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Direct Catalytic Synthesis of β-(C3)-Substituted Pyrroles: A Complementary Addition to the Paal-Knorr Reaction†

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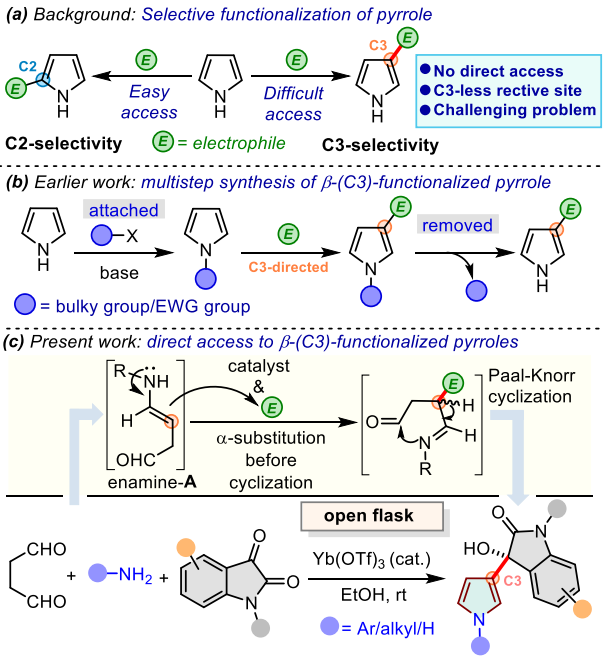
The synthesis of β-(C3)-functionalized pyrroles is a challenging task and requires a multistep protocol to achieve. An operationally simple direct catalytic synthesis of β-substituted pyrroles has been developed. This one-pot multicomponent method combined aqueous succinaldehyde as 1,4-dicarbonyl, primary amines, and isatins to access hydroxyl-oxindole β-tethered pyrroles. Direct synthesis of the β-substituted free NH-pyrrole is the central intensity of this work. DFT-calculations and preliminary mechanism investigation support the possible reaction pathway.

Pyrrole is a basic unit in numerous natural products,[1] pharmaceutical,[2] and functional materials.[3] Consequently, the synthesis of functionalized pyrrole is of continued interest that includes metal-catalyzed reactions,[4] multicomponent reactions,[5] and classical techniques.[6] Due to mitigated nucleophilicity, the C3-position is usually considered as a non-reactive site in conventional pyrrole chemistry (Scheme 1a). Notably, the selective access to β-(C3)-substituted pyrrole is often challenging to realize. The interest in the β-functionalized pyrroles not only steams from their embedding in several natural products,[7] functional materials,[8] but also serve as suitable precursors to access other bioactive compounds.[9] Few specific strategies[10] are known to access this unit that mainly relied on the prior functionalization of pyrrole, either with the electron-withdrawing[11] or sterically bulky[12] groups to adjust incoming electrophile (Scheme 1b). Additional approaches have been developed to access β-functionalized pyrrole that includes metal-catalyzed C-H functionalization,[13] β-alkylation using N-alkyl pyrroles,[14] and others.[15] Despite significant synthetic efforts, the development of a general protocol to access β-functionalized pyrrole directly from readily available materials, without attachment and removal of the directing group, is highly desired.

For many reasons, Paal–Knorr reaction[16] is still the most convenient way to access pyrroles, and an asymmetric version of this reaction was recently developed by Tan and co-workers.[17] Notably, access to β-substituted pyrrole required elaborately designed 1,4-dicarbonyls as starting material that may not be easily accessible depending on the nature of the substituent. We envisioned that the β-functionalized pyrrole, even a more challenging free NH-pyrrole, could be accessed directly through a slight variation in this reaction. The successful development of this hypothesis relies on the utilization of



Scheme 1. (a) Background, (b) Earlier work to access β-substituted pyrrole, (c) Direct access to β-(C3)-functionalized pyrroles.

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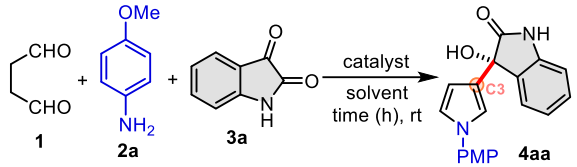
Table 1. Optimization of reaction conditions[a]



Entry	Solvent	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	DMSO	TFA (10)	10	20
2	DMSO	$Bi(OTf)_3$ (10)	16	41
3	DMSO	$Yb(OTf)_3$ (10)	16	67
4	DMF	$Yb(OTf)_3$ (10)	20	45
5	CH_3CN	$Yb(OTf)_3$ (10)	18	35
6	**EtOH**	**$Yb(OTf)_3$ (10)**	**12**	**80**
7	EtOH	No catalyst	24	trace

[a]Unless otherwise indicated, the reaction was carried out with succinaldehyde **1** (3.0 M sol, 0.6 mmol), *p*-anisidine **2a** (0.3 mmol), Isatin **3a** (0.3 mmol), Catalyst (10 mol%), Solvent (3.0 mL), rt. [b]Isolated yield of **4aa** refers to **3a** (≤10% of Paal-Knorr reaction *N*-PMP-pyrrole **5** was also obtained).

intermediate enamine-**A**, *in situ* generated through the condensation of succinaldehyde with an amine, with a suitable electrophile for the α-substitution,[18] prior to Paal-Knorr reaction, to furnish β-functionalized pyrrole (Scheme 1c). Our previous efforts to functionalized pyrroles[19] using 1,4-dicarbonyls encouraged us to explore this idea. Herein, we report a general and direct multicomponent synthesis of substituted β-(C3)-oxindole-tethered pyrrole under mild reaction conditions.

Based on our hypothesis, we commenced the multicomponent investigation using aqueous succinaldehyde **1**, p-anisidine **2a**, and isatin **3a** as a suitable electrophile (Table 1). An initial attempt using TFA (10 mol%) in DMSO at room temperature delivered the desired product **4aa** with low yield (entry 1, Table 1). An improvement in the reaction yield (41%, entry 2, Table 1) and (67%, entry 3, Table 1) was observed using catalytic $Bi(OTf)_3$ and $Yb(OTf)_3$ in DMSO, respectively. Next, varying the solvents like DMF and CH_3CN failed to improve the reaction yields (entries 4-5, Table 1). Pleasingly, compound **4aa** was obtained with 80% yield in EtOH using $Yb(OTf)_3$ (10 mol%) (entry 6, Table 1). No desired product was observed in the absence of catalyst (entry 7, Table 1). Other Lewis acid and solvents lead to poor results (for full screening of Lewis acids & solvents; see Table S1, ESI†). Collectively, the best result concerning the reaction yield was obtained in entry 6 (Table 1).

With the optimal conditions in hand, we examine the scope of the reaction with various amines, isatins (Table 2). A broad range of electronically differentiated isatins **3a-3o** was used for reaction with aqueous succinaldehyde **1,** and p-anisidine **2a** to furnish corresponding C3-pyrroles (**4aa-4ao**, 70-83% yields). Suitably substituted as well as alkyl-protected (Me, allyl, benzyl) isatins were well tolerated and potentially allowing for further functionalizations. Besides, other aromatic amines were employed successfully to furnished similar products **4ba-4fa** and **4gl** in good yields. Next, various alkylamines were examined with varying isatins; and interestingly, alkylamines emerged as a better substrate than aryl-amines and took less time for reaction completion. A wide range of alkyl-amines was successfully applied to furnished the corresponding pyrroles

Table 2. Reaction scope with primary amines **2** and substituted isatins **3**.[a]

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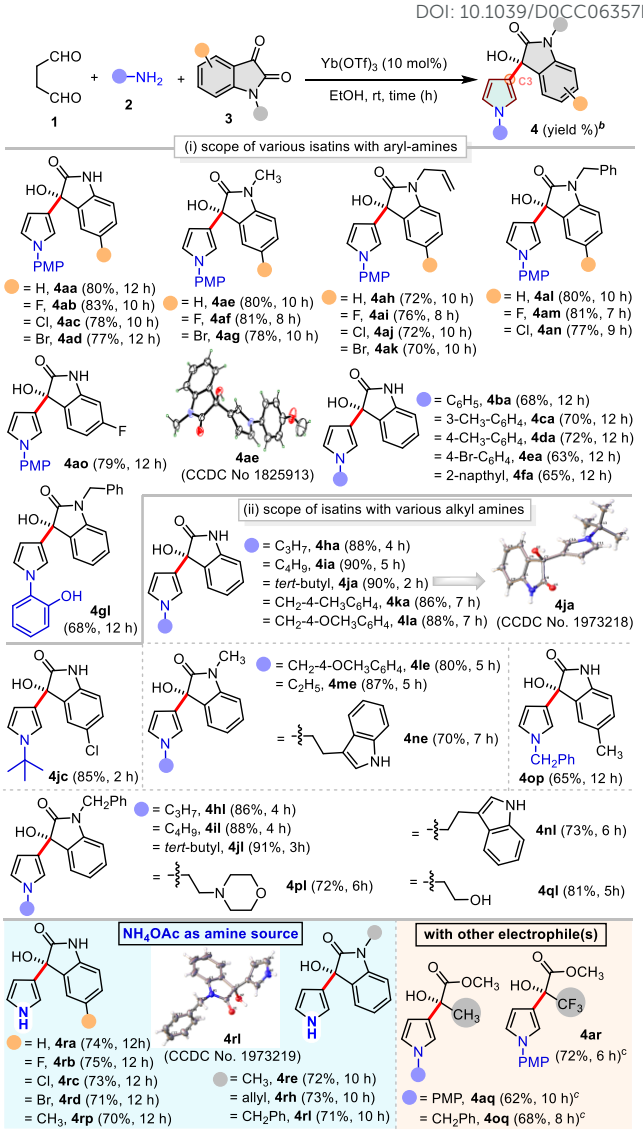
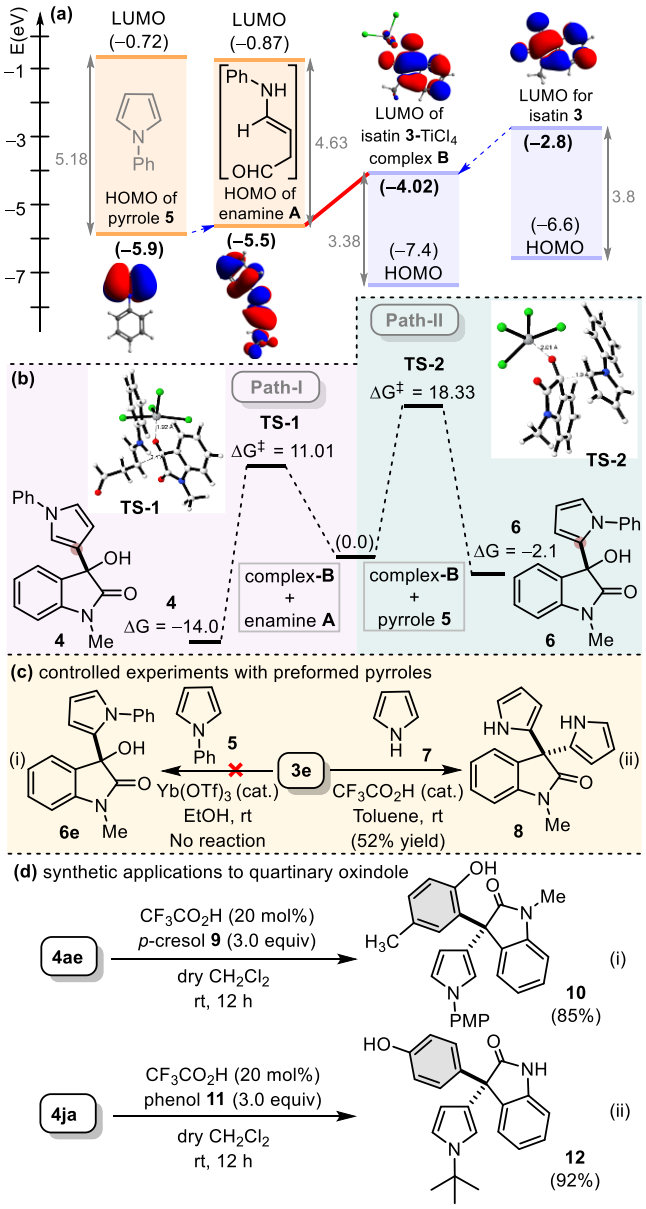


[a]Unless otherwise indicated, reaction was carried out with succinaldehyde **1** (3.0 M sol, 0.6 mmol), aryl/alkyl amine (0.3 mmol)/NH_4OAc **2** (0.6 mmol), isatin **3** (0.3 mmol), $Yb(OTf)_3$ (10 mol%), EtOH (3.0 mL), rt, 2-12 h. [b]Isolated yields of **4** refer to **3**. [c]Keto-esters (0.3 mmol) were used instead of isatin. (PMP = 4-$OMeC_6H_4$)

(**4ha-4ql**, Table 2) in excellent yields (up to 91%). Sterically bulky *tert*-butyl amine (**2j**) furnished products **4ja** (90% yield), **4jm** (91% yield); while biorelevant alkylamines (**2n** and **2o**) and unprotected polar functional amine (**2q**) gave related products **4ne**, **4nl**, **4pl**, and **4ql**, respectively, in high yields. Notably, isatins protected with electron-withdrawing groups, such as Ts, Cbz, Bz, failed to give the expected product, and corresponding imines condensed with primary amine were obtained, probably due to the high reactivity of isatin. The single-crystal X-ray analysis further confirmed the structure of **4ae** and **4ja**.[20] Next, we get excited to explore the direct synthesis of the C3-substituted free-NH-pyrrole. For this purpose, NH_4OAc was selected as an amine source under optimized conditions, after examining other amine sources separately (see Table S2, ESI†). Excitingly, succinaldehyde **1**, NH_4OAc **2r**, and variously substituted isatin **3**, furnished the corresponding free



Scheme 2. (a) The HOMO & LUMO of pyrrole **5**, enamine **A**, isatin **3** and isatin-$TiCl_4$ complex **B**. (b) Transition State Geometries and Relative Activation Energies for the two possible ways of reacting partners. Path-I: access to C-3 substituted pyrrole via reaction of enamine-**A** with complex-**B** (**TS-1**), Path-II: access to C2-substituted pyrrole via Friedel-Crafts reaction of pyrrole **5** with complex-**B** (**TS-2**). Gibbs activation energies ($\Delta G^{\ddagger}$, kcal/mol) and Gibbs reaction energies (ΔG, kcal/mol) are shown. (c) Model reactions between isatin **3e** and preformed pyrroles **5** and **7**. (d) Synthesis of quaternary substituted oxindoles **10** and **12**.

NH-pyrroles **4ra**-**4rd**, **4rp**, **4re**, **4rh**, and **4rl** in good yields (up to 75%). The single-crystal X-ray analysis confirmed the structure of compound **4rl**.[20] These preliminary results for the direct access to β-functionalized free NH-pyrrole are novel and offer an opportunity to stitch other functionality at this position. Besides, methyl pyruvate **3q** and correspnding trifluoro-compound **3r**, were also examined as a suitable electrophile with aryl/alkyl-amine, and furnished corresponding β-substituted pyrroles **4aq** (68%), **4oq** (68%), and **4ar** (72%) under optimized conditions (Table 2).

DFT-calculations were performed (B3LYP/def2-TZVP) to gain more mechanistic insight for reaction outcome (for detailed optimized structures, see ESI†). The reactivity of pyrrole **5**, and in situ generated enamine-**A** was examined with activated isatin-$TiCl_4$ complex **B** (Scheme 2). The HOMO of enamine-**A** (–5.5 eV) was found higher by 0.4 eV than the HOMO of pyrrole **5** (–5.9 eV), thus displaying enhanced nucleophilicity. Similarly, the LUMO of isatin-complex-**B** (–4.02 eV) was found to be lowered by –1.22 eV, compared to LUMO (–2.8 eV) of isatin **3**, resulting in a greater electrophilicity. Thus, a superior interaction is expected between enamine-**A** and isatin-complex-**B** with an energy gap of 1.48 eV (Scheme 3a). Next, the reactions of complex-**B** with enamine-**A** and pyrrole **5** were examined by keeping the Gibbs free energy (G) for reacting species at 0.0 kcal/mol (Scheme 3b). Enamine-**A** reacts with complex-**B** *via* TS-**1** ($\Delta G^{\ddagger}$ = 11.01 kcal/mol) to furnished β-(C3)-pyrrole **4** (ΔG = –14.0 kcal/mol) after cyclization, while the Friedel-Crafts reaction of pyrrole **5** with complex-**B** *via* TS-**2** ($\Delta G^{\ddagger}$ = 18.33 kcal/mol) gave α-(C2)-pyrrole-**6** (ΔG = –2.1 kcal/mol). Thus, a more favourable nature of path-I was attributed to the lower energy barrier of TS-**1** over TS-**2** as well as a higher stability of **4** over **6**. A separate set of DFT-calculations were performed with $Yb(OTf)_3$ at PW91/ZORA-def2-SVP level (see ESI). Next, model reactions between isatin **3e** and pyrroles were performed to find more information about the reaction pathway. Interestingly, no reaction was observed between **3e** and pyrrole **5** under optimized conditions (Scheme 2c(i)), while bis-pyrrole-indolin-2-one **8** was obtained by a reaction between **3a** and pyrrole **7** under acidic conditions (Scheme 2c(ii)). Thus, DFT-calculations and controlled experiments validate the involvement of enamine-intermediate in the reaction path. Based on theoretical study, controlled experiments, and in situ HRMS study (see Scheme S1, ESI†), a detailed mechanism has been proposed for this transformation (see Scheme S2, ESI†). The synthetic utility of the developed protocol was shown at the gram-scale to access **4ja** (1.69 g, 92% yield), and **4qa** (1.30 g, 89% yield) by simple filtration (>95% purity by HPLC). Next, the acid-catalyzed Friedel-Crafts reaction of compounds **4ae** and **4ja** with p-cresol **9** and phenol **11**, respectively, furnished the corresponding all-carbon quaternary-center oxindoles **10** (85%) (Scheme 2d(i)) and **12** (92%) (Scheme 2d(ii)).

Conclusions

In summary, the first direct catalytic synthesis of β-functionalized pyrroles has been developed. This multicomponent protocol highlights the simplicity of stitching together aqueous succinaldehyde, primary amines, and isatins to access β-(C3)-oxindole-tethered pyrroles under mild conditions. DFT-calculations further supported the experimental outcome. The synthetic applicability was shown (i) for the gram-scale synthesis, and (ii) synthesis of quaternary-center oxindoles. This method represents a valuable resource to secure other electrophiles at the β-position of pyrrole asymmetrically, particularly for free NH-pyrrole. Efforts in this direction are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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20 The X-ray crystallographic structures for **4ae** (CCDC NO. 1825913), **4ja** (CCDC NO. 1973218), and **4rl** (CCDC NO. 1973219) have been deposited at the Cambridge Crystallographic Data Centre (CCDC) (for more details see ESI†).

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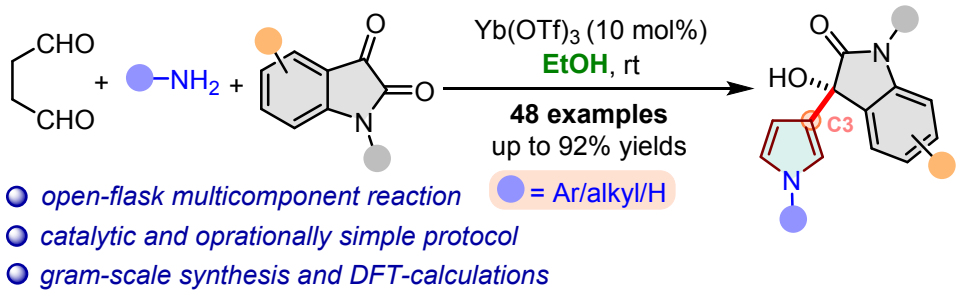
Graphical Abstract



A Lewis-acid catalyzed direct multicomponent synthesis of β-(C3)-substituted pyrroles is developed in good to high yields, using aqueous succinaldehyde, primary amines, and isatins under mild conditions. Direct access to the β-substituted free NH-pyrrole is the main strength of the work along with DFT-calculations.