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RCM in indoles. A new entry to the mitosene skeleton

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Abstract—The RCM metathesis reaction catalyzed by Grubbs' ruthenium catalyst is used with a series of 1,2-disubstituted indoles leading with excellent yields to tricyclic compounds. When applied to 1-allyl-2-vinylindoles this methodology allows a new entry to the mitosene skeleton. © 2002 Elsevier Science Ltd. All rights reserved.

RCM reactions catalyzed by ruthenium methylene complexes have become an important tool in the synthesis of natural products.[1] Among the myriade of synthetic applications reported to date, there are very few examples that use suitable functionalized indoles.[2] Following our project directed to the synthesis of polycycloindoles related to natural alkaloids,[3] we herein describe the metathesis of 1-allylindoles bearing vinyl or alkenyl chains at the 2 position. These reactions lead to azepino[1,2-*a*]-, pyrido[1,2-*a*]- and pyrrolo[1,2-*a*]indoles. The latter compounds have the skeleton of mitosenes.

The mytomicine family is a group of metabolites from *Streptomices* that have attracted much attention due to their potent antitumoral and antibacterial activity (Fig. 1).[3] Several synthesis of mitomycine and other mitosenes have been reported.[4] Access to the pyrrolo-[1,2-*a*]indole skeleton which is common for these compounds is generally carried out by radical cyclizations,[5] metal carbene insertion,[6] nitrone cycloadditions[7] or intramolecular cyclizations[8] but until now the RCM reaction has not been used.

We have first obtained a series of indolic substrates conveniently functionalized to give RCM reactions. Thus, starting from indole-2-carboxylic acids **1a**–**b**, the 1-allyl-2-indolecarbaldehydes **2a**–**b** were obtained in four steps with excellent global yield. Compound **2c** was obtained from 3-methylindole **3** by means of an allylation and a Vilsmeier reaction (Scheme 1).

Keywords: indoles; mitosenes; ring closing metathesis; ruthenium.

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The reaction of **2a** with vinyl or allylmagnesiumbromide gave the corresponding alcohols **4** and **5**, which decomposed partially when we tried to purify them by chromatography. Thus, metathesis reactions were carried out with the crude products and gave the pyrido- and azepinoindoles **6** and **7** in excellent yields. Alternatively, protection of the hydroxy group in **4** and **5** with TBDMSCl gave compounds **8** and **9**, which were purified and submitted to RCM to give **10** and **11**. This three-step procedure gave lower overall yields (Scheme

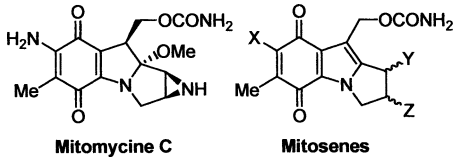
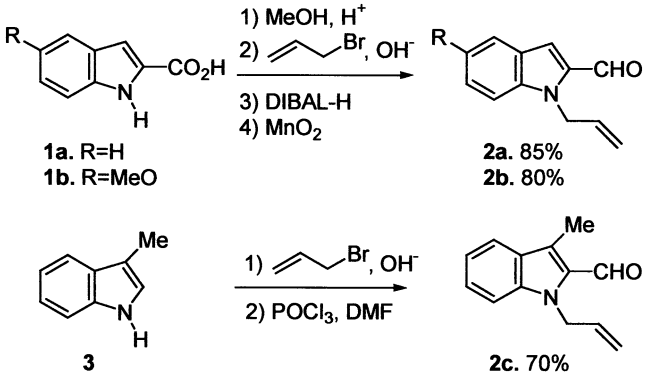


Figure 1.



Scheme 1.

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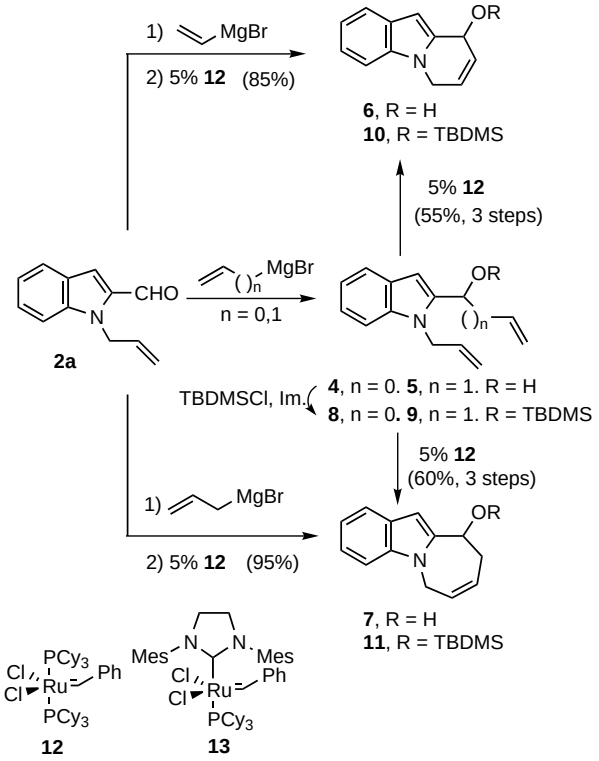
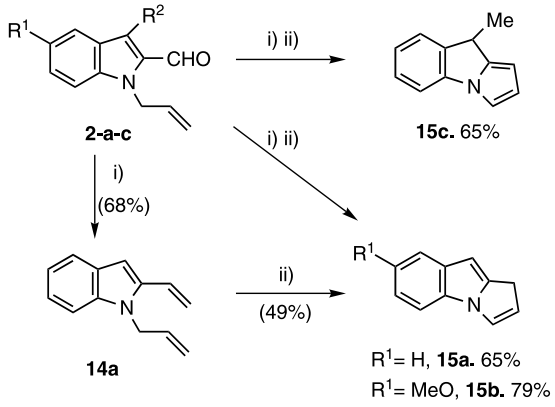
2). We also used several reaction conditions. The best solvent among toluene, benzene and DCM was the latter and the amount of catalyst used was 5%. We compared in particular the result with ruthenium catalyst **12** and second generation catalyst **13**. The results with the four substrates depicted in Scheme 2 were similar (87 and 90% yield for the obtention in one-pot of **6** and **7**, respectively, when using 5% of **13**), and thus commercial complex **12** was used for the rest of the work.

In order to effect the synthesis of pyrrolo[1,2-*a*]indoles, we submitted compound **2a** to a Wittig reaction obtaining **14a**. This allylvinylindole was unstable and decomposed in hours although it could be purified by chromatography on alumina. The RCM reaction of **14a** gave **15a** with 34% global yield from **2a**. We then tried the tandem Wittig-metathesis reaction[9] and succeeded in obtaining pyrroloindole **15a** in 65% yield. The triphenylphosphine oxide present in the reaction did not affect the metathesis process (Scheme 3). Compounds **15b–c** were obtained following this method.

As depicted in Scheme 3, the double bond emerging from the metathesis reaction shifts towards the indole nitrogen. This surprising behavior occurs in the three examples. The structures of **15a–b** were assigned according to the NMR signal of the methylene (for **15a** ^{1}H: 3.80 ppm; ^{13}C: 28.9 ppm), whereas in compounds similar to the expected isomer, previously described in the literature,[5] this methylene appears at ca. 4.60 ppm. Compound **2c**, on the other hand, leads to **15c** in which the indolic double bond has shifted also, as shown by the signal of the methyl that appears as a doublet ($J=7.1$ Hz).[10]



Scheme 2.



Scheme 3. *Reagents and conditions*: (i) $Ph_3P{=}CH_2$; (ii) 5% **12**. DCM.

In summary metathesis reactions of alkenylindoles lead to interesting intermediates in the synthesis of alkaloids. Some of the starting materials for these reactions are unstable but this problem is circumvented by the use of an efficient cascade Wittig-metathesis reaction. Use of this methodology for the obtention of natural products is underway.

Acknowledgements

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9. Experimental procedure for the synthesis of **15a** is as follows: To a suspension of methyltriphenylphosphonium bromide (0.87 g, 2.43 mmol) in THF (20 mL), KHMDS (0.5 M in toluene, 4.22 ml, 2.1 mmol) was added. The resulting suspension was stirred vigorously at room temperature and under argon for 30 min. The ylide was then added dropwise via cannula to a solution of **2a** (0.30 g, 1.60 mmol) in THF (15 mL). The mixture was stirred for 20 min at room temperature, and then poured to a mixture of ether–H_2O (1:1). The organic layer was dried ($MgSO_4$), filtrated and evaporated in vacuum. The residue was purified by column chromatography of basic alumina using hexane as eluent to give 0.20 g (68%) of 1-allyl-2-vinylindole **14a** as a colorless oil. Alternatively, the crude residue was dissolved in DCM (50 mL) and Grubbs' catalysts **12** was added (0.066 g, 0.08 mmol) and the mixture was stirred at room temperature overnight. The reaction was filtrated through Celite and the solvent was evaporated in vacuum. The residue was purified by column chromatography using hexane as eluent to give 0.24 g (1.58 mmol, 65%) of **15a** as a white solid (mp 87–88°C). Spectroscopic data for **15a**: ^{1}H NMR ($CDCl_3$) δ (ppm): 3.80 (s, 2H), 6.09–6.11 (m, 1H), 6.38 (dd, 1H, $J_1=3.3$ Hz, $J_2=2.8$ Hz), 7.04–7.09 (m, 2H), 7.21–7.31 (m, 2H), 7.37 (d, 1H, $J=7.2$ Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 141.1, 135.4, 134.9, 127.3, 125.8, 122.9, 113.0, 109.7, 109.6, 101.6, 28.9. IR (KBr) ν 2960, 1620, 1490 cm^{-1}.
10. Spectroscopic data for **15c**: ^{1}H NMR ($CDCl_3$) δ (ppm): 1.50 (d, 3H, $J_1=7.1$ Hz), 4.01 (q, 1H, $J_1=7.1$ Hz), 6.08–6.09 (m, 1H), 6.36–6.38 (m, 1H), 7.04–7.05 (m, 1H), 7.10 (td, 1H, $J_1=7.7$ Hz, $J_2=1.6$ Hz), 7.23–7.31 (m, 2H), 7.36 (d, 1H, $J=8.2$ Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 141.7, 140.7, 140.3, 127.4, 124.7, 123.1, 113.0, 109.6, 109.4, 100.8, 35.5, 19.0. IR (neat) ν 2980, 2860, 1620, 1500 cm^{-1}.