Rhodium Carbenoid Induced Cycloadditions of Diazo Ketoimides Across Indolyl π-Bonds

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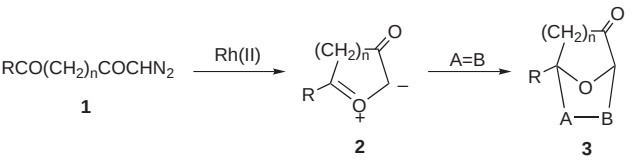
Abstract: A series of diazo ketoimides prepared from (1*H*-indol-3-yl)acetyl chloride and alkyl 2-diazo-3-(3-substituted-2-oxopiperidin-3-yl)-3-oxopropanoates were treated with rhodium(II) acetate. Attack of the imido carbonyl oxygen at the resultant rhodium carbenoid center produced a transient push–pull carbonyl ylide dipole which underwent an intramolecular dipolar cycloaddition across the indole π-bond. In most cases, the resulting cycloadduct is the consequence of *endo*-cycloaddition with respect to the dipole and this is fully in accord with the lowest energy transition state. Interestingly, when a *tert*-butyl acetate substituent is located at the ring juncture of the starting diazo ketoimide, the *exo*-cycloadduct was the exclusive product obtained. In this case, the bulky *tert*-butyl ester functionality blocks the *endo*-approach thereby resulting in the cycloaddition taking place from the less congested *exo*-face.

Key words: rhodium(II), diazo, catalyst, carbonyl ylide, dipolar cycloaddition, indole, kopsifoline, alkaloid

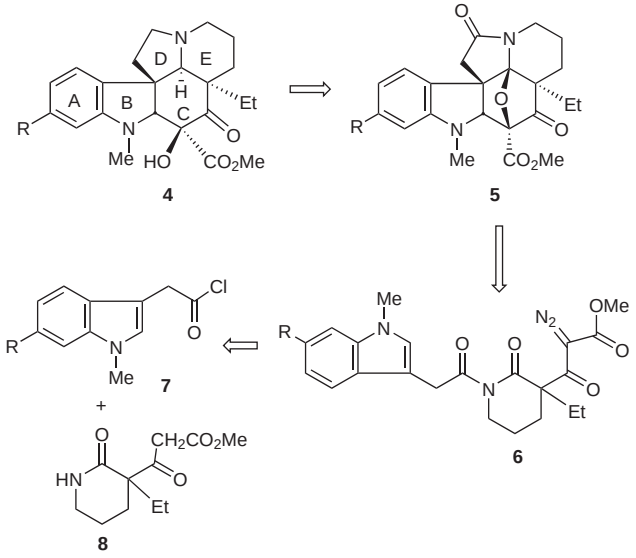
Nitrogen-containing heterocycles are abundant in nature and exhibit diverse and important biological properties.[1,2] Accordingly, novel strategies for the stereoselective synthesis of azapolycyclic ring systems continue to receive considerable attention in the field of synthetic organic chemistry.[3–9] Tandem methodology for heterocyclic synthesis represents a powerful approach for the rapid build-up of molecular complexity from potentially simple starting materials.[10–12] In the ongoing search for new domino processes, emphasis has been laid on sequential reactions which proceed cleanly and without forming by-products.[13–15] In 1986, we started work in our laboratory to synthesize bridged heterosubstituted bicycloalkanes from the Rh(II)-catalyzed cyclization cascade of diazo carbonyl compounds.[16] The domino reaction was shown to proceed by the formation of a rhodium carbenoid intermediate and a subsequent transannular cyclization of the electrophilic carbon onto an adjacent carbonyl group to generate a cyclic carbonyl ylide dipole. This was followed by a 1,3-dipolar-cycloaddition reaction[17] (Scheme 1). The primary spatial requirement for carbonyl ylide formation is that the distance between the two reacting centers be sufficiently close so that effective overlap of the lone pair of electrons of the carbonyl group with the metallocarbenoid can occur.[18] The resulting cyclic dipole (i.e., **2**) always contains a carbonyl group within the ring. We[19] and others[20] have found that intramolecular trapping of



Scheme 1

carbonyl ylide dipoles with tethered alkenes represents an effective method for the synthesis of a variety of natural products.

As an extension of these earlier studies, we developed a new approach to the construction of the pentacyclic skeleton of the aspidosperma ring system which involves the use of a related cyclization–cycloaddition cascade sequence.[21–25] This strategy was successfully applied to the synthesis of desacetoxy-4-oxo-6,7-dihydrovindorosine (**4**).[21] The approach used is outlined in Scheme 2 and is centered on the construction of the key oxabicyclic intermediate **5**. We found that **4** was accessible by reduction of the *N*-acyliminium ion derived from **5**, which in turn was available by a tandem rhodium(II)-catalyzed cyclization cycloaddition of α-diazoimide **6**. Cycloaddition of the initially formed dipole across the pendant indole π-system[22] results in the simultaneous generation of the CD-rings of the aspidosperma skeleton.[23] The



Scheme 2

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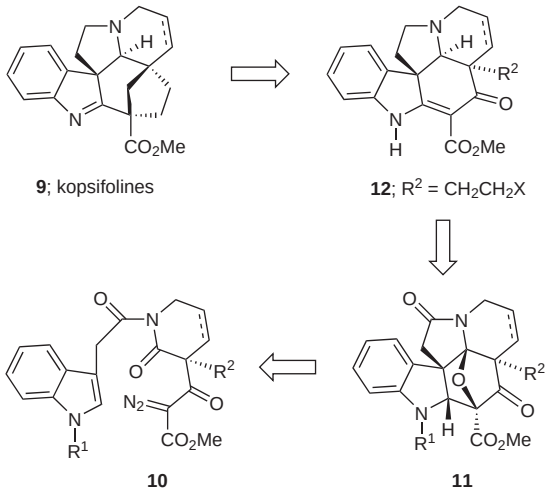
stereospecific nature of the internal cycloaddition reaction leads to the correct relative stereochemistry of the four chiral centers about the C-ring.

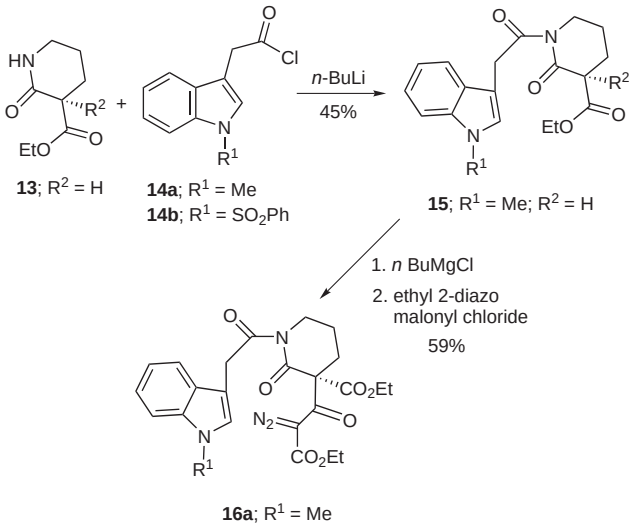
Prompted by our earlier studies dealing with the internal dipolar-cycloaddition reaction of push–pull carbonyl ylides for the synthesis of the aspidosperma skeleton, we became interested in determining whether a related process could be used to assemble the carbon framework of a new group of hexacyclic monoterpenoid indoline alkaloids known as the kopsifolines (i.e., **9**).[24] The key step in our planned approach to this family of alkaloids involves a 1,3-dipolar cycloaddition of a carbonyl ylide dipole derived from diazo ketoimide **10** across the indole π-bond.[25] Reductive ring opening of the resulting cycloadduct **11** followed by dehydration and N-deprotection would lead to the key precursor **12** necessary for the final F-ring closure (Scheme 3).[26]



Scheme 3

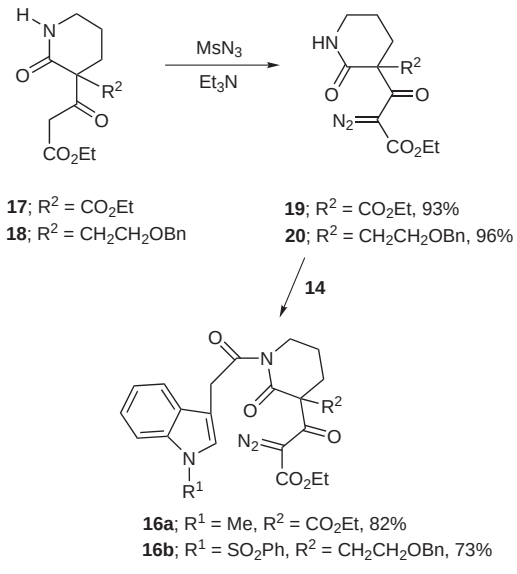
We first carried out a model study using diazo ketoimide **16a** in order to test the reliability of the key dipolar-cycloaddition reaction. Several methods for preparing the diazo imides necessary for dipole formation have been explored. One option that we have used involves treating the commercially available 3-carboethoxy-2-piperidone (**13**) with *n*-BuLi at –78 °C followed by the addition of an indole acid chloride such as **14a**. This results in the joining of the two fragments to give imide **15** in 45% yield. A subsequent reaction of **15** with *n*-butyl magnesium chloride in THF at 0 °C followed by the addition of ethyl 2-diazomalonyl chloride[27] afforded the indolyl-substituted diazo imide **16a** in 59% yield (Scheme 4).

Since the overall yield of diazo imide **16a** obtained by this method was somewhat low, we opted to study an alternate procedure to prepare several of the starting diazo substrates of interest. With this in mind, diazo imide **16a** could also be synthesized in the manner outlined in Scheme 5. This involved the initial preparation of a methyl 2-diazo-3-(3-substituted 2-oxopiperidin-3-yl)-3-oxopropanoate (i.e., **19** or **20**) and then coupling it with the



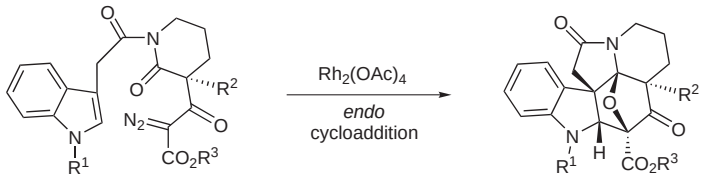
Scheme 4

appropriate indole acid chloride **14**.[28] By carrying out the synthesis of the indolyl-substituted diazo imide in this manner, the Regitz diazo-transfer reaction[29] can be avoided in the final step thereby simplifying the synthesis. Thus, piperidinones such as **17** and **18** were easily converted to the corresponding diazo lactams **19** and **20** in excellent yield.[29] These compounds, in turn, were treated with an N-substituted indolyl acid chloride (i.e., **14)** which resulted in the formation of the desired diazo imides **16a** and **16b** in 82% and 73% yield, respectively. A related set of reactions was used to prepare the other substituted diazo imides **16c**–**f** outlined in Scheme 6.



Scheme 5

Gratifyingly, heating a sample of **16a** with $Rh_2(OAc)_4$ in benzene at 80 °C afforded cycloadduct **21a** in 90% yield as a single diastereomer (Scheme 6). Bolstered by this positive result, we next examined the Rh(II)-catalyzed behavior of several related indolyl-substituted diazo amides

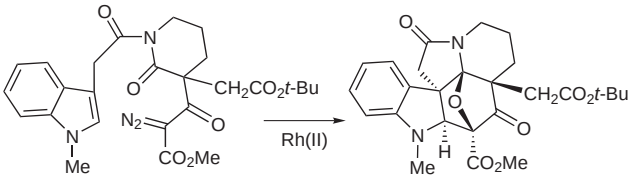


16a; R^1 = Me, R^2 = CO_2Et , R^3 = Et
16b; R^1 = SO_2Ph, R^2 = CH_2CH_2OBn, R^3 = Et
16c; R^1 = Me, R^2 = Et, R^3 = Me
16d; R^1 = Me, R^2 = CH_2CH_2OBn, R^3 = Me
16e; R^1 = SO_2*p*-tol, R^2 = CH_2CH_2OBn, R^3 = Me
16f; R^1 = SO_2*p*-tol, R^2 = CH_2CO_2Me, R^3 = Me

21a; R^1 = Me, R^2 = CO_2Et , R^3 = Et, 90%
21b; R^1 = SO_2Ph, R^2 = CH_2CH_2OBn, R^3 = Et, 90%
21c; R^1 = Me, R^2 = Et, R^3 = Me, 95%
21d; R^1 = Me, R^2 = CH_2CH_2OBn, R^3 = Me, 96%
21e; R^1 = SO_2*p*-tol, R^2 = CH_2CH_2OBn, R^3 = Me, 90%
21f; R^1 = SO_2*p*-tol, R^2 = CH_2CO_2Me, R^3 = Me, 98%

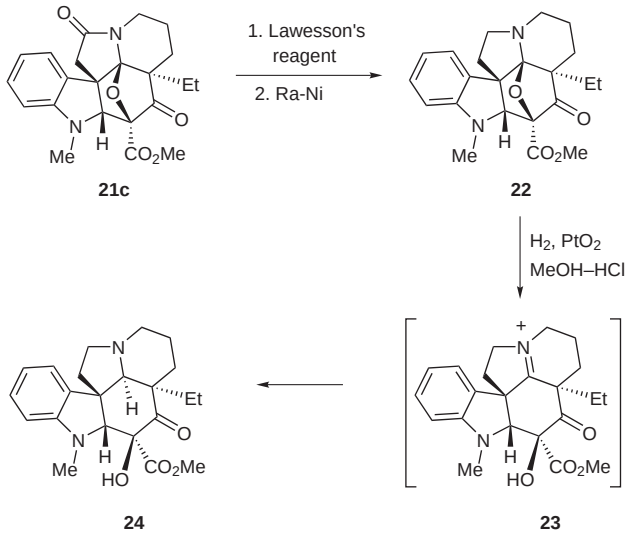
Scheme 6

(**16b**–**f**) and were pleased to find that the Rh(II)-catalyzed cycloadditions proceeded in excellent yield (i.e., 90–98%). All of the cycloadducts are formed with complete diastereoselectivity and correspond to *endo* cycloaddition with respect to the dipole and *anti* with respect to the substituent group at the ring juncture. The *endo* diastereoselection for the dipolar cycloaddition can be attributed to a conformation (strain) preference dictated by the dipolarophile tether since it mirrors the relative energy of the four possible products. The stereochemical assignment was unambiguously established by an X-ray crystal structure[30] of the ring-opened alcohol **24** derived from cycloadduct **21c** (Scheme 7). Thus, treatment of **21c** with Lawesson's reagent furnished the expected thiolactam in 85% yield which was cleanly reduced to pyrrolidine **22** on treatment with Raney-Ni at 25 °C in THF. A subsequent hydrogenation of **22** over PtO_2 in acidic methanol gave **24** in 94% yield as a single diastereomer. The overall reduction proceeds by an acid-catalyzed ring opening of the N,O-acetal to generate a transient iminium ion **23** which is hydrogenated from the least congested face. We have also investigated the Rh(II)-catalyzed cycloaddition of diazo ketoimide **25** (Scheme 8). In marked contrast to the results encountered with diazo ketoimides **16a**–**f**, the *exo*-cycloadduct **26** was the exclusive product isolated from this reaction. The relative stereochemistry of **26** was assigned on the basis of an X-ray crystal structure of the ring-opened alcohol.[30] In this case, the bulky *tert*-butyl ester functionality blocks the *endo*-approach thereby resulting in the cycloaddition taking place from the less congested *exo*-face. Interestingly, intermolecular cycloaddition of five-membered cyclic carbonyl ylides with indole was also found to proceed by an *exo*-cycloaddition[31] attesting to the sensitivity of the dipolar-cycloaddition reaction to steric factors in the transition state.



25 **26** (*exo* cycloaddition)

Scheme 8



21c **22** **24** **23**

Scheme 7

In conclusion, we have demonstrated that the Rh(II)-catalyzed reaction of diazo ketoimides containing tethered indolyl groups undergo successful 1,3-dipolar cycloadditions across the heteroaromatic π-bond to provide novel oxa-bicyclic compounds. This tandem intramolecular cyclization–cycloaddition sequence is particularly attractive for the synthesis of the kopsifoline class of alkaloids as four stereocenters and two carbon–carbon bonds are formed in a single step with a high degree of stereocontrol under mild experimental conditions. Further studies on transforming the cycloadducts to the kopsifoline family of alkaloids are in progress and will be reported at a later date.

Acknowledgment

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(28) In a typical general procedure, 1.1 equiv of the appropriate 3-indoleacetic acid was dissolved in CH_2Cl_2 and 4.0 equiv of oxalyl chloride was added dropwise. The solution was stirred overnight and then concentrated under reduced pressure. The resulting solid was taken up in THF, which was immediately added to a vigorously stirred mixture containing 1.0 equiv of the diazo lactam (i.e. **19** or **20**) and 4 Å MS in THF. After stirring for 12 h, the mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The crude material was purified by flash silica gel column chromatography to give the desired

coupled product. Using this procedure, 3-{3-(2-benzyloxyethyl)-1-[2-(1-methyl-1*H*-indol-3-yl)acetyl]-2-oxopiperidin-3-yl}-2-diazo-3-oxopropionic acid methyl ester (**16d**) was obtained as a colorless oil in 82% yield. IR (neat): 2143, 1718, 1685, 1332, 1146 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.65–1.75 (m, 1 H), 1.85–2.02 (m, 2 H), 2.19–2.30 (m, 3 H), 3.46–3.53 (m, 1 H), 3.61–3.80 (m, 2 H), 3.70 (s, 3 H), 3.76 (s, 3 H), 4.15–4.21 (m, 1 H), 4.24 (s, 2 H), 4.37 (d, 1 H, *J* = 15.8 Hz), 4.41 (d, 1 H, *J* = 15.8 Hz), 6.88 (s, 1 H), 7.07–7.11 (m, 1 H), 7.17–7.32 (m, 7 H), 7.54 (d, 1 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 30.2, 32.7, 34.7, 35.5, 44.5, 52.5, 59.3, 67.2, 73.0, 107.9, 109.3, 119.1, 119.2, 121.6, 127.6, 127.7, 128.2, 128.3, 128.5, 136.9, 138.4, 161.6, 173.6, 176.4, 190.8.

To a solution of 0.2 g of the diazoimide **16d** in 10 mL of benzene under N_2 was added 2 mg rhodium(II) acetate, and the mixture was heated at reflux for 1 h. The mixture was allowed to cool to r.t. and was filtered through a pad of Celite®. The solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give 0.16 g (96%) of the dipolar-cycloaddition product **21d**.

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