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[A0023]

Efficient allylation of 4-silyloxy quinolinium triflates and other positively charged heteroaromatic systems

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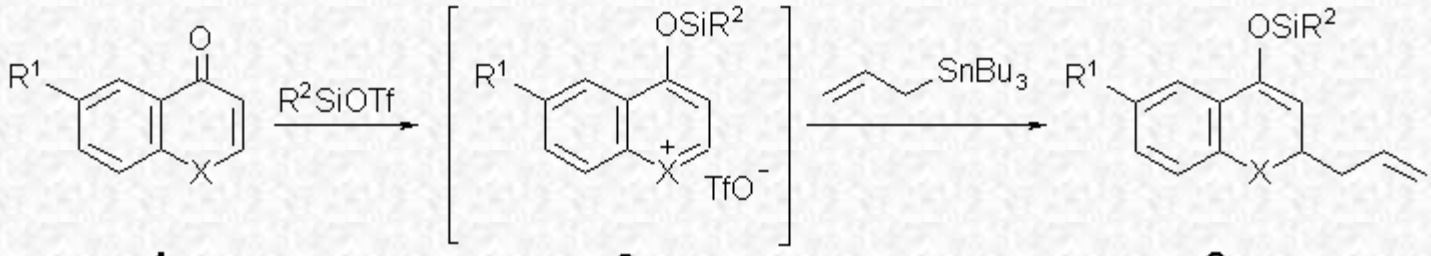
Abstract

The regioselective allylation of 4-silyloxy quinolinium triflates with allyltri-*n*-butyltin has been performed to give 2-allyl-4-silyloxy-1,2-dihydroquinolines with excellent yields. Similiar results were obtained with 4-silyloxy benzopyrylium triflates and 4-silyloxy benzothiopyrylium triflates.

Introduction

The 1,2-addition of allylic organometallic reagents to aldehydes, ketones and imines is one of the most important C-C-bond forming reactions as the allyl group represents a versatile functional carbon substituent [1]. This is why numerous protocols for this transformation have been developed. In most cases Lewis acids have been employed as activating reagents, because allylations without activation do not proceed under mild conditions [2]. In comparison, fewer conjugate additions of allylic organometallic reagents have been reported and the conjugate addition to vinylogous lactones, thiolactones and lactames remains unexplored. The allylation of azaaromatics is of great importance for the synthesis of biologically active nitrogen compounds, including alkaloids. Here the activation typically is achieved by use of the corresponding *N*-acyliminium salts that can be produced by reaction of the azaaromatics with acyl chlorides [3-5]. Using this approach, however, the allylation of vinylogous lactames like 4-quinolones cannot be achieved.

Results and Discussion



1 **2** **3**

We have reported that the conjugate addition of several nucleophiles to 4-quinolones can be efficiently performed when the 4-quinolones are transformed into the corresponding 4-silyloxy quinolinium triflates. Using this strategy the regioselective 1,2-addition of nucleophiles like silyl enol ethers [6] and enamines [7] as well as organolithium and organomagnesium reagents [8] to the $C=N^+$-bond of the 4-silyloxy quinolinium triflates delivered the conjugate addition products without any side products. Here we report the regioselective allylation of several positively charged 4-silyloxy substituted heteroaromatics corresponding to the conjugate allylation of vinylogous lactames, lactones and thiolactones.

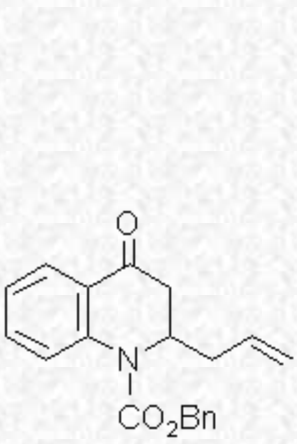
First the allylation of 4-silyloxy quinolinium triflates **2a-e**, which can easily be obtained *in situ* by reaction of the *N*-protected 4-quinolones **1a,b** with a trifluoromethanesulfonic acid trialkylsilyl ester under mild conditions, was investigated. Treatment of the *N*-benzyloxycarbonyl- as well as the *N*-ethoxycarbonyl protected quinolinium triflates **2a-e** with 1.3 eq. allyltri-*n*-butyltin at room temperature gave the 2-allyl-4-silyloxy-1,2-dihydroquinolines **3a-e** with high yields as single products (Table, Entries 1-5).

Table: The allylation of 4-silyloxy substituted positively charged heteroaromatics **2**.

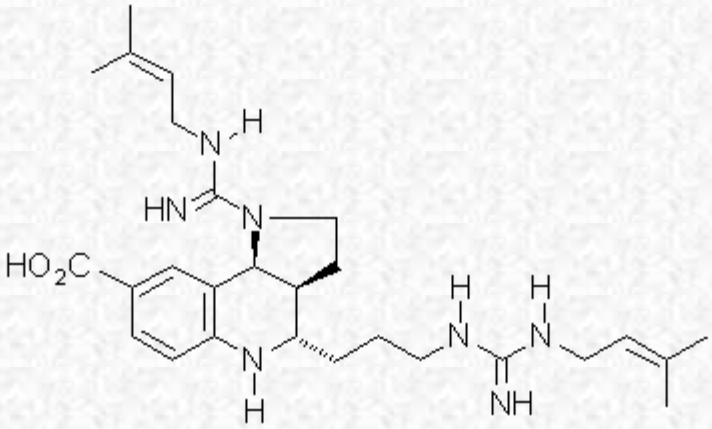
Entry	**1**	X	R^1	**2**	R^2	**3**[a]	Yield **3** [%][b]
1	**a**	N-CO_2Bn	H	**a**	Me_3	**a**	52[c]
2	**a**	N-CO_2Bn	H	**b**	Et_3	**b**	88
3	**b**	N-CO_2Et	H	**c**	Et_3	**c**	94
4	**a**	N-CO_2Bn	H	**d**	(*i*-Pr)$_3$	**d**	80
5	**b**	N-CO_2Et	H	**e**	(*i*-Pr)$_3$	**e**	86
6	**c**	N-CO_2Bn	Br	**f**	(*i*-Pr)$_3$	**f**	84
7	**d**	N-CO_2Et	Br	**g**	(*i*-Pr)$_3$	**g**	90
8	**e**	N-CO_2Bn	CO_2Bn	**h**	(*i*-Pr)$_3$	**h**	78
9	**f**	N-CO_2Et	CO_2Bn	**i**	(*i*-Pr)$_3$	**i**	89
10	**g**	O	H	**j**	(*i*-Pr)$_3$	**j**	86
11	**h**	S	H	**k**	(*i*-Pr)$_3$	**k**	91

a All new compounds were identified by their ^{1}H NMR, ^{13}C NMR, IR, UV and mass spectrometric data. The elemental analysis and/or high-resolution mass spectrometric data are consistent with the calculated data. *b* The yields refer to analytically pure compounds. *c* Due to its hydrolytic instability, **3a** could not be obtained analytically pure. Besides **3a** 28 % of the corresponding tetrahydroquinolone **4a** was isolated.

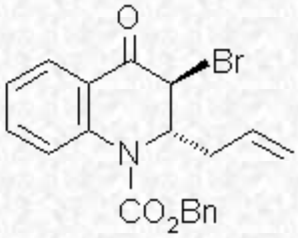
It was found that this transformation can be performed with trifluoromethanesulfonic acid trialkyl silyl esters like TMSOTf, TESOTf and TIPSOTf. In almost all cases the addition products could be isolated and purified without any difficulties. The only exception was the reaction of the trimethylsilyloxy derivative **2a**; here, the resulting trimethylsilyl enol ether **3a** undergoes partial hydrolysis to the corresponding 2-allyl quinolone **4a** upon isolation and purification (Table, Entry 1). Quinolones **4** can also be obtained by hydrolysis of the corresponding triisopropylsilyl esters. As an example, treatment of **3d** with 2 *N* sulfuric acid affords the tetrahydroquinolone **4a** with 70 % yield. Allyltrimethylsilane, which has been widely used as an allylating reagent [1] does not react with **2a-i** under a variety of reaction conditions, indicating that allylic silicon reagents are not sufficiently nucleophilic to react with an 4-silyloxy quinolinium triflate [9].



4a



5



6

Also, exclusive a -functionalization and high yields were observed with the allylation of 4-silyloxy benzopyrylium- and 4-silyloxy benzothiopyrylium triflates **2j** and **2k** (Table, Entries 10, 11). These results show that this method is not restricted to the functionalization of 4-quinolones, but can be used for the selective allylation of vinylogous lactones and thiolactones like **1g** and **1h**, too. The structure of all products **3** was established by NMR spectroscopy.

Martinellic acid (**5**) and related compounds are of great interest in the field of medicinal chemistry as they represent the first nonpeptide natural products that have been identified as bradykinin receptor antagonists [10]. In connection with studies towards the synthesis of **5** the allylation with 6-substituted 4-quinolones like **1c-f** was investigated. Again, the regioselective allylation occurred and the corresponding 2-allylated 1,2-dihydroquinolines **3c-f** could be isolated in yields from 78 - 90 % (Table, Entries 6-9). The silyl enol ether functionality in **3** offers numerous perspectives for further functionalization at C-3 and C-4. Preliminary experiments show that treatment of **3a** and **3b** with *N*-bromosuccinimide (NBS) at -78 °C proceeds diastereoselectively as only the 2,3-*trans*-disubstituted compound **6** was formed. With respect to the synthesis of **5** further studies will concentrate on radical transformations of **6** as well as reactions of silyl enol ethers **3** with *C*-electrophiles.

Experimental

Typical experimental procedure for the allylation of quinolones 1; preparation of 3i: 0.30 ml (1.11 mmol) TIPSOTf was added dropwise to 300 mg (0.85 mmol) **1f** and the mixture was held at room temperature for 1h under argon. After the successive addition of 1.5 ml dichloromethane, 0.13 ml (1.11 mmol) 2,6-lutidine and 0.34 ml (1.11 mmol) allyltri-*n*-butyltin at 0 °C the resulting solution was stirred for 3h at room temperature. The reaction mixture was poured into 20 ml icecold 5% aqueous potassium hydrogen carbonate and extracted with cold dichloromethane (3 x 30 ml). The combined organic phases were dried over magnesium sulfate and the solvent was removed at reduced pressure on a rotary evaporator. Finally the crude product was purified by flash chromatography on silica gel (cyclohexane / ethyl acetate = 9 : 1) to yield 420 mg (89 %) **3i** as a colourless oil.

Selected spectral and analytical data for 3i: ^{1}H NMR (270 MHz, $CDCl_3$): d = 1.07 [d, *J* = 7.0 Hz, 18 H, 3 x

$CH(CH_3)_2$], 1.16 - 1.33 [m, 6H, 3 x $CH(CH_3)_2$, CH_2CH_3], 2.06 - 2.26 (m, 2H, $CH_2CH=CH_2$), 4.16 - 4.31 (m, 2H, CH_2CH_3), 4.93 [d, *J* = 18.5 Hz, 1H, (*E*)-CH=CHH], 4.97 [d, *J* = 10.5 Hz, 1H, (*Z*)-CH=CHH], 5.05 (q, *J* = 6.5 Hz, 1H, 2-H), 5.19 (d, *J* = 6.5 Hz, 1H, 3-H), 5.30 (m, 2H, $CO_2CH_2C_6H_5$), 5.70 (m, 1H, $CH_2CH=CH_2$), 7.26 - 7.45 (m, 5H, $CO_2CH_2C_6H_5$), 7.63 (d, *J* = 8.5 Hz, 1H, 8-H), 7.94 (dd, *J* = 2.0 Hz, *J* = 8.5 Hz, 1H, 7-H), 8.28 (d, *J* = 2.0 Hz, 1H, 5-H) - ^{13}C NMR (68 MHz, $CDCl_3$): d = 12.64 [$CH(CH_3)_2$], 14.38 ($CO_2CH_2CH_3$), 17.96, 17.99 [$CH(CH_3)_2$], 39.27 ($CH_2CH=CH_2$), 52.46 (C-2), 62.32 ($CO_2CH_2CH_3$), 66.63 ($CO_2CH_2C_6H_5$), 105.06 (C-3), 117.81 ($CH_2CH=CH_2$), 123.81 (C-8), 124.21 (C-5), 125.16 (C-6), 126.20 (C-4a), 128.13 (C-4'), 128.16 (C-3', C-5'), 128.52 (C-2', C-6'), 129.36 (C-7), 133.59 ($CH_2CH=CH_2$), 136.04 (C-1'), 139.65 (C-4), 145.63 (C-8a), 153.85 ($CO_2CH_2CH_3$), 166.03 ($CO_2CH_2C_6H_5$). - $C_{32}H_{43}NO_5Si$ (549.8): calcd. C 69.91, H 7.88, N 2.55; found C 70.19, H 7.95, N 2.54.

Selected spectral and analytical data for 3j: ^{1}H NMR (270 MHz, $CDCl_3$): d = 1.11 [d, *J* = 7.0 Hz, 18H, 3 x $CH(CH_3)_2$], 1.23 [m, 3H, 3 x $CH(CH_3)_2$], 2.34 - 2.61 (m, 2H, $CH_2CH=CH_2$), 4.81 (d, *J* = 3.5 Hz, 1H, 3-H), 4.95 (dt, *J* = 3.5 Hz, *J* = 6.5 Hz, 1H, 2-H), 5.06 - 5.15 (m, 2H, $CH_2CH=CH_2$), 5.77 - 5.94 (m, 1H, $CH_2CH=CH_2$), 6.76 (dd, *J* = 1.0 Hz, *J* = 7.5 Hz, 1H, 8-H), 6.87 (dt, *J* = 1.0 Hz, *J* = 7.5 Hz, 1H, 6-H), 7.12 (dt, *J* = 1.5 Hz, *J* = 7.5 Hz, 1H, 7-H),), 7.39 (dd, *J* = 1.5 Hz, *J* = 7.5 Hz, 1H, 5-H) - ^{13}C NMR (68 MHz, $CDCl_3$): d = 12.73 [$CH(CH_3)_2$], 18.04, 18.05 [$CH(CH_3)_2$], 40.72 ($CH_2CH=CH_2$), 75.35 (C-2), 100.78 (C-3), 115.69 (C-8), 117.71 ($CH_2CH=CH_2$), 120.64 (C-6), 121.69 (C-4a), 122.47 (C-5), 129.49 (C-7), 133.65 ($CH_2CH=CH_2$), 145.92 (C-4), 154.66 (C-8a) - $C_{21}H_{32}O_2Si$ (344.6): calcd. C 73.20, H 9.36; found C 73.10, H 9.49.

Selected spectral and analytical data for 3k: ^{1}H NMR (270 MHz, $CDCl_3$): d = 1.10 [d, *J* = 7.0 Hz, 18H, 3 x $CH(CH_3)_2$], 1.24 [m, 3H, 3 x $CH(CH_3)_2$], 2.39 (t_{br}, *J* = 7.0 Hz, 2H, $CH_2CH=CH_2$), 3.63 (q, *J* = 7.0 Hz, 1H, 2-H), 5.00 - 5.10 (m, 2H, $CH_2CH=CH_2$), 5.19 (d, *J* = 6.0 Hz, 1H, 3-H), 5.78 (m, 1H, $CH_2CH=CH_2$), 7.06 - 7.14 (m, 2H, 6-H, 8-H), 7.18 - 7.23 (m, 1H, 7-H), 7.58 - 7.63 (m, 1H, 5-H) - ^{13}C NMR (68 MHz, $CDCl_3$): d = 12.78 [$CH(CH_3)_2$], 18.07, 18.09 [$CH(CH_3)_2$], 38.51 (C-2), 40.79 ($CH_2CH=CH_2$), 104.26 (C-3), 117.47 ($CH_2CH=CH_2$), 124.14 (C-6), 125.09 (C-8), 127.13 (C-7), 128.12 (C-5), 131.63 (C-4a), 132.67 (C-8a), 134.71 ($CH_2CH=CH_2$), 149.06 (C-4) - $C_{21}H_{32}OSSi$ (360.6): calcd. C 69.94, H 8.94; found C 69.87, H 8.84.

Acknowledgements

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