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Tandem Hydroformylation/Fischer Indole Synthesis: A Novel and Convenient Approach to Indoles from Olefins

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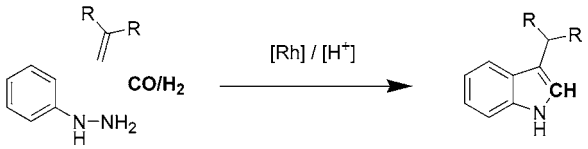
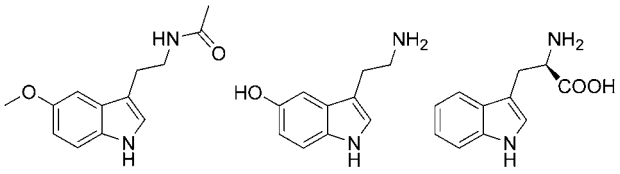
ABSTRACT



A novel one-pot synthesis of indole systems via tandem hydroformylation/Fischer indole synthesis starting from olefins and arylhydrazines is described. This tandem procedure leads directly to 3-substituted indoles if unsubstituted phenylhydrazine is used and to 3,5- respectively 3,7-disubstituted indoles if para- or ortho-substituted arylhydrazines are used.

Due to the great variety of indole units in natural products and pharmaceutical compounds, even today the development of new syntheses is the subject of considerable efforts.[1] Thus, numerous indole derivatives with biological activity like the tissue hormone melatonin (**1**), the neurotransmitter serotonin (**2**), and the essential amino acid tryptophane (**3**) have been synthesized by new methods.[1]



Fischer indole synthesis is one of the most important approaches to indoles.[2−4] In this reaction, aldehydes or ketones condense with arylhydrazines to arylhydrazones, which undergo a [3,3]-sigmatropic rearrangement to indoles in the presence of a Brønstedt resp. Lewis acid. Since under these conditions aldehydes tend toward side reactions, acetals or aminals are often used instead with in situ generation of the free aldehydes.[3,4]

For the synthesis of aldehydes, hydroformylation of olefins is known as an industrially important method[5] and, in various cases, this procedure has been used to generate the aldehydes required for the Fischer indole synthesis. Thus, hydroformylation of ortho nitro styrenes yields branched aldehydes and, under the same conditions, the nitro group is reduced to an amino group. Intramolecular condensation leads then to the indole core.[6] More recently, Sheldon et al. reported a one-pot synthesis of melatonin **1** starting from *N*-allylacetamide via regioselective hydroformylation and Fischer indole synthesis, although in this procedure reaction vessels were changed as well as the reaction conditions.[7] Following our own interests in tandem hydroformylation procedures,[8] we envisaged a protocol allowing the indole formation to proceed directly under the hydroformylation conditions in the presence of the aryl hydrazine and a Brønstedt, resp. Lewis acid. This tandem approach includes three steps: the

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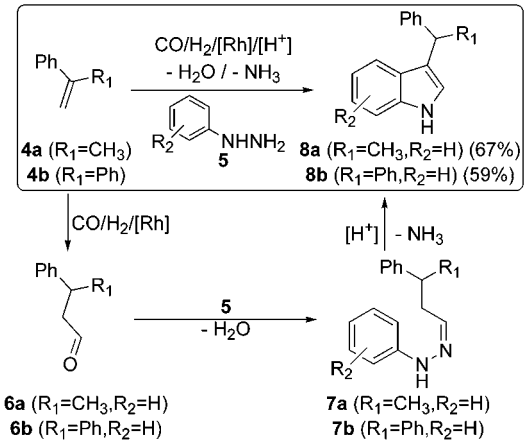
in situ generation of oxo aldehyde **6**, its conversion to aryl hydrazones **7**, and the [3,3]-sigmatropic rearrangement to the final product **8**. For this, if starting from a terminal olefin **4**, hydroformylation must regioselectively lead to aldehyde **6**. This, without isolation or side reactions, must selectively condense under the same reaction conditions with the aromatic hydrazine **5** to give the aryl hydrazone **7,** which again without isolation or hydrogenation should cyclize to the indole **8** (Scheme 1).

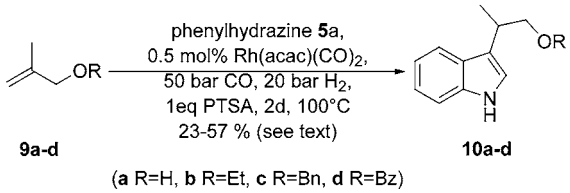
Scheme 1. Tandem Hydroformylation/Fischer Indole Synthesis of Styrenes **4** with Aryl Hydrazines **5** to Indoles **8**



We started our own investigations with studies to perform the individual steps under optimized hydroformylation conditions and then combining them to a tandem sequence. First we tested the indolization of preformed arylhydrazones with different Brønstedt acids under hydroformylation conditions. The indolization with 1 equiv of *p*-toluenesulfonic acid (PTSA) proceeded smoothly in good yields and without loss of hydrazone due to hydrogenation. In the next step, we combined formation of the arylhydrazone and the Fischer reaction. Therefore, the oxo aldehyde of α-methylstyrene (**4a**) was converted to the indole in the presence of phenylhydrazine and PTSA under hydroformylation conditions. Finally, we merged all three steps together into a single procedure starting from α-methylstyrene (**4a**) and 1,1-diphenylethene (**4b**). These nonfunctionalized 1,1-disubstituted olefins, upon hydroformylation, preferably form the linear aldehydes, whereas hydroformylation of monosubstituted olefins leads to a mixture of linear and branched regioisomers and therefore requires additional regiocontrolling P ligands (see below). Under the optimized conditions (0.5 mol % $[RhCl(cod)]_2$ or $Rh(CO)_2(acac)$, 50 bar CO + 20 bar H_2, 100−120 °C), α-methylstyrene (**4a**) and 1,1-diphenylethene (**4b**) in the presence of equimolar amounts of phenylhydrazine (**5a**) and PTSA gave the substituted indoles **8a** and **8b** in 59−67% yield (Scheme 1).[9]

Encouraged by these first examples of successful tandem hydroformylation/Fischer indole sequence starting from alkenes and phenylhydrazine, we extended the procedure to functionalized olefins such as methallylic alcohols and amines. Both allow *n*-selective hydroformylation, and their Fischer indolization would lead to pharmaceutically interesting tryptophole and tryptamine derivatives. Use of methallyl alcohol (**9a**) provided only a 28% yield of the desired indole **10a** (Scheme 2). To prevent potential side reactions such as

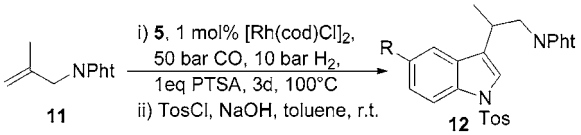
Scheme 2. Tandem Hydroformylation/Fischer Indole Synthesis of Methallylic Alcohols **9** to Tryptopholes **10**



intramolecular hemiacetalization, followed by acid-catalyzed elimination and hydrogenation, the use of protecting groups appeared to be necessary. While the use of ether groups, like in ethyl ether **9b** or in benzyl ether **9c**, did not increase the yields (25% for **10b** and 23% for **10c**), the use of electron-withdrawing groups, like the benzoyl group **9d**, improved the performance to 57% isolated yield **10d** (Scheme 2).

Similar results were obtained with use of methallylic amines. Here the use of nonprotected amines is not possible, since it is known that primary and secondary amines undergo condensation with oxo aldehydes to imines and enamines, which are then hydrogenated under hydroformylation conditions in an overall "hydroaminomethylation".[8] Of all tested N-protecting groups (benzyl, acetyl, benzoyl, phthalimide), only phthalimide **11**, as the strongest electron-withdrawing group, led to a successful tandem hydroformylation/Fischer indole reaction to form **12a** in 60% yield (Table 1). To simplify purification, the crude products were tosylated.[3,4]

Table 1. Tandem Hydroformylation/Fischer Indole Synthesis of Methallylic Phthalimide (**11**) to Tryptamines **12**



hydrazine **5**	yield
5a (R = H)	60% (**12a**)
5b (R = 4-Cl)	53% (**12b**)
5c (R = 4-*tert*-butyl)	48% (**12c**)

Substituents at the aryl nucleus of the hydrazine are tolerated, thus 4-chloro-phenylhydrazine **5b** and the 4-*tert*-butyl analogue **5c** lead to indoles **12b** (53%) resp. **12c** (48%).

(9) For further experimental details, see Supporting Information.

(Table 1). Substituents of this type are found in various pharmaceutically active compounds. No side products were found in these conversions, which led to protected tryptophole and tryptamine derivatives in satisfying yields.

For further optimizations, we thought to protect the hydrazine unit also, since it was observed that in various cases the initial reaction mixtures turned solid after a short period of time, due to protonation of aryl hydrazine. A heterogeneous system, however, could hamper the performance of the whole tandem sequence. An additional protection of the hydrazine could circumvent this problem if an acid-sensitive group is chosen that liberates the hydrazine to allow condensation with the in situ-formed oxo aldehyde. The benzhydrylidene group appeared to be compatible with these needs. Buchwald et al. had demonstrated that benzhydrylidene aryl hydrazines can be synthesized from aryl halides by using the palladium-catalyzed amination protocol. The products were directly converted via Fischer indolization.[10] Thus, for a tandem hydroformylation/Fischer indole procedure, various new aryl hydrazines can be synthesized directly in their protected form starting from aryl iodides or aryl bromides and benzophenone hydrazone using Buchwald−Hartwig methodology. On the other hand commercially available aryl hydrazines are easily protected by condensation with benzophenone.

For initial investigations, the conversion of α-methylstyrene (**4a**) with 4-chloro-phenylhydrazine (**5b**) resp. its benzhydrylidene derivative **5d** under hydroformylation conditions was compared. As shown in Scheme 2, use of the protected hydrazine increases the yield of indole **13** from 18 to 68%. The conversion appeared to proceed much smoother with fewer side reactions, and workup was facilitated without requiring NH protection via tosylation. Consequently, the same methodology was applied to methallylic phthalimide (**11**) and the protected phenylhydrazines **5d**−**h** to obtain tryptamines **12d**−**h** with yields up to 78% (for **12d**). Again, considerably higher yields are achieved if compared with the results in Table 2. Various halogen substituents are tolerated in different positions, thus offering access to further conversions using palladium-catalyzed cross-coupling reactions with wide variability. Pharmaceutically active tryptamines and tryptopholes usually contain linear side chains in the 3-position of the indole core. In contrast to other established tryptamine syntheses, the tandem hydroformylation/Fischer indole procedure allows flexible access to systems with different chain lengths and branched or substituted side chains depending on the alkene availability.

On the other hand, nonbranched tryptopholes and tryptamines should be obtainable, if starting from allylic alcohols and amines via *n*-selective hydroformylation. Typically, allylic alcohols and amines, however, tend to lower *n/iso* ratios if compared to normal terminal alkenes, due to intramolecular coordination of the hydroformylation catalyst to the allylic functionality. Therefore, sterically demanding bidentate ligands such as BIPHEPHOS or XANTHPHOS are usually added to the reaction mixture leading to higher *n/iso* ratios and requiring considerably milder hydroformylation conditions. For our initial investigations, various protected allylic alcohols and the phthalimide-protected allylic amine were used. The results are compiled in Table 3.

Indeed, with BIPHEPHOS these allylic systems exclusively gave the indoles derived from the *n*-products, although only in much lower yields as compared to the results with the analogous methallylic. It is assumed that elimination

Scheme 3. Use of Benzhydrylidene-Protected Aryl Hydrazine **5d** in Tandem Hydroformylation/Fischer Indole Synthesis.

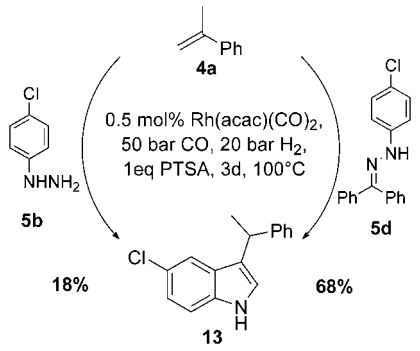
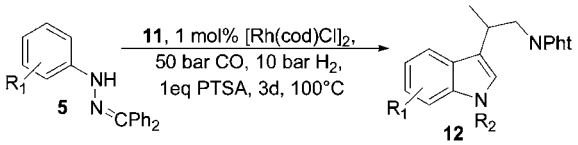


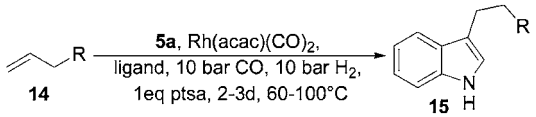
Table 2. Use of Benzhydrylidene-Protected Aryl Hydrazines **5** in the Tandem Hydroformylation/Fischer Indole Synthesis of Methallylic Phthalimide (**11**) to Tryptamines **12**



hydrazine **5** yield

hydrazine **5**	yield
5d (R_1 = 4-Cl)	78% (**12d**; R_1 = 5-Cl; R_2 = H)
5e (R_1 = H)	76% (**12e**; R_1 = H; R_2 = H)
5f (R_1 = 2-CH_3)	48% (**12f**; R_1 = 7-CH_3,R_2 = H)
5g (R_1 = 4-Br)	50% (**12g**; R_1 = 5-Br; R_2 = H)
5h (R_1 = 2-Cl)	42% (**12h**; R_1 = 7-Cl; R_2 = H)

Table 3. Allylic Alcohols and Allylic Phthalimide **14** in the Tandem Hydroformylation/Fischer Indole Synthesis Leading to Tryptopholes and Tryptamines **15**



olefin ligand yield

olefin	ligand	yield
14a (R = OH)	BIPHEPOS	17% (**15a**)
14b (R = OBn)	BIPHEPOS	20% (**15b**)
14c (R = OBz)	BIPHEPOS	13% (**15c**)
14d (R = NPhth)	BIPHEPOS	26% (**15d**)
14d (R = NPhth)	XANTHPHOS	46% (**15d**)

reactions of the products to form sensitive vinyl indoles are responsible. Indeed, when using allylic alcohol as the starting olefin, 3-ethylindole was isolated as a product of tryptophole (**15a**) formed via dehydration and hydrogenation of the resulting 3-vinylindole. Protection of the alcohol functionality could only insufficiently suppress these consecutive reactions and did not increase the yields (up to 23% for **15b** and **15c**). If allylic phthalimide tryptamine was used, **15d** was obtained with only 26% yield and an *n*/*iso* ratio of 2:1. The poor *n*/*iso* ratio may be caused by the fact that phosphite ligands are less stable in the presence of aldehydes and undergo acid-catalyzed decomposition.[11] Therefore, either an increase in the ligand-to-catalyst ratio or a more stable ligand may solve this problem. Use of the biphosphane ligand XANTHPHOS instead of the biphosphite BIPHEPHOS indeed led to complete *n*-regioselectivity with increased yields of tryptamine **15d** (46%) (Table 3).[12] At present, until further optimizations are successful, the stepwise procedure is advantageous for higher yields and regioselectivities. Thus, in various examples, the stepwise hydroformylation of allylic amines in the presence of aryl hydrazines led to the corresponding hydrazones with complete *n*-selectivity and quantitative yields. Their indolization allows a fast and high-yielding approach to pharmaceutically potent tryptamine derivatives and numerous analogues.

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Supporting Information Available: Experimental procedures and full spectroscopic and analytical characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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