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Synthesis of Indoles by Intermolecular Cyclization of Unfunctionalized Nitroarenes and Alkynes: One-Step Synthesis of the Skeleton of Fluvastatin

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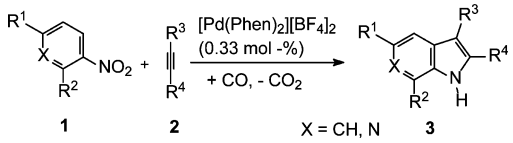
The addition of $Ru_3(CO)_{12}$, dimethyl carbonate, or both to the reaction mixture improves the selectivity of the palladium/phenanthroline-catalyzed reaction of nitroarenes, arylalkynes, and CO to give 3-arylindoles. When 4-fluorophenylacetylene and nitrobenzene are used as substrates, the indole skeleton of Fluvastatin and other pharmaceutically active compounds is obtained in one step.

Introduction

The indole skeleton is central to many pharmaceutically active compounds, and its synthesis continues to attract the attention of many researchers.[1] We have recently reported that palladium/phenanthroline complexes catalyze the reaction of nitroarenes (**1**) with arylalkynes (**2**) under CO pressure to give 3-arylindoles (**3**) (Scheme 1).[2,3]



1 2 3

Scheme 1.

The reaction is completely regioselective; no 2-arylindole was detected, and the reaction does not require any prefunctionalization of the *ortho* position of the nitroarene. The palladium catalyst showed a much higher activity (ca. 500-fold) with respect to the ruthenium–cyclopentadienyl catalyst originally reported by Nicholas for the same reaction,[4] but the selectivity remained moderate. The reaction likely proceeds by the intermediate formation of *N*-hydroxyindoles,[2,5] and this kind of product can be isolated if the reaction is performed employing nitrosoarenes as substrates, in the absence of CO and any catalyst.[5] More recently, Nicholas and coworkers proposed that the accumulation of hydroxyindoles is responsible for the moderate yields because of their easy oxidative dimerization.[6] When nitrosoarenes are used as substrates, the problem was apparently solved by working in the presence of dimethyl sulfate, which methylates *N*-hydroxyindoles to afford more stable *N*-methoxyindoles.[6] However, nitrosoarenes are much less friendly starting materials than nitroarenes and very few of them are commercially available. In this paper we report our approaches to the improvement of the catalytic reaction by employing nitroarenes as substrates. The application of the optimized reaction conditions to the synthesis of the indole skeleton of important pharmaceutically active compounds is also discussed.

Results and Discussion

When the reaction between 4-nitrotoluene (**1b**, R^1 = Me, R^2 = H, X = CH; Scheme 1) and phenylacetylene (**2a**, R^3 = Ph, R^4 = H) was performed under the previously[2] optimized conditions (Table 1, Run 7), the ^{1}H NMR spectrum of the solid obtained after evaporation of the solvent (Supporting Information) showed the presence of just one outstanding signal in the aliphatic region due to 5-methyl-3-phenylindole (**3b**). However its integration against an internal standard (2,4-dinitrotoluene) showed it to correspond to only 44% of the starting nitrotoluene and at least eight more small signals of comparable intensity were also present, whose total integration precisely matched the 56% missing mass balance. Only four of these signals could be assigned to known compounds. Because the final indole was shown to be quite stable under the reaction conditions, it is clear that the other byproducts are derived from a side reaction of a reaction intermediate, and we agree with Nicholas that the most likely species responsible for alternative reaction pathways are *N*-hydroxyindoles, although under our conditions the byproduct identified in his work can at best be one of several possibilities. To speed up the conver-

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Table 1. Synthesis of 3-arylindoles from nitroarenes, phenylacetylene, and CO catalyzed by $[Pd(Phen)_2][BF_4]_2$ and $Ru_3(CO)_{12}$.[a]

Run	$ArNO_2$	t [h]	$[Pd(Phen)_2][BF_4]_2$/ $Ru_3(CO)_{12}$ [mol ratio]	Conversion of $ArNO_2$ [%][b]	Selectivity of Indole [%][c]
1	$PhNO_2$	6	1:0	100	45
2	$PhNO_2$	6	1:1	100	53
3	$PhNO_2$	6	0:1	5.0	–
4[d]	$PhNO_2$	6	1:1	100	43
5	$PhNO_2$	6	1:2	100	46
6	$PhNO_2$	3	1:1	100	54
7	$TolNO_2$	3	1:0	100	44
8	$TolNO_2$	3	1:1	100	55
9	$TolNO_2$	3	1:0.5	100	45
10	$TolNO_2$	3	1:1.5	100	56
11	$TolNO_2$	1.5	1:1	88	57
12[d]	$TolNO_2$	3	0:1	9.0	–

[a] Experimental conditions: $[Pd(Phen)_2][BF_4]_2 = 4.7 \times 10^{-3}$ mmol [except for Runs 3 and 12, where no palladium was present and $Ru_3(CO)_{12}$ (4.7×10^{-3} mmol) was employed as the only catalyst]; mol ratio Pd/Phen/$ArNO_2$/PhC≡CH, 1:20:300:1800; T = 170 °C; P_{CO} = 60 bar; 1,2-dimethoxyethane (10 mL). [b] Calculated with respect to the initial $ArNO_2$. [c] Calculated with respect to the reacted $ArNO_2$. [d] Ph-BIAN [mol ratio Ph-BIAN/$Ru_3(CO)_{12}$ = 4.5] was also added.

sion of *N*-hydroxyindoles into other products, we investigated two different strategies, which are described in the following.

During the reaction, *N*-hydroxyindoles are reduced to the corresponding indole by carbon monoxide. To the best of our knowledge, very little precedent exists for this reaction.[5,7] Several years ago, work in our group showed that *N*-hydroxyindoles were formed during an intramolecular cyclization reaction catalyzed by $Pd(Phen)(TMB)_2$ (TMB = 2,4,6-trimethylbenzoate, Phen = 1,10-phenanthroline) and that prolonging the reaction time led to reduction of these compounds to the corresponding indoles.[7] It was noted in the literature[5] that *N*-hydroxyindoles can be reduced by CO with the use of $[Cp^*Ru(CO)_2]_2$ as catalyst, but no experimental results were reported and no comparison with other catalysts was apparently attempted. Thus, no study has been reported in the literature on the optimization of the reduction of hydroxyindoles by CO, but the related hydroxyamines are likely intermediates in the reduction of nitroarenes by CO/H_2O, a reaction for which ruthenium carbonyl complexes show a much higher activity than palladium compounds.[8] Because the latter are more active for the activation of nitroarenes in most cases,[9] we attempted to use $[Pd(Phen)_2][BF_4]_2/Ru_3(CO)_{12}$ mixtures in different proportions as catalysts for the process in Scheme 1 with the idea that palladium may catalyze the formation of *N*-hydroxyindoles and ruthenium their reduction. Results are reported in Table 1. Both nitrobenzene (affording 3-phenylindole, **3a**) and 4-nitrotoluene [affording 3-(4-tolyl)indole, **3b**] were employed as substrates, with phenylacetylene as the alkyne, to better identify possible byproducts by gas chromatography ($PhNO_2$) and ^1H NMR spectroscopy ($TolNO_2$). The results were quite comparable with the two different substrates.

Data clearly show that $Ru_3(CO)_{12}$ alone does not catalyze indole formation, at least when added in such a low (0.33 mol-%) amount (Table 1, Run 3), even in the presence of Ph-BIAN [Table 1, Run 12; Ph-BIAN = 1,2-bis(diphenylimino)acenaphthene], the ligand which is more effective in activating it towards both the reduction of nitroarenes to anilines[10] and the synthesis of allylic amines by reaction of nitroarenes with olefins.[11–13] However, the addition of $Ru_3(CO)_{12}$ to the palladium catalyst increases the indole selectivity by 8–11% (Table 1, compare Runs 1, 2 vs. 7, 10). The best $Ru_3(CO)_{12}/[Pd(Phen)_2][BF_4]_2$ ratio is between 1 and 1.5. Surprisingly, the addition of Ph-BIAN in the presence of both metals caused a decrease in the selectivity (Table 1, Runs 2 and 4). Apparently some interference occurred. The reaction time has a very minor influence (Table 1, Runs 2, 6 vs. 8, 11), indicating that the produced indole is stable under the reaction conditions. The fact that the selectivity is unchanged even when the nitroarene conversion is not complete (Table 1, Run 11) and the fact that no new peak was observed in the ^1H NMR spectrum at the end of this reaction indicates that reduction of the *N*-hydroxyindoles is relatively fast and no detectable accumulation of it was observed.

As a second strategy to improve selectivity, we employed the same approach reported by Nicholas. Since the beginning it was obvious to us that the use of dimethyl sulfate may not be compatible with our catalytic system, because it could methylate phenanthroline. This was indeed found to be true and dimethyl sulfate almost completely inhibited any catalytic activity (Table 2, Run 1). We thus resorted to a milder methylating agent, dimethyl carbonate. The latter is surely compatible with our catalytic system, because palladium–phenanthroline complexes or their bipyridyl analogues are among the catalysts that have been reported to be active for the synthesis or organic carbonates by oxidative carbonylation of alcohols.[14–17] With respect to dimethyl sulfate, dimethyl carbonate has the additional advantage of being much less toxic. Moreover, as the monomethyl ester of carbonic acid is unstable and spontaneously decomposes to CO_2 and methanol, no base should be necessary to neutralize the formed acid. Results are shown in Table 2.

First of all it is clear that, as expected, dimethyl sulfate almost completely inhibits the reaction (Table 2, Run 1). In contrast, the addition of dimethyl carbonate in the proper

Table 2. Synthesis of 3-arylindoles from nitroarenes, phenylacetylene, and CO catalyzed by $[Pd(Phen)_2][BF_4]_2$ in the presence of dimethyl carbonate.[a]

Run	$ArNO_2$	t [h]	Me_2CO_3/Pd [mol ratio] or Me_2CO_3 volume	Base (base/Pd)	Selectivity of Indole [%][b]
1[c]	$PhNO_2$	6	1200 (Me_2SO_4)	K_2CO_3 (600)	traces
2[d]	$PhNO_2$	6	300	–	48
3[d]	$PhNO_2$	6	1200	–	54
4[d]	$PhNO_2$	6	1800	–	41
5	$PhNO_2$	6	10 mL (neat)	–	42
6	$PhNO_2$	6	5 mL (+5 mL DMF)	–	14
7	$PhNO_2$	3	1200	–	47
8	$PhNO_2$	6	1200	K_2CO_3 (600)	44
9	$TolNO_2$	6	1200	–	51
10	$TolNO_2$	6	1200	NEt_3 (100)	42
11[e]	$TolNO_2$	3	1200	–	47

[a] Experimental conditions: $[Pd(Phen)_2][BF_4]_2 = 4.7 \times 10^{-3}$ mmol; mol ratio Pd/Phen/$ArNO_2$/PhC≡CH, 1:20:300:1800; T = 170 °C; P_{CO} = 60 bar; 1,2-dimethoxyethane (10 mL). $ArNO_2$ conversion was always complete except for Runs 1 and 11. [b] Calculated with respect to the reacted $ArNO_2$. [c] $PhNO_2$ conversion = 5.0%. [d] Compare with Run 1 in Table 1, where no DMC is present. [e] $TolNO_2$ conversion = 95.0%. Compare with Run 7 in Table 1, where no DMC is present.

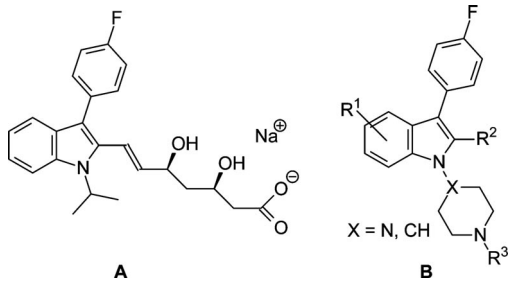
amount increases the indole selectivity (compare Table 1, Run 1 vs. Table 2, Runs 2–5; Table 1, Run 7 vs. Table 2, Run 9), although the increase is limited (9% at best). The ideal ratio of Me_2CO_3/Pd is 1200. The presence of dimethyl carbonate slows down the reaction somewhat. Indeed, while in its absence the conversion was always complete even in 3 h, in its presence the conversion of nitrotoluene was not complete in this time (Table 2, Run 11) and the indole selectivity was lower in the case of nitrobenzene after 3 h then after 6 h (Table 2, Runs 7 and 3).

Because dimethyl carbonate is less polar than dimethoxyethane used as solvent, we also tested a mixture of dimethyl carbonate and the more polar DMF, but the presence of the latter solvent gave much lower selectivity of indole and azo- and azoxybenzene predominated.[18,19]

The addition of either inorganic or organic bases is not necessary, and it even lowers the selectivity (Table 2, Runs 8 and 10).

Most importantly, the effect of the two strategies described above can be summed up. When the reaction of nitrotoluene with phenylacetylene was performed under the conditions of Run 9 in Table 2, but with the addition of $Ru_3(CO)_{12}$ (4.7×10^{-3} mmol), complete conversion was observed, with a 60.0% selectivity in indole (**3b**). It is worth noting that although the total selectivity increase is only about 16% with respect to the maximum possible yield, it corresponds to a more sensible 36% increase in the amount of obtained indole.

At this stage, we did not test the effect of the modified procedure on all the substrates reported in our previous paper. However, on the basis of the general reactivity of nitroarenes in reductive carbonylation reactions[8] and on that of dimethyl carbonate,[20] no problem is expected except for the reaction with 4-aminophenylacetylene, where the free amino group would probably be methylated or methoxycarbonylated by dimethyl carbonate under the reaction conditions. We rather tested the efficiency of our reaction in the reaction of nitrobenzene with 4-fluorophenylacetylene (**2b**) to give 3-(4-fluorophenyl)indole (**3c**). This indole constitutes the skeleton of many pharmaceutically active compounds, among which Fluvastatin (Lescol®, a cholesterol-lowering agent, **A** in Scheme 2) is that produced on the largest scale, although other compounds of type **B** in Scheme 2 (which are active 5-HT_2 antagonists)[21] are also important.



Scheme 2. Some pharmaceutically relevant compounds based on the 3-(4-fluorophenyl)indole (**3c**) skeleton.

The modified conditions described in this paper {$[Pd(Phen)_2](BF_4)_2 = 4.7 \times 10^{-3}$ mmol; mol ratios Pd/$Ru_3(CO)_{12}$/Phen/$ArNO_2$/PhC≡CH/dimethyl carbonate, 1:1:20:300:1800:1200; T = 170 °C; P_{CO} = 60 bar; 1,2-dimethoxyethane (10 mL); 6 h} were found to be especially effective for this reaction and **3c** was obtained in a 71% spectroscopic yield (only 37% if ruthenium and dimethyl carbonate were not present). Although a compound completely free from any impurity could be obtained by column chromatography, we also identified a nonchromatographic separation technique suitable for larger-scale applications (see Experimental Section).

Compared to its synthetic importance as an intermediate in the synthesis of several important drugs, very little has been reported in the free or patent literature on the preparation of **3c**.[22] Only two papers (and apparently no patent) describe its preparation from compounds that are either commercially available or whose synthesis has been fully described.[23,24] Walkup and Linder reported that **3c** can be obtained in 44% yield starting from α-chloro-*p*-fluoroacetophenone and aniline,[24] whereas Cacchi and coworkers reported a higher 71% yield for the same product by palladium-catalyzed cyclization of *o*-ethynyltrifluoroacetanilide in the presence of 4-fluoroiodobenzene,[23] but the starting material needs three synthetic steps to be prepared.[25] An alternative approach was also mentioned, in which **3c** is obtained by copper-catalyzed decarboxylation of the corresponding 2-indole-carboxylic acid.[21,26] Although a 77% yield was reported for the decarboxylation step, several synthetic steps were needed to prepare the starting material and details and yields for this substrate were not given. Our procedure compares favorably to the alternative synthetic

strategies in terms of number of steps, global yield, and, where relevant, amounts of precious metal required.[27–38]

The published characterization of **3c** is also surprisingly incomplete, as only its ^{1}H NMR spectrum (in [D$_6$]DMSO) has been reported in the literature. We have run several NMR spectra of **3c** in $CDCl_3$ and found that the ^{1}H NMR spectrum is strongly dependent on indole concentration. In particular, the signals due to the benzo-fused ring of the indole skeleton are shifted to lower fields upon an increase in concentration. The ^{13}C NMR, ^{19}F NMR and several 2D spectra are reported in the Supporting Information. Although it is outside the scope of this paper to investigate in detail the origin of the shift, it is clear that some concentration-dependent interaction is occurring between different indole molecules. It is noteworthy that we did not observed such a phenomenon for any of the other 3-arylindoles we previously prepared,[2] although we must acknowledge that we did not intentionally perform a variable concentration study for all of them. It is quite stimulating to note that although the 3-arylindole skeleton is mentioned as a generic scaffold in several patents concerning pharmaceutically active compounds, when it comes to specific examples the 4-fluorophenyl group is invariably present (e.g., see ref.[26]). That the most (or perhaps only) active compounds are those containing the moiety for which an unusual intermolecular interaction is observed is a coincidence that may be worth deeper investigation, although it is obvious that the aggregation in chloroform can be only a reference point for that occurring under physiological conditions.

Conclusions

Two independent approaches, the addition of a ruthenium compound and that of a methylating agent, were tested in the attempt to improve the selectivity of the palladium/phenanthroline catalytic system for the synthesis of 3-arylindoles from nitroarenes, alkynes, and carbon monoxide. Both were successful, and importantly, they can be used together showing additivity of the improvements. The new approach is especially important in the synthesis of 3-(4-fluorophenyl)indole, the scaffold of several pharmaceutically important drugs, for which it allowed an almost doubling of the yield.

Experimental Section

Catalytic Reactions: In a typical reaction, the reagents (see Tables 1 and 2) were quickly weighed in a glass liner. The liner was placed inside a Schlenk tube with a wide mouth under dinitrogen and frozen at –78 °C with dry ice, evacuated and filled with dinitrogen, after which the solvent was added. After the solvent was also frozen, the liner was closed with a screw cap having a glass wool-filled open mouth, which allowed exchange of gaseous reagents, and then rapidly transferred to a 200-mL stainless steel autoclave with magnetic stirring. The autoclave was then evacuated and filled with dinitrogen three times. CO was then charged at room temperature at the required pressure, and the autoclave was immersed in an oil bath preheated at the required temperature. Other experimental conditions are reported as captions to the tables. At the end of the reaction, the autoclave was cooled with an ice bath and vented. Reactions involving nitrobenzene were analyzed by gas chromatography (naphthalene as an internal standard, Equity 5 column). Aniline, azobenzene, and azoxybenzene were always detected in small amounts as byproducts. In the case of reactions involving 4-nitrotoluene, 2,4-dinitrotoluene was added as an internal standard, and the solution evaporated in vacuo. The residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR spectroscopy by using a delay of 10 s. In the case of **3c**, ^{19}F NMR spectroscopy was used to measure the reported spectroscopic yield. To this aim, CF_3CH_2OH was employed as an internal standard (in this case the standard was added after elimination of the reaction solvent).

Nonchromatographic Purification of 3c: The solution after the end of the reaction was evaporated in vacuo (the excess amount of the alkyne was evaporated with the solvent, and this mixture could be reused for further syntheses), the solid residue was then charged onto a short pad of silica gel and washed with hexane. This removed other nonpolar and nonvolatile byproducts, such as alkyne dimers. Finally, the pad was washed with dichloromethane/hexane (4:6) [polar byproducts such as bis(4-fluorophenyl)urea, the catalyst, and the excess amount of phenanthroline ligand were not eluted under these conditions], and the filtrate was evaporated in vacuo to give a product (62% yield), whose ^{1}H NMR spectrum (Supporting Information) is almost indistinguishable from that of a sample purified by a lengthier and less-scalable chromatography.

Supporting Information (see footnote on the first page of this article): NMR and mass spectroscopic data for 3-(4-fluorophenyl)-indole (**3c**).

Acknowledgments

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