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Facile and Efficient Synthesis of Pyrroles and Indoles *via* Palladium-Catalyzed Oxidation of Hydroxy-Enamines and -Amines

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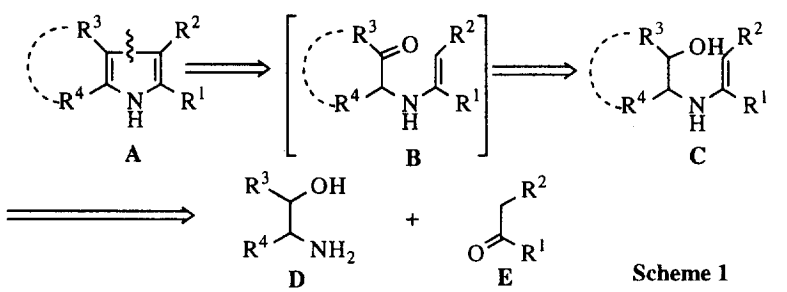
Abstract: The palladium-catalyzed oxidation of hydroxy-enamines, which were obtained by the condensation of β–aminoalcohols and carbonyl compounds, proceeded to give the corresponding polysubstituted pyrroles and 4,5,6,7-tetrahydroindoles in good yields. The treatment of *o*-(2-hydroxyethyl)aniline with the palladium catalyst also gave indole in 78% yield.

Highly functionalized pyrroles are subunits of considerable importance in heme, chlorophyll, related natural products such as the bile pigments, vitamin B_{12} and the pyrrole alkaloids from marine sources.[1] Recently, there has been considerable interest in the development of methodology for accessing these compounds. Therefore, since Knorr reported the first synthesis of pyrroles at the end of the last century,[2] a variety of syntheses for substituted pyrroles has been described.[1] Also, alternative pyrrole syntheses have been developed. For example, the pyrrole synthesis based on the Lewis acid-mediated reaction of readily available 2-acetoxypropanal *N, N*-dimethylhydrazone with cyclic and open chain silyl enol ethers was reported by Enders *et al.*[3] On the other hand, Fürstner *et al.* described the low-valent titanium-mediated approach to pyrroles. [4] In addition, the pyrrole synthesis *via* [2+3] cycloaddition reactions of *S*-methyl *N*-(benzotriazol-1-ylmethyl)-thioimidate with α,β-unsaturated esters, ketones, nitriles, and vinylpyridines was described.[5] The convenient synthesis of 2-cyanopyrroles from isocyanoacetonitrile has also been reported.[6]

The efficient palladium-catalyzed oxidation of alcohols to carbonyl compounds with carbon tetrachloride and aryl bromide was reported by Tsuji *et al.*[7] and Yoshida *et al.*,[8] respectively. Further, Choudary *et al.* reported the palladium acetate-catalyzed oxidation of primary and secondary alcohols to aldehydes and ketones at room temperature under phase transfer conditions.[9] During our research on the palladium-catalyzed reactions, we have found that the oxidation of β-hydroxy-enamine and *o*-(2-hydroxyethyl)aniline by utilizing the palladium-catalyzed oxidation systems reported by Yoshida and Tamaru[8] gave the corresponding pyrroles and indoles. In this communication, we wish to describe the alternative facile and efficient synthesis of pyrroles and indoles *via* the palladium oxidation of β-hydroxy-enamine and *o*-(2-hydroxyethyl)aniline.

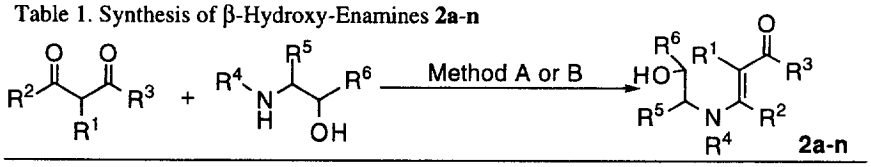


Scheme 1

As indicated in Scheme 1, pyrrole **A** is considered to be produced *via* cyclization of the β-keto-enamine **B**, a common key intermediate between the Knorr's synthesis and the present procedure, which should be obtained by the palladium-catalyzed oxidation of the β-hydroxy-enamine **C**. Finally, the retrosynthetic analysis of intermediate **C** should trace us back to the β-aminoalcohol **D** and β-dicarbonyl compound **E**.

The synthesis of the β-hydroxy-enamines was carried out according to the usual procedures (Methods A and B) (Table 1). Namely, the condensation of commercially available β-dicarbonyl compounds with β-amino alcohols, which are prepared by the reduction of amino acids with lithium aluminum hydride,[10] gave the corresponding β-hydroxy-enamines in good to excellent yields.

Table 1. Synthesis of β-Hydroxy-Enamines **2a-n**



2a-n

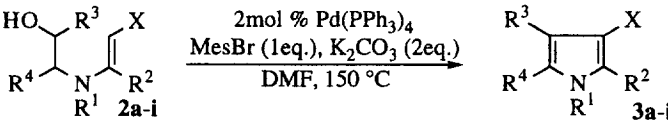
	Ketones			β-Amino alcohols				
Entry	R^1	R^2	R^3	R^4	R^5	R^6	Methods[a]	Products **2** (Yields %)[b]
1	H	Me	OEt	H	Bn	H	A	**2a** (96)
2	H	Me	OEt	H	Ph	H	A	**2b** (97)
3	H	Me	OEt	H	^{i}Pr	H	A	**2c** (93)
4	H	Me	OEt	H	H	H	A	**2d** (73)
5	H	Me	OEt	H	H	Me	A	**2e** (84)
6	H	Me	OEt	H	H	Ph	A	**2f** (99)
7	H	Me	Me	H	Me	H	A	**2g** (77)
8	H	Ph	OEt	H	Bn	H	B[c]	**2h** (50)
9	H	Me	OEt	Me	H	H	B	**2i** (52)
10	H	Me	OEt	$-(CH_2)_3-$		H	A	**2j** (97)
11	$-(CH_2)_3-$		OEt	H	Bn	H	A	**2k** (54)
12	$-(CH_2)_4-$		OEt	H	Bn	H	B	**2l** (97)
13	H	Me	OEt	H	$-(CH_2)_4-$		A	**2m** (93)
14	H	$-(CH_2)_3-$		H	H	H	B[d]	**2n** (60)

[a] Method A: A THF solution (20 ml) of ketone (7.9 mmol), β-amino alcohol (9.4 mmol), and molecular sieves 4Å (5.0 g) was stirred at room temperature for 7 days under argon. Method B: A benzene solution (30 ml) of ketone (11.7 mmol), β-amino alcohol (14.9 mmol), and molecular sieves 4Å (15.0 g) was refluxed for 12 hrs under argon. [b] Isolated yields. [c] p-TsOH•H_2O was employed. [d] THF was used as the solvent instead of benzene.

Next, in the presence of a palladium catalyst, the oxidation of β-hydroxy-enamine **2a** was examined under several reaction conditions. When a mixture of β-hydroxy-enamine **2a**, tetrakis(triphenylphosphine)-palladium, mesityl bromide, potassium carbonate, and *N,N*-dimethylformamide (DMF) was heated at 150 °C, the pyrrole **3a** was obtained in 82 % yield. In the absence of either base, aryl bromide, or the palladium catalyst, this reaction did not proceed. Consequently, it has been found that the combination of tetrakis(triphenyl-phosphine)palladium as a catalyst, mesityl bromide as an oxidant, and potassium carbonate as a base gave the best result. Furthermore, the palladium-catalyzed oxidation of the β-hydroxy-enamines **2b-h** gave the corresponding pyrroles **3b-h** in moderate to good yields (Entries 2-8 in Table 2).[11] On the other hand, other oxidations such as Swern, PCC, and PDC oxidation of β-hydroxy-enamine **2e** led to decomposition. The pyrrole **3i** was obtained in low yield (Entry 9 in Table 2), since nucleophilic activity of *N*-susbstituted β-hydroxy-enamine **2i** is supposed to be lower.

To apply this reaction to the synthesis of the bicyclic pyrrole systems such as pyrrolizine, 4,5,6,7-tetrahydroindole, and unsubstituted indole skeletons, the oxidation of β-hydroxy-enamines **2j**, **m-n** and *o*-(2-hydroxyethyl)aniline **2o** was examined. While the pyrrolizine **3j** was obtained in low yield, 4,5,6,7-tetrahydroindoles **3m-n** and the unsubstituted indole **3o** were produced in moderate to good yields. Compounds **3m-n** are important intermediates for the synthesis of 4-substituted indoles such as pindolol.[12]

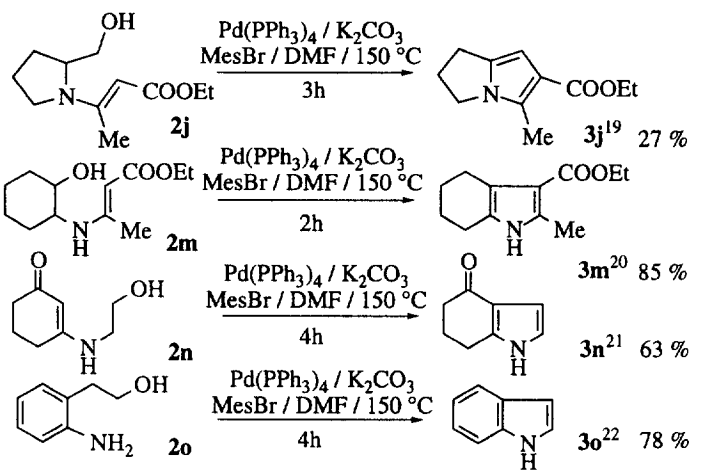
Table 2. Synthesis of Pyrroles **3a-i**



2a-i → **3a-i**

Entry	Substrates (2a-i)	R^1	R^2	X	R^3	R^4	Reaction Time (h)	Pyrroles (3a-i)[a] (Yields %)[b]
1	**2a**	H	Me	CO_2Et	H	Bn	2	**3a** (82)
2	**2b**	H	Me	CO_2Et	H	Ph	5	**3b**[13] (67)
3	**2c**	H	Me	CO_2Et	H	^iPr	4	**3c** (83)
4	**2d**	H	Me	CO_2Et	H	H	1	**3d**[14] (74)
5	**2e**	H	Me	CO_2Et	Me	H	3	**3e**[15] (76)
6	**2f**	H	Me	CO_2Et	Ph	H	5	**3f**[16] (80)
7	**2g**	H	Me	CO_2Me	H	Me	3.5	**3g**[17] (57)
8	**2h**	H	Ph	CO_2Me	H	Bn	4	**3h** (84)
9	**2i**	Me	Me	CO_2Et	H	H	2	**3i**[18] (36)

[a] All new compounds were fully characterized by ^{1}H-NMR, Mass and Ir spectometries. Satisfactory microanalyses were obtained. [b] Isolated yields.



Scheme 2

In conclusion, alternative, facile and efficient syntheses of pyrroles, 4,5,6,7-tetrahydroindoles, and indole have been developed. Compared with preexisting methods, the present one, which employs inexpensive and readily available starting materials such as amino acids, and proceeds in moderate to good yields, leads to a great practical value. Further work on the application of the present procedure for the synthesis of natural products is in progress.

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11. General procedure: The mixture of β-hydroxy-enamines or *o*-(2-hydroxyethyl)aniline (1mmol), mesityl bromide (1mmol), tetrakis(triphenylphosphine)palladium (0.025 mmol), potassium carbonate (2 mmol), and DMF (5 ml) was heated at 150 °C for the time listed in Table 2. The resulting mixture was poured into ice-water. The aqueous layer was extracted with Et_2O (20 ml x 3), and the combined organic solvent was dried over Na_2SO_4. The organic solvent was evaporated under reduced pressure to give an oily residue, which was purified by medium pressure liquid chromatography to give the corresponding pyrroles and indoles.
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22. Spectral datum of the synthetic **3o** were identical to those of a commercially available sample.

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