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Structure and Mechanism Revision of a Catalyzed Cyclization of Benzaldehyde Bearing Alkyne-Nitrile

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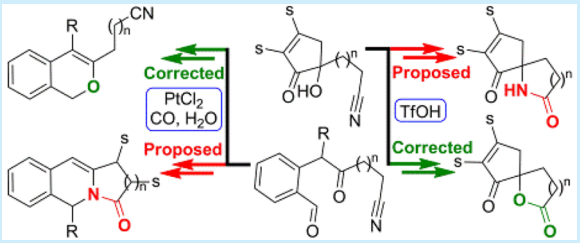
Supporting Information

ABSTRACT: Pt(II)-catalyzed carbocyclization of benzaldehyde containing a keto-nitrile functionality resulted in the formation, respectively, of isochromenes and spiro-lactones instead of fused lactams and spiro-lactams as was previously reported. The reaction mechanism was proposed, and the products were identified by multidimensional NMR, IR, and X-ray analysis. The structure of these new products was also confirmed by their synthesis in an unambiguous manner using practical and short approaches.



Our group has been interested for a very long time in the construction of enantiopure nitrogen fused 5/6- and 6/6-membered bicyclic ring systems. These form the basic skeleton of indolizidine[1−4] and quinolizidine[5] alkaloids which show a wide range of biological properties (Figure 1).[6]

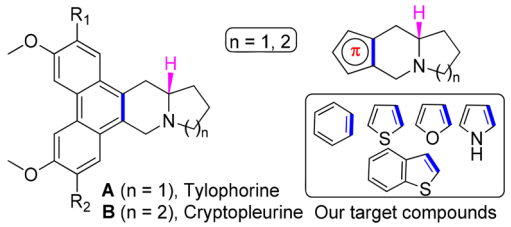
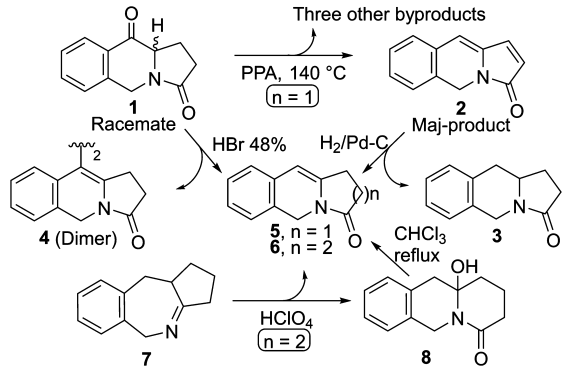


Figure 1. Model natural compounds and our targets.

During our studies on the synthesis of tylophorine (**A**) and cryptopleurine (**B**) analogues, the preparation of tricyclic enamides **5**,**6** as advanced synthetic platforms was planned. Entries into such compounds that are already published are summarized in Scheme 1. Rigo et al.[7] reported that by heating ketone **1a** (n = 1) in 48% HBr, it was possible to isolate isoquinolinone product **5** as a byproduct in only 5% yield accompanied by other products including traces of dimer **4**. With PPA at 140 °C, instead of 48% HBr, the same ketone **1a** provided **2** as the sole major reaction product. The latter upon catalytic hydrogenation (H_2/Pd−C) furnished a 2:3 ratio of inseparable **3** and **5**. Product **5** was also obtained by the same authors in two steps from ketone **1a** by Merwein−Verley−

Scheme 1. Known Strategies To Reach Cyclic Olefins 5 and 6



Ponndorf reduction followed by thermal dehydration at 180 °C, but unfortunately, the product was found to be unstable and decomposed quickly.[8] Schumann and Naumann[9] prepared, for their part, compound **6** by oxidation of benzazepine **7**. The reaction provided a mixture of two separable compounds **6** (24%) and **8** (56%). If heated, the alcohol **8** provides the elimination product **6** almost quantitatively. However, the total yield of this multistep reaction was only 3% (Scheme 1).

Because the above-mentioned published syntheses of lactams **5**, **6** (n = 1, 2) are lengthy and impractical for scale up, we wish

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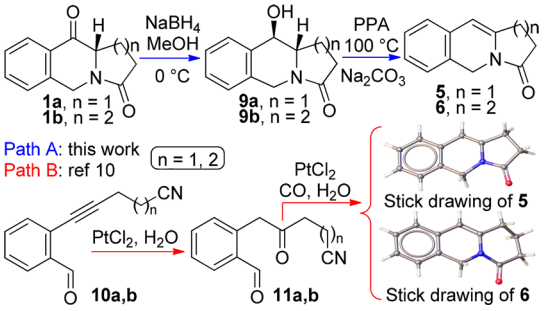
to present herein a simple and scalable approach to these systems. This is accompanied by a corrigendum of structures described in an important recent report.[10] The approach used is based on two innovative hydrative carbocyclizations of oxa-alkyne-nitrile functionalities with a $PtCl_2/CO/H_2O$ system (Scheme 2).

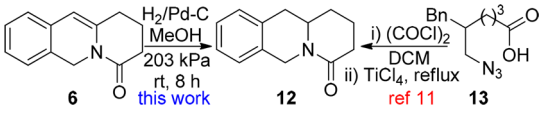
Scheme 2. Two-Step Sequences Leading to Cyclic Olefins 5 and 6 and Stick Drawings of Their X-ray Structures



Based on our earlier reports on the asymmetric hydrogenation of indolizidindiones and their use to obtain indolizidinols and their salts with glycosidase inhibitory potential,[2,4] we have chosen to attempt an elimination reaction from alcohols **9a,b**, easily prepared by diastereoselective reduction of ketones **1a,b**. This approach constitutes an ineffective (loss of chirality!) but the quickest and most reliable route to these platforms **5**, **6** (Scheme 2, Path A). In this sense, the water elimination leading to enamides was achieved by PPA at 100 °C in a yield of 48% for **5** (31% from **1a**) and 57% for **6** (34% from **1b**).

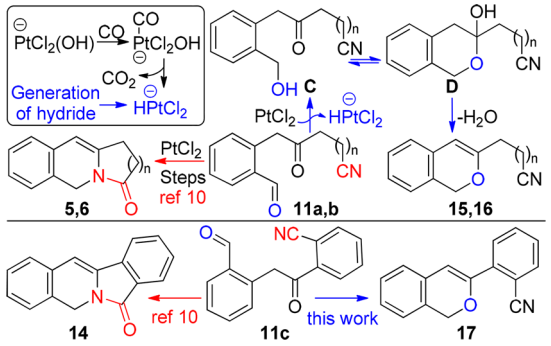
A total synthesis together with a basic characterization of these cyclic enamides **5**, **6** has already been reported starting from the oxa-alkyne-nitriles **10** using two consecutive carbocyclizations catalyzed by Pt(II) (Scheme 2, Path B).[10] To our surprise, the reported NMR data of these tricycles **5** and **6** did not match the routine NMR spectra of our elimination products. The identity of these compounds with the structures of **5**, **6** was confirmed by a detailed NMR analysis and by a comparison with other published spectra.[7,8] Ultimately, these structures were confirmed by single crystal X-ray analysis for compounds **5**, **6**, rendering the two-step sequence from **10a,b**[10] inoperative (Scheme 2). The structure of **6** was also established chemically in an unambiguous way by its catalytic hydrogenation into a well-known compound **12** (Scheme 3), previously obtained from azido-carboxylic acid **13**, and by comparison of spectral data with those from the literature.[11]

Scheme 3. Additional Chemical Proof of Quinolizinone 6



By repeating the reported synthetic protocol from **11a,b**,[10] the reaction yields 1*H*-isochromenes **15**, **16** instead of the isoquinolinones **5**, **6** as assigned in the literature (Scheme 4).[10] In fact, as both the expected structures **5** (or **6**) and **15** (or **16**) share an identical number of ^1H and ^{13}C nuclei, an inconvenient attribution without the use of correlation NMR experiments can be inadvertently carried out. The structure of

Scheme 4. Proposed Mechanism for Hydrative Carbocyclizations into Lactams 5, 6 Using $PtCl_2/CO/H_2O$ System



16 was identified by a set of standard 2D NMR spectra supported by a $^1H-^{15}N$-gHMBC spectrum. The obtained ^{15}N chemical shift (−135.1 ppm; situated in the region of ^{15}N NMR shifts of nitriles) and only one multiple-bond correlation in the spectrum definitely proved the presence of a nitrile group at the end of an aliphatic side chain. This was also indicated by the characteristic vibration of a CN group at 2246 cm^{-1} in the IR spectrum of the studied sample. The ^{15}N chemical shift of the corresponding tricyclic lactam derivative **6** was −243.6 ppm as observed in its ^{15}N NMR spectrum and through four multiple-bond correlations in the $^1H-^{15}N$-gHMBC spectrum. This study could be also extended to other published lactams, e.g. aromatic benzonitrile leading under these conditions to isochromene **17** in place of known **14**[12] as reported[10] (Scheme 4).

The reaction mechanism proposed by the authors[10] for the formation of **5**, **6**, and **14** is based on the hydrolysis of the nitrile function into primary amide (Scheme 4, red path) followed by the amide nitrogen attack onto the ketone function. As indicated by the compounds' true structures **15**–**17** described herein, it indicated that both of the above-mentioned steps are quite unlikely due to difficult hydrolysis of the nitrile group[13] as well as the very low reactivity of amides toward carbonyl compounds.[14]

For our part, we described a chemically more plausible path (Scheme 4, blue path). The formation of isochromenes **15**, **16** instead of lactams **5**, **6** can be explained by the $PtCl_2/CO$ catalyzed alkyne hydration of the starting alkynyl-nitrile **10a,b** to corresponding keto-nitrile **11a,b** (Scheme 4).[10] These rather unstable compounds can be isolated in 53–57% yield for **11a** and 58–61% yield for **11b** after careful column chromatography purification (each reaction was performed four times). In the literature,[10] for **11b**, yields of 78% using $AuCl_3$, 88% using $AuBr_3$, and 91% using the $PtCl_2/CO$ system were reported. The chemoselective reduction of aldehydes **11a,b** with a platinum hydride anion or with a plausible HPt-Cl_2 species (Scheme 4) takes place to form the alcohol **C** which undergoes intramolecular cyclization to unstable hemiacetal **D**. Finally the dehydration at this stage led to the expected isochromenes **15** and **16** in 68% and 79% yield, respectively.

Alternatively we have found that isochromenes **15**, **16** can also be advantageously prepared from alcohols **18a,b** by $NaBH_4$ reduction of alkyne-benzaldehydes **10a,b** (Scheme 5). In a highly selective conversion catalyzed by $PtCl_2$, **18a,b** without an atmosphere of CO underwent the expected 6-*endo-dig* cyclization to yield the same isochromenes **15** (68%) and **16** (48–79%). This protocol was earlier reported for the synthesis

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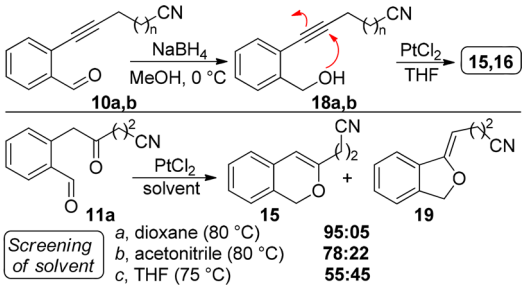
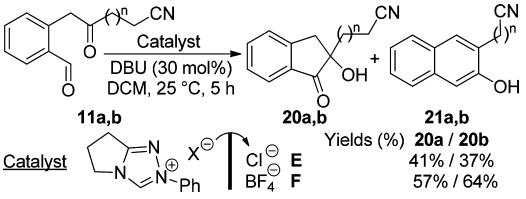
Scheme 5. Alternative Approaches to Isochromenes 15, 16



of 3-methyl-1*H*-isochromene.[15] Related 3-propylisochromene could also be prepared from 2-pentynylphenylmethanol by Gold-catalyzed ring closure in low yield (27−31%).[16] During our investigations, we also found that using the "NHC-catalyzed" cyclization protocol of **11a** (n = 1), in contrast to **11b** (n = 2), is highly dependent on the solvent (Scheme 5). Cyclization in all cases provides a mixture of two inseparable isomers (6-*endo* **15** and 5-*exo* **19**), as determined by ^{1}H NMR spectra and comparison with those of similar structures.[17] Unlike chromenes,[18] 1*H*-isochromenes are less common natural metabolites.[19] Their synthesis has been studied less frequently due to their instability and tendency toward polymerization.[20] Interestingly, similar properties were observed for the prepared isochromenes **15** and **16**.

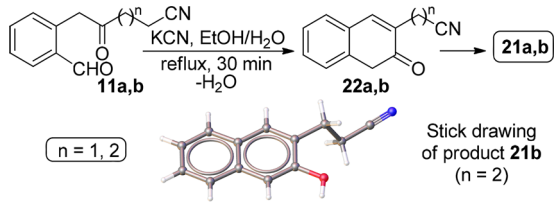
The syntheses and fundamental characterization of 10 other spiro-lactam derivatives (see Supporting Information (SI) for details) based on the same intermediates as for the above-mentioned isochromenes were reported (Scheme 4).[10] In this context, we thus turned our attention to the synthesis of 2,3-dihydro-1*H*-inden-1-ones **20a,b**. Thus, according to the reported conditions,[10] keto-aldehydes **11a,b** were subjected to a ring-closure benzoin condensation with azolium salt **E** (Scheme 6). Their cyclization was also carried out in the presence of azolium salts, B_1-vitamin, thiazolium or imidazolium salts, and other bases including KCN (see SI).

Scheme 6. Optimization of the Ring Benzoin Condensation



The best results were obtained using catalyst **F**[21] (57% for **20a** and 64% for **20b**). When we repeated the published procedure with the same catalyst **E**, essentially lower yields were observed (41% and 37% instead of the reported 77% and 82%) for **20a** and **20b**, respectively, accompanied by other reaction products. The most interesting results were however obtained when KCN (see SI) was used, since only novel 3-substituted-2-naphthols **21a,b** were isolated whose structure was identified on the basis of NMR spectra and by comparison with the spectra of similar compounds.[22] It is evident that in this case the cyanide anion acts as a base forming ketone enolate. Based on these results, it was revealed that the ring-closure benzoin condensation is a rather complex process. This is due to the high reactivity and instability of keto-aldehydes **11a,b**, as documented by the complexity of the ^{1}H NMR spectrum showing the appearance of three new compounds, even after 10 h of pure **11a,b** standing in the NMR tube. Screening other reaction parameters also demonstrated that the condensation depended strictly on the purity of the keto-aldehyde, the type of catalyst, and the amount of the base used. The best yields of **20a,b** were obtained by using an equimolar amount of catalyst **F** and DBU. Interestingly, when we repeated the reaction exactly as reported,[10] excess use of the base led to a complex mixture, from which we were able to isolate in addition to the main products **20a,b** also 2-naphthols **21a,b** (Schemes 6, 7).

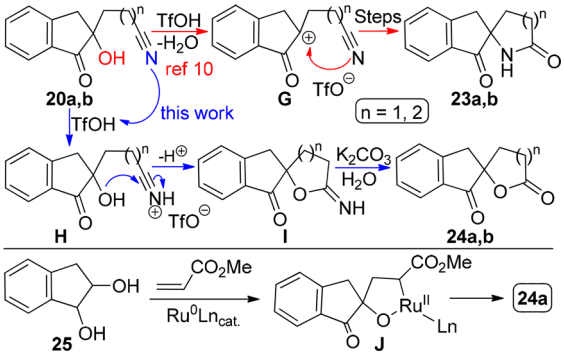
Scheme 7. One-Step Access to 21a,b and Stick Drawing of the X-ray Structure of 21b



The formation of the new compounds **21a,b** was confirmed by the independent reaction of **11a,b** with KCN, a weak base, which proved sufficient to remove the proton at the carbonyl α-position. This interestingly gives **21a,b** via the ketone intermediates **22a,b**, as the sole reaction products in high yields. Finally, the proposed structure of these entities was determined by X-ray crystal structure analysis of compound **21b** (Scheme 7).

With the oxo-2,3-dihydro-1*H*-indenes (**20a,b**) in hand, we focused our attention on the subsequent target spiro-lactams **23a,b** (Scheme 8). The formation of these products from

Scheme 8. Suggested Mechanism for Cyclization of 20a,b



indenyl-alkanenitrile **20a,b** is not explained in the literature,[10] but it is assumed that carbocation **G** should be formed in the first step of reaction. This then undergoes *endo-dig* cyclization, hydration, and tautomerization to provide finally spiro-lactams **23a,b**.

In contrast to the suggested mechanism leading to spiro-lactams **23a,b** (Scheme 8, red), we believe that the reaction begins with protonation of the CN group of **20a,b** to form **H** (Scheme 8, blue). This is subsequently attacked by the OH group to provide **I** after deprotonation. The resulting imine is hydrolyzed to afford final spiro-lactones **24a,b**. Lactone **24a** was also prepared by McInturff et al.[23] through Ru(0)-catalyzed hydroxyalkylation of acrylate. This provided transient oxa-

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ruthena-cycle **J** that cyclized easily to form the lactone **24a** (Scheme 8). Spectral data of lactone **24a** are identical with the declared spectra of lactam **23a** in the literature.[10] As the authors furnished only the HRMS analysis without elemental analysis for lactam **23a**, the structure of lactone **24a** cannot be reasonably excluded (see SI for 10 other corrected structures).

In conclusion, during our investigations on the synthesis of tylophorine (**A**) and cryptopleurine (**B**) analogues, we have prepared standards of dihydropyrrolo[1,2-*b*]isoquinolinones and pyrido[1,2-*b*]isoquinolinones as advanced platforms for molecular diversity. Upon checking the literature, we were highly surprised by the spectral data attributed to these products, obtained by a Pt(II)-catalyzed carbocyclization of benzaldehyde containing an alkyne-nitrile functionality.[10] Careful reexamination of the reported procedure with some substrates resulted in the structure revision of a set of compounds from fused lactams into new and scarce isochromenes. In the same context, the initially assigned spiro-lactams which were obtained from the same intermediates generated by benzaldehyde containing an alkyne-nitrile functionality were also revised into spiro-lactones. The confirmation of these new structures was based on an unambiguous chemical synthesis of certain isochromenes and spiro-lactones and via IR analysis and thorough NMR studies as well as single crystal X-ray analysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01881.

Experimental procedures and characterization data for all new compounds (PDF)

X-ray crystallographic data for compounds **5**, **6**, and **21b** (CIF)

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Notes

The authors declare no competing financial interest.

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