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Rhodium-catalyzed decomposition of indole-substituted α-diazo-β-keto esters: three different reactions based on indole oxidation state

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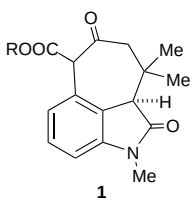
Abstract—Rhodium(II)-catalyzed decomposition of three indole-substituted α-diazo-β-keto esters affords three different types of intramolecular reactions based on the oxidation state of the indole. © 2001 Published by Elsevier Science Ltd.

In an approach to the synthesis of the tricyclic model system **1** of the important multiple-drug resistance (MDR) reversing agent *N*-methylwelwitindolinone C isothiocyanate **2**,[1] we decided to examine the possibility of cyclizing some α-diazo-β-keto esters derived from 3-substituted indoles, e.g. **3**, using rhodium(II) as a possible way of preparing the key cycloheptane ring system via an aryl CH insertion at C4 of the indole. Wood has published a clever Rh(II)-promoted cyclization of an α-diazo-β-cyclopropylketone in the presence of a Lewis acidic clay to prepare a similar cyclohexane system for the same target molecule in good yield.[2] In addition, several other groups have reported synthetic work on this target using different approaches.[3] We report herein the novel course of the reaction of three distinct α-diazo-β-keto esters derived from 3-substituted indoles in which the mode of reaction varies completely depending on the oxidation state of the indole unit.



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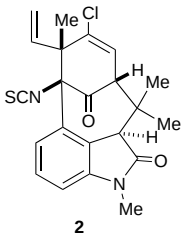

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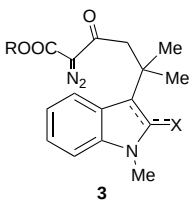

3

Keywords: Rhodium(II)-catalyzed reactions of diazo esters; cyclopropanation of indole double bond; oxindole reaction with carbenoids; oxidation of indoline to indole using carbenoid.

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The substrates for the cyclization studies were all prepared by starting with *N*-methylindole **4** (Scheme 1). Ytterbium triflate-catalyzed Michael addition of *N*-methylindole **4** to mesityl oxide **5** was carried out using a modification of the Kerr procedure (4% $Yb(OTf)_3$ and 4 equiv. of **5**)[4] to give the desired 4-(3-indolyl)-4-methyl-2-pentanone **6** in 81% yield. Treatment of this ketone with NaH in toluene and dimethyl carbonate afforded the β-keto ester **7a** in 39% yield. Standard diazo transfer[5] using tosyl azide and triethylamine converted **7a** into the desired α-diazo-β-keto ester **8a** having an *N*-methylindole unit. The oxindole substrate **8b** was prepared from the indolyl ketone **6** by initial oxidation to the oxindole **9** using HCl in DMSO in 71% yield, followed by carboethoxylation using LDA in THF, followed by addition of HMPA and then ethyl cyanoformate[6] to give the β-keto ester **7b** in 87% yield. Final diazo transfer then afforded the substrate **8b** in 95% yield. The final indoline substrate was harder to prepare.[7] Reduction of the ketone of **6** afforded in quantitative yield the secondary alcohol **10**, the indole ring of which was reduced with sodium cyanoborohydride and acetic acid to give the indoline alcohol **11** as a 65:35 mixture of diastereomers in 91% yield. Reoxidation under modified Swern conditions using TFAA and DMSO gave, in 56% yield, the ketone **12** which was carboethoxylated as before to give the β-keto ester **7c** in 100% yield. Diazo transfer as before furnished the substrate **8c** in 87% yield.

The results of the reaction of these three substrates with dirhodium tetraacetate in dichloromethane at 25°C for 10 h are shown in Scheme 2. In no case did we see any evidence of cyclization involving insertion of the carbenoid into the C4 aryl C–H bond, which would have

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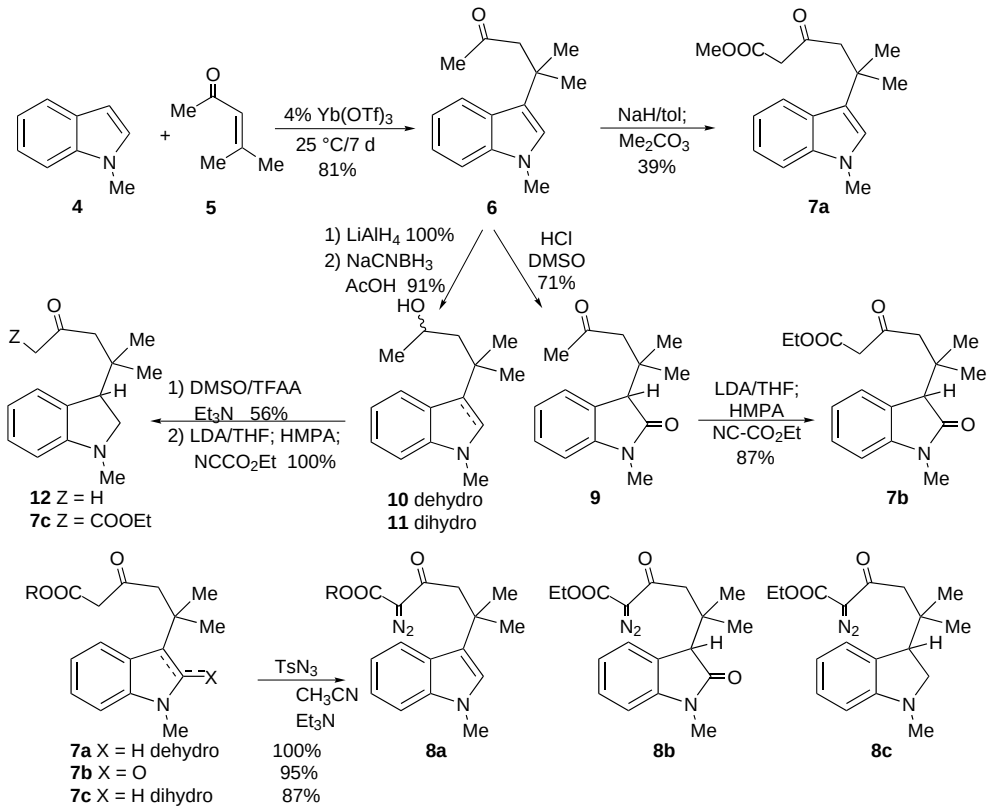


Scheme 1.

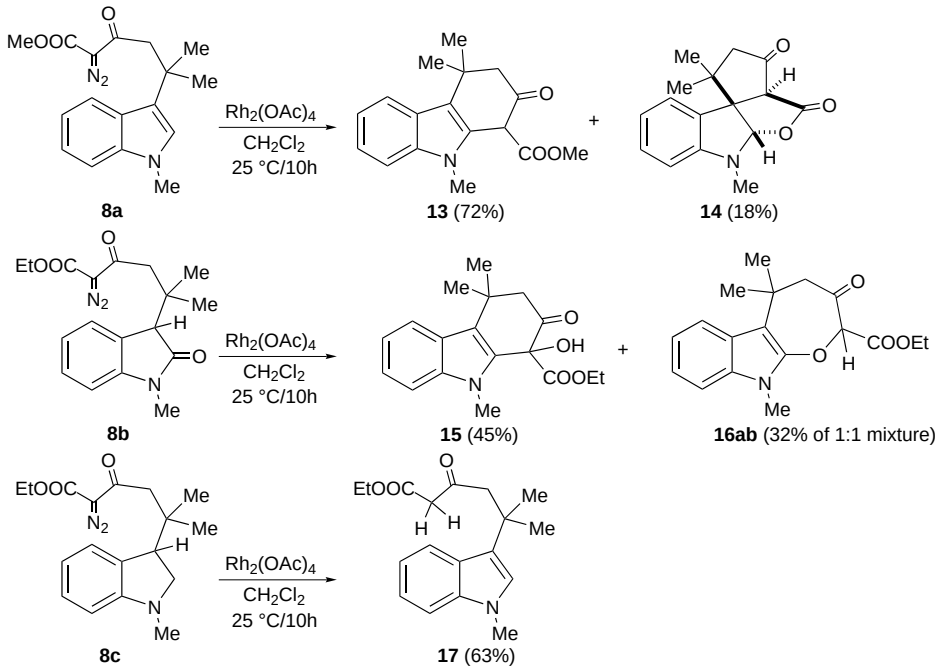
given us intermediates for our target molecule. Instead, all of the substrates reacted on the indole side of the molecule. The indole substrate **8a** afforded two products in high yield, namely 72% of the tetrahydrocarbazole derivative **13** and 18% of the novel tetracyclic β-ketolactone **14**. The oxindole substrate **8b** afforded a completely different set of products, with the α-hydroxy tetrahydrocarbazole β-keto ester **15** being the major product (45%) and a 1:1 mixture of the novel oxa seven-membered β-keto ester and its enol form **16ab** in 32% yield. Finally, the indoline substrate **8c** gave no cyclization at all but rather the product of an internal oxidation–reduction, namely the indole β-keto ester **17** in 63% yield.

The likely pathway for the formation of **13** and **14** from the α-diazo-β-keto ester **8a** involves initial formation of the rhodium carbenoid **I** which would then cyclize to the cyclopropane **II** (Scheme 3). Although simple adducts of indole containing cyclopropanes are known, e.g. the adduct of ethyl diazoacetate and *N*-carbomethoxy indole,[8] one would not expect the bridged compound **II** to be stable. Opening of the cyclopropane ring to relieve ring strain by either of two routes, bonds **a** or **b**, would then lead to the products. Breaking bond **a** would give the stabilized zwitterion **III** which would then suffer an internal protonation–deprotonation to give the tetrahydrocarboline β-keto ester **13**. Alternatively, breaking bond **b** would also lead to a very stabilized zwitterion **IV** which would cyclize via the ester enolate to the strained tetracyclic system **V**. On aqueous workup, the enol ether would hydrolyze to give only one diastereomer of the lactone, presumably the more stable one **14**.[9]

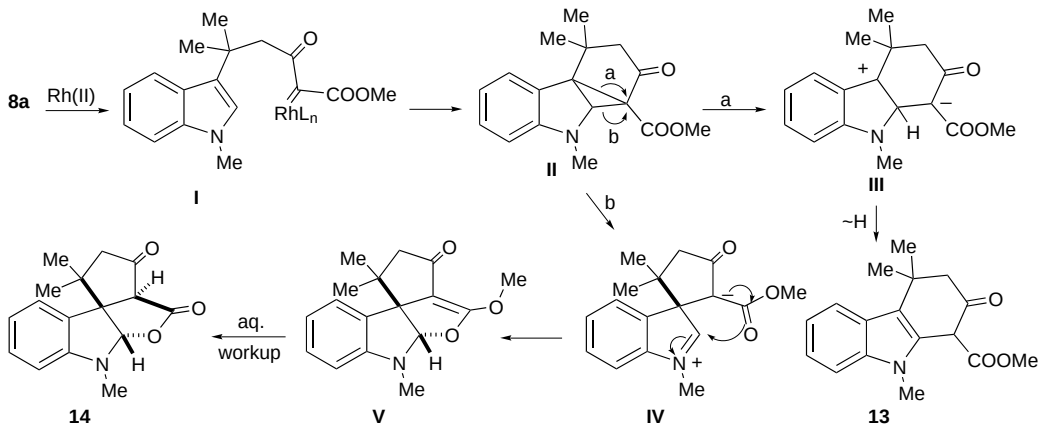
A possible route for the formation of the unusual products from the oxindole substrate **8b** is shown in Scheme 4, where the initially formed rhodium carbenoid **VI** would be attacked by the oxygen of the oxindole to produce the stabilized zwitterion **VII**, containing an oxepine ring system. Internal protonation–deprotonation would then generate the indolooxepine **16a** which would exist in equilibrium with its enol form **16b**.[10] Cyclization of the anion of the β-keto ester onto the iminium salt in **VII** would afford the novel spiro epoxide **VIII**, which is perfectly set up to open the strained epoxide bond to give the stabilized zwitterion **IX**, which would again suffer an internal protonation–deprotonation to give the observed α-hydroxy β-keto ester **15**.

The final substrate **8c** would give the rhodium carbenoid **X** which would undergo an intramolecular hydride transfer to generate the iminium enolate internal salt **XI** (Scheme 5). Although this intermediate could cyclize to the hexahydrocarboline, it undergoes an internal protonation–deprotonation to generate the product **17** instead, presumably due to the stability of the indole aromatic system.

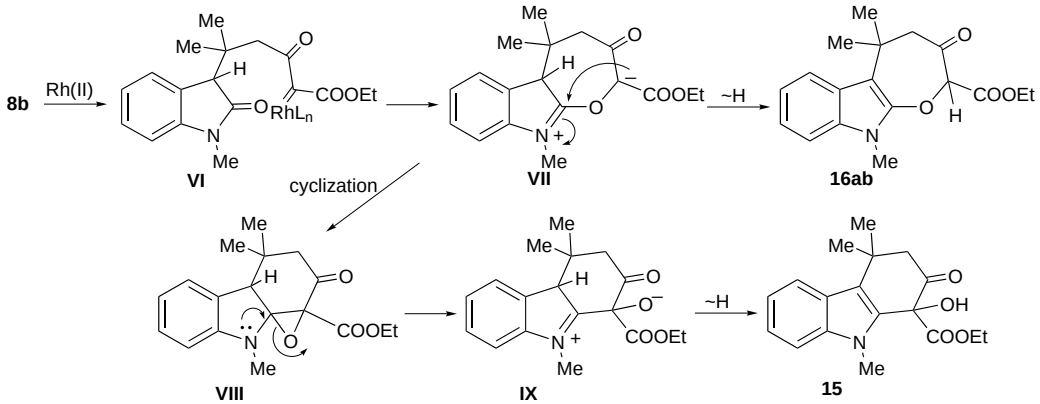
Thus, all three substrates **8abc** undergo completely different reaction processes depending on the oxidation state of the indole unit and afford products derived from cyclopropanation, amide attack followed by rear-



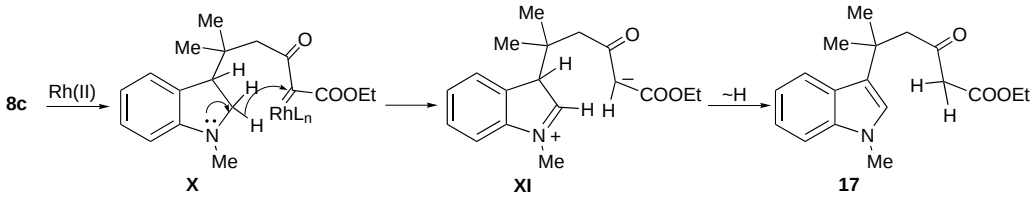
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

rangement, and internal oxidation–reduction. Further work on the synthesis of tricyclic intermediates, such as **1** for the preparation of *N*-methyl-welwitindolinone C isothiocyanate **2**, is currently underway in our laboratories.

Acknowledgements

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