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Synthesis of Indoles by Palladium-Catalyzed Reductive Cyclization of β-Nitrostyrenes with Carbon Monoxide as the Reductant

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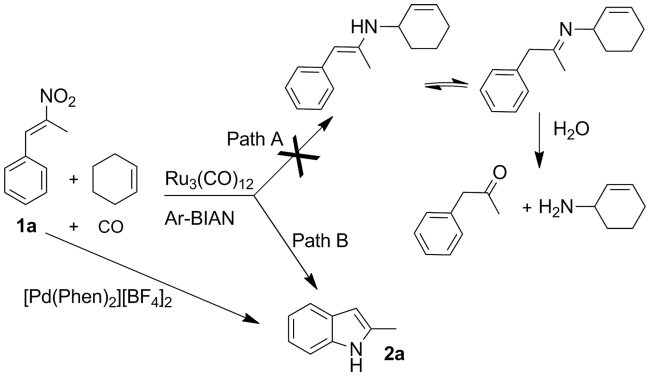
An efficient catalytic cyclization of β-nitrostyrenes to indoles was developed. The reaction was applied to the synthesis of 3-arylindoles and 2-alkylindoles. Given that in the latter case the starting β-nitrostyrenes can be easily obtained by a Henry reaction, the present method allows indoles to be obtained in a two-step sequence starting from cheap reactants.

Introduction

The indole skeleton is central to many biologically active pharmaceutical drugs and natural alkaloids,[1] and its synthesis continues to attract the attention of many researchers.[2] Many syntheses of indoles are catalyzed by transition metals, but in most cases they require substrates bearing two suitable functional groups *ortho* to each other, and the preparation of these starting materials often requires several synthetic steps. An example relevant for this work is the reductive cyclization of *o*-nitrostyrenes to indoles catalyzed by Pd/phosphine/$SnCl_2$,[3] Pd/phosphine,[4] and Pd/phenanthroline[5] systems. Several years ago, we investigated the possibility of using β-nitrostyrenes as aminating agents for olefins by employing a protocol previously devised for nitroarenes[6] and based on the use of a ruthenium/bis(aryl)-acenaphthenequinonediimine (Ar-BIAN) catalyst. The aim was to obtain a vinylic amine that, after tautomerization, could be easily hydrolyzed to result in the overall introduction of an NH_2 group in the allylic position (Scheme 1, path A). Despite some efforts, we never observed the formation of the allylic amine. A mixture of products was obtained, among which 2-methylindole was always present (Scheme 1, path B).

The deoxygenative cyclization reaction of β-nitrostyrenes to indoles has been reported to occur with $P(OEt)_3$ as the reducing agent only if the α position of the styrene bears a substituent, most commonly a second aryl group.[7] The reaction is only of little interest owing to the need for a very large excess amount of the trialkylphosphite and the consequent difficulty in its elimination from the product. No method has been reported for the efficient deoxygenative cyclization of **1a** or related β-nitrostyrenes lacking additional substituents in the α position.[8] The possibility of conducting the reaction under catalytic conditions intrigued us, as the use of β-nitrostyrenes as substrates in indole synthesis is very interesting. In fact, in most cases, they can be easily prepared from an aldehyde and a nitroalkane by the Henry reaction, which overcomes problems associated with the complex preparation of the substrates.



Scheme 1. Palladium- and ruthenium-catalyzed cyclization of β-methyl-β-nitrostyrene.

The indole yield was low with the use of a catalytic system based on ruthenium, but better results were obtained by employing $[Pd(Phen)_2][BF_4]_2$ in the presence of an excess amount of 1,10-phenanthroline (Phen). This system was previously reported to give very good results in other carbonylation reactions, such as the reductive carbonylation of nitroarenes[9] and several types of inter- and intramolecular reductive cyclization reactions of nitroarenes.[5b,10]

Results and Discussion

Encouraged by these preliminary results, we optimized the reaction conditions by employing commercially avail-

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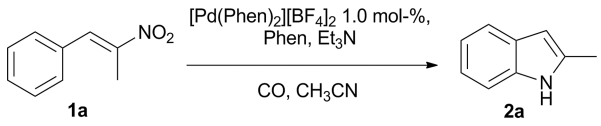
able *trans*-β-methyl-β-nitrostyrene (**1a**) as a model substrate (Scheme 2, see also Table S1 in the Supporting Information). The main results of the optimization study are the following: (1) After an initial screening of solvents (i.e., DMF, THF, toluene), CH_3CN was identified as the best solvent. (2) The reaction does not need any co-catalyst to proceed, but the addition of an organic base leads to an enhancement in the activity of the system and to an increase in indole selectivity. 1,4-Diazabicyclo[2.2.2]octane and triethylamine were tested, and the latter gave higher selectivities. The concentration of the base was preliminarily optimized, and the best results were obtained with a Et_3N concentration of 0.17 M. (3) The selectivity for indole is almost independent of the CO pressure between 20 and 40 bar (1 bar = 100 kPa); however, the reaction is strongly inhibited over 40 bar, whereas the indole selectivity decreases at pressures lower than 20 bar. (4) The selectivity is almost constant in the range of 150 to 170 °C but decreases at lower temperatures. (5) Complete conversion is reached after 2.5 h, after which only decomposition of the product occurs. (6) The amount of phenanthroline was also optimized, and the best results were obtained with a Phen concentration of 0.012 M.[11]



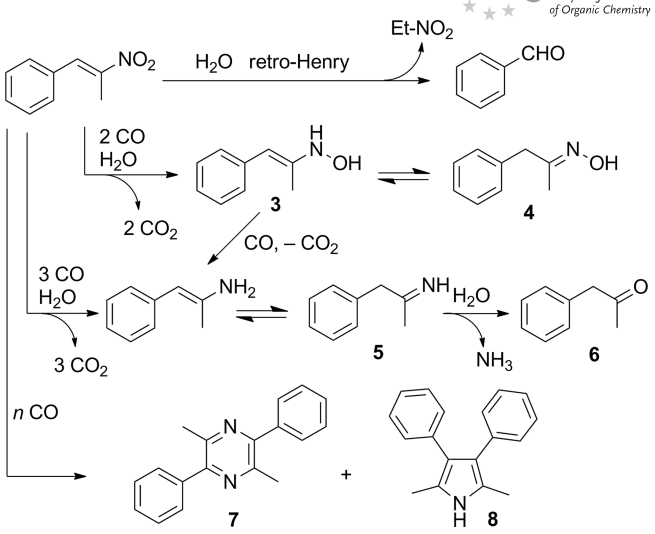
Scheme 2. Palladium-catalyzed reductive cyclization of **1a** by CO.

With the use of the optimized conditions, we were able to completely convert **1a** into **2a** with 88% selectivity (measured by gas chromatography; Table S1, entry 5) and to isolate the product[12] with just a 2% loss with respect to the GC yield.

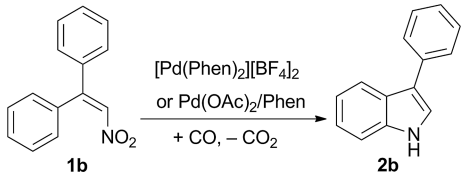
We previously mentioned that cyclization of **1a** to **2a** by using $P(OEt)_3$ as the reductant is not known. To test if indole could be obtained by this methodology to some extent, we heated **1a** at 150 °C in neat $P(OEt)_3$. A mixture of products was obtained, among which the indole was not present (GC analysis, detection limit <1%).

During the optimization study, we were able to identify by GC–MS some of the side products of the reaction. Under the optimized conditions, their amount was very low and it was not possible to quantify them. The likely pathways for the formation of these side products are reported in Scheme 3. Compounds **7** and **8** may be derived from dimerization of a radical anionic intermediate;[13] the dimer is then further reduced by carbon monoxide. The formation of **8** was previously reported to occur by reduction of the β-nitrostyrene with aqueous $TiCl_3$.[13] Even if the formation of the above-mentioned side products can be almost suppressed under the optimized conditions, some unidentified high-boiling side products still form to some extent.

A few years ago, Hsieh and Dong reported a study on the palladium-catalyzed reductive cyclization of α-aryl-β-nitrostyrenes.[14] $Pd(OAc)_2$ was used as the catalyst, the molar ratio of cat/Phen/substrate was 1:2:50, and the reaction was performed in DMF at 110 °C and 1 bar overpressure of CO for 3 h; excellent yields were obtained. We reproduced the reaction by employing 1,1-diphenyl-2-nitroethene (**1b**, Scheme 4) as the substrate and obtained a very similar result (82% conversion and 92% indole selectivity in our hands, instead of 97% yield as reported; Table S2, entry 1).[15] However, the previously reported conditions appear to be suitable only for the very limited class of α-aryl-β-nitrostyrenes, and upon using **1a** as the substrate under the same experimental conditions, both the conversion and selectivity were very poor (Table S2, entry 2; indole **2a** yield = 6.8%). By using our optimized conditions, excellent results were obtained with both substrates **1a** and **1b** (Table 1). The use of a different Pd^{II} precursor {$Pd(OAc)_2$ or $[Pd(Phen)_2][BF_4]_2$} did not affect the system performance (Table S2, entries 4 and 5).



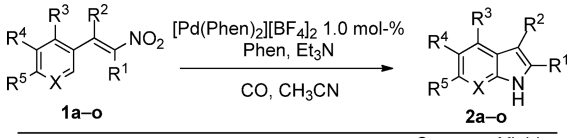
Scheme 3. Pathways for the formation of side products for substrate **1a**.



Scheme 4. Palladium-catalyzed reductive cyclization of **1b**.

The difference in reactivity between substrates **1a** and **1b** is due to two reasons: the higher reduction potential of β-substituted β-nitrostyrenes[16] relative to β-nitrostyrene (**1i**) owing to tilting of the nitro group out the olefin plane, and the presence of a more extended π system in **1b**. In fact, given that reduction of the nitro group should involve initial single-electron transfer from the metal to the nitroalkene with the formation of a radical anion[17] (**A** in Scheme 5), a high degree of conjugation of the π system should favor radical delocalization and thus the subsequent formation of nitroso compound **B**, which is proposed to be the aminating species, by analogy with what occurs in the cyclization of *o*-nitrostyrenes.[18] Eventually, hydroxyindole **C**, formed by

Table 1. Scope of the reaction.[a]

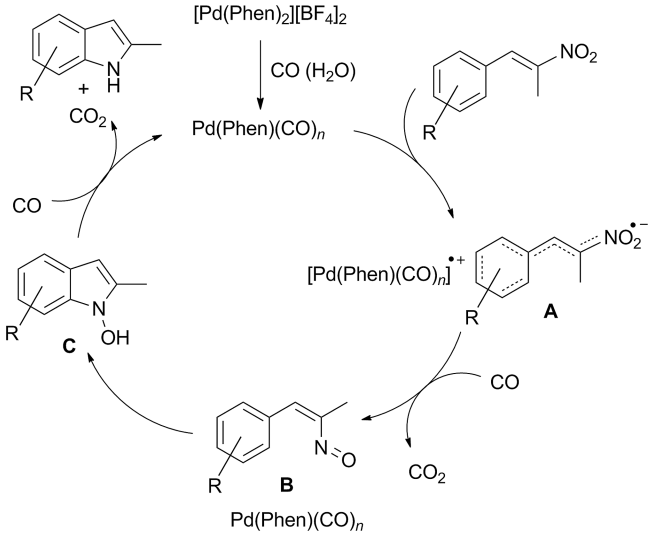


1a–o 2a–o

Substrate	Product	Conv. (%)[b]	Yield (%)[c]
1a	2a	100	86
1b	2b	100	93
1c	2c	>99	70
1d	2d	>99	75
1e	2e	95	50
	2e'		11[d]
1f	2f	94	59
1g	2g	100	51
1h	2h	100	21
	2h'		20
1i	2i	64	3[b]
1j	2j	100	50
1k	2k	16	-
1l	2l	96	47
1m	2m	93	41
1n	2n	100	57
1o	2o	100	61

[a] Reaction conditions: $[Pd(Phen)_2][BF_4]_2 = 1.10 \times 10^{-2}$ mmol, mol ratio substrate/Phen/$[Pd(Phen)_2][BF_4]_2$ = 100:16:1, 150 °C, 20 bar of CO, $[Et_3N]$ = 0.17 M, CH_3CN (15 mL), 2.5 h. [b] Determined by GC analysis. [c] Yield of isolated product. [d] Determined by ^1H NMR spectroscopy by using anisole as an internal standard.

amination, is reduced to the indole by carbon monoxide. The formation of the radical anion allows easy rotation around the double bond and explains why good selectivities in indole could be obtained even upon employing *trans*-β-nitrostyrenes that are selectively formed by the Henry reaction. The presence of a second aryl group in **1b** is expected to favor the cyclization step, because it maximizes the chances of proper orientation of the nitroso and phenyl groups, in accord with the observation that **1b** gave the highest selectivity among all tested nitrostyrenes (see above).



Scheme 5. Proposed reaction mechanism.

The scope of the reaction was then explored (Table 1). The best results were obtained for substrate **1b** owing to the presence of the phenyl ring, as mentioned above. For other substrates lacking an aryl group in the α position, the presence of a substituent in the β position was fundamental for indole formation, and its absence (i.e., for **1i**) resulted in low reactivity and the formation of palladium black. In this case, an insoluble solid derived from polymerization of the starting β-nitrostyrene[19] was found as the main product of the reaction, whereas 3,4-diphenylpyrrole was detected by GC–MS as the major product in solution. Both electron-withdrawing and electron-donating substituents can be present in the *para* position of the aryl ring. However, as expected, the presence of strongly electron-releasing groups, such as methoxy (i.e., compound **1f**) and even more diethylamino (i.e., compound **1k**), led to reduced reactivity because of slower reduction of the nitro group.[10c]

It is especially notable that good results were obtained with substrate **1e**. Indeed, azaindoles are very important molecules.[20] Cyclization of the nitroso intermediate is an electrophilic process, and attack on the electron-poor 2- or 4-position of the pyridine ring should be disfavored. The 80% regioselectivity in 2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**2e**), the most disfavored product from an electronic point of view, may be ascribed to partial coordination of the substrate to the metal center. On the contrary, reductive cyclization of chloro derivative **1h** is not regioselective.

Conclusions

The reaction described herein enables the synthesis of a wide range of indoles from easily accessible and often commercially available aldehydes and nitroalkanes. Given that nitroalkanes are much more difficult to reduce than nitroalkenes, it is conceivable that the Henry condensation and the following cyclization could be performed in one pot. Preliminary results showed that this is indeed the case, but selectivities were poor because of difficulties in finding a solvent mixture that was suitable for both the Henry condensation and the following cyclization. Further efforts will be done in this direction in the future.

Acknowledgments

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