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Versatile Base-Catalyzed Route to Polycyclic Heteroaromatic Compounds by Intramolecular Aza-Michael Addition

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A catalytic new synthetic approach to 3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-ones by intramolecular 1,4-addition of readily available α,β-unsaturated esters, is described. Here, the use of a range of organic as well as inorganic bases (5–10 mol-%) allowed a fast (30 min) and regioselective ring-closing reaction to be performed in high yields under simple operational conditions. Moreover, the protocol was effectively employed, as the key step, in the synthesis of the dibromopyrrolo alkaloid derivative *N*-Bn-longamide b.

Development of new catalytic and eco-sustainable synthetic routes to the formation of functionalized physiologically active polycyclic scaffolds is a longstanding goal for numerous research teams. Feasibility on several scales and generality in scope are among the most important aspects addressed during the design of synthetic strategies. Pyrroles and their benzo-fused analogous indoles are present in a large number of biologically active compounds[1] and over the past decades catalytic intramolecular as well as intermolecular protocols have featured prominently the direct and selective functionalization of these aza-aromatic systems.[2]

In this scenario, emerging classes of molecular fragments in medicinal chemistry are 3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-ones (**1**) and 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones (**2**, Figure 1).[3,4] Here, despite the growing interest for these compounds, no examples of direct catalytic and regioselective strategies for their preparation have been reported to date.[5]

Taking advantage of our recent reports on catalytic intramolecular regioselective *C3*-alkylations of indoles through indolyl enones (Michael reaction)[6] and allyl indolyl carbonates (allylic alkylation),[7] we envisaged an intramolecular *N1*-alkylation variant for the construction of the title molecular motifs **1** and **2**.

After several efforts, we individuated, in the indole-2-carboxamide **5a**, a potentially useful acyclic precursor for pyrazino-indolones **1**. The reliability of the pathway arises from the ready availability of precursors **3a** and **4**[8] that furnished **5a** in 76% yield (40 min) without the need for chromatographic purification (Scheme 1).

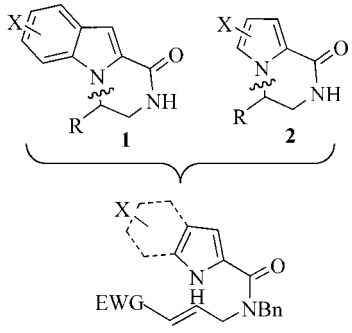
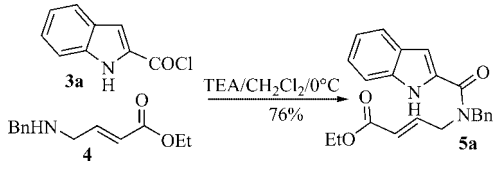


Figure 1. Intramolecular Michael addition as a key step in the synthesis of polycyclic indole- and pyrrole-based compounds.



Scheme 1. Synthesis of pyrazino-indol-1-one precursor **5a**.

Suitable crystals of **5a** for single-crystal X-ray diffraction (Supporting Information) were obtained by slow diffusion of hexane into a solution of **5a** in CH_2Cl_2 (room temp., 3 d) and the molecular packing revealed the existence of tight dimeric adducts stabilized by complementary strong intermolecular hydrogen-bonding interactions between the N1-H atom and the carbonyl (amide) moiety of the coupled molecule.[9] Then, the strong acidity of the indole N1-H atom in **5a**,[10] probably ascribable to the presence of the electron-withdrawing group (EWG) at the C2 position, sug-

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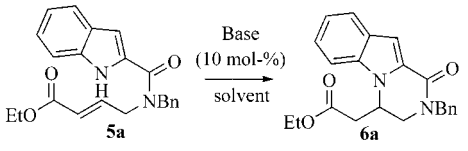
gested that mild basic conditions could promote the ring-closing step through deprotonation of the indolyl ring. At the same time, the EWG would guarantee a high regioselectivity toward *N1*-annulation (kinetic control) by decreasing the nucleophilicity of the competitor C3 site (thermodynamic control).[1a,7a] Efforts in this direction have been already reported by Banwell and co-workers who proposed an intramolecular 1,4-addition/alkylation of pyrroles promoted by 3 equiv. of NaOMe to obtain the cyclized compound in 45% isolated yield.[11]

Since that paper had appeared, several studies appeared in the literature focusing on the N-ring-closing reaction for the synthesis of polycyclic heteroaromatic compounds; however, no catalytic versions with general scope of substrates were reported to date.

At the outset of optimization of the reaction conditions, we considered the intramolecular conjugated addition of **5a** in the presence of catalytic amounts of DABCO (10 mol-%) that furnished the N-cyclized compound **6a** regioselectively.[12] The data collected in Table 1 (Entries 1–3) highlight the expected influence of the reaction medium on the final outcome.[1a] In particular, by changing the solvent from weakly (CH_2Cl_2) to strongly coordinating ones (CH_3CN, DMSO) the reaction rate increased due to the formation of solvent-separated ion pairs. Among them, the highest reaction rates were reached in DMSO that guaranteed 71% conversion into **6a** within 4 h. Remarkably, (–)-sparteine proved to be efficient in the ring-closing reaction of **5a** (30 min, 92% yield, Entry 4) with the possibility to increase the operational simplicity of the protocol by running the title Michael addition in open-air vials and with reagent-grade DMSO (Entry 5). However, the absence of stereoinduction in **6a** prompted us to test less expensive catalysts, and a brief survey of additives led us to K_2CO_3 as the optimal catalytic species (10 mol-%, 30 min, conv. > 98%, Entry 6).[13]

Table 1. Optimization of the reaction conditions for the base-catalyzed intramolecular Michael reaction of **5a**.[a]



Entry	Base	Solvent	*T* [h]	Conv. to **6a** [%][b]
1	DABCO	CH_2Cl_2	24	< 20
2	DABCO	CH_3CN	4	53
3	DABCO	DMSO	4	71
4	(–)-sparteine	DMSO	0.5	98 (92)
5	(–)-sparteine[c]	DMSO	3	95
6	K_2CO_3	DMSO	0.5	> 98
7	K_2CO_3[d]	DMSO	1	> 98
8	–	DMSO	24	5

[a] All reactions were carried out at room temp. under anhydrous conditions in the presence of 10 mol-% of catalyst, unless otherwise specified. [b] Determined by HPLC. Isolated yields are given in parentheses. In all cases the *N*/*C*-alkylation ratio was found to be >50:1. [c] Commercial-grade DMSO was used. [d] 5 mol-% of K_2CO_3 was employed.

Proofs for the molecular structure of the cyclized product came from the X-ray diffraction analysis of single crystals (AcOEt, slow diffusion, room temp., 5 d) of **6a** that unambiguously showed the operating regiospecific, kinetic *N*-alkylation pathway (Figure 2).

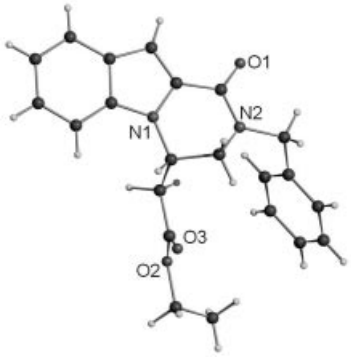
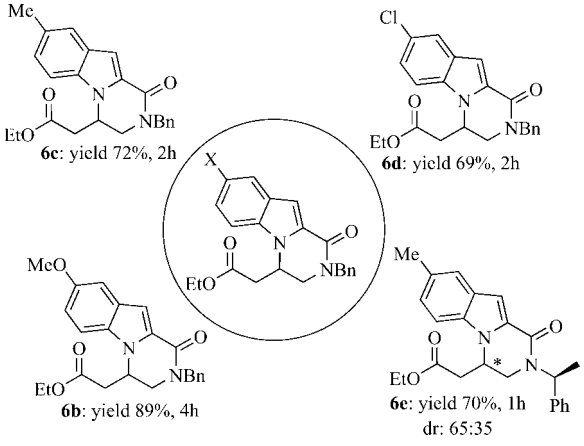


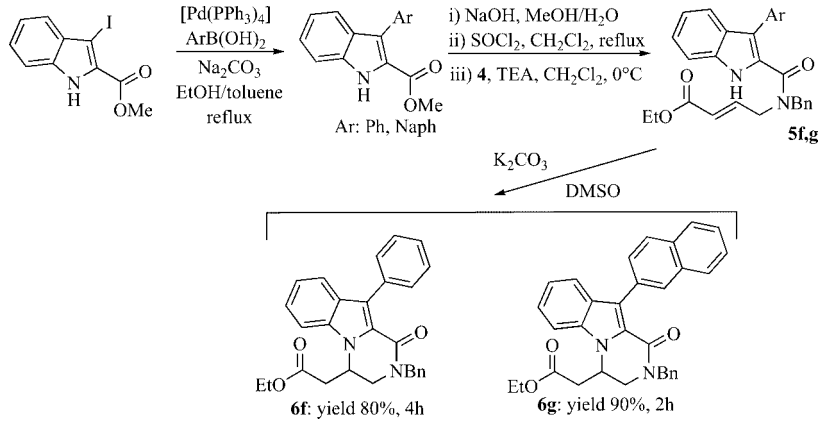
Figure 2. X-ray structure of (±)-**6a** (only one enantiomer is shown).

With the optimized reaction parameters in hand, we envisioned the generality of the protocol by subjecting a range of variously functionalized indolyl precursors to cyclization (K_2CO_3, 10 mol-%, room temp.), and the final outcome is summarized in Scheme 2. High tolerance toward both electron-withdrawing and electron-donating groups at the C5 position (X = Cl, Me, MeO) is highlighted by the high yields obtained in the cyclization of **5b**–**d** (see Supporting Information) to **6b**–**d** (69–82%). Also enantiomerically pure precursor **5e** containing a (*S*)-phenylethylamine unit was cyclized successfully under optimal conditions (conv. 93%); however, **6e** was isolated with only moderate diastereoselectivity (*dr* = 65:35).



Scheme 2. Catalytic synthesis of functionalized dihydropyrazino[1,2-*a*]indol-1(2*H*)-ones.

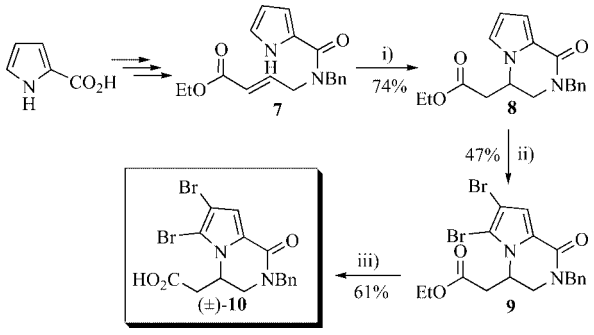
Then, in the light of recent findings that underline the beneficial role of aryl groups in the C3 position of the indole core (antibacterial activity), we synthesized the corresponding acyclic precursors **5f**,**g** by Suzuki cross-coupling reaction {[$Pd(PPh_3)_4$]/$ArB(OH)_2$/Na_2CO_3} in good overall yield (see Supporting Information). Gratifyingly, the N-cyclization does not seem to be significantly affected by the presence of the aryl substituents at the C3 position, furnish-



Scheme 3. Synthesis of 3-aryl-dihydropyrazino-indolinones **6f**,**g** by K_2CO_3-catalyzed ring-closing reaction.

ing the desired polycyclic compounds (**6f**,**g**) in high isolated yields (80–90%, Scheme 3).

In the perspective of exploiting the present catalytic system for the synthesis of important naturally occurring secondary metabolites bearing a 4,5-dibromopyrrolyl core,[14] pyrrole-2-carboxamide **7** was readily prepared starting from commercially available pyrrole-2-carboxylic acid (yield 53%) and subsequently smoothly cyclized in the presence of K_2CO_3 (10 mol-%, DMSO, room temp., 20 min) to provide **8** in 74% isolated yield (Scheme 4) The regioselective bromination of the pyrrole ring led to substituted 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one **9** (47%), a molecular skeleton embedded in numerous pyrrole alkaloids of Agelasida sponges, that was finally hydrolyzed to the derivative *N*-Bn-longamide b (**10**)[4a] in 61% yield.



Scheme 4. Racemic synthesis of *N*-Bn-longamide b. Reagents and conditions: i) K_2CO_3 (10 mol-%), DMSO, room temp., 20 min; ii) NBS, CH_2Cl_2, room temp.; iii) KOH, MeOH/H_2O, reflux, 16 h.

Conclusion

We described a practical and effective catalytic strategy for the preparation of unprecedented polycyclic indole/pyrrole compounds by intramolecular 1,4-addition. The complete regioselectivity observed was guaranteed by the use of catalytic amounts of K_2CO_3 that furnished *N*-alkylated compounds in a short reaction time. With an unprecedented scope for both indole and pyrrole rings, this protocol allowed a range of variously functionalized dihydropyrazinindolones to be readily prepared under mild conditions with the possibility to extend the method to important pyrrole-based secondary metabolites such as longamide b. Studies addressed toward the development of stereocontrolled versions of this intramolecular Michael addition are under way.

Experimental Section

Typical Procedure for the Synthesis of Indolcarboxamides 5: In a three-necked round-bottomed flask, equipped with a dropping funnel, the ester **4** (2.6 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL). The mixture was cooled to 0 °C when TEA (3.9 mmol) was added followed by a solution of the corresponding chloride **3** (2.0 mmol), dissolved in CH_2Cl_2 (5 mL). The reaction mixture was kept at 0 °C for 1 h, then the reaction was quenched with H_2O (8 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by washing with an appropriate solvent.

Typical K_2CO_3-Catalyzed Cyclization for the Synthesis of Pyrazino Compounds 6: In a flame-dried two-necked flask, the indolyl precursor **5** (0.05 mmol) was dissolved in anhydrous DMSO (1 mL) and 10 mol-% of K_2CO_3 was added. After stirring at room temp. for the specified time (complete consumption of **5** was judged by TLC and HPLC), the reaction mixture was diluted with AcOEt (3 mL) and washed with H_2O (3 × 5 mL). After evaporation of the volatiles, the crude product was purified by flash chromatography.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures, analytical and spectral characterization data for all the compounds.

CCDC-623047 (for **5a**) and -623048 (for **6a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

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[1] a) R. J. Sundberg, in *Indoles*, Academic Press, San Diego, CA (USA), **1996**; b) A. Fürstner, *Angew. Chem. Int. Ed.* **2003**, *42*, 3582–3603.
[2] a) M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett* **2005**, 1199–1222; b) M. Bandini, E. Emer, S. Tommasi, A. Umani-Ronchi, *Eur. J. Org. Chem.* **2006**, 3527–3544.
[3] J. M. Bentley, P. Hebeisen, M. Muller, H. Richter, S. Roever, P. Mattei, S. Taylo, PCT Int. Appl. WO 2001-EP8520 20010724, **2002**.
[4] a) F. Cafieri, E. Fattorusso, O. Tagliatela-Scafati, *J. Nat. Prod.* **1998**, *61*, 122–125; b) K. G. Poullennec, D. Romo, *J. Am. Chem. Soc.* **2003**, *125*, 6344–6345.
[5] For Pd-catalyzed oxidative synthesis of pyrazino[1,2-*a*]indoles and pyrrolo[1,2-*a*]pyrazinones, see: a) G. Abbiati, E. M. Beccalli, G. Broggini, C. Zoni, *J. Org. Chem.* **2003**, *68*, 7625–7628; b) E. M. Beccalli, G. Broggini, M. Martinelli, G. Paladino, *Tetrahedron* **2005**, *61*, 1077–1082.
[6] a) M. Agnusdei, M. Bandini, A. Melloni, A. Umani-Ronchi, *J. Org. Chem.* **2003**, *68*, 7126–7129; b) M. Angeli, M. Bandini, A. Garelli, F. Piccinelli, S. Tommasi, A. Umani-Ronchi, *Org. Biomol. Chem.* **2006**, *4*, 2391–3296.
[7] a) M. Bandini, A. Melloni, A. Umani-Ronchi, *Org. Lett.* **2004**, *6*, 3199–3202; b) M. Bandini, A. Melloni, F. Piccinelli, R. Sinisi, S. Tommasi, A. Umani-Ronchi, *J. Am. Chem. Soc.* **2006**, *128*, 1424–1425.
[8] A. Barco, S. Benetti, C. Spalluto, A. Casolari, G. P. Pollini, V. Zanirato, *J. Org. Chem.* **1992**, *57*, 6279–6286.
[9] This network of interactions has been recognized also to be fundamental in the pharmaceutical activity of structurally analogous non-peptidic HLE inhibitors: C. A. Veale Jr, J. R. Damewood, G. B. Steelman, C. Bryant, B. Gomes, J. Williams, *J. Med. Chem.* **1995**, *38*, 86–97.
[10] **5a:** ^{1}H NMR ($CDCl_3$): δ = 9.6 (N1-H) ppm (c.f. unsubstituted indoles: δ = 8.2–8.4 ppm).
[11] M. G. Banwell, A. M. Bray, A. C. Willis, D. J. Wong, *New J. Chem.* **1999**, *23*, 687–690.
[12] a) Y.-L. Shi, M. Shi, *Org. Lett.* **2005**, *7*, 3057–3060; b) Y.-L. Shi, M. Shi, *Chem. Eur. J.* **2006**, *12*, 3374–3378.
[13] M. Shi, L.-Z. Dai, Y.-L. Shi, G.-L. Zhou, *Adv. Synth. Catal.* **2006**, *348*, 967–972.
[14] a) G. Papeo, M. A. Gómez-Zurita Frau, D. Borghi, M. Varasi, *Tetrahedron Lett.* **2005**, *46*, 8635–8638; b) A. P. Ilyn, J. A. Kuzovkova, V. V. Potapov, A. M. Shkirando, D. I. Kovrigin, S. E. Tkachenko, A. V. Iachtchenko, *Tetrahedron Lett.* **2005**, *46*, 881–884; c) C. Pöverlein, G. Breckle, T. Lindel, *Org. Lett.* **2006**, *8*, 819–821; d) J. Patel, N. Pelloux-Léon, F. Minassian, Y. Vallée, *Tetrahedron Lett.* **2006**, *47*, 5561–5563, and references cited therein.

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