Pyrrole Synthesis

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Multicomponent Synthesis of Pyrroles from Cyclopropanes: A One-Pot Palladium(0)-Catalyzed Dehydrocarbonylation/Dehydration**

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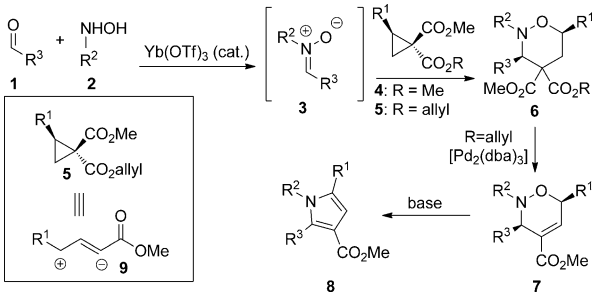
Since 1834 when Runge described a substance that was found in coal tar and bone oil and turned red upon application to acid-moistened pine splinters,[1] chemists have been fascinated with the pyrrole moiety, which is found in a wide range of bioactive natural products.[2] In addition to its ubiquity in nature, the tremendous therapeutic and commercial impact of pyrrole-containing drugs, such as Lipitor (atorvastatin calcium), has driven the development of vast numbers of new synthetic methods for the synthesis and functionalization of this heterocycle.[3] Herein, we report a new and powerful synthetic method for the generation of tetrasubstituted pyrroles from tetrahydro-1,2-oxazines, which are in turn prepared in excellent yields from donor/acceptor cyclopropanes.[4]

Previous work reported by our group has shown that the reaction of a nitrone **3** with a 1,1-cyclopropanediester **4** results in the smooth formation of tetrahydro-1,2-oxazines **6** (Scheme 1).[5] Although the use of an isolable nitrone is an option, the reaction is often conveniently performed as a three-component coupling of an aldehyde **1**, a hydroxylamine **2**, and a cyclopropane **4**.[5g] This cycloaddition has been useful in our preparation of several natural products.[6]



Scheme 1. The formation of tetrahydro-1,2-oxazines, dihydro-1,2-oxazines, and pyrroles. dba = dibenzylideneacetone, Tf = trifluoromethanesulfonyl.

During our recently reported synthesis of isatisine A,[7] we converted one of the geminal diesters in an adduct (a furan in that case) into an allyl ester and then used a Tsuji dehydrogenative decarbonylation (dehydrocarbonylation)[8] to introduce the required alkene moiety. It occurred to us that use of a cyclopropane substituted with an allyl ester (**5**) would give, upon dehydrocarbonylation of the tetrahydro-1,2-oxazine **6**, access to dihydro-1,2-oxazines **7.** In essence, the cyclopropane would have a preinstalled unit of unsaturation, thus behaving as synthon **9** in the overall conversion of **3** into **7**. The allyl ester moiety would serve both as an activating group as well as a group capable of undergoing elimination in the adduct. This idea could be used to access unsaturated analogues of a variety of donor/acceptor cyclopropane adducts. Moreover, it also occurred to us that when treated with base **7** may undergo conversion into highly functionalized pyrroles **8**. Herein, we report a convenient synthesis of 4,5-dyhydro-1,2-oxazines and their facile conversion into a wide variety of tetrasubstituted pyrroles.

Our study commenced with the synthesis of a variety of 1-carboallyloxy-1-carbomethoxy cyclopropanes **5** and their reaction with a variety of nitrones **3** by either a 2- or 3-component protocol (Scheme 2). The requisite cyclopropanes were prepared by monosaponification[9] of the appropriate bis(methylester) followed by treatment of the hemimalonate with base and allyl bromide.[10] The decision on whether to use a preformed nitrone or to generate it in situ is sometimes determined by the stability of the hydroxylamine or nitrone, but is more-often determined by the preference of the chemist. The tetrahydro-1,2-oxazines are, for the most part, formed in excellent yields and as a near 1:1 mixture of epimers at the geminal diester center. This lack of selectivity is ultimately inconsequential since the chirality at this center is lost in subsequent transformations. It should be noted that the formation of adducts **6l** and **6o** (Scheme 2) required the use of the slightly more Lewis acidic $Sc(OTf)_3$ to effect efficient reaction. This requirement can be explained by the absence of a donor group vicinal to the diester moiety.

With the tetrahydro-1,2-oxazines in hand, we submitted them to the dehydrocarbonylation conditions described by Tsuji and co-workers.[8] Scheme 3 shows the results of the dehydrocarbonylation of five selected allyl esters **6** from Scheme 2. The yields are generally good and are typical of the reported yields for this type of reaction. Notably, the reactions are 100% regioselective (to our levels of detection) for the Δ^4 isomer (alkene in the 4,5-position). The reasons for this are not clear at this time, however as the last step in the putative mechanism is a β-hydride elimination of a carbon-bound palladium enolate, perhaps the β hydrogen at the oxazine 3-

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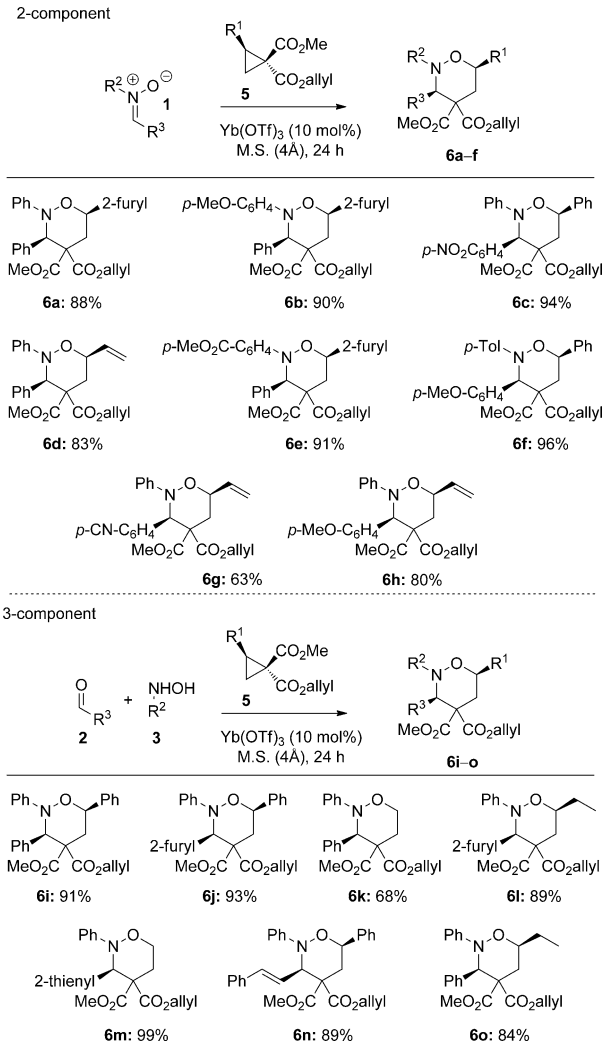
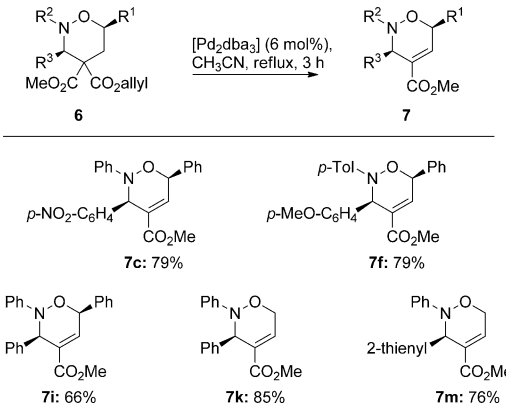


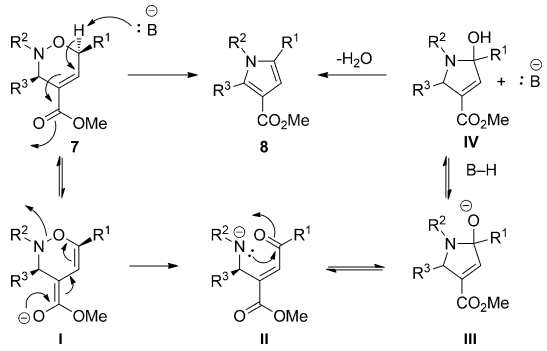
Scheme 2. Synthesis of tetrahydro-1,2-oxazines. Yields are for the isolated products. M.S. = molecular sieves.



Scheme 3. Dehydrocarbonylation to dihydro-1,2-oxazines. Yields are for the isolated products.

position lacks the stereoelectronic requirements for the process. Also worthy of note is that an alkyl *N*-substituent was not tolerated, presumably as a result of the increased Lewis basicity of the nitrogen atom and subsequent catalyst poisoning. This issue was not overcome by performing the reaction on the ammonium salt of the oxazines.

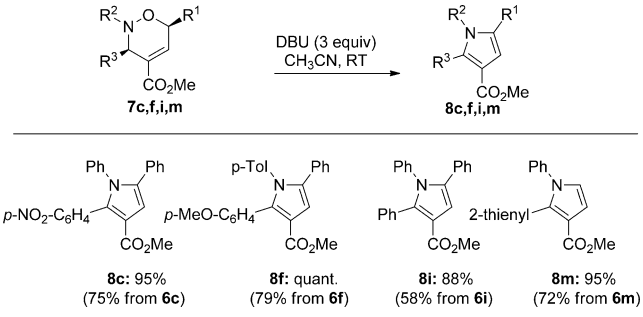
During attempts to use the dihydro-1,2-oxazines **7** in subsequent transformations (cross-coupling to the 5-position, for example) we noted that the compounds had a propensity to rearrange with loss of water to pyrroles; the ease of pyrrole formation was surprising. Scheme 4 shows a mechanism by



Scheme 4. Mechanism of pyrrole formation.

which a general base may promote the formation of such a pyrrole. Although the mechanism shown is illustrated as proceeding by an E1cb process (**I**→**II**), a mechanism proceeding via an enol (rather than an enolate) is also a distinct possibility. We also cannot rule out a direct E2-style elimination across the C–O bond. Ring closure of **II** to **III** followed by dehydration of hemiaminal **IV** leads to pyrrole **8**. Although rarely seen synthetically,[11] this type of transformation has been reported as a side reaction in other processes.[12]

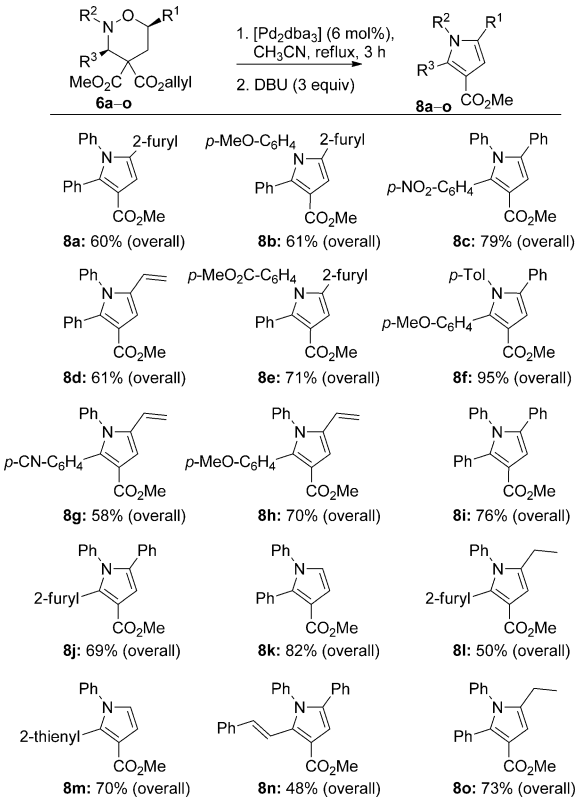
Scheme 5 shows the facile conversion of the dihydro-1,2-oxazines **7** into pyrroles **8** by using an excess amount of DBU at room temperature. Although the reaction proceeds with catalytic base, the use of an excess of base allows for a more expedient conversion.



Scheme 5. Conversion of dihydro-1,2-oxazines into pyrroles. Yields are for the isolated products. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

As the transformation of **7** into **8** was so facile, it occurred to us that the addition of a small amount of base to the dehydrocarbonylation reaction mixture (the conversion of **6** into **7**) might effect a one-pot synthesis of pyrroles from the

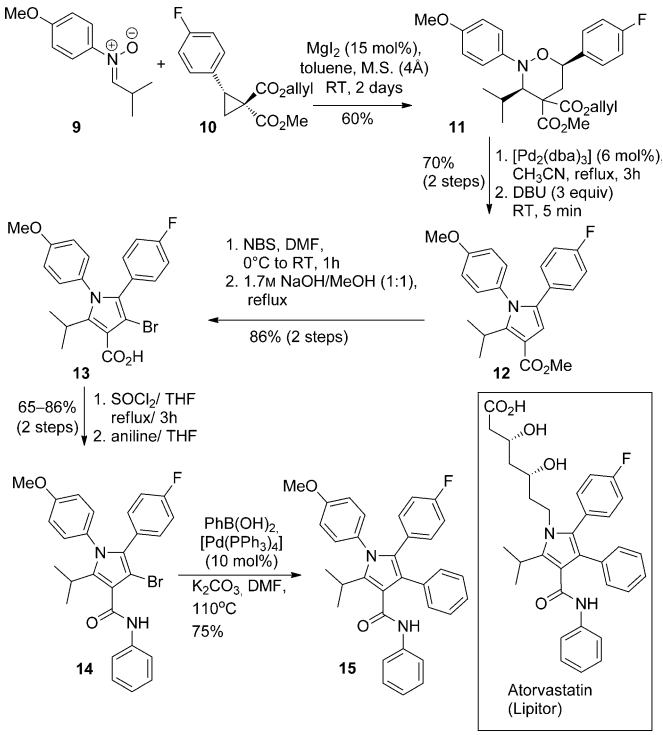
tetrahydro-1,2-oxazines **6**. This was indeed the case and Scheme 6 shows the results of this modified reaction. In the event, upon completion of the dehydrocarbonylation (3 h),



Scheme 6. One-pot conversion of tetrahydro-1,2-oxazines into pyrroles. Yields are for the isolated products.

the reaction mixture was cooled to room temperature and DBU (3 equiv) was added. After a short time (usually 5 min) the conversion to the pyrrole was complete and the reaction was worked up. It is noteworthy to compare the yields of the one-pot syntheses of **8c**, **8f**, **8i**, and **8m** (Scheme 6) with the corresponding overall yields for the two-pot conversion of **6** into **8** (in parentheses in Scheme 5). In all cases the one-pot procedure is at least as efficient as the two-pot procedure, thus obviating the need for isolation of the dihydro-1,2-oxazine en route to the pyrrole. In the cases where $R^1 = H$ or Et (**8k**, **8m**, **8l**, and **8o**), the reaction mixture was kept at either 40 °C (24 h) or 60 °C (0.5 h) to effect conversion into the pyrrole. The need for different reaction conditions was presumably due to the decreased acidity of the C6 hydrogen (Scheme 4) in these instances.

To show the utility of this route to pyrroles we applied the preceding two-pot strategy to the synthesis of the atorvastatin (Lipitor) pyrrole unit. Scheme 7 shows our synthesis of this compound. We were surprised to find that the desired cycloaddition did not occur under the usual reaction conditions. Gratifyingly however, condensation of nitrone **9** and cyclopropane **10** occurred under the catalytic influence of MgI_2 to give tetrahydro-1,2-oxazine **11** in 60% yield.[13] Treatment of **11** with $[Pd_2dba_3]$ followed by addition of



Scheme 7. Synthesis of the atorvastatin pyrrole. DMF = *N*,*N*′-dimethylformamide, NBS = *N*-bromosuccinimide.

DBU under the usual reaction conditions gave pyrrole **12** in 70% overall yield. Bromination of the remaining vacant pyrrole position proceeded in near quantitative yield to give, after hydrolysis, bromoacid **13** (86% yield overall). Conversion into anilide **14** took place in variably good yields (65–86%) via the acid chloride. Suzuki coupling of the bromopyrrole **14** with phenylboronic acid gave the target pyrrole **15** in 75% yield. Deprotection of the pyrrole would provide a substrate suitable for conversion into atorvastatin and a variety of related compounds. Although arguably comparable with regards to the number of steps to the industrial (Paal–Knorr) synthesis of the pyrrole unit, the value of the route described herein lies in its modularity, allowing access to a wide variety of substitutions on the pyrrole ring.

In summary, we have described a new pyrrole synthesis which will allow the preparation of a plethora of heterocyclic compounds. The starting materials are inexpensive and readily available and the method is technically simple. Further applications of this method will be reported in due course.

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