in Fig. 1.



Scheme 3.

The use of *o*- or *p*-substituted anilines resulted in the formation of quinoline derivatives having a functional group at the 6- or the 8-position, respectively. In these cases, the crude product of the Diels–Alder reaction was treated with DDQ to give the corresponding quinoline derivative, since some of the dihydroquinoline derivatives were fairly labile (Scheme 4).[8]



Scheme 4.

In conclusion, biscarbamates and *N*-aryl imine derivatives, which were prepared from α-(alkynylsiloxy)aldehydes, underwent intramolecular hetero Diels–Alder reactions under acidic conditions to give bicyclic compounds in good yield. Since α-(alkynylsiloxy)aldehydes, including optically active ones, can be easily prepared from the corresponding 1,2-alkanediols, the present reactions would provide a useful pathway for the synthesis of naturally occurring, nitrogen-containing compounds.

Acknowledgements

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5. Preparation of **2a**: A mixture of aldehyde **1a** (0.60 g, 1.7 mmol), urethane (0.45 g, 5.1 mmol), and camphorsulfonic acid (78 mg, 0.34 mmol) in benzene (3.4 mL) was stirred at room temperature for 24 h. A saturated aqueous solution of $NaHCO_3$ was added, and the mixture was separated. The aqueous layer was extracted with ether, and the combined organic layer was dried over $MgSO_4$. Concentration under reduced pressure followed by purification by flash chromatography afforded 0.82 g (92%) of biscarbamate **2a**. IR (neat) 3350, 1739, 1558, 1471, 1224, 1060 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, $J=7.1$ Hz, 3 H), 0.90 (t, $J=7.1$ Hz, 3 H), 1.04 (s, 18 H), 1.16–1.80 (m, 14 H), 2.29 (t, $J=7.0$ Hz, 2 H), 3.92–4.32 (m, 5 H), 5.20–5.50 (m, 2 H), 5.84 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.93, 14.05, 19.64, 20.61, 20.69, 22.49, 22.61, 22.71, 27.56 (6C), 28.29, 28.44, 31.19, 31.54, 60.58, 60.83, 61.13, 76.36, 79.34, 111.19, 155.02, 155.42.
6. Synthesis of ketocarbamate **4a**: A mixture of biscarbamate **2a** (0.23 g, 0.46 mmol) and $BF_3{\cdot}OEt_2$ (0.23 mL, 1.8 mmol) in dichloroethane (1.2 mL) was stirred at room temperature for 5 h. Usual work-up (see above) afforded cycloadduct **3a**, which was treated with PPTS (12 mg, 0.05 mmol) in dichloroethane (2.3 mL) at room temperature for 10 h. Usual work-up followed by purification by flash chromatography afforded 153 mg (84% from **2a**) of biscarbamate **4a**. IR ($CDCl_3$) 3440, 1720, 1510, 1420, 1270 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, $J=7.1$ Hz, 3 H), 0.91 (t, $J=7.3$ Hz, 3 H), 0.97 (s, 9 H), 1.18 (s, 9 H), 1.20–1.78 (m, 14 H), 2.45 (dt, $J=1.6$, 7.0 Hz, 2 H), 3.72–4.24 (m, 5 H), 4.92 (bs, 1 H).
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8. Synthesis of quinoline derivative **9**: A mixture of aldehyde **1a** (33 mg, 0.09 mmol), *p*-anisidine (13 μL, 0.11 mmol), and MS4A (65 mg) in benzene (0.45 mL) was stirred at room temperature for 3 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude imine was treated with trifluoromethanesulfonic acid (10 μL, 0.11 mmol) in dichlolomethane (0.45 mL) at –78°C for 30 min. Usual work-up afforded the corresponding dihydroquinoline derivative, which was treated with DDQ (25 mg, 0.11 mmol) in dichloroethane (0.45 mL) at room temprature for 1 min. Concentration under reduced pressure followed by purification by flash chromatography afforded 39 mg (91% from **1a**) of **9**: IR (neat) 1575, 1560, 1495, 1470, 1390, 1360, 1330, 1225, 1090, 1050 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (t, $J=7.3$ Hz, 3 H), 0.95 (t, J = 7.3 Hz, 3 H), 1.02 (s, 9 H), 1.13 (s, 9 H), 1.20–1.90 (m, 14 H), 2.10–2.40 (m, 1 H), 2.94–3.29 (m, 2 H), 3.94 (s, 3H), 5.10 (dd, $J=3.6$, 10.2 Hz, 1 H), 7.28 (d, $J=3.3$ Hz, 1 H), 7.37 (dd, $J=3.3$, 10.5 Hz, 1 H), 7.96 (d, $J=10.5$ Hz, 1 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.12, 14.32, 20.56, 22.49, 22.65, 22.86, 27.87 (3C), 28.32 (3C), 28.66, 30.16, 30.74, 31.63, 37.77, 38.22, 55.48, 82.05, 102.79, 121.51, 125.58, 126.72, 131.05, 145.08, 152.68, 156.74, 169.47.