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$TiCl_4$/*t*-$BuNH_2$-Promoted Hydroamination/Annulation of δ-Keto-acetylenes: Synthesis of Novel Pyrrolo[1,2-*a*]indol-2-carbaldehydes

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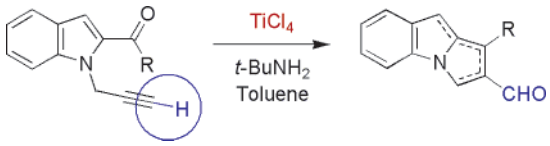
ABSTRACT



An original $TiCl_4$/*t*-$BuNH_2$-mediated hydroamination/annulation domino reaction of δ-keto-acetylenes is described. The synthesis of pyrrolo-[1,2-*a*]indole-2-carbaldehydes, starting from 2-carbonyl-1-propargyl-1*H*-indoles runs under mild reaction conditions. A conceivable mechanism is also discussed. $TiCl_4$ has proved to be an effective multiactivity reagent: catalyst/Lewis acid/water scavenger. Some unpublished 2-carbonyl-1-propargyl-1*H*-indoles are prepared by means of Suzuki- and Negishi-type reactions.

The study of the synthesis and activity of polycyclic indoles is a research field in continuous growth. The importance of these derivatives is related to the widespread occurrence of an indole subunit in a plethora of natural and synthetic compounds characterized by a variety of biological and pharmacological activities.[1]

From a synthetic point of view, the opportunity to prepare complex polycyclic molecules by means of a small number of steps is an exciting goal for every modern organic chemist. Moreover, the demand to decrease the consumption of reagents, solvents, and energy together with the requirement to reduce reaction times and waste production prompt every researcher sensible to economical and environmental issues to explore the pathway of domino reactions.[2]

For many years, we have been interested in the synthesis of polycyclic indole derivatives.[3] In particular, *N*-alkynyl indoles containing a proximate carbonyl group proved to be versatile building blocks for domino transformations. For example, in a few studies devoted to the synthesis of *a*-fused indoles, some new pyrazino[1,2-*a*]indoles[4] were prepared by sequential imination/annulation reactions. Starting from the same building blocks, we recently reported a simple and efficient entry to the [1,4]oxazino[4,3-*a*]indole nucleus through a tandem nucleophilic addition/annulation reaction.[5]

In connection with our ongoing interest in the synthesis of *a*-fused polycyclic indoles through domino reactions of δ-carbonyl-alkynes, we present here a mild $TiCl_4$/*t*-$BuNH_2$-mediated synthesis of pyrrolo[1,2-*a*]indole-2-carbaldehydes, starting from 2-acyl-1-propargyl-1*H*-indoles. A similar sys-

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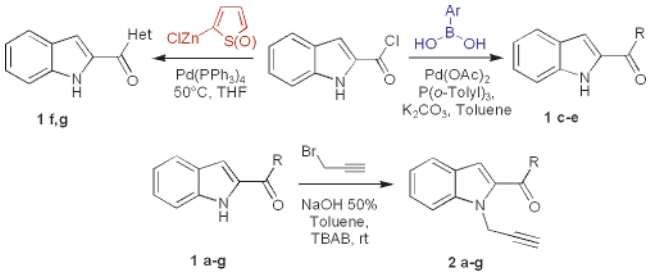
tem including $TiCl_4$ and *t*-$BuNH_2$ has been recently used for a transformation which involves an intermolecular hydroamination and a Lewis acid catalyzed reaction.[6]

The interest of the pyrrolo[1,2-*a*]indole skeleton is connected to its structural relationship with mitomycins,[7] an important class of antibiotics characterized by noteworthy antitumoral activity. Several approaches for the synthesis and functionalization of this system have been explored.[8] Recently, some interesting syntheses were reported, starting from simple *N*-allyl-indole-2-carbaldehydes via inter-/intramolecular 1,3-dipolar-[9] or hetero Diels−Alder-type[10] cycloadditions and via Ru-catalyzed RCM reactions.[11] Moreover, intramolecular Pauson−Khand reaction of *N*-allyl-2-ethynilindole promoted by molecular sieves gave the corresponding condensed pyrrolo[1,2-*a*]indole.[12] Finally, pyrrolo[1,2-*a*]indole-2,3-dicarboxylate was easily obtained by a one-pot reaction among indol-2-carbaldehyde, triphenylphosphine, and acetylene dicarboxylate.[13]

Otherwise, our approach is characterized by some outstanding features: (1) the use of easily accessible building blocks, (2) the cheapness of reagents involved, and (3) the capability to obtain in a single step several pyrrolo[1,2-*a*]-indole scaffolds differently substituted on C-1 and bearing an aldehydic function on C-2 susceptible to further transformations.

Starting materials were prepared using both traditional and catalytic strategies. The 2-acetylindole[14] **1a** and the 2-benzoylindole[15] **1b** were prepared in good yields by standard methods. 2-Acylindoles **1c**−**g** were prepared starting from the indole-2-carboxylic acid chloride, easily obtained in almost quantitative yield by reaction of the corresponding acid with oxalyl chloride. Thus, 2-aroylindoles **1c**,**d** and 2-heteroaroylindole **1e** were synthesized in good yield through a Suzuki-type coupling reaction in anhydrous toluene at 50−60 °C using a ratio of acid chloride/boronic acid/K_2CO_3/$Pd(OAc)_2$/P(*o*-tolyl)$_3$ equal to 1:1.2:3:0.05:0.07 (Scheme 1). Unfortunately, this strategy failed in the synthesis of derivatives **1f** and **1g**; this is probably due to the low nucleophilicity of C-2 with respect to C-3 in the furan- and thiophen-boronic acids.[16] Otherwise, compounds **1f** and **1g** were prepared in moderate to good yield via a

Scheme 1. Synthesis of Starting Materials



R	compound	yield %	compound	yield %
methyl	**1a**	98	**2a**	98
phenyl	**1b**	85	**2b**	98
p-tolyl	**1c**	89	**2c**	92
m-tolyl	**1d**	70	**2d**	79
thiophen-3-yl	**1e**	74	**2e**	70
thiophen-2-yl	**1f**	85	**2f**	86
furan-2-yl	**1g**	50	**2g**	69

Negishi-type coupling; the suitable furane- and thiophene-2-zinc-halide[17] were prepared in situ and reacted with indole-2-carboxylic acid chloride in anhydrous THF at 50 °C in the presence of 0.04 equiv of $Pd(PPh_3)_4$ (Scheme 1). Afterward, 2-carbonyl-indoles **1a**−**g** were converted into the corresponding *N*-propargyl derivatives **2a**−**g** in good to excellent yield by means of PTC nucleophilic substitution in toluene/50% aqueous NaOH and tetrabutylammonium bromide (TBAB) as the catalyst[18] (Scheme 1).

Before reacting the whole series of *N*-propargyl-2-carbonylindoles **2a**−**g**, we investigated the optimal reaction conditions to obtain pyrrolo[1,2-*a*]indole-2-carbaldehydes **3**, taking **2b** as the model compound and modifying consecutively the solvent, the metal salt, the temperature, the energy source, and the ratio among reaction partners (Table 1). Two considerations prompted us to engage this screening: (1) the initial reaction conditions, besides a moderate yield of 3*H*-pyrrolo[1,2-*a*]indole-2-carbaldehydes **3b**, gave a significant amount of unreacted starting product **2b** (entry 1) and (2) the study of the optimal reaction conditions could help us to understand the reaction mechanism involved in this original domino cyclization.

Any modification of the combination $TiCl_4$/*t*-$BuNH_2$/toluene gave worse results. A different titanium salt as well as the use of polar protic and aprotic solvents gave a complex mixture of unidentified products (entries 2−4). Although a huge number of articles and reviews[19] testify that microwaves[20] can speed up reactions and improve the yields, our reaction did not seem to be positively influenced by the use of this nonconventional energy source (entries 5−7); in

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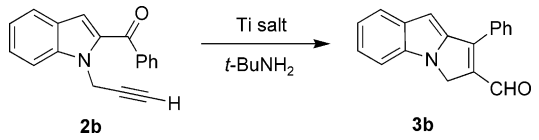
Table 1. Reaction Conditions Screening



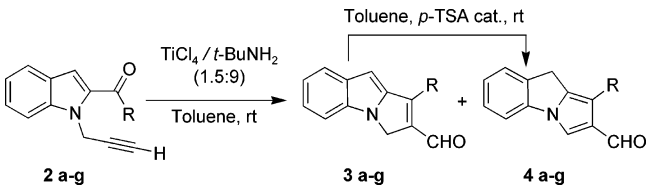
entry	solvent	Ti salt	ratio **2b**/Ti/base	T (°C)	t (h)	yield %[a] **3b** (**2b** rec.)
1	toluene	$TiCl_4$	1:0.5:3	80	12	63 (28)
2	toluene	$Ti(O\text{-}i\text{-}Pr)_4$	1:0.5:3	100	48	
3	ethanol	$TiCl_4$	1:0.5:3	80	48	
4	DMF	$TiCl_4$	1:0.5:3	80	15	
5	toluene	$TiCl_4$	1:0.5:3	110 μw[b]	0.5	35 (48)
6	toluene	$TiCl_4$	1:0.5:3	140 μw[b]	0.5	46 (29)
7	toluene	$TiCl_4$	1:0.5:3	180 μw[b]	0.5	21 (38)
8	toluene	$TiCl_4$	1:0.5:6	80	7	45 (40)
9	toluene	$TiCl_4$	1:1:6	25	20	63
10	toluene	$TiCl_4$	1:1.5:9	25	6	87

[a] Yields refer to isolated products. [b] μw = microwave.

particular, an excessive rise in temperature gave a dropout of overall yield, maybe as a consequence of a thermal degradation of products (entry 7). Better results were obtained by increasing the ratio among the reagents (entries 8−10); in particular, a ratio of substrate/$TiCl_4$/t-$BuNH_2$ of 1:1.5:9 gave the best results already at room temperature (entry 10).

The optimized method was then extended to all derivatives **2**. The results are reported in Table 2.

Table 2. Synthesis of Pyrrolo[1,2-*a*]indole-2-carbaldehydes



entry	**2**	R	t (h)	yield %[a] **3**	yield %[a] **4**
1	**a**	methyl	0.3	50	-
2	**b**	phenyl	6	87	-
3	**c**	*p*-tolyl	6	75	-
4	**d**	*m*-tolyl	6	91	-
5	**e**	thiophen-3-yl	2	89	-
6	**f**	thiophen-2-yl	2	-	75
7	**g**	furan-2-yl	2	-	77

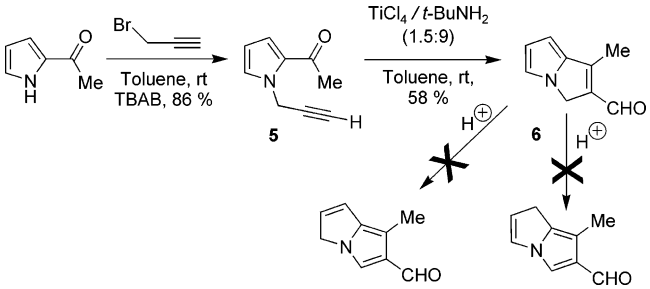
[a] Yields refer to isolated products.

The reaction of 2-acetyl derivative **2a** took place quickly and gave the corresponding 3*H*-pyrrolo[1,2-*a*]indole-carbaldehyde **3a** in moderate yields (entry 1). Better yields were obtained using 2-benzoyl-1-propargylindoles (entries 2−4). The reaction allows also a heteroaryl substituent on C=O (entries 5−7), but when reacting thiophen-2-yl and furan-2-yl derivatives **2f**−**g**, only the isomeric 9*H*-pyrrolo[1,2-*a*]-indole-carbaldehydes **4f**−**g** (fluorazene form) were isolated (entries 6 and 7).

Furthermore, we found that all 3*H*-pyrrolo[1,2-*a*]indole-carbaldehyde derivatives **3** isomerize in the more stable tautomeric fluorazene form **4** standing in a $CDCl_3$ solution at room temperature for 24 h. The same result was obtained by stirring at room temperature a solution of **3b** in toluene for 40 min in the presence of a catalytic amount of *p*-TSA (Table 2).

Finally, with the aim to explore the scope and limitation of this synthetic approach, we did a preliminary test on a different substrate. The reaction of 2-acetyl-1-propargyl pyrrole **5** under optimized conditions gave the corresponding 1-methyl-3*H*-pyrrolizin-2-carbaldehyde **6** in moderate yields as a single product; interestingly, the treatment of **6** with *p*-TSA acid did not give any of the possible tautomers (Scheme 2).

Scheme 2. Synthesis of 1-Methyl-3*H*-pyrrolizin-2-carbaldehyde



All compounds were identified on the basis of analytical and spectral data. Proposed structures are in agreement with experimental evidence of similar compounds reported in the literature.[21] In particular, the structures of tautomers were clearly established for the couple **3b**/**4b** and **6** via 2D NMR experiments (NOESY, HETCOR, HMBC) and extended by analogy to the entire series. Diagnostic NOE interactions and ^3J(C,H) coupling constants are reported in Figure 1.

The proposed reaction mechanism involves three steps in which $TiCl_4$ has a multiplicity of activities (Scheme 3). The first step is a $TiCl_4$-catalyzed hydroamination of alkyne[22] with the formation of an enamine intermediate (I). The addition is highly regioselective in anti-Markovnikow fashion, due to the steric hindrance of the *tert*-butyl moiety of amine.[23] According to recent Ackermann studies, the catalytically active species is probably generated in situ by reaction

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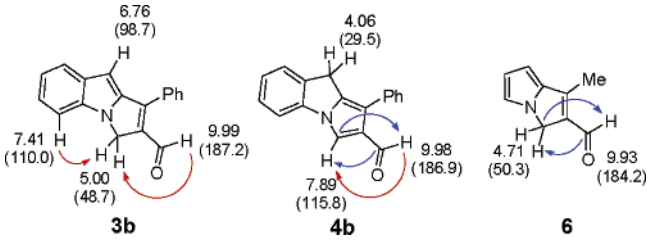

Figure 1. Compounds **3b**, **4b**, and **6**: diagnostic NOE interactions (red arrows) and ^3J(C,H) coupling constants (blue arrows), besides significant proton (and carbon) chemical shifts.

between $TiCl_4$ and *t*-$BuNH_2$.[24] The second step is an aldol-type intramolecular reaction: the nucleophilic addition of the β-carbon of enamine (I) on the carbonyl group gave the intermediate (II). An analogous mechanism was reported by Okada and co-workers for the intramolecular addition of the enamine electron-rich carbon on a C═O activated by the presence of a trifluoromethyl group.[25] Differently, in our reactions, the carbonyl group is activated by $TiCl_4$ as a Lewis acid catalyst.[26] It is worth noting that the carbonyl group reacts in preference with enamine in regard to its direct reaction with *t*-$BuNH_2$. This behavior is related to the well-known inertia of ketones toward bulky amines.[27] In the third step, the imine **7** could be formed by intramolecular elimination of $HOTiCl_3$ and deprotonation or by a N−O proton shift followed by elimination of water and $TiCl_4$. Either way, the driving force of this step is the formation of a new C═C double bond stabilized by the conjugation with the heterocyclic ring. Also in this case, $TiCl_4$ could play a central role, avoiding the release of water in the reaction medium thus preventing the hydrolysis of enamine/imine intermediates.[28] Besides, the excess of amine buffers the reaction solution scavenging the acid chloride. Afterward, the usual workup leads to the hydrolysis of the imine intermediate to give the pyrrolo[1,2-*a*]indole-2-carbaldehydes **3** or **4**.

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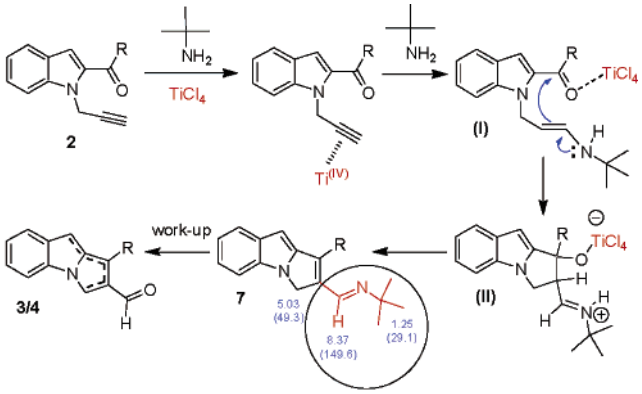
Scheme 3. Suggested Reaction Mechanism



Proton and carbon chemical shifts for R = *m*-Tolyl (**7**).

This mechanism that involves a plethora of different activities of $TiCl_4$—catalyst/Lewis acid/water scavenger—well explains the need to use an excess of this reagent. Moreover, the ^1H and ^{13}C NMR spectra of the reaction crude validates the final step of the suggested mechanism highlighting the presence of the characteristic signals of the *tert*-butyl-imine group of compound **7** (Scheme 3).

In conclusion, this preliminary report demonstrates once again the usefulness of domino addition/annulation reactions involving δ-carbonyl-acetylenes in the synthesis of heterocycles. In particular, this synthetic route to pyrrolo[1,2-*a*]indole-2-carbaldehydes represents an original example of a $TiCl_4$/*t*-$BuNH_2$-mediated hydroamination/annulation reaction in which the $TiCl_4$ performs a variety of tasks. Current efforts are now directed to widening this methodology to other δ-carbonyl-acetylenic substrates and to theoretically clarifying the tautomeric distribution of products.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C spectra for compounds **1c**−**g**, **2c**−**g**, **3a**−**g**, **4a**−**g**, and **5**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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