Novel Synthetic Method of 2-(2-Oxoethyl)-1*H*-indole-3-carbaldehydes

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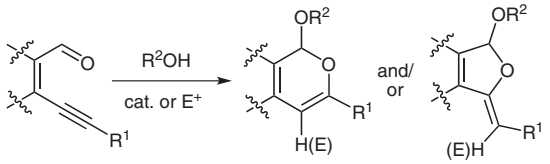
Abstract: The smooth and regioselective synthesis of 2-(2-oxoethyl)-1*H*-indole-3-carbaldehydes via silver-catalyzed 6-*endo*-dig acetalization–cyclization reaction followed by immediate hydrolysis of the unstable 1-alkoxypyrano[4,3-*b*]indole intermediates is described.

Key words: 2-alkynyl-1*H*-indole-3-carbaldehydes, 2-(2-oxoethyl)-1*H*-indole-3-carbaldehydes, acetalization, hydrolysis

Aromatic or heteroaromatic aldehydes bearing the triple bond in close proximity to a carbonyl group are versatile building blocks in organic synthesis for the preparation of various carbo- and heterocyclic compounds.[1] A variety of synthetic methodologies for the creation of new dihydrofurane and dihydropyrane rings has been developed, starting from *o*-alkynylbenzaldehydes via tandem acetalization–cyclization reactions (Scheme 1). Since the pioneering work of Yamamoto,[2] a variety of transition-metal-catalyzed,[3] base-,[4] or electrophile-induced[5] 5-*exo*-dig and/or 6-*endo*-dig acetalization–cyclization processes of *o*-alkynylbenzaldehydes and their heterocyclic analogues has been described.



Scheme 1 Literature results overview

Recently, we have developed a novel, concise, and regioselective synthetic method for constructing 5,7-dihydrofuro[3,4-*d*]pyrimidine and 5*H*-pyrano[4,3-*d*]pyrimidine frameworks via acetalization–cyclization reactions of 2,4-disubstituted 6-phenylethynylpyrimidine-5-carbaldehydes.[6] We have also demonstrated the influence of the substituent at the 4-position of the pyrimidine ring on substrate reactivity and regioselectivity of the reaction.

Overall, from the literature results and our previous studies, it is possible to conclude that base-catalyzed transformations of aromatic or heteroaromatic aldehydes having an *o*-alkynyl substituent with alcohols lead mainly to 5-*exo*-dig cyclization, for example, to the formation of the furan ring. On the other hand, reactions of acetylenic aldehydes with alcohols in the presence of transition-metal catalysts or electrophilic initiators proceed to give 6-*endo*-dig cyclization products, the corresponding alkoxypyranes.

Encouraged by literature precedent and our previous results, we envisaged that cycloisomerization of all aromatic and heteroaromatic compounds, bearing a triple bond and an aldehyde moiety in close proximity to each other would always lead to the 5-*exo*-dig and/or 6-*endo*-dig acetalization–cyclization. However, to our surprise, we observed the formation of different products during reactions of 2-alkynylindole-3-carbaldehydes, so herein we wish to report on these unexpected results.

The starting compounds **1** were synthesized by the well-known Sonogashira reaction[7] from 2-bromo-1*H*-indole-3-carbaldehydes. It should be noted that 2-phenylethynyl-1*H*-indole-3-carbaldehyde (**1a**) treated with sodium or potassium methoxide in methanol did not undergo acetalization–cyclization reactions. This result can be explained by the fact that the triple bond is electron-rich due to the neighboring electron-donating indole ring, so tandem cyclization becomes impossible. However, no changes of the starting material were observed by TLC when we used a catalytic amount of silver nitrate or trifluoroacetate as a catalyst under the same reaction conditions: boiling methanol and basic medium (1 equiv of sodium or potassium methoxide). On the other hand, the reaction of **1a** with methanol only in the presence of $AgNO_3$ or $AgCF_3CO_2$ proceeded smoothly, and formation of one major product was observed by TLC. We were intrigued that the NMR, IR, and microanalysis data of the isolated product did not correspond to any of the expected structures – (3*Z*)-3-benzylidene-3,4-dihydro-1-methoxy-1*H*-furo[3,4-*b*]indole (**3a**) or 1,5-dihydro-1-methoxy-3-phenylpyrano[4,3-*b*]indole (**4a**). The analytical data showed that during the reaction of the starting compound with methanol in the presence of silver salts 2-(2-oxo-2-phenylethyl)-1*H*-indole-3-carbaldehyde (**2a**) was formed as the sole product (Scheme 2). The same reaction result was obtained from heating of a solution of **1a** in 1,2-dichloroethane in the presence of 2 equivalents of methanol and 5 mol% of $AgCF_3CO_2$ in a microwave oven for 15 minutes.

Thus, we decided to perform a more detailed study of the reactions of 2-phenylethynyl-1*H*-indole-3-carbaldehyde (**1a**) with alcohols. It should be noted that in all successful cases 2-(2-oxo-2-phenylethyl)-1*H*-indole-3-carbaldehyde (**2a**) was formed, and no formation of 5-*exo*-dig or 6-*endo*-dig cyclization reaction products was observed. The results are summarized in Table 1.

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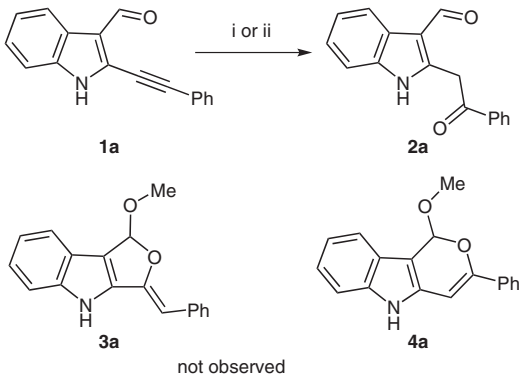


Scheme 2 *Reagents and conditions*: i) MeOH, $AgCF_3CO_2$ (5 mol%), reflux, 2 h; ii) MeOH (2 equiv), $AgCF_3CO_2$ (5 mol%), DCE, MW, 600 W, 15 min.

After the unsuccessful experiments with methanol in basic medium (Table 1, entries 1–3), it was noted that the use of 2 equivalents of methanol, silver trifluoroacetate (5 mol%) in dichloroethane, and the heating of the reaction mixture in a sealed tube in a domestic microwave oven gave the best result (Table 1, entry 5). While use of silver nitrate or ethanol provided a slightly lower yield of the desired product **2a** (Table 1, entries 6, 9), conventional heating of the reaction mixture in methanol, as well as the use of catalytic amounts of CuI and $Cu(OTf)_2$, proved to be far less effective (Table 1, entries 4, 7–8). The formation of **2a** was slower, and the conversion was not complete when 1-propanol or 1-butanol were used (Table 1, entries 10, 11). However, the use of a catalytic amount of methanol is also suitable for the synthesis of **2a** (Table 1, entry 12). On the other hand, absence of alcohol inhibited the reaction, so it can be concluded that direct addition of water to the triple bond of the starting compound does not take place (Table 1, entry 13).

Encouraged by these results we decided to perform the synthesis of a range of 2-(2-oxoethyl)-1*H*-indole-3-carbaldehydes **2**. The results are summarized in Table 2. It is noteworthy, that the nature of the alkynyl substituent normally does not have a strong influence on the result of the reaction. In the case of 2-arylethynyl-1*H*-indole-3-carbaldehydes and 2-alkynyl-1*H*-indole-3-carbaldehydes, the formation of the dicarbonyl compounds took place (Table 2, entries 1, 2, and 5–7). However, when the substituent on the alkynyl moiety contains a basic pyridine-type nitrogen (compounds **1c**,**d**, Table 2, entries 3 and 4) no changes of the starting materials were observed under the reaction conditions. This 'nitrogen-effect' can be explained by complexation of the pyridine moiety with silver ion or by the pyridine substituent acting as a base and inhibiting the process. In the case of 2-trimethylsilylethynyl-1*H*-indole-3-carbaldehyde (**1h**) and 2-ethynyl-1*H*-indole-3-carbaldehyde (**1g**), the formation of the same product 2-(2,2-dimethoxyethyl)-1*H*-indole-3-carbaldehyde (**2h**) was observed (Table 2, entries 8 and 9). Probably, the expected reaction product 3-formyl-1*H*-indole-2-acetaldehyde reacted with methanol to give the dimethyl acetal.

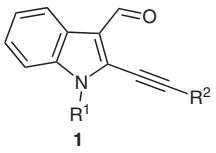
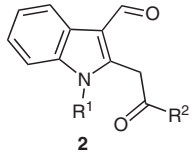
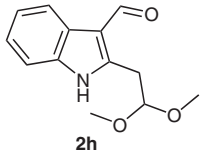
In Scheme 3 the possible mechanism of formation of 2-(2-oxoethyl)-1*H*-indole-3-carbaldehydes **2** is depicted. We

Table 1 Reaction Conditions for the Synthesis of 2-(2-Oxo-2-phenylethyl)-1*H*-indole-3-carbaldehyde (**2a**) from 2-Phenylethynyl-1*H*-indole-3-carbaldehyde (**1a**)

Entry	Reaction conditions	Time	Conv. (%)	Yield of **2a** (%)
1	MeOH, reflux	12 h	0[a]	0
2	MeOH, NaOMe (1 equiv), reflux	12 h	0[a]	0
3	MeOH, KOMe (1 equiv), reflux	12 h	0[a]	0
3	MeOH, KOMe (1 equiv), $AgCF_3CO_2$ (5 mol%), reflux	12 h	0[a]	0
4	MeOH, $AgCF_3CO_2$ (5 mol%), reflux	3 h	75	43
5	MeOH, $AgCF_3CO_2$ (5 mol%), DCE, MW, 600 W	15 min	100	84
6	MeOH, $AgNO_3$ (5 mol%), DCE, MW, 600 W	20 min	100	71
7	MeOH, CuI (10 mol%), DCE, MW, 600 W	40 min	50	23
8	MeOH, $Cu(OTf)_2$ (10 mol%), DCE, MW, 600 W	40 min	80	44
9	EtOH, $AgCF_3CO_2$ (5 mol%), DCE, MW, 600 W	20 min	100	70
10	PrOH, $AgCF_3CO_2$ (5 mol%), DCE, MW, 600 W	35 min	80	62
11	BuOH, $AgCF_3CO_2$ (5 mol%), DCE, MW, 600 W	45 min	70	52
12	MeOH (10 mol%), $AgCF_3CO_2$ (5 mol%), DCE, MW, 600 W	20 min	100	80
13	H_2O, $AgCF_3CO_2$ (5 mol%), DCE, MW, 600 W	1 h	0[a]	0

[a] Starting material **1a** was isolated.

Table 2 Synthesis of 2-(2-Oxoethyl)-1*H*-indole-3-carbaldehydes **2**[8]

Entry	Starting material	Product	Yield (%)
	 **1**	 **2**	
1	**1a** R^1 = H, R^2 = Ph	**2a** R^1 = H, R^2 = Ph	84
2	**1b** R^1 = H, R^2 = 4-EtC_6H_4	**2b** R^1 = H, R^2 = 4-EtC_6H_4	77
3	**1c** R^1 = H, R^2 = 2-pyridyl	–	n.r.[a]
4	**1d** R^1 = Bn, R^2 = 2-pyridyl	–	n.r.[a]
5	**1e** R^1 = H, R^2 = *n*-Bu	**2e** R^1 = H, R^2 = *n*-Bu	66
6	**1f** R^1 = Bn, R^2 = *t*-Bu	**2f** R^1 = Bn, R^2 = *t*-Bu	67
7	**1g** R^1 = Bn, R^2 = *c*-Pr	**2g** R^1 = Bn, R^2 = *c*-Pr	76
8	**1h** R^1 = H, R^2 = TMS	 **2h**	48
9	**1k** R^1 = R^2 = H	**2h**	78

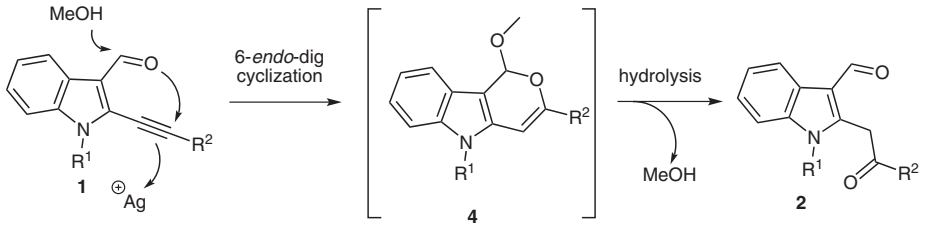
[a] The starting material was isolated after the workup of the reaction mixture.

propose that, after the complexation of the metal with the triple bond, intramolecular 6-*endo*-dig cyclization reaction takes place. The intermediate 1,5-dihydro-1-methoxypyrano[4,3-*b*]indole **4** should be unstable due to the electron-donating indole ring and therefore undergo smooth hydrolytic cleavage with traces of water leading to the formation of final dicarbonyl compounds **2**.

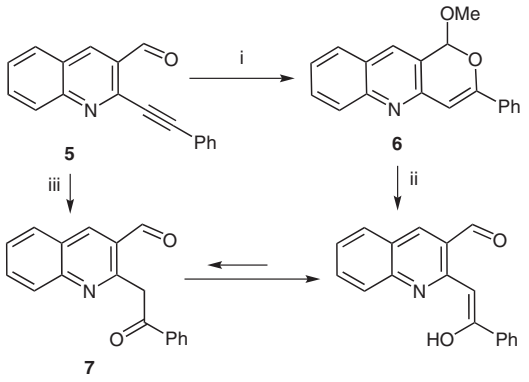
In comparison, it should be noted that 2-phenylethynyl-3-quinolinecarbaldehyde (**5**), with an electron-withdrawing quinoline core, under the same reaction conditions [MeOH (2 equiv), $AgCF_3CO_2$ (5 mol%), DCE, MW, 600 W, 15 min] formed 1-methoxy-3-phenyl-1*H*-pyrano[4,3-*b*]quinoline (**6**) in 95% yield. The latter compound is relatively stable and underwent hydrolytic pyran ring opening only after prolonged heating of **6** in aqueous acid. The product of hydrolysis 2-[(*Z*)-2-hydroxy-2-phenylethenyl]-3-quinolinecarboxaldehyde (**7**) can be obtained by direct addition of water to the electron-poor triple bond of the starting 2-phenylethynyl-3-quinolinecarbaldehyde (**5**, Scheme 4). On the other hand, electron-rich 4,5-dimethoxy-2-phenylethynylbenzene (**8**), after heating in the microwave oven with 2 equivalents of methanol in DCE in the presence of $AgCF_3CO_2$, formed 4,5-dimethoxy-2-(2-oxo-2-phenylethyl)benzene (**9**) in 89% yield (Scheme 5). So it is possible to conclude that the stability of the intramolecular acetalization 6-*endo*-dig cyclization products strongly depends on the electron density of the 2-alkoxy-2*H*-pyrane moiety.

In conclusion, we have presented a short and efficient synthesis of 2-(2-oxoethyl)-1*H*-indole-3-carbaldehydes via a tandem 6-*endo*-dig cyclization process followed by smooth hydrolysis. Taking into account that 1,5-dicarbonyl compounds can be used as useful intermediates in organic synthesis, this method can be used for preparation of various important precursors.

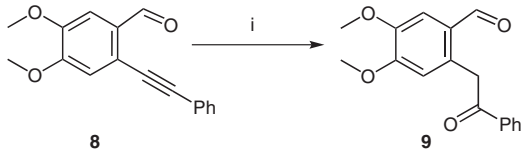
Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.[9]



Scheme 3 Possible mechanism of formation of 2-(2-oxoethyl)-1*H*-indole-3-carbaldehydes **2**



Scheme 4 *Reagents and conditions*: i) MeOH (2 equiv), $AgCF_3CO_2$ (5 mol%), DCE, MW, 600 W, 15 min; ii) HCl, H_2O, reflux, 8 h; iii) H_2O, dioxane, $AgCF_3CO_2$ (5 mol%), reflux, 1 h.



Scheme 5 *Reagents and conditions*: i) MeOH (2 equiv), $AgCF_3CO_2$ (5 mol%), DCE, MW, 600 W, 15 min.

Acknowledgment

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(8) **Typical Procedure for the Synthesis of 2-(2-Oxoethyl)-1*H*-indole-3-carbaldehydes 2**

A solution of the requisite 2-alkynyl-1*H*-indole-3-carbaldehyde **1** (0.3 mmol), MeOH (0.0192 g, 0.6 mmol), $AgCF_3CO_2$ (3.3 mg, 0.015 mmol) in DCE (3 mL) was irradiated in a closed 15 mL vessel in domestic microwave oven (model DAEWOO KOR6305A) at 600 W for 10–15 min. After heating, the solution was cooled to r.t., filtered through a silica gel pad, the solvent evaporated, and the solid residue purified by column chromatography to give **2a**–**h**. Typical analytical data are given for compounds **2a**,**f**,**h**.

2-(2-Oxo-2-phenylethyl)-1*H*-indole-3-carbaldehyde (2a)

Yield 84%; mp 156 °C. IR (KBr): ν_{max} = 3313 (NH), 1680, 1645 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.02 (2 H, s, CH_2CO), 7.30–7.34 (2 H, m, ArH), 7.45–7.47 (1 H, m, ArH), 7.53–7.59 (2 H, m, ArH), 7.65–7.70 (1 H, m, ArH), 8.14–8.17 (3 H, m, ArH), 10.20 (1 H, br s, NH), 10.41 (1 H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ = 34.9, 111.6, 119.1, 122.6, 123.5, 126.4, 128.6, 128.8, 128.9, 129.1, 134.3, 135.2, 135.8, 184.7, 196.7 ppm. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.62; H, 5.03; N, 5.18.

1-Benzyl-2-(3,3-dimethyl-2-oxobutyl)-1*H*-indole-3-carbaldehyde (2f)

Yield 67%; mp 131–131.5 °C. IR (KBr): ν_{max} = 1709, 1651 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 [9 H, s, $C(CH_3)_3$], 4.44 (2 H, s, CH_2CO), 5.35 (2 H, s, NCH_2), 6.99–7.03 (2 H, m, ArH), 7.30–7.34 (6 H, m, ArH), 8.19–8.22 (1 H, m, ArH), 10.25 (1 H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ = 26.4, 33.8, 44.8, 47.1, 110.3, 114.7, 119.5, 122.9, 123.5, 125.9, 126.5, 127.9, 129.1, 135.7, 137.0, 143.1, 184.1, 209.9 ppm. Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.40; H, 7.02; N, 4.33.

2-(2,2-Dimethoxyethyl)-1*H*-indole-3-carbaldehyde (2h)

Yield 78%(from **1k**); mp 145–146 °C. IR (KBr): ν_{max} = 3185 (NH), 1628 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.47 (2 H, d, *J* = 4.8 Hz, CH_2CH),3.48 [6 H, s, $CH(OCH_3)_2$], 4.71 [1 H, t, *J* = 4.8 Hz, $CH(OCH_3)_2$], 7.27–7.30 (2 H, m, ArH), 7.40–7.43 (1 H, m, ArH), 8.25–8.28 (1 H, m, ArH), 9.57 (1 H, br s, NH), 10.23 (1 H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ = 29.9, 54.4, 103.5, 111.2, 114.9, 120.6, 122.6, 123.5, 125.8, 135.2, 145.1, 184.5 ppm. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.00; H, 6.38; N, 6.05.

(9) The Supporting Information contains experimental procedures and characterization data for compounds **1a**–**k**, **2b**,**e**,**g**, **5**–**9**.