Novel Domino Approach to Fluorescent Pyrimido[1,6-*a*]indolones

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Abstract: Easily accessible *N*-ethoxycarbonyl-2-alkynylindoles undergo, in the presence of primary aryl amines and under $TiCl_4$/*t*-$BuNH_2$ catalysis, domino hydroamination–annulation reactions giving rise to pyrimido[1,6-*a*]indolones in good to excellent yields. The reaction involves an initial highly regio- and chemoselective hydroamination reaction. The obtained compounds show interesting fluorescence properties and could represent a new class of useful markers for bioanalytical purpose.

Key words: alkynes, titanium, hydroaminations, domino reactions, heterocycles, fluorescence

Domino reactions are now widely used to assemble simple or polyfunctionalized organic molecules.[1] Thus, domino reactions allow the formation of several new covalent bonds in a one-pot fashion, can accomplish the coupling of three or more simple building blocks in a modular approach, and, in several cases, match well also with Trost's atom-economy concept.[2] Moreover, they offer an attractive, economical, and ecologically benign alternative to classical organic transformations. In this context, transition-metal catalysis has proven to play a pivotal role for the direct construction of complicated heterocyclic and heteropolycyclic molecules from readily accessible starting materials under mild conditions.

During the last years, we focused our attention on the catalyzed and uncatalyzed domino addition–annulation reactions of 2-acyl-*N*-propargylindoles and 2-acyl-3-alkynyl(or propargyl)indoles for the synthesis of *a*- or *b*-fused polycyclic indole systems, respectively. Thus, using this synthetic approach, β-carbolines,[3] pyrazino[1,2-*a*]-indoles,[4] [1,4]oxazino[4,3-*a*]indoles,[5] pyrrolo[1,2-*a*]indol-2-carbaldehydes,[6] 1-aminocarbazoles,[7] and 9-amino-pyrido[1,2-*a*]indoles[7] have been obtained. Most of the reported reactions[3–5,7] involve in the second step, step b of the domino reaction, a nucleophilic attack onto a carbon–carbon triple bond that allows the annulation onto an existing ring (Figure 1, **A**). Furthermore, we reversed the sequence by performing a domino reaction involving in the first step, step a, a $TiCl_4$/*t*-$BuNH_2$-catalyzed hydroamination of the carbon–carbon triple bond followed by nucleophilic attack of the enamine intermediate at the carbon–oxygen double bond (Figure 1, **B**).[6]

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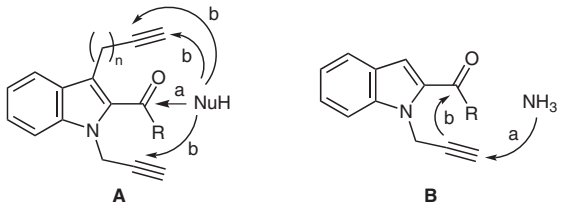


Figure 1

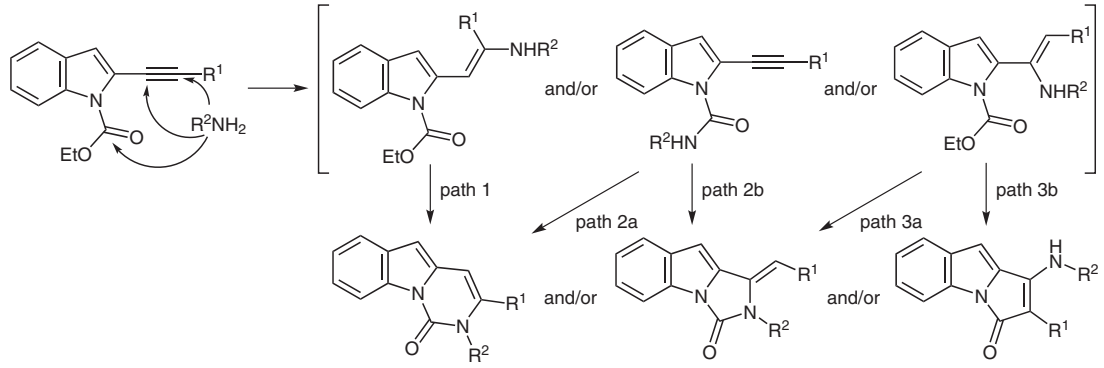
During recent years, catalyzed hydroamination reactions became a valuable tool for the synthesis of nitrogen heterocycles and complex molecules.[8] Among various catalysts employed, titanium-based catalysts are particularly attractive in terms of costs, functional group tolerability, and regioselectivities.[9] In particular, the inexpensive and user-friendly $TiCl_4$/*t*-$BuNH_2$ catalytic system has been described for the regioselective intermolecular anti-Markovnikov hydroamination of alkynes.[10]

N-Ethoxycarbonyl-2-alkynylindoles **2a–g** were synthesized in excellent yields starting from 2-trifluoromethanesulfonyloxy-indole-1-carboxylic acid ethyl ester (**1**) and terminal alkynes following the Sonogashira protocol (Table 1).[11]

On these bases, we investigated a domino sequence involving hydroamination–annulation of *N*-ethoxycarbonyl-2-alkynylindoles with primary amines. Thus, depending on the regiochemistry and the chemoselectivity of the process (Scheme 1) pyrimido[1,6-*a*]indol-1-ones (path 1 and path 2a), imidazo[1,5-*a*]indol-3-ones (path 2b and path 3a) or (path 3b) 3*H*-pyrrolo[1,2-*a*]indol-3-ones should be obtained.

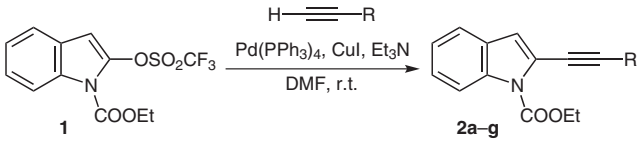
The reactivity of compounds **2** under hydroamination reaction conditions was then probed with primary anilines, along with $TiCl_4$/*t*-$BuNH_2$ as catalytic system, in dry toluene at 105 °C (Table 2). Under these conditions we were pleased to isolate, after chromatographic purification on silica gel, the pyrimido[1,6-*a*]indol-1-ones **3a–r** as the sole reaction products.[12]

Thus, the reactions proceeded in very good to excellent yields with complete chemo- and regioselectivity giving rise to compounds **3** in the presence of anilines bearing either electron-donating or electron-withdrawing groups (Table 2, entries 1–3, 5–7, 11–13). Only the reactions performed on 2-alkynylindole **2g** gave the corresponding pyrimido[1,6-*a*]indol-1-ones **3o–p** in very low yields (Table 2, entries 15, 16). In this case, beside the desired com-



Scheme 1

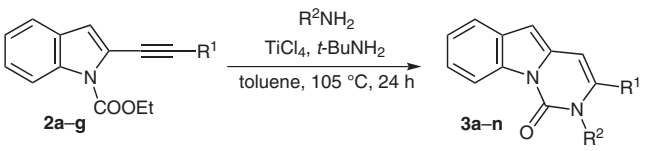
Table 1 Synthesis of *N*-Ethoxycarbonyl-2-alkynylindoles **2a–g**



Product	R	Yield (%)[a]
2a	Ph	97
2b	4-MeC_6H_4	92
2c	3-$F_3CC_6H_4$	92
2d	4-$MeOC_6H_4$	99
2e	C_5H_{11}	92
2f	C_6H_{13}	93
2g	TMS	88

[a] Reaction were carried out on a 2.0 mmol scale in 12 mL of dry DMF–Et_3N (8:4) under nitrogen atmosphere using the following molar ratios: **1**/Pd(0)/CuI = 1:0.03:0.015.

Table 2 Synthesis of Pyrimido[1,6-*a*]indol-1-ones **3a–n**



Entry	Product	R^1	R^2	Yield (%)[a,b]
1	**3a**	Ph	4-MeC_6H_4	89
2	**3b**	Ph	4-$MeOC_6H_4$	87
3	**3c**	Ph	4-ClC_6H_4	81
4	**3d**	Ph	*n*-Bu	–
5	**3e**	3-$F_3CC_6H_4$	4-MeC_6H_4	85
6	**3f**	3-$F_3CC_6H_4$	4-$MeOC_6H_4$	81
7	**3g**	3-$F_3CC_6H_4$	4-ClC_6H_4	87
8	**3h**	3-$F_3CC_6H_4$	*n*-Bu	–
9	**3i**	3-$F_3CC_6H_4$	Bn	–
10	**3j**	4-$MeOC_6H_4$	4-MeC_6H_4	93
11	**3k**	C_5H_{11}	4-MeC_6H_4	86
12	**3l**	C_5H_{11}	4-$MeOC_6H_4$	83
13	**3m**	C_6H_{13}	4-ClC_6H_4	79
14	**3n**	C_6H_{13}	*n*-Bu	–
15	**3o**	TMS	4-MeC_6H_4	13
16	**3p**	TMS	4-$MeOC_6H_4$	24

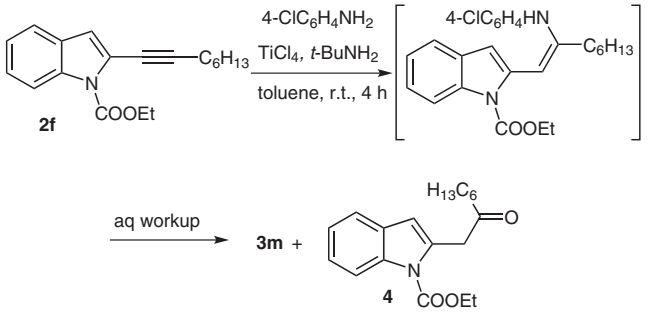
[a] Yields are referred to a single run.
[b] Reactions were carried out on a 0.60 mmol scale in 6 mL of dry toluene under nitrogen atmosphere using the following molar ratios: **2**/amine/$TiCl_4$/*t*-$BuNH_2$ = 1:1.2:0.2:1.

pounds, starting material was recovered in 55% and 57% yield, respectively. Instead, any attempt to perform these reactions in the presence of aliphatic amines failed, and indoles **2** were recovered unreacted even after prolonged heating at high temperature (170 °C instead of 105 °C; Table 2, entries 4, 8, 9, 14).

The reaction mechanism probably involves the regioselective hydroamination of the triple bond followed by intramolecular attack of the nitrogen nucleophile at the carbon–oxygen double bond and subsequent loss of ethanol (Scheme 1, path 1). An alternative route based on the reverse sequence, (Scheme 1, path 2a) can be ruled out by experimental evidence. Thus, the reaction of indole **2f** with 4-chloroaniline performed under otherwise identical reaction conditions at ambient temperature for four hours gave rise to a mixture of pyrimido[1,6-*a*]indol-1-one **3m** (38%) and ethyl 2-(2-oxooctyl)-1*H*-indole-1-carboxylate **4** (52%) after aqueous workup (Scheme 2).

The $TiCl_4$-catalyzed hydroamination–hydrolysis sequence of alkynes for the regioselective synthesis of ketones has been reported elsewhere.[9d] Moreover, the ability of $TiCl_4$ to activate carbonyl groups towards nucleophiles is well documented. Thus, an activating role of this catalyst also in the second step of the domino reaction is likely.[13]

Although several routes are available for the preparation of pyrimido[1,6-*a*]indol-1-ones, there are no reports on general methods for the synthesis of these derivatives.



Scheme 2

The reported protocols involve reactions of iminophosphoranes with heterocumulenes,[14] olefination reactions of 2-formylindole with the *N*-Cbz Schmidt reagents,[15] phosgene-mediated cyclization of 2-(1*H*-indol-2-yl)benzenamine,[16] palladium-mediated cyclization of *N*-(2-bromophenyl)- or *N*-allyl-1*H*-indole-1-carboxamide,[17] and platinum-catalyzed cascade dehydroalkoxylation–cyclization of *ortho*-alkynylphenylureas.[18]

Importantly, pyrimido[1,6-*a*]indol-1-ones **3a–c**,**e–g**,**i**,**j** bearing an aryl substituent in position 4, show interesting fluorescence properties with maximum absorption and emission wavelengths ranging from 308–320 and 420–445 nm in methanol, respectively.[19] In recent years, many heterocyclic fluorescent compounds have been utilized for labeling amino acids, peptides, proteins, DNA, and other organic biomolecules for bioanalytical purposes.[20] Detection and measurement of protein–protein, as well as peptide–peptide and peptide–protein interactions based on fluorescence techniques have received special attention, and notable progress has been made in both fluorescence instrumentation and synthesis of new fluorophores. The linked organic fluorophores may form covalent or noncovalent linkages with the sample to be analyzed, producing the respective conjugates or complexes that can show fluorescence from short to very long wavelengths, depending on the marker used. Thus, the development of new fluorophores with absorption and emission at appropriate wavelengths is of utmost importance. Using our synthetic methodology a new class of heterocyclic fluorophores could be assembled and utilized as specific probe in biological studies. In particular, the structure of compounds **3** could be modified by deprotection of N-2, thereby creating useful functionality for the linkage to the target bioactive molecule (peptide, oligonucleotide, etc.). However, since the removal of the N-aryl substituent from **3** could be a complicated task an aliphatic substituent would be introduced running the reaction of **2** in the presence of an alkylamine (i.e., benzylamine) and a suitable catalytic system.[8] Moreover, in order to vary the fluorescence properties, different aryl or heteroaryl rings could be introduced in position 3 on the heteroaromatic scaffold, the core indole nucleus could be modified by the introduction of other heteroatoms and the fundamental tricyclic compound could be transformed into a polycyclic derivative by annulation reactions in 3,4-position (Figure 2).

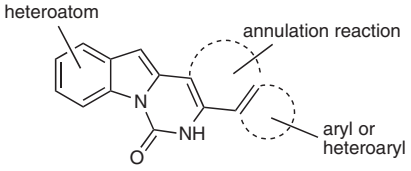


Figure 2

These reactions are now under investigations in our laboratories.

In conclusion, we reported a new efficient domino reaction involving a highly regio- and chemoselective $TiCl_4$-catalyzed addition of anilines onto carbon–carbon triple bonds followed by intramolecular annulation reaction, which allowed for the synthesis of a new class of fluorescent pyrimidoindolones.

References and Notes

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(12) **Representative Procedure - Synthesis of 3a**
In a 25 mL Schlenk tube, a solution of *t*-$BuNH_2$ (49.83 mg, 71.6 μL, 0.673 mmol) in dry toluene (3 mL) was stirred at 0 °C under nitrogen. To the cooled solution $TiCl_4$ (25.53 mg, 14.76 μL, 0.135 mmol) was added dropwise via syringe. The obtained mixture was stirred at 0 °C for 15 min, and then a solution of **2a** (194.5 mg, 0.673 mmol) and 4-methylaniline (86.5 mg, 0.808 mmol) in dry toluene (3 mL) was slowly added via cannula under a nitrogen atmosphere. The reaction mixture was warmed at 105 °C and stirred overnight. After cooling the reaction mixture was poured in 0.1 N HCl (20 mL), the organic layer was separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The collected organic

phases were dried over Na_2SO_4 and concentrated at reduced pressure. The resulting crude material was purified by flash chromatography on SiO_2 (EtOAc–hexane, 1:9) to afford 210 mg (89% yield) of pyrimido[1,6-*a*]indol-1-one **3a**. White solid; mp 199–200 °C. IR (KBr): 3366, 1692, 1634, 1390, 1366, 781, 754 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.69 (dd, *J* = 0.7, 7.0 Hz, 1 H), 7.65–7.71 (m, 1 H), 7.31–7.44 (m, 2 H), 7.21 (s, 5 H), 7.10 (s, 4 H), 6.61 (s, 1 H), 6.54 (s, 1 H), 2.30 (s, 3 H). ^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 149.3 (C_q), 140.9 (C_q), 138.0 (C_q), 135.7 (C_q), 135.5 (C_q), 134.5 (C_q), 133.7 (C_q), 131.1 (C_q), 129.7 (CH), 129.6 (CH), 129.2 (CH), 128.5 (CH), 128.2 (CH), 124.2 (CH), 123.0 (CH), 120.0 (CH), 116.6 (CH), 101.3 (CH), 98.8 (CH), 21.4 (CH_3). ESI-MS: *m/z* (%) = 351 (100) [MH^+]. ESI-MS/MS: *m/z* (%) = 351 (64) [MH^+], 259 (100). Anal. Calcd for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 7.99. Found: C, 82.24; H, 5.14; N, 8.03.

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(19) UV and fluorescence spectra were recorded at 25 °C in MeOH. As an example both absorption and emission spectra of compound **3c** are reported in Figure 3.

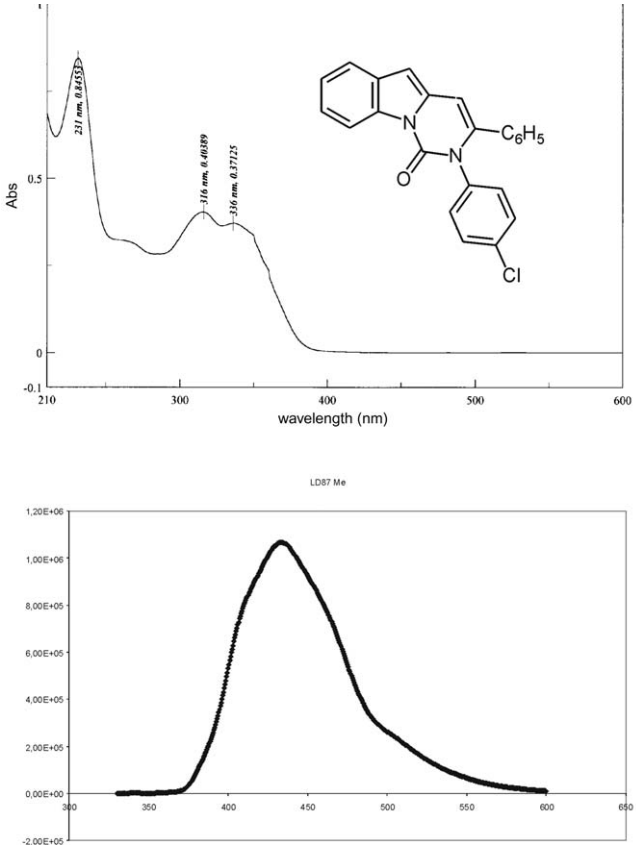

Figure 3

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