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Synthesis of vinyl spirolactones and lactams by sequential cross-coupling metathesis, [2+2] photocycloaddition and cyclobutane ring-opening

Sophie Faure,[a] Sylvie Piva-Le Blanc[a] and Olivier Piva[a,b,*]

[a] *Laboratoire de photochimie, UMR 6519 CNRS, Université de Reims, Champagne, Ardenne, BP1039 51687, Reims cedex, France*

[b] *Laboratoire de chimie organique, Photochimie et synthèse, UMR 5622 CNRS, Université Claude Bernard, Lyon I, 43, Boulevard du 11 novembre 1918, 69622 Villeurbanne, France*

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Abstract

Unsaturated oxoesters and amides have been submitted to cross-coupling metathesis with trimethylallylsilane using Grubbs' catalyst. The resulting allylsilanes underwent, under irradiation, intramolecular [2+2] photocycloaddition leading to trimethylsilylmethylcyclobutanes. By treatment with an appropriate Lewis acid, vinyl spiranic lactones and lactams were isolated in good yields. © 1999 Elsevier Science Ltd. All rights reserved.

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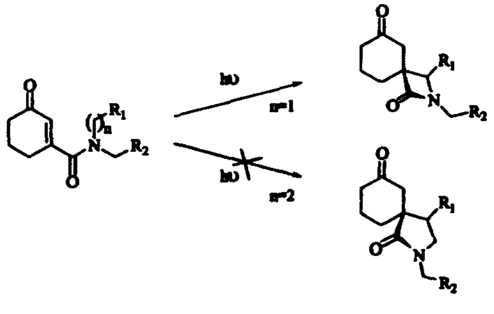
Spirocompounds are attractive derivatives not only due to their unusual geometry but also as key framework of numerous natural products including azaderivatives like perhistrionicotoxine,[1] nitramine, sibirine.[2] Some years ago, we reported, that irradiation of unsaturated oxoamides provided a direct access to spiranic β-lactams[3] with potential cholesterol absorption inhibitor properties.[4] Unfortunately, this process was not transposable to the synthesis of spiranic β-lactones or larger ring lactams (Scheme 1).[5]



Scheme 1.

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[*] Corresponding author. Fax: 00-33-(0)4-72-44-81-36; e-mail: piva@copssg.univ-lyon1.fr

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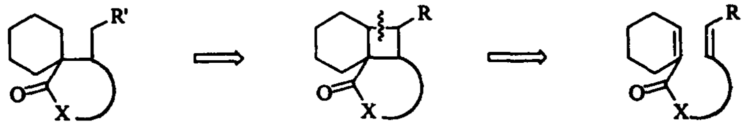
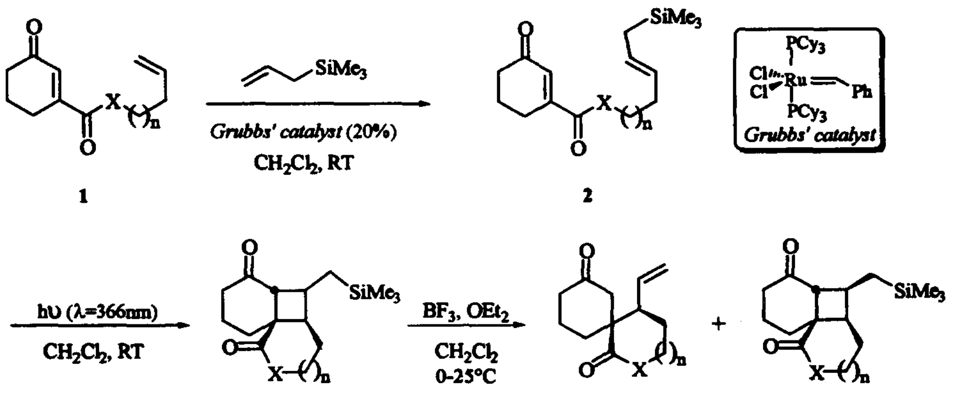
In order to find a more general method, we have searched reliable procedures starting from cyclobutane derivatives easily prepared by intramolecular [2+2] photocycloadditions.[6,7] The selective cleavage of one bond of the four-membered ring using the internal strain of the molecule could afford a direct access to the expected spiroderivatives (Scheme 2).



Scheme 2.

In our approach, we considered the use of trimethylsilylmethylcyclobutane derivatives in which selective cleavage of a C–C bond is favoured by the presence of a neighbouring keto group.[8,9] While our own work was in progress, a similar strategy involving a free radical process starting from iodomethyl compounds has been published;[10] we wish to report herein our first results. Unsaturated oxoesters and oxoamides **1** were submitted to cross-coupling metathesis[11,12] with 2 equivalents of trimethylallylsilane using Grubbs' catalyst (0.2 equiv.) and led to the formation of new allylsilane derivatives **2** (as a mixture of *E* and *Z* isomers, typically 60/40) (Scheme 3). While the yields of the reaction are moderate, the selectivities are quite high and the starting material could be recovered and reused. As expected, photocycloaddition led to [2+2] adducts in high yields as a predictable mixture of *syn* and *anti* isomers.[8] By treatment in dichloromethane with BF_3,OEt_2 (3 equiv.), we observed a slow but clean transformation of compounds **3** into spiranic vinyl compounds. The yields were especially high in the case of lactam derivatives.

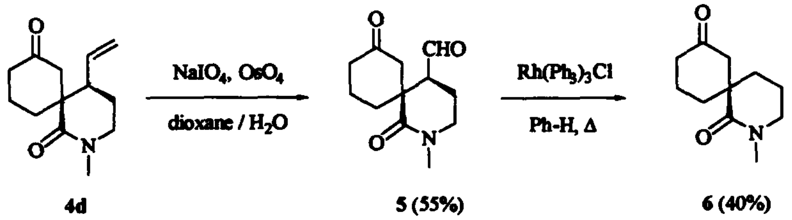


Scheme 3.

1			2	3	4	
	n	X	Yield (%)	Yield (%)	Conversion	Yield
a	1	O	58	87	>90%	60%
b	2	O	61	51	64%	36% (+ 34% S.M.)
c	1	N-CH3	43	98	>95%	84%
d	2	N-CH3	40	84	79%	70% (+ 21% S.M.)

With substrates **3b** and **3d** (n=2), the reaction was not totally completed even after 3 days. In both cases, a single diastereoisomer was recovered which was shown to be *anti* according to NOE experiments. The lower reactivity of the *anti* isomers of **3** could be attributed to an unfavourable arrangement of the keto group and the trimethylsilylmethyl unit which prevent the formation of a chair-like cyclic transition state.[9a,13]

Aiming to remove the vinyl group of the spiranic adducts, we investigated a two step sequence on compound **4d** as depicted in Scheme 4. Oxidative cleavage of the carbon–carbon double bond with osmium tetroxide and sodium periodate[14] provided aldehyde **5** which was finally decarbonylated by heating to reflux in benzene in the presence of Wilkinson's catalyst.[15]



Scheme 4.

In conclusion, we have developed a new route to vinyl-spirolactones and spirolactams by using a three step procedure: cross-metathesis with allylsilane; intramolecular photocycloaddition; and finally selective cleavage of the cyclobutane ring using a Lewis acid activation. We demonstrated also the removal of the vinyl group by oxidation/decarbonylation procedure without any change of the spiro framework.[16]

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16. Selected data for: **2c** (a mixture of two isomers). ^{13}C NMR: characteristic signals: δ −1.9 ($Si(CH_3)_3$); 31.9 and 36.3 (N-CH_3); 169.6 ($CONR_2$); 198.5 and 198.7 (C=O). MS: 293 (M+), 278 (M–CH_3). HMRS calcd for $C_{16}H_{27}O_2NSi$: 293.181. Found: 293.188. **3c** (two diastereoisomers). ^{1}H NMR: δ (diastereoisomer A): –0.03 (s, 9H), 0.70 (dd, 1H, J_{AB}=14.8 Hz and J=6 Hz), 0.76 (dd, 1H, J_{AB}=14.8 Hz and J=8.7 Hz), 1.75 (m, 2H); 1.80–2.00 (m, 2H), 2.00–2.10 (m, 1H); 2.25–2.50 (m, 4H), 2.63 (quint, 1H, J=8.5 Hz), 2.68 (d, 1H, J=9 Hz), 2.95 (s, 3H), 3.25 (dt, 1H, J_{AB}=12.6 Hz, J=4 Hz), 3.40 (ddd, 1H, J_{AB}=12.6 Hz, J=2.5 Hz, J=1.2 Hz); (diastereoisomer B): –0.01 (s, 9H), 0.38 (dd, 1H, J_{AB}=14.5 Hz and J=12.1 Hz), 0.88 (dd, 1H, J_{AB}=14.5 Hz and J=3.7 Hz), 1.60 (dt, 1H, J=13.4 and J=3.8 Hz); 1.67–1.80 (m, 2H), 1.83–2.05 (m, 2H); 2.05–2.10 (m, 1H), 2.15 (m, 1H), 2.25–2.50 (m, 4H), 3.02 (s, 3H), 3.32 (ddd, 1H, J_{AB}=12.6 Hz, J=4.5 Hz, J=6.1 Hz), 3.47 (ddd, 1H, J_{AB}=12.8 Hz, J=4.0 Hz, J=8.8 Hz). ^{13}C NMR: characteristic signals: δ (diastereoisomer A): −1.19 ($SiMe_3$), 174.03 ($CONR_2$), 210.35 (CO); (diastereoisomer B): −1.07 ($SiMe_3$), 174.51 ($CONR_2$), 211.43 (CO). **4c**: ^{1}H NMR: δ 1.70–1.76 (m, 2H), 1.85–1.95 (m, 1H), 1.95 (dd, 1H, J_{AB}=14.9 Hz, J=0.7 Hz), 1.98–2.16 (m, 1H), 2.15–2.25 (m, 2H), 2.32 (m, 1H), 2.44–2.49 (m, 2H), 2.62 (dt, 1H, J_{AB}=14.9 Hz, J=1.9 Hz), 2.92 (s, 3H), 3.28 (ddd, 1H, J_{AB}=12.5 Hz, J=6.8 Hz, J=2.9 Hz), 3.42 (ddd, 1H, J_{AB}=12.5 Hz, J=11 Hz, J=5.8 Hz), 5.17 (d, 2H, J=10 Hz), 5.74 (dt, 1H, J=17.3 and 10 Hz). ^{13}C NMR: δ 21.6 (t), 24.6 (t), 33.9 (t), 34.8 (q), 39.5 (t), 46.8 (t), 47.5 (d), 47.8 (t), 48.0 (s), 118.2 (*C*H_2=CH-), 136.3 (-*C*H=CH_2), 172.8 ($CONR_2$), 209.2 (C=O). IR: υ (cm^{-1}) 1718(C=O), 1630 ($CONR_2$). MS: 221 ($M^{+\cdot}$), 193 ($M^{+\cdot}$–28). Elemental analysis: calcd for $C_{13}H_{19}O_2N$: C 70.56, H 8.65, N 6.33. Found: C 70.47, H 8.96, N 6.24. **4a**: ^{1}H NMR: δ 1.75–1.80 (m, 1H), 1.82 (td, 1H, J=7.3 Hz and J=2.0 Hz), 1.97 (m, 2H), 2.05 (d, 1H, J_{AB}=15.1 Hz), 2.17–2.30 (m, 2H), 2.35 (m, 1H), 2.48 (dt, 1H, J=15.7 Hz and J=4.6 Hz), 2.57 (quint, 1H, J=4.8 Hz), 2.64 (dt, 1H, J_{AB}=15.1 Hz and J=1.9 Hz), 4.43 (dd, 1H, J_{AB}=11.7 Hz and J=5.4 Hz), 4.49 (ddd, 1H, J_{AB}=11.7 Hz, J=9.5 Hz, J=5.0 Hz), 5.21 (d, 1H, J=16.8 Hz), 5.24 (d, 1H, J=10 Hz), 5.79 (dt, 1H, J=16.8 Hz and J=10 Hz). ^{13}C NMR: δ 21.1 (t), 25.7 (t), 33.3 (t), 39.4 (t), 46.9 (d), 47.2 (t), 48.7 (s), 67.3 (t), 119.1 (*C*H_2=CH-), 135.3 (CH_2=*C*H-), 173.8 (*C*O_2), 207.8 (*C*=O). MS: 208 ($M^{+\cdot}$, 64), 180 ($M^{+\cdot}$–28).