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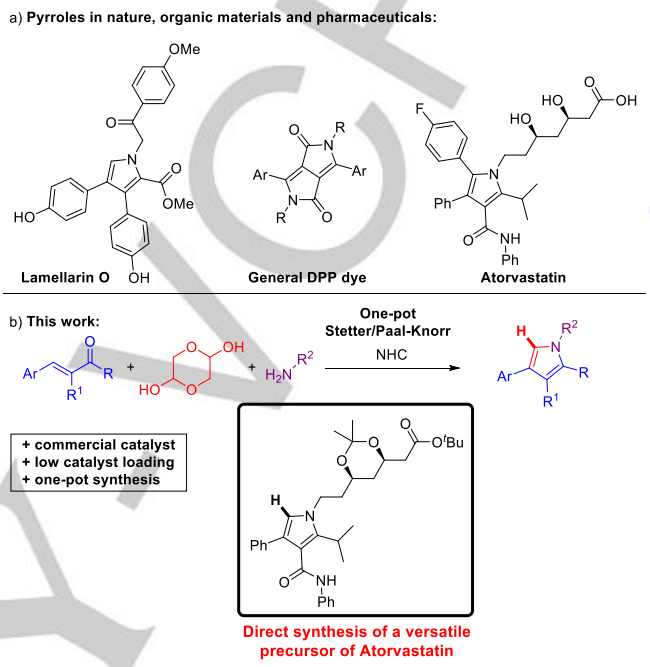
α-Unsubstituted Pyrroles by NHC-Catalyzed Three-Component Coupling - Direct Synthesis of a Versatile Atorvastatin Derivative

Mirco Fleige and Frank Glorius*[a]

Abstract: A practical one-pot cascade reaction protocol provides direct access to valuable 1,2,4-trisubstituted pyrroles. The process involves an N-heterocyclic carbene (NHC)-catalyzed Stetter-type hydroformylation using glycolaldehyde dimer as a novel C1 building-block, followed by a Paal-Knorr condensation with primary amines. The reaction makes use of simple and commercially available starting-materials and catalyst, an important feature regarding applicability and utility. Low catalyst loading under mild reaction conditions afforded a variety of 1,2,4-substituted pyrroles in a transition-metal free reaction with high step economy and good yields. This methodology is applied in the synthesis of a versatile Atorvastatin precursor which allows a variety of modifications at the pyrrole core structure.

Pyrroles represent important core structures, appearing in a variety of natural products,[1] organic materials[2] and pharmaceuticals (Scheme 1a).[3] Amongst others, 1,2,4-triarylpyrroles are key scaffolds of several bioactive compounds.[4] Consequently, it is of high relevance to create a diverse set of synthetic strategies to build up this scaffold.[5] During Paal-Knorr pyrrole synthesis, 1,4-dicarbonyl compounds condense with primary amines.[6] However, the general Paal-Knorr pyrrole synthesis for the generation of 1,2,4-trisubstituted pyrroles requires either a multi-step synthesis and/or pre-functionalization of starting materials. A multi-step synthesis of the 1,2,4-triarylsubstitued pyrroles has been achieved by Montgomery et al. from readily available enones via a sequential Ni-catalyzed reductive coupling with alkynes, followed by ozonolysis and Paal-Knorr condensation.[7] Alternatively, a Au(I)-catalyzed hydroamination cascade reaction has been established by Li and Liu et al., which gave access to differently substituted pyrroles in two steps from commercially available starting materials.[8] Less selective and efficient syntheses of 1,2,4-triarylpyrroles have also been reported using Ti[9] or Pd[10] catalysis or acid promoted hydrolysis of pyrrole-2-carboxylates.[11] Recently, Zhang reported a metal-free strategy to obtain this particular substitution pattern of pyrroles via an iodine promoted condensation/cyclization reaction of acetophenones with anilines.[12] Unfortunately, only homo-coupling of the acetophenone derivatives could be achieved.

The NHC-catalyzed Stetter-reaction is a powerful tool for hydroacylation of Michael acceptors, that can serve as pyrrole precursors.[13-15] A famous example of an industrial application of the Stetter reaction followed by a pyrrole synthesis is Pfizer's synthesis of Atorvastatin (Lipitor®), a fully substituted pyrrole. (Scheme 1a right).[16]



Scheme 1. a) Examples of pyrrole motives in natural products (left), organic materials (middle) and pharmaceuticals (right). b) One-pot Stetter-type hydroformylation and Paal-Knorr condensation.

Although the Stetter-reaction/Paal-Knorr sequence is an often applied synthetic strategy for the formation of pyrroles, an efficient one-pot three-component coupling involving an aldehyde, amine and Michael-acceptor has not been reported, to the best of our knowledge. This is attributed to the fact that the Paal-Knorr synthesis usually requires acidic reaction media, which makes it necessary to add acid after the rather basic NHC-catalyzed reaction is complete.[17] Encouraged by Chi's report on a Stetter-type hydroformylation of chalcones, which makes use of C6/C5-sugars as formaldehyde equivalents[18] we investigated other potential formaldehyde sources for NHC-catalyzed hydroformylation reactions. When we added an amine to a Stetter reaction of glycolaldehyde dimer, we surprisingly observed the Paal-Knorr reaction product under basic reaction conditions (Scheme 1b). Herein, we report this reaction as a one-pot Stetter-type hydroformylation/Paal-Knorr reaction for the synthesis of complex pyrroles.

We started the optimization of this reaction by treating 4-fluorochalcone (**1a**) with glycolaldehyde dimer (**2**), *p*-toluidine (**3a**) with 20 mol% of thiazolium salt **4** and 20 mol% K_3PO_4 in acetonitrile (0.1 M) to generate the desired pyrrole **5a** in 53% yield (table 1, entry 1). Variation to other polar solvents did not improve the yield (entry 2). Diminishing the catalyst/base loading to 5 mol% increased the formation of **5a** to 66% yield (entry 3). We speculated, that due to the lower catalyst concentration, side reactions would be suppressed and the

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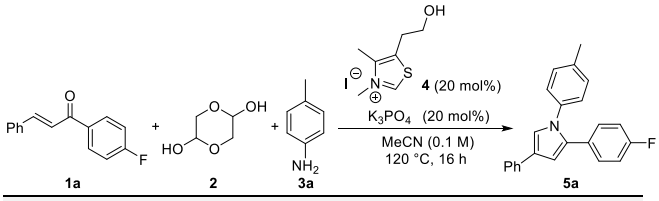
product formation could be enhanced. Switching the base (entry 4) as well as varying the temperature (entry 5) did not improve the yield (for detailed optimization data see the Supporting Information). Finally, dilution of the reaction mixture to 0.03 M improved the yield to 76% of **5a** (entry 6). Diminished yields were obtained by employing glucose and paraformaldehyde under these conditions as C1-surrogate (60%, 53%). Surprisingly, aqueous formaldehyde solution still gave access to pyrrole **5a** in 50% yield.

Table 1. Optimization of reaction conditions.

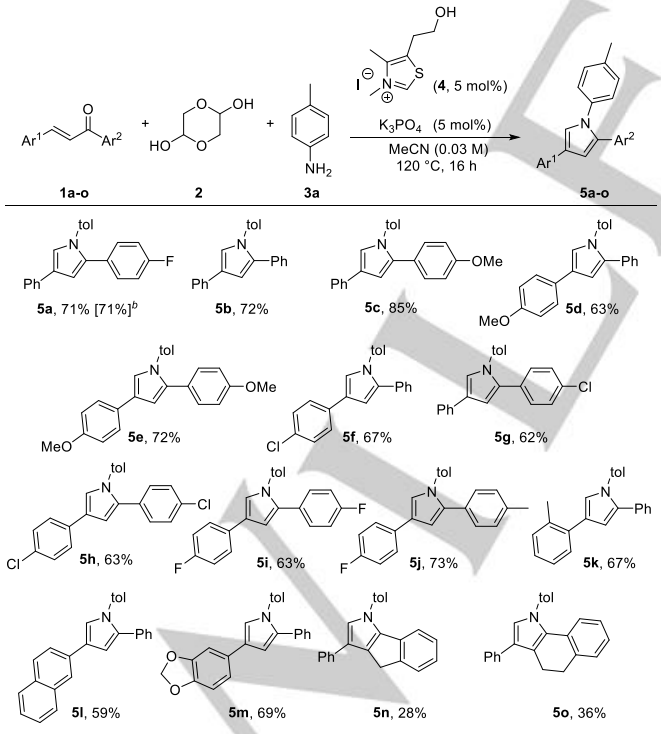


1a 2 3a 5a

Entry	Changes of initial conditions	Yield (%)[a]
1	-	53
2	DMF or DMSO or EtOH	33/28/28
3	5 mol% NHC salt/K_3PO_4	66
4	5 mol% NHC salt/K_2CO_3	60
5	5 mol% NHC salt/K_3PO_4, 100 °C or 140 °C	38/63
6	5 mol% NHC salt/K_3PO_4, 0.03 M	76

[a] Reaction conditions: 0.1 mmol **1a**, 1.0 equiv. **2**, 2.0 equiv. **3a** at 120 °C for 16 h.Yields were determined by ^{19}F NMR analysis of the crude mixture using 1-fluoronaphthalene as internal standard.

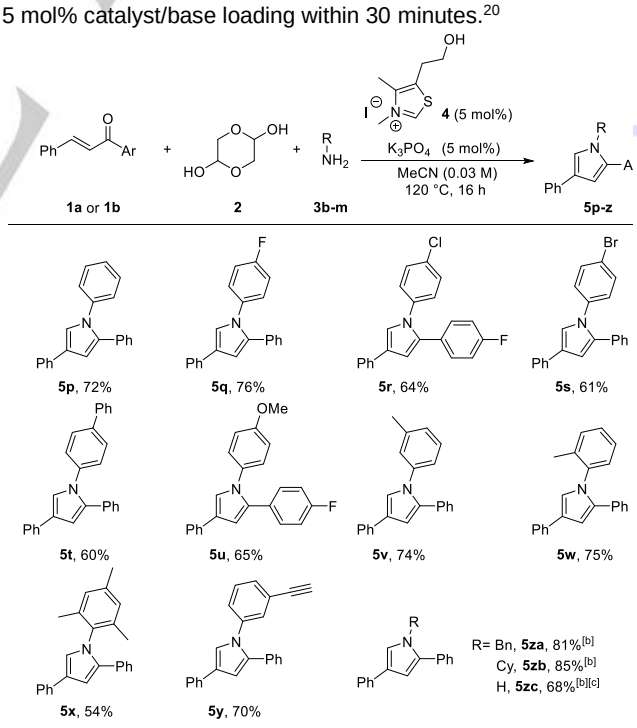
With the optimized reaction conditions in hand, we assessed the generality of the substrate scope (Scheme 2).



Scheme 2. [a] Reaction conditions: 0.3 mmol chalcone **1a**-**o**, 1.0 equiv. **2**, 2.0 equiv. **3a**, 5 mol% NHC salt **4**, 5 mol% K_3PO_4, 9 mL MeCN at 120 °C for 16 h. [b] 2.5 mol% NHC salt **4** and 2.5 mol% K_3PO_4 were employed. Isolated yields are given.

Employing unsubstituted *trans*-chalcone (**1b**) yielded pyrrole **5b** in good yield. Electron-donating substituents on both aromatic rings of the chalcone afforded the corresponding pyrroles **5c** – **5e** in 85 – 72% yield. Chalcones substituted with halides gave access to pyrroles **5f** – **5j** in good yields. *Ortho*-substitution was tolerated and yielded pyrrole **5k**. Disubstituted arenes at the chalcone were also successfully converted to the pyrroles **5l** and **5m**.[19] In addition, cyclic chalcones were successfully converted to the corresponding dihydroindenopyrrole **5n** and dihydrobenzoindole **5o** in modest yields. Gratifyingly, the catalyst/base loading for chalcone **1a** could be lowered to 2.5 mol% while maintaining the isolated yield of pyrrole **5a**.

Next, we investigated the scope of the amine coupling partner (Scheme 3). Unsubstituted aniline gave access to pyrrole **5p** in 72% yield. 4-Haloanilines led to the respective pyrroles **5q** – **5s** in 61 – 76% of yield. Electron donating substituents afforded the corresponding pyrroles **5t**, **5u** in good yields. Employing anilines with one *ortho*- or *meta*-substituent did not impede the generation of pyrroles **5v**, **5w**. Sterically encumbered mesityl aniline afforded 54% of pyrrole **5x**. Furthermore, an acetylene functionalized aniline was successfully converted to pyrrole **5y**. Gratefully, this method could also be applied for aliphatic and benzylic amines yielding pyrroles **5za** and **5zb**. Here, we observed a beneficial effect on the overall yield, when the amine was added after the hydroformylation reaction was complete. Employing ammonium acetate gave rise to the *N*-unsubstituted pyrrole **5zc** in synthetically usefull yield.[19] The reaction can also be performed in the absence of amines to afford 1,4-dicarbonyl compounds with 2.5 mol% catalyst/base loading within 30 minutes.[20]



Scheme. 3 [a] Reaction conditions: 0.3 mmol chalcone **1**, 1.0 equiv. **2**, 2.0 equiv. **3b**-**n**, 5 mol% NHC salt **4**, 5 mol% K_3PO_4, 9 mL MeCN at 120 °C for 16 h. Isolated yields are given. [b] The corresponding amine was added after 30 min of reaction time. [c] Ammonium acetate was employed as amine source.

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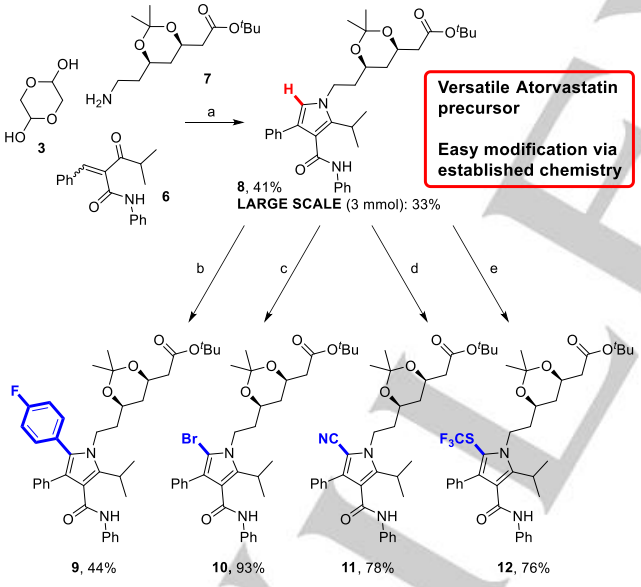
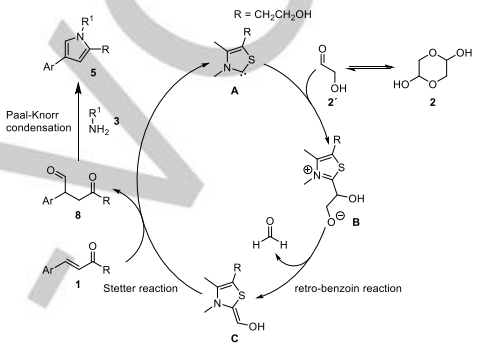
To demonstrate the synthetic applicability of the methodology, we applied the protocol for the synthesis of a versatile Atorvastatin analogue **8**. Michael acceptor **6** was transformed into pyrrole **8** via our one-pot approach in good yields. This particular Atorvastatin derivative, to the best of our knowledge, is unprecedented in the literature.[21] The practicability of this method is demonstrated by performing a large scale reaction (3 mmol) while maintaining similar yields of pyrrole **8**. In comparison to the industrially employed sequential Stetter/Paal-Knorr reaction, this method leads to an *α*-unsubstituted pyrrole which makes precursor **8** to be a versatile base structure. Furthermore, the industrial synthesis of Atorvastatin is restricted to arene moieties in the *α*-position and is much more difficult to derivatize in comparison to our method. Since the *α*-position is unsubstituted, modifications using literature protocols provided various substitution patterns of pyrrole **8**. Protected Lipitor® precursor **9** was synthesized via a Heck-type cross coupling reaction employing 1-bromo-4-fluorobenzene as reaction partner. Bromination of the *α* -positon was achieved with NBS affording **10** in excellent yield providing a handle for further derivatization. Likewise cyanated pyrrole **11** gives the possibility for further postfunctionalization of the introduced cyano-moiety to access further Atorvastatin derivatives. Fluorinated compounds tremendously influence the chemical and biological properties of pharmaceutical products.[22] The pharmaceutically relevant thiotrifluoromethyl-group was successfully installed in the *α*-position giving rise to pyrrole **12** in very good yield.



Scheme 4. Reaction conditions: [a] **6** (0.3 mmol), 1.0 equiv. **2**, 5 mol% NHC salt **4**, 5 mol% K_3PO_4, 3 mL MeCN, 120 °C, 16 h; then 2.0 equiv. **7**, 120 °C, 4 h. [b] 1.5 equiv.1-bromo-4-fluorobenzene, 1.5 equiv. KOAc, 5 mol% $Pd(OAc)_2$, DMA (0.2 M), 150 °C. [c] 1.1 equiv. NBS , THF (0.1 M), − 78 °C. [d] 1.7 equiv. CSI, MeCN:DMF (1:1 0.25 M), − 78 °C [e] 1.3 equiv. Phth-SCF_3, 10 mol% NaCl, DMF (0.2 M), 90 °C. Isolated yields are given.

Based on the literature precedent, we propose the following reaction mechanism (Scheme 5).[18,23] Free thiazol carbene **A** (generated from the thiazolium salt and K_3PO_4) adds to the carbonyl carbon atom of glycolaldehyde **2´**. After proton transfer, intermediate **B** undergoes a retro-benzoin C–C bond cleavage to generate the one carbon nucleophile **C** and one equivalent of formaldehyde. Both, the protonated species **B** and **C** could be observed by mass spectrometry, suggesting their existence in the catalytic cycle.[24] Stetter-reaction of the carbon nucleophile **C** with Michael acceptor **1** furnishes 1,4-dicarbonyl **8** and releases the catalyst. Subsequently, dicarbonyl **8** undergoes Paal-Knorr condensation with primary amine **3** to afford the desired pyrrole **5**. In addition we monitored the course of the reaction over time. It revealed that the NHC-catalyzed Stetter reaction is already completed within 10 minutes and nearly no chalcone is left. Over the period of 10 hours, the 1,4-dicarbonyl intermediate is condensed to the desired pyrrole.[24]



Scheme 5. Proposed reaction mechanism.

In summary, we have developed a direct and efficient one-pot three component-coupling to 1,2,4-trisubstituted pyrroles from readily available starting materials under mild conditions with low catalyst loadings. This approach facilitates a direct synthesis of a variety of pyrroles via rapid Stetter-type hydroformylation/Paal-Knorr three component reaction. Additionally the reaction was shown to be scalable. Furthermore, we were able to extend this methodology in the synthesis of an Atorvastatin precursor which allows a variety of unprecedented modifications of the *α*-position via straight forward procedures.

Acknowledgements

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Keywords: NHC organocatalysis • one-pot • three-component coupling • pyrroles • Atorvastatin •

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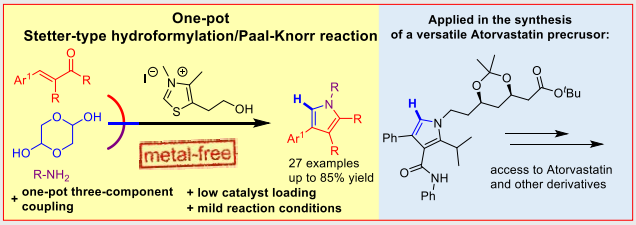

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α-Unsubstituted Pyrroles by NHC-Catalyzed Three-Component Coupling - Direct Synthesis of Versatile Atorvastatin Derivative

Three at a Stroke: Herein, we report a metal-free one-pot three-component coupling of readily available starting materials and catalyst to generate valuable pyrroles. The process involves an N-heterocyclic carbene (NHC) catalyzed Stetter-type hydroformylation using glycolaldehyde dimer as a novel C1 building-block, followed by a Paal-Knorr condensation. Furthermore, this methodology is applied in the synthesis of a versatile Atorvastatin precursor and derivatives of it.