

Regioselective Synthesis of Indoles via Reductive Annulation of Nitrosoaromatics with Alkynes

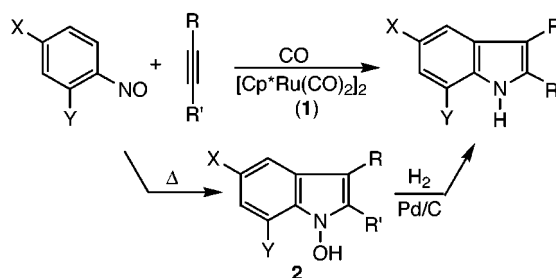
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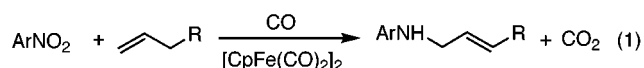
ABSTRACT



Indoles are produced regioselectively and in moderate yields by two new processes: (a) from the $[\text{Cp}^*\text{Ru}(\text{CO})_2]_2$ -catalyzed reaction of nitrosoaromatics (ArNO) with alkynes under carbon monoxide and (b) in a two-step sequence involving the (uncatalyzed) reaction of ArNO with alkynes, followed by reduction of the intermediate adduct.

The widespread natural occurrence and importance of indoles has stimulated the continuing development of new methods for their preparation.¹ Especially attractive but few in number are reactions that directly produce indoles by annulation of commercially available N-aromatic precursors, as in the Fischer indole synthesis.^{2,3} The desire for broad substrate scope, more accessible starting materials, improved regioselectivity, milder reaction conditions, and functional group tolerance has also spawned several transition metal promoted routes to indoles,⁴ most of which, however, are intramolecular reactions that require an ortho-substituted N-aromatic precursor.⁵

Our interest in metal-promoted nitrogenation reactions of hydrocarbons⁶ led us to discover the regioselective, iron-catalyzed synthesis of allylamines by the reductive amination of olefins with nitroaromatics (eq 1).⁷ We recently examined

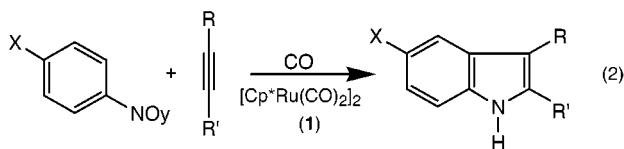


the corresponding reactions of nitroaromatics with alkynes,

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anticipating the production of propargyl and/or allenylamines, but found instead that *indoles are the major products* (eq 2, $y = 2$), the result of a novel reductive annulation reaction.⁸



These reactions feature moderate yields and high regioselectivity for 3-substituted indoles when unsymmetrical alkynes with conjugating substituents are utilized.

Given the precedented, metal-promoted deoxygenation of nitro compounds by carbon monoxide⁹ it seemed likely that *nitrosoarenes*, either free or complexed, could be intermediates in the catalytic reductive annulation of nitroarenes to indoles. To address this issue and to develop milder, more efficient annulation variants, we have examined the reactions of *nitrosoarenes* with alkynes under the above catalytic conditions. In addition, we report the discovery of a novel uncatalyzed reaction between nitrosoarenes and alkynes and its relevance to the catalytic annulation processes.

In our initial experiments phenylacetylene and nitrosobenzene were heated together with $[\text{Cp}^*\text{Ru}(\text{CO})_2]_2$ (**1**, $\text{Cp}^* = \text{C}_5\text{Me}_5$) and CO under the conditions employed for the reductive annulation of nitroarenes (benzene, 170 °C, 750 psi, 20 h). GC–MS analysis indicated the formation of a major product (m/e 193) that proved to be 3-phenylindole (eq 2; $y = 1$, $\text{R} = \text{Ph}$, $\text{R}' = \text{H}$; 53% yield).¹⁰ Lesser quantities of aniline (7%) and azo- (11%) and azoxybenzene (18%) were also produced, but none of the isomeric 2-phenyl indole was detected. For comparison, under identical conditions with **1** as the catalyst the corresponding $\text{PhNO}_2/\text{PhC}\equiv\text{CH}$ reaction achieved only 63% conversion and a 14% yield of 3-phenylindole after 36 h.

A limited survey of nitrosoarene and alkyne substrates showed that these reactions are faster and somewhat more efficient in general than the corresponding ArNO_2 annulations (24 vs 48 h or more for ArNO_2 reactions) but display comparable selectivity (eq 2, Table 1). Thus, (1) both neutral

Table 1. $[\text{Cp}^*\text{Ru}(\text{CO})_2]_2$ -Catalyzed Reaction of ArNO with Alkynes (eq 2)^a

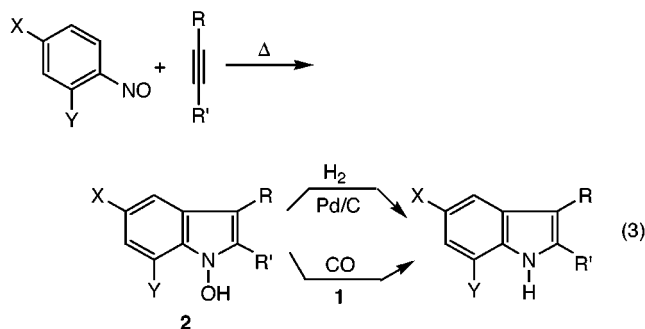
entry	Ar	R	R'	indole yield (%) ^b
1	Ph	Ph	H	53
2	Ph	Ph	CH_3	32
3	Ph	Ph	CO_2Et	21 ^c
4	$p\text{-Et}_2\text{N-C}_6\text{H}_4$	Ph	H	49 ^d

^a Procedure as described in ref/note 10. ^b Isolated yield. ^c 1.5:1 ratio of 2,3-substituted isomers. ^d 72 h reaction time.

and electron-rich nitrosoarenes are effective reaction partners (entries 1,4); (2) moderately efficient reactions occur with alkynes possessing at least one aryl or carboalkoxy group (entries 1–4); and (3) unsymmetrical alkynes react with high regioselectivity, placing the aryl substituent at the 3-position (entries 1–4). The comparable regioselectivity and faster rates of the *nitrosoarene* annulations support (but do not prove) the hypothesis that the *nitroarene* reactions pass through nitrosoarene intermediates (either free or coordinated).

To further clarify the role of complex **1** in the ArNO annulations, nitrosobenzene and excess phenyl acetylene were combined in refluxing benzene (16 h) in the *absence of 1*. Remarkably, GC and GC–MS (EI) analysis of the reaction mixture detected 68% of 3-phenylindole. However, TLC analysis of the mixture showed only traces of the indole with the major product being a polar, labile compound that tentatively has been identified as the *N*-hydroxy indole derivative **2a** ($\text{X}, \text{Y}, \text{R}' = \text{H}$, $\text{R} = \text{Ph}$, eq 3).¹¹ The formation of **2a** was not influenced by conducting the reaction in the dark or by the presence of the free radical inhibitor galvinoxyl.¹⁴ Furthermore, **2a** was converted to 3-phenyl indole when (1) injected into the GC at 250 °C, (2) heated at 80 °C with complex **1** (10 mol %) under CO (5 atm, benzene), or (3) stirred under 1 atm H_2 in the presence of 10% Pd/C (20 °C, 5 h, 62% overall). Therefore, **2a**, formed in the direct (uncatalyzed) reaction of PhNO and $\text{PhC}\equiv\text{CH}$, is a likely intermediate in the formation of the indole in the Ru-catalyzed reactions.

The regioselectivity and scope of the two-stage addition/hydrogenation process for the synthesis of indoles (eq 3) was



then examined with a set of representative nitrosoarenes and alkynes (Table 2).¹⁵ In each case the intermediate adduct **2**

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(10) **Experimental Procedure.** A stainless steel autoclave fitted with a glass liner and a magnetic spin bar was charged with catalyst (0.15 mmol), nitrosoarene (3 mmol), alkyne (12 mmol), and distilled solvent (benzene, 10 mL). In a well-ventilated fume hood the autoclave was purged with CO three times (CAUTION, toxic) and finally pressurized to 750 psi. The vessel was then heated to 170 °C for 24 h. After cooling, the autoclave was vented in the fume hood, the solvent was removed by rotary evaporation, and the products were isolated by flash chromatography over silica gel. Product characterizational data are provided in Supporting Information.

Table 2. Indole Annulation by Addition/Hydrogenolysis (eq 3)^a

entry	Ar	R	R'	indole yield (%) ^b
1	Ph	Ph	H	62
2	Ph	Ph	CH ₃	53
3	Ph	Ph	CO ₂ Et	46 ^c
4	Ph	CO ₂ Et	CO ₂ Et	29
5	Ph	CO ₂ Et	H	64
6	Ph	<i>n</i> -hexyl	H	51 ^d
7	<i>p</i> -Br-C ₆ H ₄	Ph	H	34
8	<i>p</i> -Cl-C ₆ H ₄	Ph	H	42
9	<i>p</i> -Et ₂ N-C ₆ H ₄	Ph	H	36 ^e
10	<i>o</i> -CH ₃ -C ₆ H ₄	Ph	H	39

^a Procedure as described in ref/note 13. ^b Isolated indole yield based on ArNO. ^c 1.5:1 ratio of 2,3-substituted isomers. ^d 20 h reaction time. ^e 48 h reaction time with *i*-PrOH solvent.

was isolated by flash chromatography and subjected to hydrogenolysis (H₂/10% Pd on C, 4–6 h); reported yields are for the isolated indole based on ArNO. As found for the Ru-catalyzed annulations of ArNO₂ and ArNO with alkynes, considerable electronic and steric variability is accommodated in the N-arene component (entries 1 and 7–10) with little effect on efficiency, although the electron-rich 4-NEt₂-C₆H₄NO reacted sluggishly (entry 9). Although alkynes with

(11) Data for **2a**: *R*_f 0.25 (7:3 CH₂Cl₂/petroleum ether); ¹H NMR (CDCl₃) δ 6.8–8.0 (broad m); MS (ESI, neg ion) 208 (*M* – 1 for C₁₄H₁₁NO, 100%); IR (CH₂Cl₂) 3470 (b), 1605, 1540, 1416 cm^{–1}. *N*-Hydroxyindoles, as found for **2**, are typically unstable (see ref 12a for a review of *N*-hydroxyindoles) and subject to facile autoxidation (ref 13) and hydrogenolysis to indoles (ref 12a). An alternative formulation of **2a** as 4-phenyl-1,2-benzooxazine is less consistent with the compound's high polarity and abundant (*M* – 1) MS ion.

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(14) Galvinoxyl did largely suppress the formation of the major byproduct, azoxybenzene.

(15) **Experimental Procedure.** Formation of adducts **2**. The nitrosoarene (1.0 mmol) and the alkyne (80 mmol) were refluxed in benzene (100–120 mL) under nitrogen for 12–15 h until the complete consumption of the nitrosoarene was indicated by TLC. The solvent and volatiles were evaporated in vacuo, and the intermediate **2** was isolated as a yellow oil or oily solid by flash chromatography over silica gel using 7:3 CH₂Cl₂/petroleum ether as eluant (*R*_f ca. 0.2). Hydrogenolysis of **2**. A mixture of ca. 100 mg **2** and ca. 60–70 mg of Pd/C (10%) in benzene (20–30 mL) was stirred at room temperature while H₂ was bubbled into the solution. After 5–6 h TLC analysis indicated complete consumption of **2** and clean formation of the corresponding indole; filtration to remove the catalyst and solvent evaporation provided the indole, which was pure by NMR analysis (see Supporting Information).

conjugating substituents (entries 1–5 and 7–10) are the most reactive substrates in the annulation, 1-octyne (entry 6) did undergo reasonably efficient (albeit somewhat slower) and 3-regioselective reaction. Aryl alkynes and ethyl propiolate afford indoles selectively substituted with the conjugating group at the 3-position (entries 1–3, 5, and 7–10); the regioselectivity found with PhC≡CCO₂Et (1.5:1 in favor of 2-Ph-3-CO₂Et-indole, entry 4) was comparable to that in the Ru-catalyzed reaction of PhNO₂ with PhNO.

To our knowledge the reaction of nitrosoarenes with alkynes is heretofore unknown.¹⁶ Although further insight into the mechanism of this novel transformation and the metal-catalyzed annulations awaits studies in progress, the absence of strong solvent or arene substituent effects on the reactions and their indifference to galvinoxyl argue against the involvement of ionic or radical intermediates. Its mechanism notwithstanding, the facility of the purely organic ArNO/alkyne addition and the substrate reactivity/selectivity similar to that of the Ru-catalyzed reactions suggest that this novel reaction is an integral part of the Ru-catalyzed processes and determines their regioselectivity. The primary role of the catalyst thus appears to be to promote selective reduction of the nitroarene (to nitrosoarene) and the intermediates **2** (to the indoles).

The presently disclosed novel annulation reactions provide a direct and regioselective route to indoles from nitrosoarenes. The synthetic potential of these reactions is enhanced by the ready accessibility of variously substituted nitrosoarenes (by oxidation of anilines or nitrosation of arenes)¹⁷ and the neutral reaction conditions employed. Efforts are underway to develop more efficient catalytic reductive annulations, to elucidate their mechanisms, and to demonstrate their synthetic potential.

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Supporting Information Available: Characterization data for the indole products and (partial) for the intermediates **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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