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A Versatile Synthesis of Substituted Tetrahydropyridines

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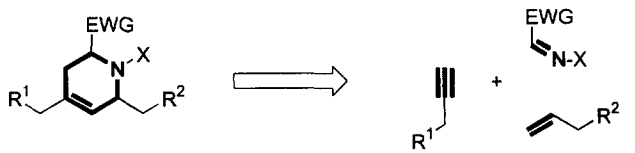
Abstract. A short and efficient synthesis of highly substituted tetrahydropyridines is achieved by a combination of enyne cross metathesis and aza-Diels-Alder reaction under high pressure. The reaction sequence shows atom economy and is compatible with a variety of functionalities being introduced by three building blocks: a monosubstituted alkyne, a terminal alkene, and an imine. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Metathesis; Diels-Alder reactions; Piperidines.

Piperidine-derived ring systems form the skeleton of many naturally occurring alkaloids. They exhibit a variety of biological activities and are found in numerous therapeutic agents.[1] Because of the ubiquitous nature of the piperidine-derived sub-structure in natural products and its biological properties much effort has been devoted to the development of synthetic strategies.[2]

Herein we report an application of olefin metathesis followed by an aza-Diels-Alder transformation as an efficient and flexible access towards tetrahydropyridines. The availability of well-defined catalysts, in particular Grubbs' ruthenium initiator[3] $Cl_2(PCy_3)_2Ru{=}CHPh$ (**[Ru]**, Cy = cyclohexyl), tolerating a variety of functional groups has considerably widened the scope of olefin metathesis as a very mild and competitive method of C,C-bond formation.[4] During our research involving metathesis reactions as key steps for new synthetic methodology we recently presented a **[Ru]**-catalyzed selective crossed metathesis reaction between terminal alkynes and terminal alkenes yielding 1,3-disubstituted butadienes.[5] We were interested in exploiting a combination of this enyne cross metathesis and an aza-Diels-Alder reaction as a very short and efficient approach towards tetrahydropyridines. The Diels-Alder reaction of imines or iminium salts with carbon dienes is a valuable method for the synthesis of substituted tetrahydropyridines.[6] However, nonactivated acyclic 1,3-dienes, as they are obtained by enyne cross metathesis, and in particular their *Z*-isomers are regarded as poor substrates in Diels-Alder reactions.[7]



Scheme 1. Synthesis of tetrahydripyridines from 3 simple building blocks by a sequence of enyne cross metathesis and aza-Diels-Alder reaction

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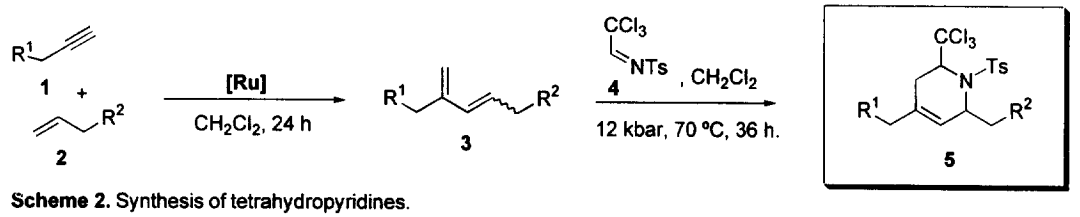
Nonetheless, this sequence could prove powerful due to atom economy being shown by the planned reaction sequence, allowing to build highly substituted tetrahydropyridines in a particular efficient way from three simple building blocks: i) a monosubstituted alkyne and a terminal alkene for the synthesis of the 1,3-diene and ii) an imine as the dienophile for the subsequent aza-Diels-Alder reaction (Scheme 1).

Although aza-Diels-Alder reactions employing various acyclic 1,3-disubstituted butadienes of type **3**, which can be obtained by enyne cross metathesis, were supposed to be problematic we started investigations on this transformation. As dienophile we chose the electron deficient N-trichloro-ethylidene-p-toluenesulfonamide (**4**)[8] and first introduced the enyne metathesis product of propargyl acetate and pentenoic acid benzyl ester as a diene. Investigating thermal and high pressure conditions best results were obtained at 12 kbar pressure and 70 °C in dichloromethane for 36 to 48 h to give tetrahydropyridine **5a** in high yield (Scheme 2, Table 1).[9] Similar conditions were applied to the synthesis of other tetrahydropyridines. The aza-Diels-Alder reactions proceed with excellent regioselectivity. However, *endo-/exo*-selectivities can not be measured, since *E/Z* mixtures resulting from enyne cross metathesis were employed as reactants in the aza-Diels-Alder reactions. For all examples given in Table 1 the two expected diastereomers are formed in a ratio varying from 0.8 to 1.5 being consistent with the *E/Z*-ratios of the metathesis products.

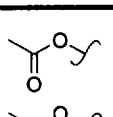
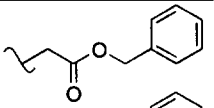
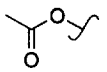
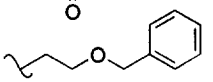
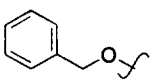
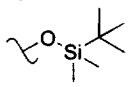
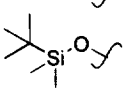
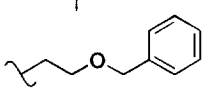
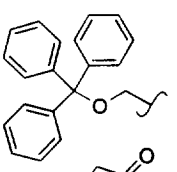
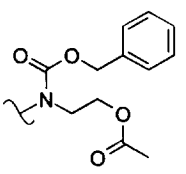
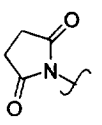
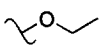
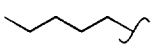
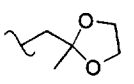
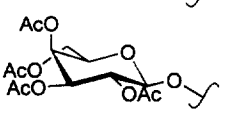
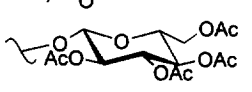


Scheme 2. Synthesis of tetrahydropyridines.

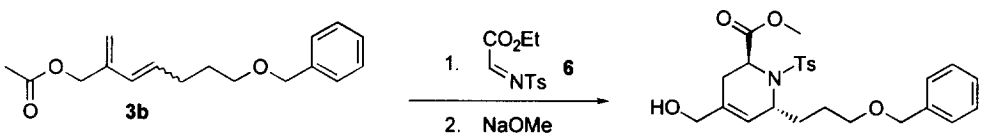
A number of enyne cross metatheses followed by aza-Diels-Alder reaction was then performed to demonstrate the generality of the described reaction sequence. Using pentenyl benzyl ether as the alkene component resulted in formation of tetrahydropyridine **5b** in comparable yield to those of **5a**. Besides the ester functionality introduced to tetrahydropyridines **5a** and **5b**, benzyl and silyl ethers have been employed as alkyne and alkene components (Table 1 entry **5c**, **5d**). The yield of the metathesis reaction seems to be affected by the steric demand of the alkyne components. Regarding the aza-Diels-Alder reaction it should be mentioned that for some cases the reaction is accompanied by competitive ene-reaction[10] of the *Z*-isomer of the 1,3-dienes obtained by enyne cross metathesis. To further demonstrate the applicability of the reaction sequence we employed additional olefinic components such as a succinimide as the alkyne and a ketal as the alkene to give the corresponding tetrahydropyridines in moderate yields (entry **5f** and **5g** respectively). A three fold orthogonal protected tetrahydropyridine (**5e**) was obtained by enyne cross metathesis of trityl protected butyn-4-ol and N-allyl- N-benzoxycarbonyl-O-acetyl-glycinol followed by aza-Diels-Alder reaction. Tetrahydropyridines of type **5** or **7** (see Scheme 3), can be regarded as potential precursors of azasugar derivatives, whose syntheses involving metathesis reactions have been of interest in our laboratory.[11] Applying the presented methodology, a protected galactopyranoside and a glycopyranoside as alkyne and alkene component respectively were employed to yield the pseudo oligosaccharide **5h** after high pressure aza-Diels-Alder transformation. The examples given in Table 1 clearly show that the presented methodology is compatible with a variety of functionalities thus representing a very mild and flexible procedure for the synthesis of tetrahydropyridines.

To demonstrate the possibility of introducing different dienophiles than **4** as the third variable component we synthesized (toluene-4-sulfonylimino)-acetic acid ethyl ester[12] (**6**). Imine **6** was employed in an aza-Diels-Alder reaction with diene **3b** under the same conditions that were used for dienophile **4** to give a pipecolic acid derivative, which was then equilibrated using sodium methoxide in methanol to give **7** as a single diastereomer in high yield (Scheme 3).

Table 1. Synthesized tetrahydropyridines **5a-h**

compound	R^1	R^2	yield of enyne cross metathesis (%)	yield of aza-Diels-Alder reaction (%)
5a			87	89
5b			80	91
5c			70	62
5d			47	60
5e			51	72
5f			52	77
5g			74	67
5h			58	61

In summary, we have presented a very mild and flexible combination of enyne cross metathesis and aza-Diels-Alder reaction. The reaction sequence shows atom economy and allows the short and efficient synthesis of highly substituted tetrahydropyridines from three readily available building blocks. The methodology presented is compatible with a variety of functionalities, which was demonstrated for a number of alkynes and alkenes to introduce the R^1 and R^2 substituents respectively and for two imines as dienophile. We are currently investigating possibilities to consolidate the stereochemistry of the metathesis products to overcome the major drawback of diastereomeric mixtures being formed in subsequent reactions.



Scheme 3. Stereoselective synthesis of a pipecolic acid derivative.

Acknowledgments

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9 All 1,3-dienes and tetrahydropyridines have been completely characterized by ^{1}H, and ^{13}C NMR, IR, and HRMS. As a representative example the synthesis of tetrahydropyridine **5b** is given: A solution of 200 mg (2.04 mmol) of propargyl acetate and 719 mg (4.08 mmol) of pentenyl benzyl ether in 10 mL of CH_2Cl_2 and 84 mg (102 μmol, 5 mol%) of Grubbs' catalyst **[Ru]** was stirred for 36 h and then concentrated and purified by column chromatography (eluent hexanes / methyl *t*-butyl ether) to give 449 mg (1.64 mmol, 80 %) of a colorless oil **3b** (*E*/*Z* = 0.8). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (tt, 7Hz, 8Hz, 4H), 2.08 (s, 3H), 2.09 (s, 3H), 2.21 (ddt, 7Hz, 1Hz, 8Hz, 2H), 2.32 (ddt, 7Hz, 1Hz, 8Hz, 2H), 3.48 (t, 7Hz, 2H), 3.49 (t, 7Hz, 2H), 4.50 (s, 2H), 4.51 (s, 2H), 4.58 (s, 2H), 4.75 (s, 2H), 5.10 (s, 2H), 5.13 (s, 1H), 5.16 (s, 1H), 5.59 (dt, 12Hz, 7Hz, 1H), 5.71 (dt, 16Hz, 7Hz, 1H), 5.81 (dd, 12Hz, 1Hz, 1H), 6.08 (dd, 16Hz, 1Hz, 1H), 7.25-7.38 (m, 10H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.9 (CH_3), 25.5 (CH_2), 29.2 (CH_2), 29.6 (CH_2), 30.0 (CH_2), 64.1 (CH_2), 66.9 (CH_2), 69.5 (CH_2), 69.7 (CH_2), 72.9 (CH_2), 115.6 (CH_2), 116,1 (CH_2), 126.7 (CH), 127.5 (CH), 127.6 (CH), 128.3 (CH),129.6 (CH), 130.8 (CH), 133.9 (CH), 138.5 (C_q), 139.8 (C_q), 130.2 (C_q), 170.6 (C_q), 170.7 (C_q). IR (ATR): ν/cm^{-1} 2938 (m), 2859 (m), 1739 (s). MS: m/z (%): 274 ([M^+], 3), 123 (24), 105 (52), 91 (100). HRMS calcd. for $C_{17}H_{22}O_3$ [M^+] m/z 274.1569, measured 274.1577.
130 mg (474 μmol) of diene **3b** and 214 mg (711 μmol) of N-trichloro-ethylidene-p-toluenesulfonamide (**4**) in 2 ml of CH_2Cl_2 were heated to 70 °C at 12 kbar pressure in a Teflon tube for 40 h. The product was then concentrated and chromatographed on silica gel (eluent hexanes / methyl *t*-butyl ether) to give 248 mg (431 μmol, 91 %) of the colorless oil **5b** (ratio of isomers 1.3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.60-1.70 (m, 2H), 1.70-1.79 (m, 1H), 1.79-1.89 (m, 2H), 1.95-2.04 (m, 1H), 2.04 (s, 3H), 2.08-2.18 (m, 2H), 2.10 (s, 3H), 2.22-2.33 (m, br, 1H), 2.44 (s, 3H), 2.45 (s, 3H), 2.59 (d, 18Hz, 1H), 2.63 (d, 18 Hz, br, 1H), 2.78 (dd, 18Hz, 8Hz, br, 1H), 3.43 (dt, 9Hz, 7Hz, br, 1H), 3.46 (dt, 9Hz, 7Hz, br, 1H), 3.55 (dt, 9Hz, 7Hz, 1H), 3.62 (dt, 9Hz, 7Hz, 1H), 4.26-4.36 (m, br, 2H), 4.42 (d, 13Hz, br, 2H), 4.47 (d, 13Hz, br, 2H), 4.49 (s, br, 2H), 4.56 (s, 2H), 5.10 (d, 8Hz, 1H), 5.30-5.42 (m, br, 1H), 5.74 (s, br, 2H), 7.24-7.40 (m, 14H), 7.69 (d, 8Hz, 2H), 7.73 (d, 8Hz, 2H). ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 20.7 (CH_3), 20.8 (CH_3), 21.5 (2xCH_3), 24.3 (CH_2), 26.7 (CH_2), 26.9 (CH_2), 27.1 (br, CH_2) 28.7 (br, CH_2), 33.0 (CH_2), 53,3 (CH), 54.7 (br, CH), 64.8 (CH), 66.3 (CH_2), 66.5 (CH_2), 67.6 (br, CH), 69.5 (CH_2), 70,1 (CH_2), 72.9 (CH_2), 94.1 (br, C_q), 102.9 (C_q), 122.5 (CH), 127.0 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 128.3 (CH), 129.5 (CH), 129.9 (CH), 131.4 (br, C_q), 136.3 (C_q), 138.4 (C_q), 138.5 (C_q), 139.5 (C_q), 143.6 (C_q), 143.9 (C_q) 170.4 (C_q), 170.5 (C_q). IR (ATR): ν/cm^{-1} 2927 (m), 2856 (m), 1739 (s). MS: m/z (%): 538 ([M^+-Cl], 3), 514 (12), 418 (40), 247 (20), 155 (56), 91 (100). HRMS calcd. for $C_{26}H_{30}Cl_2O_5NS$ [M^+-Cl] m/z 538.1222, measured 538.1222.

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