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Intramolecular Cyclization of δ-Iminoacetylenes: A New Entry to Pyrazino[1,2-*a*]indoles

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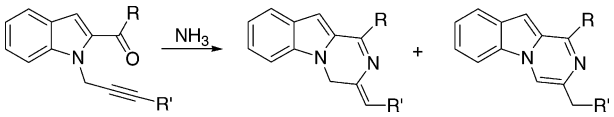

The synthesis of the pyrazino[1,2-*a*]indole nucleus was achieved by intramolecular cyclization of several 2-carbonyl-1-propargylindoles in the presence of ammonia. The reaction conditions were optimized using microwave heating and a pool of catalysts. Cyclization of 1-alkynylindole-2-carbaldehydes was easily accomplished under standard heating conditions, whereas microwave heating contributed to reduced reaction times and improved overall yields. Moreover, a fine-tuning of the microwave irradiation time made possible the selective synthesis of both pyrazino[1,2-*a*]-indole isomers. $TiCl_4$ proved the catalytic system of choice to achieve pyrazinoindoles in satisfactory yields starting from 1-alkynyl-2-acetylindoles and 1-alkynyl-2-benzoylindole derivatives. Also in these cases, microwave heating contributed to faster reactions and improved yields. The uncatalyzed versus catalyzed reaction mechanism is discussed.

Introduction

Polycyclic indoles represent the framework of a large number of compounds characterized by a wide range of biological activities.[1] The isolation from natural sources, synthesis, and the study of the biological properties of these molecules is still a research field of great interest and continuous evolution. For instance, the explosive growth of the carbazole chemistry is demonstrated by the many reviews and monographs that appeared in the literature.[2] In addition, nitrogen analogues of carbazole—commonly called carbolines—are under active investigation for their potential pharmacological activities,[3] in particular the β[4] and γ[5] forms. Although *a*-fused azapolycyclic indoles are less studied than the *b*-fused, recently some papers related to the chemistry and the pharmacology of pyrazino[1,2-*a*]indole nucleus have appeared in the literature. Whereas the synthesis of 1-oxopyrazino[1,2-*a*]indole derivatives was widely explored,[6] the preparation of simple pyrazino-[7] and 3,4-dihydropyrazino[1,2-*a*]indoles[8] has been less examined. For example, Hegedus[7a] prepared the pyrazinoindole nucleus

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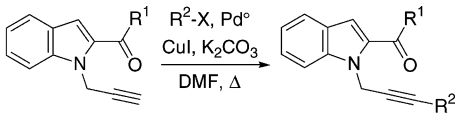
in moderate yield starting from *N*-allylskatole by activation of the olefin moiety with a strong electrophilic palladium complex as $Pd(MeCN)_4(BF_4)_2$ followed by treatment with acetonitrile. Some pyrazino[1,2-*a*]indoles have been obtained by heating skatole[2,1-*c*]-1,4-oxazinium salts[7b] or 2-acyl-*N*-methylcarbonylskatoles[7c] with ammonia, whereas a series of 3,4-dihydropyrazino[1,2-*a*]indoles were synthesized according to Hendi[8a] through $POCl_3$-promoted cyclodehydration of 1-(2-amidoethyl)-3-phenylindoles. Moreover, the relevance of pyrazinoindole compounds, as potential serotoninergic and antitumoral agents, is further demonstrated by the number of recent patents appearing in the literature.[9]

For many years, we have been interested in developing new synthetic strategies for the construction of heterocycles from alkynes.[10] Recently, we focused on the synthesis of nitrogen containing rings by sequential addition/annulation reactions of γ-ketoalkynes with benzylamine or ammonia. In particular, 5-*exo-dig* cyclization of 4-pentynones[11] and 2-propynyl-1,3-dicarbonyl[12] compounds gave polysubstituted and fused pyrrole derivatives. The presence of a γ-ketoalkyne moiety in an aromatic framework is responsible for the 6-*endo-dig* cyclization of 5-acetyl-4-alkynylthiazoles[13] and 2-acyl-3-alkynylindoles[14] to pyrido[3,4-*c*]thiazoles and pyrido[3,4-*b*]indoles, respectively. Furthermore, an original one-pot synthesis of pyridines was developed through a sequential amination/6-*endo-dig* cyclization/aromatization of carbonyl compounds and propargylamine.[15]

In a recent short communication,[16] we reported our preliminary investigations on the synthesis of pyrazino-[1,2-*a*]indoles through a thermal sequential imination/annulation of 1-alkynylindole-2-carbaldehydes **1a**−**d** and 2-acetyl-1-alkynyl-indoles **1f**,**h**−**j** in the presence of ammonia (Table 1, 2). The main drawbacks of these reactions were the long times required for the cyclization of 2-acetyl derivatives and the formation of isomeric mixtures of pyrazino and dihydropyrazino indoles. Thus, the target of this new work was to develop and optimize this approach through the reduction of reaction times for the 2-acetyl derivatives, the extension of this methodology to some new 2-acetyl-, 2-formyl-, and 2-benzoylindoles (Table 1, **1e**,**g**,**k**−**o**), and the selective preparation of both isomeric pyrazinoindoles. We now report the full details of the results we have obtained, as well as scope and limitations of this synthetic strategy. It is worth noting that, although intramolecular cyclization reactions involving 2-substituted-1-alkynylpyrrole or indole derivatives have been described in the synthesis of indolophenanthridine and isoindoloindole derivatives,[17] pyrrolizines,[18] pyrrolophenanthridines,[19] 2a-azacyclopentafluorenes,[20] pyridopyrrolizines, and 10-aza-indenoindoles,[21] our methodology represents the first example of intramolecular cyclization of *N*-alkynyl-substituted heterocycles with proximate nitrogen nucleophiles.

TABLE 1. 1-Alkynyl Derivatives 1 Prepared[a]



1a R^1= H
1f R^1= Me
1k R^1 = Ph

1b-e R^1 = H
1g-j R^1 = Me
1l-o R^1 = Ph

	R^1	R^2	X	Yield %[b]
1b	H	Ph	I	78
1c	H	*p*-Cl-Ph	I	88
1d	H	*m*-CF_3-Ph	I	88
1e	H	*p*-MeO-Ph	I	61
1g	CH_3	Ph	I	73
1h	CH_3	*p*-Cl-Ph	I	83
1i	CH_3	*m*-CF_3-Ph	I	91
1j	CH_3		Br	84
1l	Ph	Ph	I	90
1m	Ph	*p*-Cl-Ph	I	83
1n	Ph	*m*-CF_3-Ph	I	81
1o	Ph	*p*-MeO-Ph	I	86

[a] Reaction conditions: molar ratio indole **1a**, **f**, **k**/aryl-halide/K_2CO_3/CuI/$Pd(PPh_3)_4$ = 1:1.01:5:0.04:0.02; DMF, N_2, 60 °C. [b] Isolated yields.

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Results and Discussion

The 1-propargyl-1*H*-indole-2-carbaldehyde **1a**,[22] the 2-acetyl-1-propargyl-1*H*-indole **1f**, and the 2-benzoyl-1-propargyl-1*H*-indole **1k** were synthesized by standard procedures,[23] starting from readily accessible 1*H*-indole-2-carbaldehyde,[24] 2-acetyl-1*H*-indole[25] and 2-benzoyl-1*H*-indole,[26] respectively. The corresponding 1-alkynyl-1*H*-indole-2-carbaldehydes **1b**−**e**, 2-acyl-1-alkynyl-1*H*-indoles **1g**−**j**, and 2-benzoyl-1-alkynyl-1*H*-indoles **1l**−**o** (Table 1) were synthesized from 1-propargylindoles **1a**, **1f**, and **1k** by palladium-catalyzed Sonogashira−(Hagihara) coupling with aryl halides.[27]

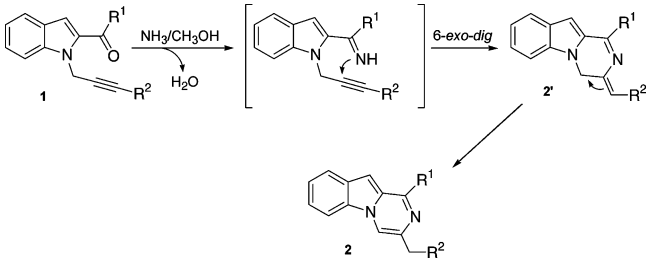
As reported in ref 16, when 1-propargyl derivatives **1a** and **1f** and 1-alkynyl derivatives **1b**−**d** and **1h**−**j** were treated in a sealed tube at 100 °C with 2 M ammonia in methanol, **1a** and **1f** gave the corresponding pyrazino-[1,2-*a*]indoles **2a** and **2f** in good yields, whereas 1-alkynyl derivatives **1b**−**d** and **1h**−**j** afforded a mixture of isomeric pyrazino[1,2-*a*]indoles **2b**−**d** and **2h**−**j** and 3,4-dihydropyrazino[1,2-*a*]indoles **2′b**−**d** and **2′h**,**i** (Table 2, entries 1−8). Moreover, the cyclization reactions of the newly prepared 2-benzoyl derivatives **1k** and **1n** took place very awkwardly giving rise to the corresponding pyrazino derivatives **2k** and **2′n** in very poor yields (Table 2, entries 9,10). The reaction times vary from 3 to 4 h for the carbaldehyde derivatives **1a**−**d** (entries 1−4), to 50−200 h for the 2-acetyl derivatives **1f**,**h**−**j** (entries 5−8) and 240-387 h for 2-benzoyl derivatives **1k**,**n** (entries 9−10).

All compounds were identified on the basis of analytical and spectral data (IR, ^{1}H NMR, ^{13}C NMR, MS). In particular, the stereochemistry around the exocyclic double bond of dihydro derivatives was clearly established for compound **2′h** through 2D NOESY experiments and extended by analogy to the entire series. Diagnostic NOE interactions and proton chemical shifts are reported in Figure 1.

The suggested reaction mechanism involves the formation of an imine intermediate that undergoes a stereoselective 6-*exo-dig* cyclization to 3,4-dihydropyrazinoindole **2′** followed by partial isomerization to give pyrazinoindole **2** (Scheme 1).

The ratio between compounds **2** and **2′** is switched toward the formation of the fully conjugated rings in the experiments performed with 1-propargyl derivatives **1a**, **1f**, and **1k** (Table 2, entries 1, 5, and 9) or with 1-alkynyl-2-acylindoles **1h**−**j** (Table 2, entries 6−8), whereas dihydro derivatives were the main products when the reactions are performed with 1-alkynylindole-2-carbaldehydes **1b**−**d** (Table 2, entries 2−4) or with 1-alkynyl-2-benzoylindole **1n** (Table 2, entry 10). Moreover, the

SCHEME 1



dihydro isomers **2′** derived from 2-acetyl- and 2-formylindoles can be converted, in almost quantitative yields, to the corresponding fully conjugated isomers **2** under basic conditions (NaOMe/MeOH 15%, reflux). The same reaction failed when performed on dihydro isomers derived from 2-benzoylindoles.

In our opinion, the experimental evidence could be related to two main features: the mutual stability of pyrazinoindoles with respect to dihydropyrazino derivatives and the divergent reaction times required by the different substituted substrates. The formation of dihydropyrazino derivatives is a kinetically governed process, whereas pyrazinoindoles are the thermodynamically controlled products, and as is well-known, prolonged reaction times promote the formation of second ones. These statements were confirmed by the theoretical calculations performed on derivatives **2a**,**b**,**f**,**g**,**k**,**l** and **2′a**,**b**,**f**,**g**,**k**,**l** at the DFT[28] level (Table 3).

As expected, the pyrazinoindoles derivatives **2** were thermodynamically favored with respect to the corresponding dihydro isomers **2′**. It is worth noting that the energetic differences among the isomers derived from cyclization of 1-propargyl derivatives **1a**, **1f**, and **1k** are significantly higher (13.41−14.98 kcal/mol) than those calculated for cyclization products of 1-alkynyl derivatives **1b**, **1g**, and **1l** (7.51−8.94 kcal/mol). This is related to the stabilizing effect caused by the aryl substituents conjugated with the exocyclic double bonds on compounds **2′b**, **2′g,** and **2′l**. The lack of this stabilization on hypothetical methylene derivatives **2′a**, **2′f**, and **2′k** make them so unfavored that they can never be isolated. In addition, it is worth noting that the energy difference between 2-benzoyldihydropyrazino derivatives **2′k**,**l** and the corresponding fully conjugated isomers **2k**,**l** are the lowest in the series.

With the aim to maximize the efficiency of this synthetic approach in terms of reaction times (2-acetyl and 2-benzoyl derivatives), overall yields (2-benzoyl derivatives), and the internal ratio between dihydro and fully conjugated compounds, we customized the methodology according to two different strategies: (1) the employ of a different energy source and (2) the support of catalysts.

Microwave[29] heating as a nonconventional energy source has become a very popular and valuable technology in organic chemistry. Although the subsistence of a "specific microwave effect" (nonthermal effect) is an argument of active discussion in the scientific com-

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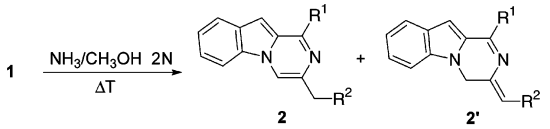
TABLE 2. Thermal Cyclization of 1-Alkynyl Derivatives 1[a]



Entry	1	T (°C)	t (h)	2 (yield %)[b]	2' (yield %)[b]
1	**1a**	100	4	**2a** (80)	**2'a** (-)
2	**1b**	90	3.5	**2b** (12)	**2'b** (35)
3	**1c**	110	3	**2c** (30)	**2'c** (58)
4	**1d**	90	3	**2d** (26)	**2'd** (46)
5	**1f**	100	50	**2f** (73)	**2'f** (-)
6	**1h**	100	200	**2h** (58)	**2'h** (31)
7	**1i**	100	160	**2i** (76)	**2'i** (12)
8	**1j**	100	100	**2j** (69)	**2j** (-)
9	**1k**	100/150	240	**2k** (14)	**2'k** (-)
10	**1n**	100	387	**2n** (-)	**2'n** (10)

[a] Reaction conditions: molar ratio indole **1**/2 M NH_3 in MeOH = 1:20, sealed tube. [b] Isolated yields.

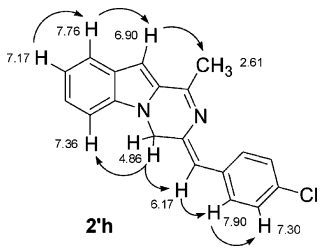


FIGURE 1. NOE interactions and proton NMR chemical shifts for derivative **2′h**.

munity,[30] a huge number of articles and reviews[31] testifies that microwave heating can speed up reactions and improve the yields by decreasing decomposition of products, substrates, and reagents. These remarks prompted

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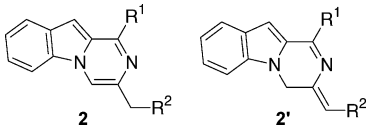
TABLE 3. Calculated Energies for Pyrazinoindoles 2a,b,f,g,k,l and Dihydropyrazinoindoles 2′a,b,f,g,k,l

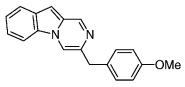
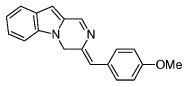


2 **2'**

2	R^1	R^2	*E* DFT[a] (kcal/mol)	E_{rel} DFT[a] (kcal/mol)
2a	H	H	−359521.04	0
2′a	H	H	−359506.46	14.58
2f	Me	H	−384201.37	0
2′f	Me	H	−384186.39	14.98
2k	Ph	H	−504544.33	0
2′k	Ph	H	−504530.92	13.41
2b	H	Ph	−504540.44	0
2′b	H	Ph	−404532.23	8.21
2g	Me	Ph	−529219.35	0
2′g	Me	Ph	−529210.41	8.94
2l	Ph	Ph	−649562.46	0
2′l	Ph	Ph	−649554.95	7.51

[a] B3LYP/6−311+G**//HF/6-31+G*.

TABLE 4. Microwave-Assisted Cyclization of 1-Alkynyl Derivatives 1a−f[a]

Entry	1	t[b] (min)	2 (yield %)[c]	2' (yield %)[c]
1	**1a**	40	**2a** (100)	**2'a** (-)
2	**1b**	45	**2b** (55)	**2'b** (3)
3	**1c**	60	**2c** (74)	**2'c** (24)
4	**1d**	40	**2d** (90)	**2'd** (8)
5	**1e**	25	 **2e** (-)	 **2'e** (95)
6	**1e**	40	**2e** (65)	**2'e** (-)
7	**1f**	300[d]	**2f** (29)	**2'f** (-)

[a] Reaction conditions: molar ratio indole **1**/2 M NH_3 in MeOH = 1:20, sealed tube, 150 °C. [b] Including 15 min "ramp time" ≅ 10 °C/min. [c] Isolated yields. [d] 34% of unreacted starting product **1f** was recovered.

us to test the cyclization of our substrates under microwave heating. Thus, a solution of the appropriate alkynyl indole in 2 M ammonia in methanol was heated in a multimode microwave oven at 150 °C until no more starting product was detectable by TLC analysis. The results are summarized in Table 4.

The microwave-assisted reaction of carbaldehyde derivatives **1a**−**e** took place quicker than conventional-heated ones (cf. Table 2, minutes vs hours), and overall yields were incremented by 11−36% (entries 1−6). The ratio between dihydropyrazinoindoles (**2′**) and pyrazinoindoles (**2**) was shifted toward the fully conjugated system. Moreover, it is interesting to note that the synthesis of a single pyrazino isomer is achieved through longer reaction times (entries 5 and 6). When **1e** was reacted for 25 min, under usual reaction conditions, the dihydro derivative **2′e** was obtained as the sole reaction product in 95% yield (entry 5), whereas with a reaction time of 40 min the fully conjugated isomer **2e** was isolated in 65% yield (entry 6). Unfortunately, under these reaction conditions no yield improvement was observed for the cyclization of 2-acetyl-1-propargylindole **1f** in a reasonable reaction time (entry 7). This latter result discouraged us from attempting the microwave methodology on 2-benzoyl-1-propargylindole derivatives.

As depicted in Scheme 1, the cyclization reactions of 1-propargyl-2-carbonylindole derivatives proceed in two key steps: (1) the formation of an imine intermediate and (2) the addition of the nitrogen nucleophile to the triple bond. It is well-known that ketones (in particular if aromatic and/or sterically hindered) react with amines and ammonia more slowly than aldehydes to form imines. This process can be accelerated by protons and Lewis acid catalysts and/or by water removal from the reaction mixture.[32] In the literature, a great number of examples of imine synthesis promoted by a variety of agents such as molecular sieves,[33] zinc chloride,[34] titanium tetrachloride,[35] alumina,[36] and other Lewis acids[37] are reported.

On the other hand, considering the annulation step, a number of recent reviews suggest that catalytic hydroamination of multiple bonds is a powerful synthetic method to obtain nitrogen-containing compounds.[38] In particular, a variety of protocols are available for the intermolecular hydroamination of alkynes,[39] and a number of metal complexes of group 4[40] and organolanthanides[41] as well as various metal salts of group 9, 10, and 11 have been reported to successfully catalyze the intramolecular addition of nitrogen nucleophiles to alkynes.[11f,42]

Based on these accounts, we tested a variety of water scavengers/catalytic systems. The screening was performed by heating, in a silicon oil bath, a sealed tube containing a solution of the 1-alkynyl-2-acetylindoles **1h** or **1i** in 2 M ammonia in methanol and in the presence of suitable Lewis acids, water scavengers, or metal catalytic systems. The obtained results are summarized in Table 5.

The reaction performed at 150 °C and in the presence of molecular sieves failed, giving rise to the corresponding mixture of pyrazino indoles in very low yields and a large amount of starting material (entry 3). Activation of the intermediate imine function and/or triple bond was then tentatively achieved by means of palladium/phosphane catalyst or with phosphane-free silver or copper catalysts (entries 4−7). However, such reactions ran worse and were slower than the corresponding uncatalyzed reactions (entries 4 and 5) or did not produce significant improvements (entries 6 and 7). Surprisingly, the gold-(III) salt, which acts as a Lewis acid and also increases

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TABLE 5. Screening of Water Scavengers/Catalytic Systems[a]

entry	1	*T* (°C)	t (h)	water scavenger/catalytic system	1 (rec, %)[b]	2 (yield, %)[b]	2′ (yield, %)[b]
1[c]	**1h**	100	200			**2h** (58)	**2′h** (31)
2[c]	**1i**	100	160			**2i** (76)	**2′i** (12)
3	**1h**	150	48	molecular sieves 3 Å (1.0 g)	**1h** (75)[d]	**2h** (10)[d]	**2′h** (15)[d]
4	**1i**	100	137	$Pd(OAc)_2$ (0.05 mol), PPh_3 (0.10 mol)		**2i** (60)	**2′i** (14)
5	**1h**	100	158	$Pd(OAc)_2$ (0.05 mol), PPh_3 (0.10 mol)		**2h** (44)	**2′h** (16)
6	**1i**	100	172	$AgNO_3$ (0.10 mol)	**1i** (36)	**2i** (18)	**2′i** (21)
7	**1i**	100	112	CuI (0.10 mol)	**1i** (18)	**2i** (40)	**2′i** (22)
8	**1h**	100	94	$NaAuCl_4$ (0.04 mol)	**1h** (23)	**2h** (27)	**2′h** (28)
9	**1i**	100	160	$NaAuCl_4$ (0.10 mol)		**2i** (77)	**2′i** (12)
10	**1h**	100	36	$AlCl_3$ (1 mol)	**1h** (45)[d]	**2h** (20)[d]	**2′h** (35)[d]
11	**1h**	100	36	$ZnCl_2$ (1 mol)		**2h** (20)	**2′h** (60)
12	**1h**	100	8.5	$TiCl_4$ (0.50 mol)	**1h** (29)	**2h** (18)	**2′h** (52)

[a] Reaction conditions: molar ratio indole derivatives **1h** or **1i**/2 M NH_3 in MeOH = 1:20, water scavenger/cat., sealed tube, conventional heating. Workup: flash column chromatography (petroleum ether/ethyl acetate = 98:2). [b] Unless other stated, isolated yields. [c] To simplify the evaluation, entries 1 and 2 report once more the results of uncatalyzed thermal cyclization of compounds **1h** and **1i**. [d] Yields determined by analysis of the proton NMR spectrum of the reaction mixture.

the electrophilicity of the triple bond by coordination, seems to be irrelevant for the reaction outcome (entries 8 and 9). Instead, reasonable reduction of reaction time can be achieved working in the presence of Lewis acids catalyst/water scavengers such $AlCl_3$, $ZnCl_2$, and $TiCl_4$ (entries 10−12). Among these catalysts, titanium tetrachloride was selected for further investigation in order to establish the most advantageous ratio substrate/catalyst with respect to reaction time and conversion yields. Derivative **1h** was reacted under standard conditions in the presence of 0.5, 1, 2, 3 equiv of $TiCl_4$ and TLC analysis, run at regular intervals, and showed that an indole/$TiCl_4$ ratio of 1:3 gave a faster conversion time (disappearance of **1h** in ca. 2 h).

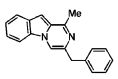
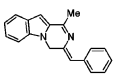
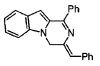
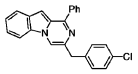
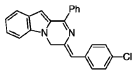
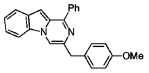
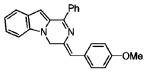
The optimized methodology was then applied to 2-acyl and 2-benzoyl derivatives using either conventional or microwave heating. The obtained results are summarized in Table 6.

The obtained results show that titanium tetrachloride, under mild conventional heating conditions, accelerates the cyclization of 2-acetylindoles (entries 1, 3, 4, 6, and 7) and allowed the cyclization of 2-benzoylindoles with good yields and reasonable reaction times (entries 9, 11, 14, and 15). Moreover, reaction times were further reduced by microwave heating (entries 2, 5, 8, 10, 12, 13, and 16). On the whole, the overall yields on pyrazinoindoles **2/2′** appeared slightly improved with respect to reactions performed without catalyst. Finally, titanium tetrachloride catalyzed cyclization of internal alkynes gave preferentially (entries 3, 4, 6, and 12) and sometimes exclusively (entries 7, 8, 11, and 13−16) the dihydropyrazino derivatives **2′**.

To better understand this behavior, we performed a semiquantitative kinetic study via ^{1}H NMR. In two sealed tubes, two identical samples (**A** and **B**) containing 154 mg of derivative **1h** in 5 mL of 2 M ammonia in methanol were prepared. Three equivalents of $TiCl_4$ were added to sample **B**, and then both samples were heated in an oil bath at 100 °C for several hours. The ratio among starting material **1h**, dihydro derivative **2′h**, and pyrazino derivative **2h** was detected by sampling the reaction at different reaction times via ^{1}H NMR and comparing the integrals of characteristic methylene signals of **1h** (δ = 5.72 ppm), **2′h** (δ = 4.85 ppm), and **2h** (δ = 4.08 ppm). The results are reported in Figure 2.

After an induction time of 4 h, the uncatalyzed reaction (sample A) runs very slowly. Although the conversion of **2′h** to **2h** is a slow process, the sluggishness of cyclization of **1h** under thermal uncatalyzed conditions allows for the tautomerization of **2′h** to the more stable isomer **2h**. Therefore, after 210 h of reaction, when **1h** was nearly

TABLE 6. $TiCl_4$-Catalyzed Cyclization of 2-Acyl and 2-Benzoyl Derivatives

Entry	1	Heating	Time (min)	2 (yield %)[a]	2' (yield %)[a]
1	**1f**	conventional[b]	135	**2f** (90)	**2'f** (-)
2	**1f**	microwave[c]	43[d]	**2f** (81)	**2'f** (-)
3	**1g**	conventional[b]	135	 **2g** (19)	 **2'g** (51)
4	**1h**	conventional[b]	135	**2h** (8)	**2'h** (89)
5	**1h**	microwave[c]	73[d]	**2h** (40)	**2'h** (40)
6	**1i**	conventional[b]	180	**2i** (22)	**2'i** (59)
7	**1j**	conventional[b]	120	**2j** (-)	**2'j** (85)
8	**1j**	microwave[c]	43[d]	**2j** (-)	**2'j** (68)
9	**1k**	conventional[b]	600	**2k** (77)	**2'k** (-)
10	**1k**	microwave[c]	223[d]	**2k** (73)	**2'k** (-)
11	**1l**	conventional[b]	840	 **2l** (-)	 **2'l** (82)
12	**1l**	microwave[c]	313[d]	**2l** (18)	**2'l** (67)
13	**1m**	microwave[c]	313[d]	 **2m** (4)	 **2'm** (88)
14	**1n**	conventional[b]	1020	**2n** (-)	**2'n** (86)
15	**1o**	conventional[b]	600	 **2o** (-)	 **2'o** (79)
16	**1o**	microwave[c]	313[d]	**2o** (-)	**2'o** (88)

[a] Isolated yields. [b] Reaction conditions: molar ratio indole derivative **1**/2 M NH_3 in MeOH/$TiCl_4$ = 1:20:3, sealed tube, 100 °C (silicon oil bath). [c] Reaction conditions: molar ratio indole derivative **1**/2 M NH_3 in MeOH/$TiCl_4$ = 1:20:3, sealed tube, 130 °C (microwave oven). [d] Including 13 min "ramp time" ≅ 10 °C/min.

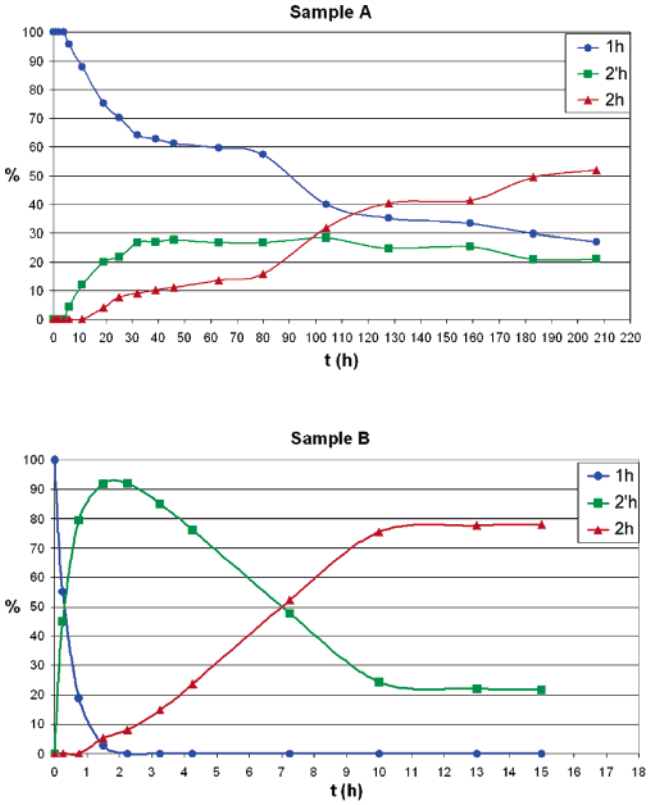
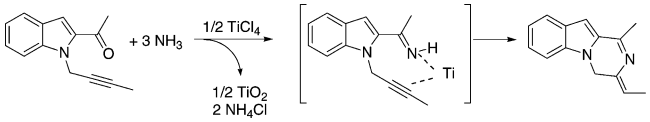


FIGURE 2. Kinetic study of uncatalyzed (sample A) and $TiCl_4$-catalyzed (sample B) cyclization of **1h**.

SCHEME 2



consumed, the ratio between **2h** and **2′h** was significantly shifted toward the first one (Figure 2, sample A).

On the contrary, the titanium-catalyzed reaction (sample B) runs quickly and the conversion of **1h** in the dihydro isomer **2′h** is almost complete within 2 h. In this short segment, only a small amount of **2′h** can turn in to the thermodynamic isomer **2h**; thus, by stopping the reaction at this point it is possible to isolate the kinetic isomer **2′h** in nearly quantitative yield. Consequently, to observe the formation of a significant amount of **2h** a longer heating time is required (Figure 2, sample B).

On the basis of these findings, we hypothesize that titanium tetrachloride affects both critical steps of pyrazinoindole formation (Scheme 2). First, it can promote the imine intermediate formation through the double activity of vigorous water scavenger as well as useful Lewis acid.[35] In the second instance, $TiCl_4$ or a catalytically active species generated in situ from $TiCl_4$ and ammonia[43] can promote the cyclization step through the coordination between the triple bond and imine.[44] Moreover, this dual activity of $TiCl_4$ justifies the high catalyst/substrate ratio required.

(43) For a recent example, see: Ackermann, L. *Organometallics* **2003**, *22*, 4367−4368.

(44) For an example of a complex among titanium, alkynes, and carbonyl compounds, see: Kabalka, G. W.; Ju, Y.; Wu, Z. *J. Org. Chem.* **2003**, *68*, 7915−7917.

Conclusions

In conclusion, the synthesis of the pyrazino[1,2-*a*]indole nucleus, achieved by intramolecular cyclization of 2-carbonyl-1-alkynylindoles in the presence of ammonia, demonstrates once again the efficiency of annulation reactions involving alkynes with neighboring nucleophiles.

The cyclization reactions of 1-alkynylindole-2-carbaldehydes **1a**−**e**, in the presence of ammonia, run well under conventional heating giving rise to isomeric pyrazino[1,2-*a*]indoles **2a**−**e** and 3,4-dihydropyrazino[1,2-*a*]-indoles **2′a**−**e** in good yields. Nevertheless, reaction times can be reduced and yields can be improved by the aid of microwave heating.

Also the 1-propargyl-2-acetylindole **1f** reacts easily with ammonia to give in good yields the corresponding pyrazino[1,2-*a*]indole **2f** whereas for the less reactive 1-alkynyl-2-acetylindoles **1g**−**j** and 1-alkynyl-2-benzoylindoles **1k**−**o** the use of an inexpensive catalyst such $TiCl_4$ allowed to achieve the corresponding isomeric pyrazino-[1,2-*a*]indoles **2** and 3,4-dihydropyrazino[1,2-*a*]indoles **2′** in satisfactory yields with reasonable reaction times. Furthermore, also in $TiCl_4$-catalyzed reactions microwave heating efficiently contributed to a widespread reduction of reaction times and improvement of yields.

Finally, it has been demonstrated that $TiCl_4$ catalysis drastically modifies the cyclization kinetics for the 1-alkynyl-2-acetylindoles, allowing for the almost selective isolation of both isomers by appropriate choice of the reaction times.

Experimental Section

General Procedure for the Synthesis of 1-Propargylindoles 1f and 1k. To a well-stirred solution of the appropriate 2-acetyl- or 2-benzoyl-1*H*-indole (6.0 mmol), propargyl bromide (0.93 g, 7.8 mmol, corresponding to 1.16 g, 0.87 mL of 80% w/w toluene solution), and tetrabutylammonium bromide (0.097 g, 0.30 mmol) in toluene (18 mL), a 50% w/w aqueous solution of sodium hydroxide (3.5 mL) was slowly added at room temperature. The reaction was vigorously stirred for 5 h until no more starting product was detectable by TLC analysis. After that, the reaction mixture was diluted with toluene (10 mL) and washed with water (2 × 20 mL). The organic layer was dried over sodium sulfate and the solvent removed at reduced pressure. The resulting crude was used without further purification.

1-(1-Prop-2-ynyl-1*H*-indol-2-yl)ethanone 1f. Yield: 1.15 g, 98%. Dark yellow solid. Mp: 98−101 °C. IR: ν = 3276, 2100, 1647, 1614 cm^{-1}. ^1H NMR: δ = 2.26 (t, 1H, ≡C-H, ^4J = 2.6 Hz), 2.66 (s, 3H, CH_3), 5.51 (d, 2H, CH_2, ^4J = 2.6 Hz), 7.23 (m, 1H, arom), 7.36 (s, 1H, C3-H arom), 7.23 (m, 1H, arom), 7.45 (m, 1H, arom), 7.53 (d, 1H, arom, ^3J = 8.0 Hz), 7.74 (d, 1H, arom, ^3J = 8.0 Hz) ppm. ^{13}C NMR: δ = 27.9, 34.3, 71.9, 78.9, 110.8, 113.5, 121.5, 123.2, 126.2, 126.6, 133.7, 139.5, 191.6 ppm. ESI-MS *m/z*: 198 [M^+ + 1] (100), 154 (45), 130 (19), 100 (73).

Phenyl(1-prop-2-ynyl-1*H*-indol-2-yl)methanone 1k. Yield: 1.55 g, 98%. Light brown solid. Mp: 120 °C. IR: ν = 3271, 2124, 1634, 1610 cm^{-1}. ^1H NMR: δ = 2.30 (t, 1H, ≡C-H, ^4J = 2.2 Hz), 5.50 (d, 2H, CH_2, ^4J = 2.2 Hz), 7.09 (s, 1H, C3−H arom), 7.22 (m, 1H, arom), 7.44−7.65 (m, 5H, arom), 7.72 (d, 1H, arom, ^3J = 8.0 Hz), 7.96 (m, 2H, arom) ppm. ^{13}C NMR: δ = 34.4, 72.5, 79.1, 110.9, 116.5, 121.7, 123.5, 126.5, 126.7, 128.5, 130.0, 132.6, 134.2, 139.4, 139.9, 188.7 ppm. ESI-MS *m/z*: 260 [M^+ + 1] (100), 100 (32).

General Procedure for the Synthesis of 2-Carbonyl-1-alkynylindoles 1b−e,g−j,l−o. Under a nitrogen atmosphere, a solution of **1a** or **1f** or **1k** (1.0 mmol), the appropriate aryl halide (1.01 mmol), potassium carbonate (0.69 g, 5 mmol),

CuI (7.6 mg, 0.04 mmol), and tetrakis(triphenylphosphine)-palladium(0) (23.1 mg, 0.02 mmol) in dry DMF (2 mL) was stirred at 60 °C until no more starting product was detectable by TLC analysis. Then, the reaction mixture was diluted with HCl 0.1 M solution (100 mL) and extracted with ethyl acetate (2 × 30 mL). The organic layer, dried over sodium sulfate, was evaporated to dryness and the crude purified by flash chromatography over a silica gel column.

1-(3-Phenylprop-2-ynyl)-1*H*-indole-2-carbaldehyde 1b. Reaction time: 1 h. Eluent for chromatography: PE/EtOAc (95:5). Yield: 202 mg, 78%. Yellow solid. Mp: 76 °C. IR: ν = 1668, 1613 cm^{-1}. ^{1}H NMR: δ = 5.71 (s, 2H, CH_2), 7.22−7.41 (m, 7H, arom), 7.51 (m, 1H, arom), 7.65 (dd, 1H, arom, ^3J = 8.6, ^4J = 1.1 Hz), 7.79 (dd, 1H, arom, ^3J = 8.1, ^4J = 1.1 Hz), 9.94 (s, 1H, CHO) ppm. ^{13}C NMR: δ = 35.0, 84.0, 84.5, 111.4, 118.9, 121.7, 122.7, 123.8, 126.9, 127.6, 128.5, 128.7, 132.1, 134.8, 140.5, 183.0 ppm. ESI-MS *m/z*: 260 [M$^+$ + 1] (100), 199 (15). Anal. Calcd for $C_{18}H_{13}NO$ (259.30): C, 83.37; H, 5.05; N, 5.40. Found: C, 83.31, H, 5.05; N, 5.38.

1-[1-(3-Phenylprop-2-ynyl)-1*H*-indol-2-yl]ethanone 1g. Reaction time: 3 h. Eluent for chromatography: PE/EtOAc (98:2). Yield: 200 mg, 73%. White solid. Mp: 112−113 °C. IR: ν = 1663, 1614 cm^{-1}. ^{1}H NMR: δ = 2.65 (s, 3H, CH_3), 5.71 (s, 2H, CH_2), 7.16−7.28 (m, 4H, arom), 7.32−7.40 (m, 3H, arom), 7.44 (m, 1H, arom), 7.59 (d, 1H, arom, ^3J = 7.7 Hz), 7.72 (d, 1H, arom, ^3J = 7.7 Hz) ppm. ^{13}C NMR: δ = 28.2, 35.2, 83.9, 84.7, 111.2, 113.5, 121.5, 122.9, 123.3, 126.4, 126.6, 128.4, 128.5, 132.0, 133.9, 139.8, 191.7 ppm. ESI-MS *m/z*: 274 [M$^+$ + 1] (100), 232 (10). Anal. Calcd for $C_{19}H_{15}NO$ (273.33): C, 83.49; H, 5.53; N, 5.12. Found: C, 83.41; H, 5.49; N, 5.14.

Phenyl[1-(3-phenylprop-2-ynyl)-1*H*-indol-2-yl]methanone 1l. Reaction time: 1.5 h. Eluent for chromatography: PE/EtOAc (95:5). Yield: 320 mg, 90%. Yellow oil. IR: ν = 1635, 1614 cm^{-1}. ^{1}H NMR: δ = 5.71 (s, 2H, CH_2), 7.07 (s, 1H, C3-H arom), 7.18−7.36 (m, 6H, arom), 7.42−7.72 (m, 6H, arom), 7.96 (dd, 2H, arom, ^3J = 6.6, ^4J = 1.5 Hz) ppm. ^{13}C NMR: δ = 35.2, 84.2, 84.6, 111.2, 116.3, 121.5, 122.8, 123.4, 126.5, 126.6, 128.4, 128.5, 128.6, 130.0, 132.0, 132.5, 134.3, 139.5, 140.0, 188.8 ppm. ESI-MS *m/z*: 336 [M$^+$ + 1] (100), 251 (38). Anal. Calcd for $C_{24}H_{17}NO$ (335.40): C, 85.94; H, 5.11; N, 4.18. Found: C, 86.21; H, 5.18; N, 4.13.

General Methods for Cyclization Reactions of 2-Carbonyl-1-alkynylindoles 1. Conventional Thermal Cyclizations. A stirred solution of the appropriate indole **1** (0.3 mmol) in dry ammonia in methanol (NH_3/MeOH 2 M solution, 3 mL) was heated at 90−150 °C in a sealed tube for 3−387 h until no more starting product was detectable by TLC. The solvent was then evaporated under reduced pressure. The crude product was purified by flash chromatography over silica gel column yielding progressively 3,4-dihydropyrazino[1,2-*a*]-indoles **2′** and/or pyrazino[1,2-*a*]indole **2** (for yields, times, and temperatures, see Table 2).

Microwave-Assisted Cyclizations. A stirred solution of the appropriate indole **1** (0.3 mmol) in dry ammonia in methanol (NH_3/MeOH 2 M solution, 3 mL) was heated at 150 °C in a sealed tube for 25−300 min in a multimode microwave oven until no more starting product was detectable by TLC. The solvent was then evaporated under reduced pressure. The crude product was purified by flash chromatography over silica gel column yielding progressively 3,4-dihydropyrazino[1,2-*a*]-indoles **2′** and/or pyrazino[1,2-*a*]indole **2** (for yields and times, see Table 4).

$TiCl_4$-Catalyzed Cyclizations. In a sealed tube, to a solution of the appropriate indole **1** (0.3 mmol) in dry ammonia in methanol (NH_3/MeOH 2 M solution, 3 mL), was carefully added $TiCl_4$ (171 mg, 99 μL, 0.9 mmol) (caution!). The stirred reaction mixture was warmed at 100 °C with a silicon oil bath for 120−1020 min, or alternatively heated at 130 °C in a multimode microwave oven for 43−313 min, until no more starting product was detectable by TLC. The solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography over silica gel column yielding progressively 3,4-dihydropyrazino[1,2-*a*]indoles **2′** and/or pyrazino[1,2-*a*]indole **2** (for yields and times, see Table 6).

3-[1-Phenylmeth-(*Z*)-ylidene]-3,4-dihydropyrazino[1,2-*a*]indole 2′b. Eluent for chromatography: PE/EtOAc (98:2). Dark yellow solid. Mp: 121 °C. IR: ν = 1612, 1560 cm^{-1}. ^{1}H NMR: δ = 4.94 (d, 2H, CH_2, ^4J = 1.5 Hz), 6.34 (s, 1H, =C-H), 6.84 (s, 1H, C10-H arom), 7.16−7.45 (m, 6H, arom), 7.72 (d, 1H, arom ^3J = 7.7 Hz), 7.91 (d, 2H, arom ^3J = 7.3 Hz), 8.36 (s, 1H, C1-H arom) ppm. ^{13}C NMR: δ = 44.5, 105.2, 109.5, 121.2, 123.1, 125.2, 126.0, 127.8, 128.3, 128.5, 128.9, 130.8, 136.1, 137.9, 138.0, 149.1 ppm. Anal. Calcd for $C_{18}H_{14}N_2$ (258.32): C, 83.69; H, 5.46; N, 10.84. Found: C, 83.58; H, 5.42; N, 10.80.

3-Benzylpyrazino[1,2-*a*]indole 2b. Eluent for chromatography: PE/EtOAc (98:2). Dark yellow solid. Mp: 89 °C. IR: ν = 1619, 1530 cm^{-1}. ^{1}H NMR: δ = 4.14 (s, 2H, CH_2), 6.98 (s, 1H, C10-H arom), 7.37−7.43 (m, 7H, arom), 7.84−7.93 (m, 3H, arom), 9.03 (d, 1H, C1-H arom, ^4J = 1.5 Hz) ppm. ^{13}C NMR: δ = 41.3, 95.2, 111.1, 114.5, 122.3, 122.5, 123.8, 126.8, 128.8, 128.9, 129.4, 129.8, 136.1, 139.4, 147.2 ppm (one signal obscured). ESI-MS *m/z*: 259 [M$^+$ + 1] (100). Anal. Calcd for $C_{18}H_{14}N_2$ (258.32): C, 83.69; H, 5.46; N, 10.84. Found: C, 83.57; H, 5.48; N, 10.79.

1-Methyl-3-[1-phenylmeth-(*Z*)-ylidene]-3,4-dihydropyrazino[1,2-*a*]indole 2′g. Eluent for chromatography: PE/EtOAc (98:2). Yellow oil. IR: ν = 1613, 1556 cm^{-1}. ^{1}H NMR: δ = 2.60 (s, 3H, CH_3), 4.86 (d, 2H, CH_2, ^4J = 1.1 Hz), 6.21 (s, 1H, =C-H), 6.87 (s, 1H, C10-H arom), 7.15−7.41 (m, 6H, arom), 7.68 (d, 1H, arom ^3J = 8.1 Hz), 7.92 (d, 2H, arom ^3J = 7.3 Hz) ppm. ^{13}C NMR: δ = 22.5, 44.3, 103.8, 109.8, 121.0, 122.9, 123.5, 125.0, 127.5, 127.8, 128.1, 128.2, 131.0, 136.0, 138.0, 156.9 ppm (one signal obscured). ESI-MS *m/z*: 273 [M$^+$ + 1] (100), 211 (10). Anal. Calcd for $C_{19}H_{16}N_2$ (272.34): C, 83.79; H, 5.92; N, 10.29. Found: C, 83.69; H, 5.96; N, 10.25.

3-Benzyl-1-methylpyrazino[1,2-*a*]indole 2g. Eluent for chromatography: PE/EtOAc (98:2). Dark yellow oil. IR: ν = 1617, 1517 cm^{-1}. ^{1}H NMR: δ = 2.80 (s, 3H, CH_3), 4.14 (s, 2H, CH_2), 6.98 (s, 1H, C10-H arom), 7.29−7.42 (m, 7H, arom), 7.70−7.90 (m, 3H, arom) ppm. ^{13}C NMR: δ = 22.2, 41.1, 97.0, 111.2, 113.1, 121.6, 122.4, 123.7, 126.8, 128.6, 128.9, 129.5, 130.0, 136.4, 139.1, 154.9 ppm (one signal obscured). ESI-MS *m/z*: 273 [M$^+$ + 1] (100), 195 (20). Anal. Calcd for $C_{19}H_{16}N_2$ (272.34): C, 83.79; H, 5.92; N, 10.29. Found: C, 83.74; H, 5.98; N, 10.25.

1-Phenyl-3-[1-phenylmeth-(*Z*)-ylidene]-3,4-dihydropyrazino[1,2-*a*]indole 2′l. Eluent for chromatography: PE/EtOAc (99:1). Yellow orange solid. Mp: 65 °C. IR: ν = 1613, 1527 cm^{-1}. ^{1}H NMR: δ = 4.97 (s, 2H, CH_2), 6.35 (s, 1H, =C-H), 6.87 (s, 1H, C10-H arom), 7.16−7.44 (m, 6H, arom), 7.55 (m, 3H, arom), 7.69 (dd, 1H, arom ^3J = 8.1, ^4J = 0.7 Hz), 8.06 (m, 4H, arom) ppm. ^{13}C NMR: δ = 44.1, 106.6, 109.5, 121.0, 123.0, 124.8, 124.9, 127.6, 127.8, 128.1, 128.5, 128.7, 129.4, 130.6, 130.9, 136.5, 137.6, 138.0, 138.1, 157.2 ppm. ESI-MS *m/z*: 335 [M$^+$ + 1] (100). Anal. Calcd for $C_{24}H_{18}N_2$ (334.41): C, 86.20; H, 5.43; N, 8.38. Found: C, 86.28; H, 5.45; N, 8.35.

3-Benzyl-1-phenylpyrazino[1,2-*a*]indole 2l. Eluent for chromatography: PE/EtOAc (99:1). Yellow orange solid. Mp: 145 °C. IR: ν = 1638, 1530 cm^{-1}. ^{1}H NMR: δ = 4.22 (s, 2H, CH_2), 6.83 (d, 1H, C10-H arom, ^4J = 0.8 Hz), 7.18 (m, 2H, arom), 7.20−7.60 (m, 6H, arom), 7.65 (m, 1H, arom), 7.83 (m, 2H, arom), 7.92 (m, 4H, arom) ppm. (This compound was obtained in a too low amount to perform ^{13}C NMR and elemental analysis.)

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Supporting Information Available: General experimental details, characterization data for compounds **1c**−**e**,**h**−**j**,**m**−**o**, **2a**,**c**−**f**,**h**−**k**,**m**, and **2′c**−**e**,**h**−**j**,**m**−**o**, computational methods, and details of NMR kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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