

# Domino Addition/Annulation of $\delta$ -Alkynylaldehydes and Oxygen Nucleophiles: a New Entry to [1,4]Oxazino[4,3-*a*]indoles

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**Abstract:** The unusual [1,4]oxazino[4,3-*a*]indole nucleus was prepared, under mild reaction conditions, by reacting 1-alkynyl-1*H*-indole-2-carbaldehydes with various alkoxides, generated in situ from the corresponding alkyl, benzyl, allyl and propargyl alcohols.

**Keywords:** 1-alkynyl-1*H*-indole-2-carbaldehydes; [1,4]oxazino[4,3-*a*]indole; domino addition/annulation; alcohol; sodium.

Domino reactions continue to be a matter of great interest and intensive explorations.<sup>1</sup> Their usefulness in synthetic organic chemistry is primarily correlated to the bond-forming efficiency, the increase in structural complexity, and the suitability for a general application. In this context, intra- and intermolecular reactions involving C-C double and triple bonds often represent the key step in the preparation of a wide range of original and not readily accessible carbo- and heterocycles. In the last years, we applied this synthetic strategy for the preparation of 2,4-disubstituted quinolines/naphthyridines by means of domino addition/annulation reactions<sup>2</sup> and *c*-fused polycyclic quinolines through domino cycloaddition/annulation reactions<sup>3</sup> starting from  $\beta$ -(2-aminoaryl)- $\alpha,\beta$ -ynones. Moreover, in a few studies devoted to the synthesis of *a*- and *b*-fused polycyclic indoles, pyrazino[1,2-*a*]indoles<sup>4</sup> and  $\beta$ -carbolines<sup>5</sup> were synthesized by sequential imination/annulation reactions.

In connection with our ongoing interest in the synthesis of *a*-fused polycyclic indoles through domino addition/annulation reactions of  $\delta$ -carbonyl-alkynes, in this paper we report a simple and efficient entry to the [1,4]oxazino[4,3-*a*]indole nucleus, starting from readily accessible 1-alkynyl-1*H*-indole-2-carbaldehydes.<sup>4b</sup>

Despite some sporadic studies on indolo[2,1-*c*]-1,4-oxazinium perchlorates,<sup>6</sup> oxazinoindol-1-ones<sup>7</sup> and oxazinoindol-3-ones<sup>8</sup> were recently reported, to our knowledge there are no recent examples concerning the synthesis of simple oxazinoindoles.

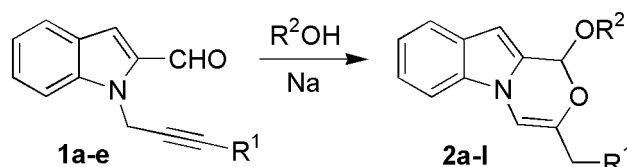
On the other hand, several synthetic strategies for the construction of the cyclic alkenyl ether framework by intramolecular cyclization of acetylenic aldehydes or ketones, have been newly published. Yamamoto and coll.<sup>11</sup> reported two neat and useful syntheses of cyclic alkenyl ethers by intramolecular cyclization of  $\gamma$ -acetylenic aldehydes in the presence of alcohols, catalyzed respectively by Pd(OAc)<sub>2</sub><sup>9(a)</sup> and CuI/DMF.<sup>9(b)</sup> Barluenga and coll. reported a remarkable multicomponent approach to iodinated heterocycles, by reaction of IPy<sub>2</sub>BF<sub>4</sub> with  $\gamma$ -acetylenic carbonyl compounds and a set of nucleophiles.<sup>10</sup> Finally, starting from the same substrates, an analogous synthesis of heterocycles was developed by Larock group under milder conditions, in the presence of K<sub>2</sub>CO<sub>3</sub>, iodine (or other electrophiles) and various nucleophiles.<sup>11</sup>

On the basis of these accounts, we tested the reactivity of **1a**, which contains a  $\delta$ -alkynyl-aldehydic framework, with methanol, under Yamamoto's conditions. Nevertheless, both the reactions

catalyzed by CuI/DMF and Pd(OAc)<sub>2</sub> failed, and **1a** was quantitatively recovered unreacted even after prolonged reaction time.

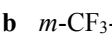
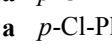
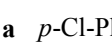
Besides, we found that the cyclization of **1a** could be easily achieved under mild reaction conditions and without catalysts, transforming the alcohol into the corresponding alkoxide nucleophile. Following this procedure oxazinoindoles **2a-l** were obtained starting from **1a-e**, in the presence of a wide set of alkoxides, generated in situ from corresponding alcohols by sodium (Scheme 1).

### Scheme 1



The reactions were performed in the presence of a three-fold excess of alkoxide. When inexpensive and low-boiling alcohols were used, the reactions were carried out using the same alcohol as solvent. When more expensive and/or high-boiling alcohols were used, the alkoxides were generated in THF.<sup>12</sup> The results are summarized in Table 1.

**Table 1.** Nucleophilic Cyclization of  $\delta$ -Acetylenic Aldehydes.

entry	<b>1</b>	R <sup>1</sup>	R <sup>2</sup> -OH	t (h)	T (°C)	<b>2</b>	yield <sup>a</sup> (%)
1 <sup>b</sup>	<b>1a</b>	<i>p</i> -Cl-Ph-	Me-OH	2	80	<b>2a</b>	71 (74)
2 <sup>b</sup>	<b>1b</b>	<i>m</i> -CF <sub>3</sub> -Ph-	Me-OH	1	100	<b>2b</b>	80
3 <sup>b</sup>	<b>1c</b>	<i>p</i> -MeO-Ph-	Me-OH	4	100	<b>2c</b>	42
4 <sup>b</sup>	<b>1a</b>	<i>p</i> -Cl-Ph-	Et-OH	2	80	<b>2d</b>	88 (92)
5 <sup>b</sup>	<b>1c</b>	<i>p</i> -MeO-Ph-	Et-OH	2	80	<b>2e</b>	33 (36)
6 <sup>b</sup>	<b>1d</b>	Ph-	Et-OH	2	80	<b>2f</b>	48
7 <sup>b</sup>	<b>1a</b>	<i>p</i> -Cl-Ph-	<i>i</i> -Pr-OH	2	80	<b>2g</b>	60
8 <sup>c</sup>	<b>1b</b>	<i>m</i> -CF <sub>3</sub> -Ph-		1	25	<b>2h</b>	62
9 <sup>c</sup>	<b>1a</b>	<i>p</i> -Cl-Ph-	Bz-OH	4	10	<b>2i</b>	44 (47)
10 <sup>c</sup>	<b>1a</b>	<i>p</i> -Cl-Ph-		1	25	<b>2j</b>	71 (78)
11 <sup>c</sup>	<b>1a</b>	<i>p</i> -Cl-Ph-		4	25	<b>2k</b>	57
12 <sup>b</sup>	<b>1e</b>	H	Et-OH	16	55	<b>2l</b>	50

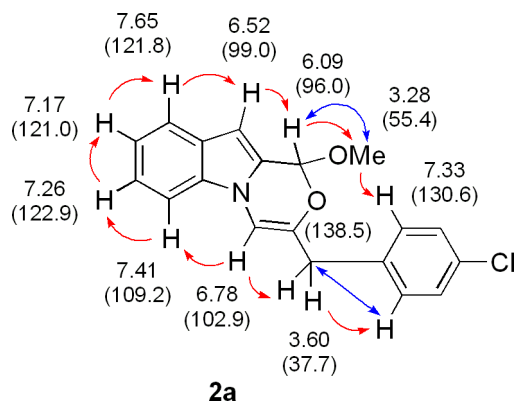
<sup>a</sup> Isolated yields referred to single run. In parenthesis, yields determined by <sup>1</sup>H NMR spectroscopy with dibromo-methane as internal standard.  
<sup>b</sup> Reaction conditions: molar ratio indole **1**/Na = 1:3, alcohol, sealed tube, N<sub>2</sub>.  
<sup>c</sup> Reaction conditions: molar ratio indole **1**/Na/alcohol = 1:3:4, THF, N<sub>2</sub>.

The reactions with nucleophiles derived from simple primary (entries 1-6) and secondary (entry 7) alcohols run smoothly, but the yields were strongly influenced by the nature of the substituent on the triple bond. As expected, the presence of an electron-donating group conjugated to triple bond reduced the reactivity of the alkynes **1c,d** towards nucleophilic attack, thus oxazinoindoles **2c,e,f** were isolated in moderate yields (entries 3, 5 and 6). On the contrary, the cyclization of alkynes **1a,b** bearing an electron-withdrawing group, gave the corresponding oxazinoindoles **2a,b,d,g** in good yields (entries 1, 2, 4 and 7). The synthetic strategy proved to be effective also in the reactions involving cyclopropyl methanol (entry 8), benzyl (entry 9), allyl (entry 10) and propargyl (entry 11) alcohols. Nevertheless, when these more reactive alcohols were used, best results were obtained working at lower temperatures. Also the presence of a terminal alkyne group was tolerated under

our reaction conditions, and the reaction of **1e** with sodium and ethanol gave the desired product **21** in 50% yield after 16 h at 55 °C (entry 12).

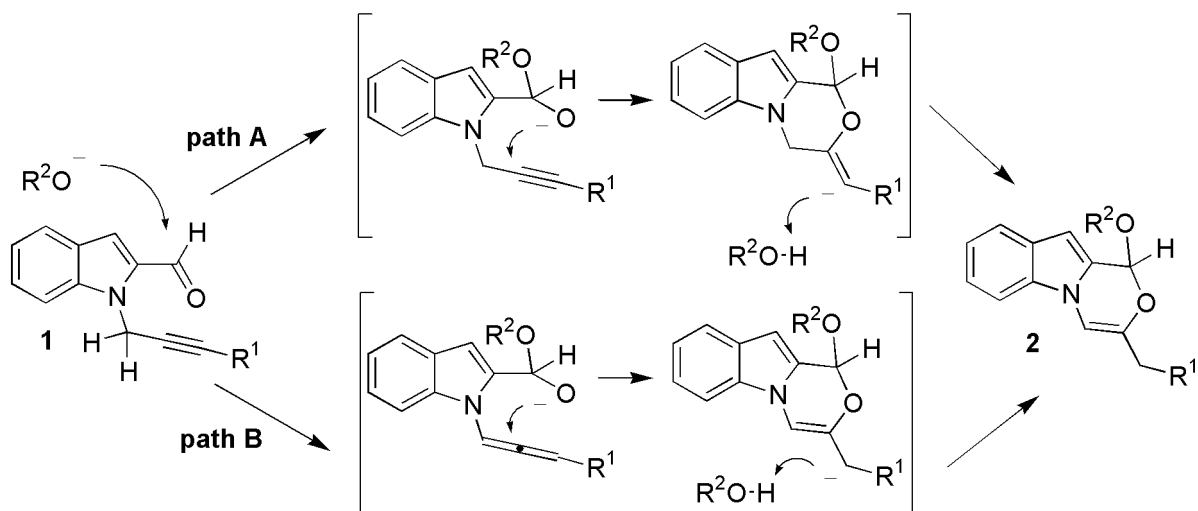
All compounds were identified on the basis of analytical and spectral data (IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, MS). In particular, the structure of [1,4]oxazino[4,3-a]indole nucleus was clearly established for compound **2a** through bidimensional NOESY, HETCOR and HMBC experiments. In particular, the positions of methyl ( $\delta$  55.4) and methylene ( $\delta$  37.7) groups were unambiguously established by an accurate analysis of NOE interactions and  $^3J(\text{C,H})$  coupling constants (Figure 1).

**Figure 1.** Derivative **2a**: diagnostic NOE interactions (red arrows) and  $^3J(\text{C,H})$  coupling constants (blue arrows), besides proton (and carbon) chemical shifts.



A proposed reaction mechanism is depicted in scheme 2. By analogy with Yamamoto's hypothesis,<sup>11(a)</sup> the first step is most probably the addition of nucleophile to aldehyde resulting to the in situ formation of a transient hemiacetal anion. There are two conceivable pathways to explain the cyclization step: (i) The hemiacetal anion undergoes a 6-exo-dig cyclization directly on the triple bond; the following isomerization leads to the formation of the final product **2** (path A). (ii) The alkaline environment promotes the isomerization of the triple bond to allene;<sup>13</sup> thus, the attack of hemiacetal anion takes place on the central carbon of the allene framework<sup>14</sup> with formation of the oxazinoindole ring (path B).

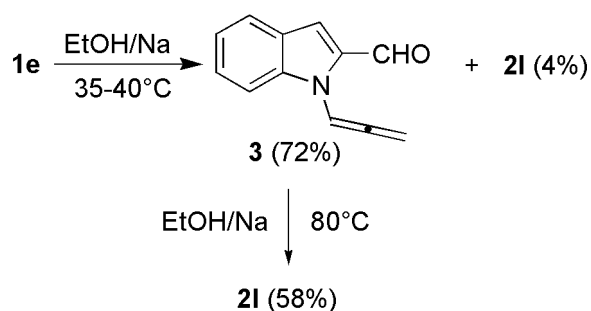
**Scheme 2**



In our opinion path A is the pathway of choice for the annulation of internal alkynes **1a-d** whereas path B seems to be the mechanism involved in the cyclisation of terminal alkyne **1e**. These statements were supported by the following experiments. A mixture of **1e** and sodium in ethanol

was stirred at 35-40 °C for 48 h; under these reaction conditions the allene **3** was the main product isolated (72% yield), beside traces of oxazinoindole **2I** (4% yield). Furthermore, the isolated allene **3** was transformed into the oxazinoindole **2I** in 58% yields, by reaction with ethoxide at 80 °C for 8 h (Scheme 3). On the contrary, the allene intermediates arising from internal alkynes<sup>15</sup> has never been isolated. All the base promoted attempts to transform **1a** into the corresponding allene derivative dramatically failed; reacting **1a** with t-BuONa in THF at 35-40 °C for 24 h, no reaction was observed, and the presence of unreacted starting material was detected by tlc analysis. Stressing the reaction conditions by heating the mixture at 80 °C for additional 12 h, a complex blend of by-products was detected by tlc analysis; a careful analysis of <sup>1</sup>H NMR spectra of reaction crude did not showed the presence of any signals referable to the allene framework.<sup>16</sup>

### Scheme 3



Even though the internal allene intermediates had never been isolated, also for cyclization reactions of derivatives **1a-d** the path B can't be ruled out once and for all. For example, this suggestion is supported by the following observation: the dihydro isomer **2'** (*Z* or *E*), directly arising from path A before the proton shift,<sup>17</sup> has never been isolated, even though the  $\Delta E$  calculated at DFT level<sup>18</sup> among **2a** and both the hypothetical dihydro isomers **2'a**(*Z*) and **2'a**(*E*) were low, in particular relatively to the former (Table 2). Further work is in progress to clarify this point.

**Table 2.** Absolute and relative ZPE corrected energies (Kcal mol<sup>-1</sup>) of **2a**, **2'a**(*Z*) and **2'a**(*E*) at B3LYP/6-31G\* level.

structure	E <sup>a</sup>	E <sub>rel.</sub>
<b>2a</b> 	-877701.4593	0
<b>2'a</b> ( <i>Z</i> ) 	-877700.6517	0.8076
<b>2'a</b> ( <i>E</i> ) 	-877698.2847	3.1746

<sup>a</sup> Isolated molecules in gas phase.

Irrespective of the precise mechanism, this preliminary report demonstrates once again the usefulness of domino addition/annulation reactions involving alkynes with neighbouring nucleophiles. Although the addition of hetero-nucleophiles to electron deficient alkyne is well documented,<sup>19</sup> this work represents an unusual example of uncatalyzed nucleophilic addition to unactivated triple bond.

Current efforts are now directed to the extension of this methodology to other reactive carbo- and hetero-nucleophiles. Furthermore, this annulation reaction could be extended to new substrates such as 3-alkynyl-indole-2-carbaldehydes and 1-alkynyl-2-acyl-indoles. For example, salts or complexes of transition metals successfully catalyze the intramolecular addition of nucleophiles to alkynes<sup>20</sup> and could be used to increase the applicability of this synthetic approach.

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- <sup>12</sup> General method for the reaction of 1-alkynyl-2-indolcarbaldehydes **1** with alkoxides: In a 25 mL round bottom flask, sodium (1.5 mmol) was dissolved in the appropriate dry alcohol (4 mL) (Table 1, entries 1-7 and 12) or in a mixture of alcohol (2 mmol.) and dry THF 4 mL (Table 1, entries 8-11) under a nitrogen atmosphere. When the sodium was completely dissolved, the appropriate 1-alkynyl-2-indolcarbaldehyde **1** (0.5 mmol) was added. The reactions performed at 80-100 °C were transferred to a sealed tube under a nitrogen atmosphere. The reaction mixture was stirred at the appropriate temperature until no more starting product was detectable by tlc, concentrated under reduced pressure, poured in a saturated solution on NaHCO<sub>3</sub> (50 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over sodium sulfate and the solvent removed at reduced pressure. The crude was purified by flash chromatography over a silica gel column (for yields, times and temperatures see Table 1). **2a**: Eluent for chromatography: PE/TEA (98:2). Brown solid. Mp: 79-80 °C. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ = 3.28 (s, 3H, CH<sub>3</sub>), 3.60 (s, 2H, CH<sub>2</sub>), 6.09 (s, 1H, C1-H), 6.52 (s, 1H, C10-H), 6.78 (s, 1H, C4-H), 7.17 (t, 1H, C8-H, <sup>3</sup>J = 7.6), 7.26 (t, 1H, C7-H, <sup>3</sup>J = 7.6), 7.33 (m, 4H, *p*-Cl-Ph-), 7.40 (d, 1H, C6-H, <sup>3</sup>J = 7.7 Hz), 7.65 (d, 1H, C9-H, <sup>3</sup>J = 7.8 Hz) ppm. <sup>13</sup>C NMR(200 MHz, CDCl<sub>3</sub>): δ = 37.7 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 96.0 (C1-H), 99.0 (C10-H), 102.9

(C4-H), 109.2 (C6-H), 121.0 (C8-H), 121.8 (C9-H), 122.9 (C7-H), 127.9 (C10a), 128.1, 132.7, 132.9, 136.0 (C arom.), 128.9, 130.6 (CH *p*-Cl-Ph-), 138.5 (C3) ppm. IR (KBr)  $\nu$  = 2928, 1632, 1465, 1041  $\text{cm}^{-1}$ . ESI-MS  $m/z$  (%): 326 [ $M^+ + 1$ ] (19), 294 (100). HRMS calcd for  $C_{19}H_{16}NO_2ClNa$  [ $M^+ + Na$ ] 348.07613, found 348.07516.

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<sup>15</sup> For some recent examples of alkaline isomerization of similar internal alkynes see (a) Nandi, B.; Kundu, N. G. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1649-1655. (b) Fortes, C. C.; Garrote, C. F. D. *Synth. Commun.* **1997**, *27*, 3917-3941. (c) Noguchi, M.; Okada, H.; Watanabe, M.; Okuda, K.; Nakamura, O. *Tetrahedron* **1996**, *52*, 6581-6590.

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