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Efficient Synthesis of *N*-Methoxyindoles via Alkylative Cycloaddition of Nitrosoarenes with Alkynes

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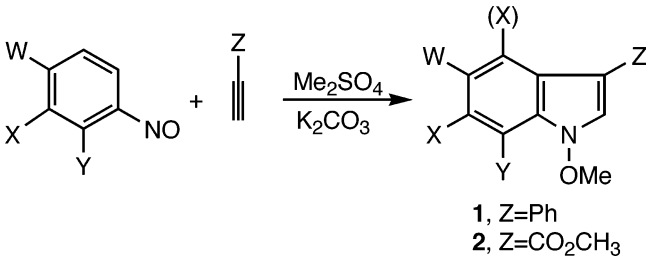
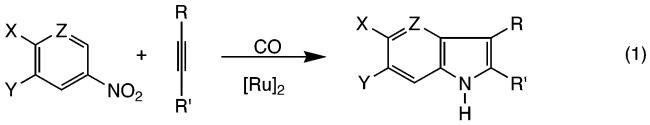


N-Methoxyindoles are produced in moderate to excellent yields from the reaction between nitrosoarenes and alkynes in the presence of $K_2CO_3/(CH_3)_2SO_4$. Terminal alkynes with conjugating substituents afford 3-substituted *N*-methoxyindoles exclusively. The analogous reactions with methyl propiolate provide a one-step preparation of phytoalexin analogues from Wasabi.

N-Oxidized derivatives of indoles, e.g., *N*-hydroxy- and *N*-alkoxyindoles, have been receiving increasing attention as novel reactive compounds, as useful synthetic intermediates, and as bioactive natural products.[1] The most established synthetic route to these compounds is Somei's method, which starts from a preformed indole via reduction (to the indoline), followed by reoxidation (tungstate-catalyzed) to the *N*-hydroxyindole.[2] Besides other less efficient or less general methods,[3] efficient Pb-promoted reductive cyclizations of *o*-nitrobenzyl ketones[4] and Sn(II)-induced reductive cyclizations of *o*-nitro-unsaturated ketoesters[5] have been recently described. Some of us reported the detection of *N*-hydroxyindoles as intermediates in Pd-catalyzed reductive cyclization of *o*-nitrostyrenes with CO.[6] All of these approaches, however, employ *o*-nitro-functionalized substrates requiring multistep preparations.

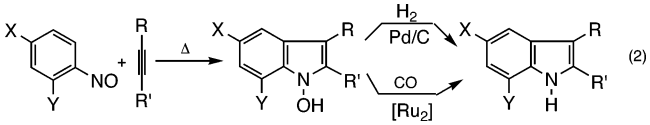
We recently discovered a novel, direct, and regioselective route to indoles via the $[Cp^*Ru(CO)_2]_2$-catalyzed reductive cycloaddition of *nitro*arenes with alkynes (eq 1).[7] A follow-up



(1)

$[Ru]_2 = [(\eta^5\text{-}C_5Me_5)Ru(CO)_2]_2$

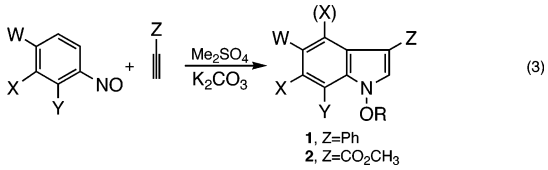
study showed that alkynes and *nitroso*arenes (potential intermediates in the Ru-catalyzed process) undergo an uncatalyzed, thermal cycloaddition to form *N*-hydroxyindoles, which by catalytic reduction are efficiently converted to indoles (eq 2).[8]



(2)

Because of the lability of *N*-hydroxyindoles and the synthetic and biological importance of the more stable *N*-alkoxyindoles, we sought a one-pot method for the preparation of the latter via an alkylative modification of the nitrosoarene/alkyne cycloaddition. Realization of this goal now provides an efficient and direct route to *N*-methoxyindoles and is highlighted by a one-step synthesis of methyl *N*-methoxyindole 3-carboxylate, an antifungal phytoalexin from Wasabi, and several analogues.

Beginning with the original reaction conditions for the *N*-hydroxyindole preparation, we conducted an optimization study of the reaction between PhNO and phenyl acetylene in the presence of various alkylating agents (CH_3I and $(CH_3)_2SO_4$), bases (Na_2CO_3, K_2CO_3, pyridine, NaOH, and KOH), and solvents (benzene, dioxane, ethanol, and 2-propanol). Thin-layer chromatography (TLC) analysis indicated the efficient formation of 3-phenyl-*N*-methoxyindole **1a** (86% after flash chromatography, eq 3) using $(CH_3)_2SO_4/K_2CO_3$ (0.75 mmol ArNO, 4.5 mmol $(CH_3)_2SO_4$, 4.5 mmol K_2CO_3, and 22.5 mmol alkyne) in refluxing benzene (6 h). As with the corresponding hydroxy-



(3)

indole-forming reaction (i.e., without base/alkylating agent), only the 3-phenyl isomer was detected. Using these conditions, the reaction of phenyl acetylene with a representative set of nitrosoarenes afforded the heretofore unknown 3-phenyl-*N*-

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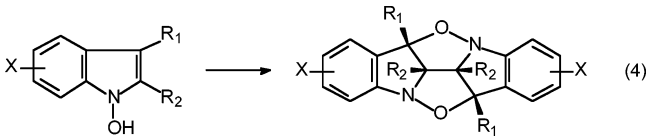
TABLE 1. ***N*-Methoxyindoles from Nitrosoarenes and Phenyl Acetylene (Z═Ph)**

entry	W	X	Y	product	yield (%)
1	H	H	H	**1a** (R═CH_3)	86
2	H	H	CH_3	**1b** (R═CH_3)	69
3	H	H	CO_2CH_3	**1c** (R═H)	84
4	H	CH_3	H	**1d** (4-CH_3),	61[a]
				1e (6-CH_3)(R═CH_3)	(48:52)
5	H	NO_2	H	**1f** (4-NO_2),	73[a,b]
				1g (6-NO_2)(R═CH_3)	(75:25)
6	CH_3	H	H	**1h** (R═CH_3)	57
7	$CO_2CH_2CH_3$	H	H	**1i** (R═CH_3)	41
8	Cl	H	H	**1j** (R═CH_3)	68
9	NO_2	H	H	**1k** (R═CH_3)	quant.
10	H	H	CF_3	**1l** (R═CH_3)	44

[a] Molar ratio determined by integration of ^{1}H NMR spectrum. [b] 4- and 6-nitro-3-phenylindole were detected in trace amounts.

methoxyindoles in moderate to good yields (Table 1). Both electron-donating and -withdrawing substituents are accommodated on the nitrosoarene, and complete 3-position regioselectivity is observed throughout. The yields of the *N*-methoxyindoles are significantly improved (20−40%) relative to those for the corresponding hydroxyindoles, probably as the result of effective trapping/stabilization of the labile hydroxyindoles by alkylation, thus avoiding the formation of kabutane derivatives (*cis*-1,10-diaza-9,20-dioxadibenzo[*b*,*g*]tetracyclo[7.2.1.0.^{4,11}0^{6,10}]-dodecane, eq 4)[9] and other decomposition products. Interest-



(4)

ingly, reaction of the *o*-nitrosoester (entry 3) afforded the stable *N-hydroxy*indole **1c** (R═H), which may be reluctant to undergo alkylation because of intramolecular N−OH−CO_2R hydrogen bonding. From 3-substituted nitrosoarenes (*m*-nitrosotoluene and *m*-nitronitrosobenzene), mixtures of 4- and 6-substituted *N*-methoxyindoles were obtained (entries 4 and 5). No appreciable regioselectivity was observed in the reaction with *m*-nitrosotoluene (Z═Me), but that with *m*-nitronitrosobenzene (X═NO_2) showed a substantial preference for the 4-substituted indole. This modest regioselectivity appears to be electronic in origin because the favored product is the more sterically hindered one.

To explore further the scope of the nitrosoarene/alkyne route to *N*-methoxyindoles, methyl propiolate was also combined with a set of substituted nitrosoarenes under the established cycloaddition/alkylation conditions (eq 3). Moderate to excellent yields of the corresponding 3-carbomethoxy-*N*-methoxyindoles **2** were obtained (Table 2). Key features include: (1) the effective participation of both electron-rich and electron-deficient nitrosoarenes; (2) the regiospecific location of the carboxyl function of the alkyne at the indole 3-position; and (3) generally higher yields from the 2-substituted nitrosoarenes relative to the 4-substituted derivatives (compare entries 2/7, 3/8, and 4/11). With the 3-substituted nitrosoarenes, *m*-nitrosotoluene and *m*-nitronitrosobenzene, modest 4/6 regioselectivity was found (entries 5 and 6), qualitatively paralleling the regioselectivity observed with these nitrosoarenes and phenyl acetylene.

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TABLE 2. ***N*-Methoxyindoles from Nitrosoarenes and Methyl Propiolate (Z═$COOCH_3$)**

entry	W	X	Y	product	yield (%)
1	H	H	H	**2a** (R═CH_3)	67
2	H	H	CH_3	**2b** (R═CH_3)	82
3	H	H	CO_2CH_3	**2c** (R═H)	75
4	H	H	NO_2	**2d** (R═CH_3)	79
5	H	CH_3	H	**2e** (4-CH_3),	65
				2f (6-CH_3)(R═CH_3)	(45:55)
6	H	NO_2	H	**2g** (4-NO_2),	59
				2h (6-NO_2)(R═CH_3)	(59:41)
7	CH_3	H	H	**2i** (R═CH_3)	58
8	$CO_2CH_2CH_3$	H	H	**2j** (R═CH_3)	60
9	Cl	H	H	**2k** (R═CH_3)	45
10	Br	H	H	**2l** (R═CH_3)	48
11	NO_2	H	H	**2m** (R═CH_3)	82

The attractiveness of this method for the preparation of 3-carboxy-*N*-alkoxyindoles, which occur naturally as Wasabi phytoalexins,[10] and their analogues is highlighted by comparison with prior syntheses of these compounds. Previously, compound **2a** (entry 1) had been prepared by the Acheson (ten steps, low yield),[11] Pedras (six steps, 6% yield),[10] Selvakumar (five steps, 16% yield),[12] and Somei (five steps, 51% yield)[13] groups. The Somei group used **2a** and subsequent electrophilic substitution to prepare several analogues.[13,14] In contrast, the present method affords 3-carboxy-*N*-alkoxyindoles in a single, moderately efficient step from starting materials that are either commercially available or one step away.

We note as well that the easily produced *N*-methoxyindoles can be converted efficiently to the corresponding N−H indoles by reduction. For example, *N*-methoxyindole **1a** was quantitatively converted to 3-phenylindole either by hydrogenolysis (1 atm H_2, 10% Pd/C, benzene, room temperature) or by reductive carbonylation (5−10 atm CO, 10 mol % [Cp*Ru$(CO)_2]_2$, benzene, 80 °C).

Although the reaction mechanism was not a focus of the present study, we consider that the insensitivity of the reaction to arene substituent effects and solvent and the strong 3-position regioselectivity are most consistent with an apolar (concerted or stepwise radical) cycloaddition pathway, then C−H to O−H tautomerism, followed by alkylation of the intermediate *N*-hydroxyindole. Efforts are continuing to further elucidate the mechanism of the nitrosoarene/alkyne cycloaddition and to extend its scope and synthetic application.

Experimental Section

General Procedure for the Preparation of *N*-Methoxyindoles. A mixture containing 0.75 mmol of nitrosoarene, 22.5 mmol of alkyne, 6 mmol of K_2CO_3, and 6 mmol of dimethyl sulfate (*Caution: toxic!*) in 80 mL of dry benzene was stirred at reflux for 6−8 h under nitrogen. After cooling, the mixture was filtered and the filtrate was concentrated by rotary evaporation. Flash chromatography of the residue over silica gel (hexane/ethyl acetate eluant) afforded the *N*-methoxyindoles, typically as oils. All new com-

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pounds were spectroscopically pure (≥95%) and exhibited appropriate ^{1}H-, ^{13}C NMR, and MS data (provided in the Supporting Information).

Preparation of 3-Phenylindole by in Situ Reduction of *N*-Methoxy-3-phenylindole (1a). A filtered benzene solution (ca. 80 mL) of *N*-methoxy-3-phenylindole (without chromatographic purification) was produced as described above. Approximately 50 mg of 10% Pd on C was added to one-half (ca. 40 mL) of the solution, and hydrogen was slowly bubbled through the stirred mixture overnight. TLC monitoring vs authentic 3-phenylindole and ^{1}H NMR analysis indicated complete and quantitative conversion to the indole.

To the remaining solution of **1a** was added 29 mg of $[Cp^*Ru(CO)_2]_2$. The solution was transferred into a glass liner with a stir bar, and the liner was placed in a stainless steel reactor. The reactor was flushed twice with CO (fume hood), pressurized to 10 atm CO, and then heated to 80 °C. After 4 h, TLC and ^{1}H NMR analysis vs authentic 3-phenylindole indicated the complete and quantitative formation of the indole.

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Supporting Information Available: Spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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