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Multifunctionalized 3-Hydroxypyrroles in a Three-Step, One-Pot Cascade Process from Methyl 3-TBSO-2-diazo-3-butenoate and Nitrones

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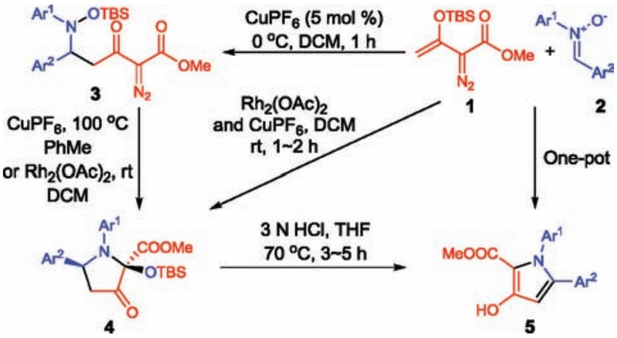
ABSTRACT



The synthesis of *N*-aryl-2-carboxyl-3-hydroxy-5-arylpyrroles has been achieved in high yield by the combination of a TBSO-substituted vinyldiazoacetate and nitrones in a one-pot cascade process involving copper-catalyzed Mannich addition, dirhodium-catalyzed dinitrogen extrusion and N-OTBS insertion, and acid-promoted aromatization (elimination).

Pyrroles are found in a broad range of bioactive molecules[1] and have multiple applications in materials science.[2,3] Efficient methods for their synthesis continue to be a topic of intense interest,[4] especially for complex systems, and recent reports have focused on polysubstituted pyrroles.[5] However, none of these methods have been designed for or are applicable to the synthesis of substituted 3-hydroxypyrroles, and there is only one recent example specific to the preparation of 3-hydroxypyrroles,[6,7] despite their well-known applications.[8] Herein we report a novel

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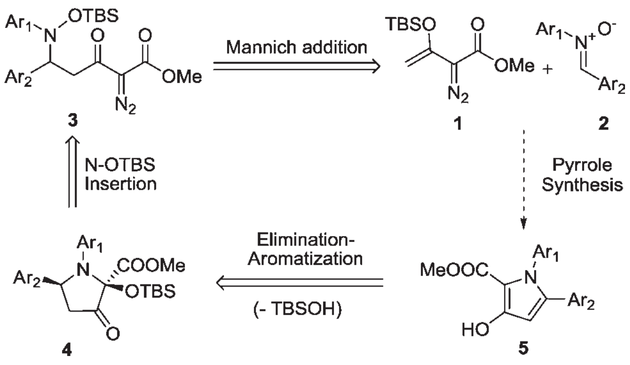
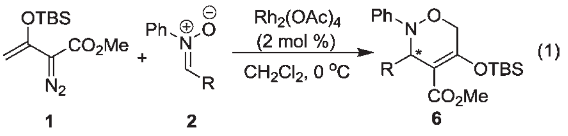
and efficient one-pot reaction for the construction of multifunctionalized 3-hydroxylpyrrole derivatives.

The Lewis acid catalyzed Mukaiyama–Mannich addition of a TBSO-substituted vinyldiazoacetate to imines[9] coupled with dirhodium(II)-catalyzed N–H insertion of δ-amido-β-keto-α-diazo esters[10] is a convenient methodology for the synthesis of 3-ketopyrrolidine derivatives. However, relatively harsh conditions are required to convert pyrrolidine derivatives to pyrroles.[11] Based on the success of the Mannich/N–H insertion process, we considered this combination of steps together with mild dehydration as a combined methodology for the synthesis of 3-hydroxypyrroles (Scheme 1). To accomplish this transformation we adopted nitrones, instead of imines, as Mannich addition acceptors. Nitrones have been used in Mannich-type reactions with keteneacetals catalyzed by Lewis acids.[12] Hydroxylamines **3** were anticipated from reactions of nitrones with **1** that, following unprecedented dirhodium catalyzed N-OTBS insertion, would produce 2-hydroxy-3-oxopyrrolidines **4**. Dehydration of **4** to the multifunctionalized pyrrole **5** is known to occur under acidic conditions.[13] Although insertion into the N–O bond of a hydroxylamine is unprecedented,[14] insertion into the isoxazole N–O bond has recently been reported.[15]

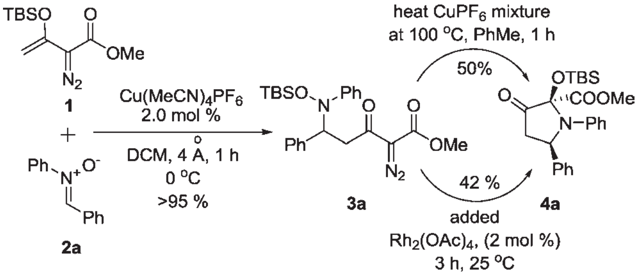
Scheme 1





When TBSO-substituted vinyldiazoacetate **1** is treated with *N*,α-diphenylnitrone (**2a**, R = Ph) in dichloromethane at 0 °C in the presence of a catalytic amount of dirhodium tetraacetate, formal [3 + 3] addition occurs to form methyl *N*,3-diphenyl-3,6-dihydro-1,2-oxazine **6** in > 95% yield (eq 1).[16] Under the same conditions, however, only Mannich addition occurs between these substrates in the presence of catalytic copper(I) hexafluorophosphate. By warming the reaction mixture containing $CuPF_6$ to 100 °C or by adding $Rh_2(OAc)_4$ at room temperature, **3a** underwent formal N-OTBS insertion to produce pyrrolidin-3-one **4** as a single diastereoisomer in moderate yield (Scheme 2). The structure of the pyrrolidine product was confirmed by single-crystal X-ray diffraction analysis of its *p*-bromo-substituted derivative (Figure 1).

Scheme 2. Access to Pyrrolidin-3-one **4a** by a Two-Step Process



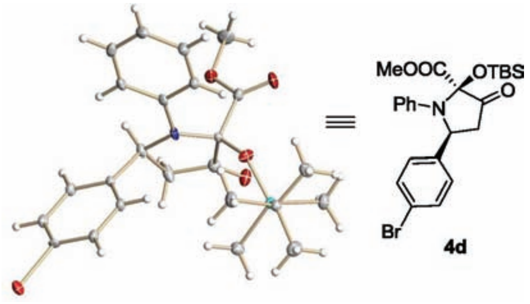


Figure 1. Crystal structure of compound **4d**. The *p*-bromophenyl and OTBS functionalities are on the same side of the five-membered ring.

Carbene insertion into a saturated N–O bond is unprecedented, so efforts were undertaken to further understand this process. As a first experiment, we investigated the outcome of the reaction with the TBS group of **3a** replaced by hydrogen. In this case there is potential competition between N–OH insertion and O–H insertion and, indeed, both are observed (eq 2), with O–H insertion being the preferred process. However, the lower stereoselectivity in this case (9:1 with **10a** versus > 20:1 for **4a**) led us

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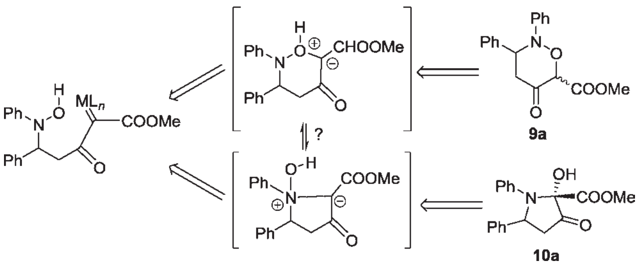
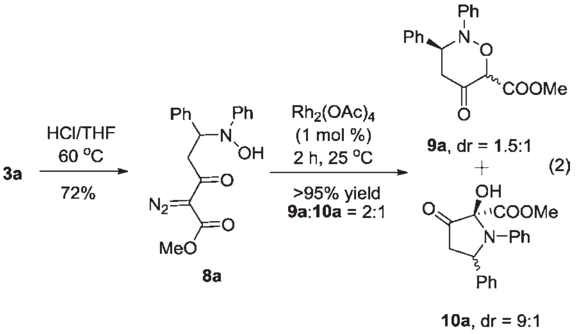
Scheme 3. NO−H versus N−OH Insertion via Ylide Intermediates



to the conclusion that the TBS attachment is critical for high stereocontrol in product formation. The mechanism of these processes probably involves ylide intermediates, either as an oxonium ylide leading to **9** or as an ammonium ylide leading to **10** (Scheme 3).[17] Why the six-membered ring O−H insertion product is preferred over the five-membered ring N−OH insertion product is uncertain, but this competition and selectivity may be related to the rate of hydrogen versus hydroxyl shift, which would be associated with a common intermediate or equilibrium between the oxonium and ammonium ylides.



(2)

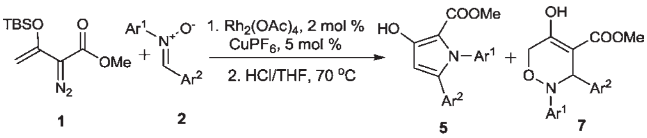
With the assumption that copper and rhodium catalysts act independently, so that the combination of TBSO-substituted vinyldiazoacetate **1** and nitrone could achieve the formation of **4** under one set of reaction conditions, we treated **1** with *N*,α-diphenylnitrone (**2a**) in the presence of catalytic amounts of rhodium acetate and copper(I) hexafluorophosphate at room temperature. As anticipated, pyrrolidine **4a** was formed with only a trace amount of **6** and was isolated as a pure product in 76% yield (Table 1, entry 1). Obviously, the role of $CuPF_6$ as a Lewis acid in these reactions is pronounced, and the possibility exists that coordination of $CuPF_6$ with **1** or **3** inhibits its use as a catalyst for dinitrogen extrusion,[17] which is successfully compensated with the addition of $Rh_2(OAc)_4$ that is not inhibited by reactant or product. Further attempted optimization in the amount of Lewis acid employed (entries 1−3) with a constant 2 mol % of $Rh_2(OAc)_4$ showed that a lower Lewis acid catalyst loading was advantageous. The use of alternative Lewis acid cocatalysts in combination with dirhodium acetate was also explored. An outcome comparable to that from the use of $CuPF_6$ could be obtained with $Sc(OTf)_3$ (entry 5). However, use of other Lewis acids, including copper(II) triflate, led to a decrease in the relative percentage of pyrrolidine **4a** (entries 4,6−7). In the absence of $Rh_2(OAc)_4$ all Lewis acids employed catalyze the Mannich reaction of **1** with **2** to form **3** at various rates.

Table 1. Optimization of Reaction Conditions for the Synthesis of **4a**[a]

entry	Lewis acid	**3a**:**4a**:**6**[b]	yield (%)[c]
1	$CuPF_6$	0:98:2	76
2	$CuPF_6$ (5 mol %)	0:95:5	78
3	$CuPF_6$ (10 mol %)	47:50:3	92
4	$Zn(OTf)_2$	0:71:29	80
5	$Sc(OTf)_3$	0:96:4	77
6	$Cu(OTf)_2$	0:55:45	88
7	$Yb(OTf)_3$	0:67:33	86
8	$CuPF_6$	0:98:2	72[d]

[a] Reactions were carried out on a 0.25 mol scale: **1** (0.30 mmol), **2** (0.25 mmol), 4 Å MS (0.10 g), $Rh_2(OAc)_4$ (2.0 mol %), Lewis acid cocatalyst (2.0 mol %), in DCM (2.0 mL) at 0 °C. [b] Determined by ^1H NMR of the crude reaction mixture. [c] Isolated yield of **3a**, **4a**, and **6**. [d] Yield of the corresponding pyrrole **5a** after 3 N HCl was treated with the crude reaction mixture of entry 1.

Table 2. Substrate Generality of the One-Pot Cascade Reaction for the Pyrrole Synthesis[a]



entry	Ar^1/ Ar^2	product	**5**:**7**[b]	yield[c]
1	C_6H_5/C_6H_5	**5a**	<98:2	72
2	$4\text{-}BrC_6H_4/4\text{-}ClC_6H_4$	**5b**	<98:2	79
3	$4\text{-}MeOC_6H_4/C_6H_5$	**5c**	<98:2	76
4	$C_6H_5/4\text{-}BrC_6H_4$	**5d**	<98:2	77
5	$C_6H_5/4\text{-}CF_3C_6H_4$	**5e**	<98:2	85
6	$C_6H_5/4\text{-}FC_6H_4$	**5f**	<98:2	75
7	$C_6H_5/4\text{-}ClC_6H_4$	**5g**	<98:2	80
8	$C_6H_5/3\text{-}ClC_6H_4$	**5h**	<98:2	85
9	$C_6H_5/2\text{-}ClC_6H_4$	**5i**	<98:2	87
10	$C_6H_5/4\text{-}MeC_6H_4$	**5j**+**7j**	67:33	88
11	$C_6H_5/4\text{-}MeOC_6H_4$	**6k**	10:90	90[d]

[a] The reaction was carried out in 0.25 mol scale: **1** (0.30 mmol), **2** (0.25 mmol), 4 Å MS (0.10 g), $Rh_2(OAc)_4$ (2.0 mol %), $CuPF_6$ (5.0 mol %), in DCM (2.0 mL) at 0 °C for 1 h with stirring another 2 h at room temperature; then the solvent was replaced with THF (5 mL) followed by 3 N HCl (5 mL), and the mixture was warmed to 70 °C for another 3 h. [b] Determined by ^1H NMR of the crude reaction mixture. [c] Isolated yield of **5** and **7** based on **2**. [d] Isolated yield of **6** (skip the step with HCl) based on **2**.

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The aromatization step for pyrrole synthesis was conveniently achieved by refluxing **4a** in THF with 3 N HCl for 3–5 h to give 100% conversion.[13] A one-pot three-step pyrrole synthesis was achieved by performing the catalytic Mannich addition and N-OTBS insertion in dichloromethane, replacing that solvent with THF, adding 3 N HCl, and heating at 70 °C for 3 h to give pyrrole product **5a** in 72% isolated yield (Table 1, entry 8).

Substrate generality for the one-pot synthesis of 3-hydroxypyrroles with various arylnitrones was determined from the yields and selectivities that are reported in Table 2. All substrates gave high to excellent product yields from reactions using moderate amounts of the combined catalysts and subsequent aromatization. Pyrrole **5** was the only product observed with all *N*-arylnitrones having electron-withdrawing substituents on the α-aryl group. In contrast, nitrones with electron-donating substituents on the α-aryl group formed both six- and five-membered ring products with moderate chemoselectivity but also in high yield (entries 10–11). The N-OTBS insertion product **4** was formed with high diastereoselectivity; in the case of entry 3 (Ar_1 = *p*-$MeOC_6H_4$) and entry 4 (Ar_2 = *p*-BrC_6H_4) the pyrrolidin-3-one products were single diastereoisomers with the aryl and OTBS functionalities on the same side of the five-membered ring.

In conclusion, we have developed a general and efficient three-step, one-pot methodology for the construction of *N*-aryl-2-carboxyl-3-hydroxy-5-arylpyrroles from TBSO-substituted vinyldiazoacetate **1** and nitrones in high yield. This cascade reaction involves Lewis acid catalyzed Mannich addition, a novel dirhodium tetraacetate catalyzed *N*-OTBS insertion, and acid-promoted aromatization (elimination). Efforts are underway to assess the generality of methodology for the synthesis of heterocycles and to generalize N–O and related bis-heteroatom insertion reactions.

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Supporting Information Available. General experimental procedures, X-ray structures of **4d** and **5g**, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.