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Rhodium-Catalyzed Carbonylation of 2-Alkynylaniline: Syntheses of 1,3-Dihydroindol-2-ones

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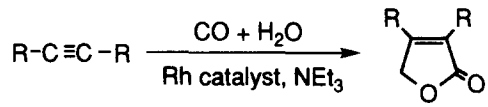
abstract: Rhodium-catalyzed carbonylation of 2-alkynylanilines under water-gas shift reaction conditions gives 3-alkyl-1,3-dihydroindol-2-ones **2** in good yields along with a small amount of 2-quinolone derivatives **4**. The reaction under carbonylation conditions without additive water yields 3-(E)-alkylidene-1,3-dihydroindol-2-ones **3**, indicating that the formation of **2** involves two steps; simultaneous cyclization with carbonylation of a triple bond by the participation of an adjacent amino group and subsequent hydrogenation.

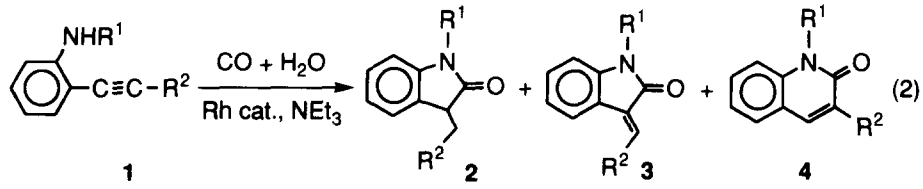
Carbonylation reactions are very important and useful for organic syntheses.[1] The carbonylation of acetylenic compounds is one of the most extensively investigated reactions and is applied to an industrial field.[2] Previously we have shown that furan-2(5H)-ones are selectively formed from the carbonylation of acetylenes under water-gas shift reaction conditions with a rhodium catalyst (eq. 1).[3] The reaction has a wide application to a variety of aromatic and aliphatic acetylenes.[4] In such the reaction furanones are yielded from the incorporation of one molecule of acetylene, two molecules of carbon monoxide and one molecule of hydrogen of which the latter comes from water.[3]



(1)

In the course of our study on a neighboring group effect in the above furanone synthesis we have found a new cyclization reaction where an amino group takes part in the reaction of acetylenes with carbon monoxide and hydrogen. Here we report that 2-alkynylanilines (**1**) undergoes carbonylation, cyclization and hydrogenation in sequence to give 3-substituted-1,3-dihydroindol-2-ones (**2**) along with 3-substituted-2-quinolones (**4**), both of which have significant biological activities.

In a typical experiment, 2-phenylethynylaniline (**1a**) was treated with carbon monoxide (100 atm) in 1,4-dioxane containing water and triethylamine at 175 °C for 14 h in the presence of a $Rh_6(CO)_{16}$ catalyst. After usual work-up the products were separated by column chromatography on silica gel (CH_2Cl_2/AcOEt=11/1),

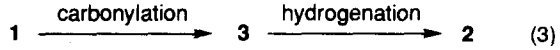


a: R^1= H, R^2= Ph **b**: R^1= H, R^2= C_6H_4OMe-*p*

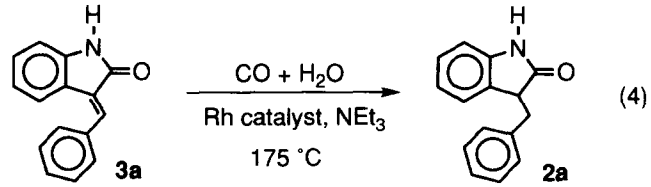
c: R^1= H, R^2= C_6H_4Me-*p* **d**: R^1= H, R^2= C_6H_4CN-*p*

e: R^1= H, R^2= *tert*-Bu **f**: R^1= Me, R^2= Ph

and recrystallization from ethanol gave 3-benzyl-1,3-dihydroindol-2-one (**2a**)[5] in 83% yield and 3-phenyl-2-quinolone (**4a**)[6] in 11% yield (entry 1 in Table 1). It should be noted that acetylene **1a** bearing an amino group at an ortho position do not give furanones at all, but instead products incorporated by an amino group, though 4-phenylethynylaniline afforded furanone derivatives having an intact amino group under the same reaction conditions. Experiments on the effect of reaction conditions have revealed that the reaction temperature strongly affects the product distribution as summarized in Table 1. On lowering the reaction temperature to 80 °C (entry 4), the main product is not **2a**, but non-hydrogenated product, (E)-3-benzylidene-1,3-dihydroindol-2-one (**3a**), which has been identified by spectral analyses.[7] This result suggests that **3a** is initially produced and then hydrogenated to **2a** at higher temperatures. Thus, the reaction giving **2a** proceeds via two steps; that is, carbonylation accompanied with cyclization of substrate **1a** takes place to afford **3a** and



4a, and then the hydrogenation of **3a** occurs to give **2a**. In order to confirm the reaction path, the reaction of **1a** was carried out without additive water and triethylamine (entry 2). As expected, **3a** was produced as a main product, but a small amount of **2a** was also formed because of difficulty to remove a trace of water contained in the supplied carbon monoxide gas. The reaction at a lower temperature almost selectively produced **3a** (entry 5). The hydrogenation of **3** to **2** at higher temperatures may reasonably be understood because the rhodium catalyst is effective for the hydrogenation of activated olefins such as α,β-unsaturated ketones under water-shift reaction conditions.[8] Actually in a separate experiment **3** was hydrogenated under the same reaction conditions at 175 °C to give **2** quantitatively (eq. 4). However, quinolones **4** seem to resist to hydrogenation probably due to its cyclic enone structure.



The present reaction may be applicable to several 2-alkynylanilines (**1b-1e**) including 2-arylethynyl- and 2-*tert*-butylethynylaniline and the corresponding dihydroindol-2-ones are obtained in good yields (Table 1). N-Alkyl-substituted aniline derivatives like N-methyl-2-phenylethynylaniline can also be used as a substrate. Product **3** having a five membered ring is formed by the cyclization at the α-carbon of the acetyleneic bond in **1**, while the cyclization at the β-carbon constructs the six-membered ring of **4**. When R^2 is a phenyl group, the substituent on the phenyl ring exhibits no appreciable influence on the product ratio **4/2** (entries 6-8). The substitution of R^1 or R^2 with an alkyl group results in a somewhat increase of the ratio (entries 9 and 10). As a catalyst, rhodium complexes such as $Rh_6(CO)_{16}$, $RhCl(CO)(PPh_3)_2$ and $RhCl_3{\cdot}xH_2O$ showed a good activity, while $Co_2(CO)_8$, $Ru_3(CO)_{12}$ and $PdCl_2(CH_3CN)_2$ are almost inactive for the dihydroindol-2-one synthesis.

Table 1: Syntheses of **2**, **3**, and **4** from 2-alkynylanilines (**1**)[a]

entry	subst.	temp (°C)	H_2O (eqiv.)	Et_3N (eqiv.)	yield (%)[b]		
					2	**3**	**4**
1	**1a**	175	4	1	86(83)	0	12(11)[b]
2	**1a**	175	0	0	13	61	7
3	**1a**	100	4	1	74	0	11
4	**1a**	80	4	1	9	66	3
5	**1a**	80	0	0	2	85	0
6	**1b**	175	4	1	81(66)	0	- (8)[c]
7	**1c**	175	4	1	85(68)	0	5(4)
8	**1d**	175	4	1	83(61)	0	- (3)[c]
9	**1e**	175	4	1	71(42)[d]	0	21(4)[d]
10	**1f**	175	4	1	60(23)[d]	0	26(4)[d]

[a] Conditions: substrate, 1 mmol; $Rh_6(CO)_{16}$, 0.3 mol%; dioxane, 15 ml; 14 h.

[b] Yields are based on 2-alkynylanilines and determined by GLC; parentheses indicate isolated yields.

[c] Yields could not be determined by GLC because of its non-volatility.

[d] The low isolated yields are due to the difficulty of separation between **2** and **4** by column chromatography on silica gel.

The present new reaction may provide the first examples of direct syntheses of dihydroindol-2-ones starting from acetylenic compounds. Since the starting acetylenic substrates, 2-alkynylanilines, can easily be prepared by the palladium-catalyzed cross-coupling between 2-haloanilines and acetylenes,[9] the reaction may have a wide application to the synthesis of a variety of dihydroindol-2-ones. It is of special interest that 4-alkynylanilines give furanone derivatives according to eq. (1) without any participation of the amino group, whereas a neighboring amino group causes a dramatic change of the reaction features and participates in cyclization constructing a five- or six-membered heterocycle.

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