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New synthetic approaches to CNS drugs. A straightforward, efficient synthesis of tetrahydroindol-4-ones and tetrahydroquinolin-5-ones via palladium-catalyzed oxidation of hydroxyenaminones[†,‡]

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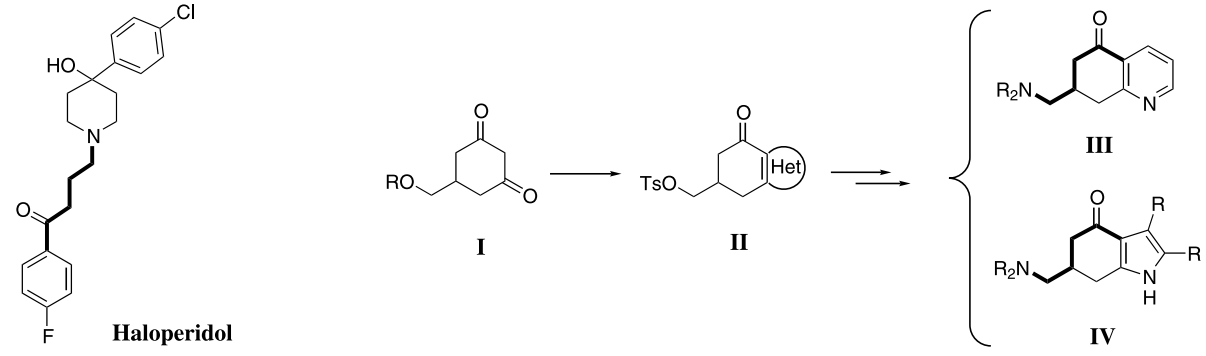
Abstract—We have developed a facile and efficient synthesis of new conformationally restricted butyrophenones in the indole and quinoline series via palladium-catalyzed oxidation of hydroxyenaminones, and subsequent cyclization followed by spontaneous aromatization.

Haloperidol (Haldol®, Jannsen 1959) is the prototype of a group of butyrophenone derivatives with a potent and antipsychotic activity. For some time, we have been interested in the utilization of cyclohexanedione **I** as a versatile synthon in the preparation of condensed heterocyclic systems as intermediates in the synthesis of butyrophenone-type CNS agents. In previous papers[1–3] we have reported the preparation (and in most of them, the antipsychotic activity as well) of heterocyclic constrained butyrophenones by nucleophilic substitution of the tosylate group in the corresponding heterocyclic condensed systems **II** with CNS amine building blocks.

Now, we want to study its use in the synthesis of tosylates of 7-hydroxymethyltetrahydroquinolin-5-ones and 6-hydroxymethyltetrahydroindol-4-ones as intermediates in the synthesis of conformationally constrained aminobutyrophenones in the tetrahydroquinoline and tetrahydroindole series (**III**, **IV**).

In previous papers[4,5] we have reported the preparation of 4,5,6,7-tetrahydroindol-4-one derivates by applying the Knorr pyrrole synthesis methodology to several 5-substituted-1,3-cyclohexanediones. For the synthesis of 2,3-unsubstituted tetrahydroindoles, a modification



Keywords: cyclic ketones; enamines; tetrahydroquinolines; tetrahydroindoles.

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‡ Dedicated to Professor B. S. Thyagarajan of the University of San Antonio (Texas) on the occasion of his retirement.

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of the Knorr method reported by Bobbit et al.[6] was used, giving the desired compounds in low yields.[4] The successful synthesis of pyrroles and indoles via palladium-catalyzed oxidation of hydroxyenaminones reported by Ohta[7] prompted us to extend this procedure to the preparation of our above mentioned compounds.

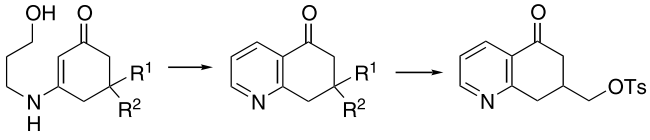
On the other hand, we have previously reported the preparation of several 7-aminomethyltetrahydroquinolin-5-ones with high affinity on CNS receptors, by using some strategies leading to the quinolinone ring.[2] Now, we have studied the application of the palladium-catalyzed oxidation of γ-hydroxyenaminones as a new approach to the synthesis of the above mentioned heterocycles.

In this communication we describe the alternative efficient synthesis of tetrahydroquinolin-5-ones and tetrahydroindol-4-ones from cyclohexanediones via palladium-catalyzed oxidation of β- and γ-hydroxyenaminones, respectively. The key step of the synthesis of tetrahydroquinolin-5-ones **4a–d** was the palladium-catalyzed oxidation of the hydroxyenaminones **3a–d** (Table 1) which were prepared by condensation of the β-dicarbonyl compounds **1a–d** with the corresponding β- or γ-aminoalcohols **2a–d** (Table 1), and subsequent cyclization followed by spontaneous aromatization.

The oxidation of the hydroxyenaminones **3a–d** in the presence of a palladium catalyst was examined under several reaction conditions. The best results were achieved when a mixture of hydroxyenaminone, mesityl bromide as oxidant, potassium carbonate, palladium acetate, and triphenylphosphine as cocatalyst, in DMF were heated at 150°C.[8] The amount of triphenylphosphine is a crucial factor for the success of the reaction; an excess greater than 3 equiv. considerably decreases the reaction rates. Other catalysts as tetrakis(triphenylphosphine)palladium(0) or dichlorobis(triphenylphosphine)palladium(II) proved to be less efficient. In the absence of either base, aryl bromide or palladium catalyst, the reaction did not proceed. Thus, the palladium-catalyzed oxidation of the γ-hydroxyenaminones gave the corresponding quinolin-5-ones in moderate yields (Table 2). The preparation of the sulfonate ester **5c**[9] was carried out from tetrahydroquinolin-5-one **4c** by BBr_3 demethylation and subsequent tosylation of the resulting crystalline alcohol, affording the white crystalline sulfonate ester **5c** (mp 119.5–120.5°C, toluene).

β-Hydroxyenaminones **3e–g** were prepared by condensation of 5-methoxymethyl-1,3-cyclohexanedione **1c** with β-aminoalcohols **2b–d** (3-amine-2-butanol **2c** was prepared by reduction of 3-nitro-2-butanol with ammonium formate and 2-amine-3-pentanol by synthesis of the α-oximinoketone of 3-pentanone and subsequent lithium aluminium hydride reduction). As in above, the key step was the cyclization of hydroxyenaminones, which was examined under several reaction conditions. The best yields were achieved when a mixture of β-hydroxyenaminones **3e–g**, in DMF and tetrakis(triphenylphosphine)-palladium(0), mesityl bromide, potassium carbonate was heated at 150°C.[10] Tetra-

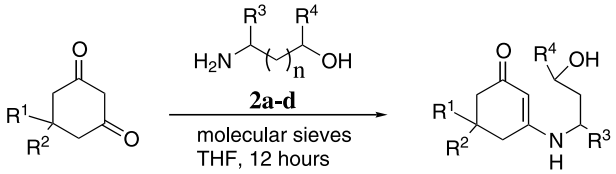
Table 2. Synthesis of tetrahydroquinolin-5-ones **4a–d**



3a-d **4a-d** **5c**

Entry	Substrate			Tetrahydroquinolin-5-one (Yield%)
		R^1	R^2	
1	**3a**	H	H	**4a** (30)
2	**3b**	CH_3	CH_3	**4b** (35)
3	**3c**	H	CH_2OCH_3	**4c** (35)
4	**3d**	H	CH_2OBn	**4d** (35)

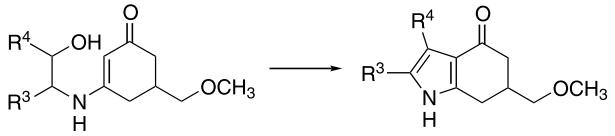
Table 1. Synthesis of hydroxyenaminones **3a–g**



1a-d **3a-g**

Entry	Ketone			Aminoalcohol				Product
		R^1	R^2		R^3	R^4	*n*	(Yield%)
1	**1a**	H	H	**2a**	H	H	1	**3a** (60)
2	**1b**	CH_3	CH_3	**2a**	H	H	1	**3b** (60)
3	**1c**	H	CH_2OCH_3	**2a**	H	H	1	**3c** (60)
4	**1d**	H	CH_2OBn	**2a**	H	H	1	**3d** (60)
5	**1c**	H	CH_2OCH_3	**2b**	H	H	0	**3e** (86)
6	**1c**	H	CH_2OCH_3	**2c**	CH_3	CH_3	0	**3f** (86)
7	**1c**	H	CH_2OCH_3	**2d**	CH_3	C_2H_5	0	**3g** (92)

Table 3. Synthesis of tetrahydroindol-4-ones **6e–g**



3e-g **6e-g**

Entry	Substrate			Tetrahydroindol-4-one	
		R^3	R^4	(Yield%)	Mp (°C)
1	**3e**	H	H	**6e** (40)	87–89
2	**3f**	CH_3	CH_3	**6f** (60)	141–142
3	**3g**	CH_3	C_2H_5	**6g** (70)	157–158

hydroindol-4-ones **6e–g** were thus obtained as white crystalline solids in moderate to good yields (Table 3).

In order to obtain the sulfonate esters, demethylation of **6e–g** was carried out by using 1 equiv. of BBr_3 at −70°C to +20°C affording the alcohols **7e–g** in good yields (Table 4). Tosylation of **7e–g** by using *p*-toluenesulphonyl chloride in pyridine gave the corresponding sulfonate esters **8e–g**[11] as white crystalline solids (Table 4).[12]

In conclusion, we have developed a facile and efficient synthesis of new conformationally restricted butyrophenones in the indole and quinoline series via palladium-catalyzed oxidation of hydroxyenaminones and subsequent cyclization followed by spontaneous aromatization. Because of the simplicity of the methodology and the shorter reaction times than those expected, this synthetic procedure proved to be attractive and of great practical value. This methodology provides a new approach to the synthesis of potential CNS-active agents. Work in progress in our Laboratory will be reported in due course.

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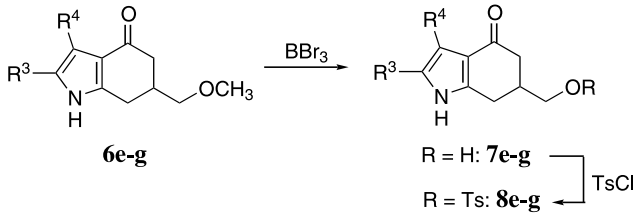
8. General Procedure: A mixture of the γ-hydroxyenaminone **3a–d** (1 mmol), mesityl bromide (1.1 mmol), palladium acetate (0.03 mmol), triphenylphosphine (0.06 mmol), potassium carbonate (1.2 mmol) and DMF (5 ml) was heated at 150°C for 4 h. The resulting mixture was filtered through a Celite pad and then evaporated under reduced pressure to give an oily residue, which was purified by column chromatography to give the corresponding quinolines.
9. Compound **5c**: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.68 (dd, 1H, $J=4.8$, 1.8 Hz, H-2), 8.24 (dd, 1H, $J=7.8$, 1.8 Hz, H-4), 7.78 (d, 2H, $J=8.3$ Hz, Ar), 7.35 (d, 2H, $J=8.1$ Hz, Ar), 7.30 (dd, 1H, $J=7.8$, 4.8 Hz, H-3), 4.10 (d, 2H, $J=5.5$ Hz, CH_2OTs), 2.93–2.83 (m, 1H, aliphatics), 2.65–2.55 (m, 4H, aliphatics), 2.46 (s, 3H, CH_3-Ph).

Table 4. Synthesis of 6-(*p*-toluenesulfonyloxymethyl)-4,5,6,7-tetrahydroindol-4-ones **8e–g**



6e-g

Entry	Substrate			Alcohol		Tosylate	
		R^3	R^4		Mp (°C)		Mp (°C)
1	**6e**	H	H	**7e**	169–171	**8e**	162–164
2	**6f**	CH_3	CH_3	**7f**	213–214	**8f**	207–209
3	**6g**	CH_3	CH_2CH_3	**7g**	178–180	**8g**	188–189

10. General Procedure: To a solution of the β-hydroxyenaminone **3e–g** (1 mmol) in 5 ml of DMF, mesityl bromide (1 mmol), tetrakis(triphenylphosphine)palladium(0) (0.025 mmol), and potassium carbonate (2 mmol) was added, and the mixture heated at 150°C for 2 h. After cooling, the mixture was filtered through a Celite pad and evaporated in vacuo to give an oily residue, which was purified by column chromatography to yield the corresponding indoles.
11. Compound **8f**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (s, 1H, NH), 7.78 (d, 2H, $J=8.3$ Hz, Ar), 7.35 (d, 2H, $J=8.2$ Hz, Ar), 4.01–3.99 (m, 2H, CH_2OTs), 2.93–2.83 (m, 1H, aliphatics), 2.64–2.56 (m, 2H, aliphatics), 2.46 (s, 3H, CH_3-Ph), 2.35–2.25 (m, 2H, aliphatics), 2.16 (s, 3H, CH_3), 2.11 (s, 3H, CH_3).
12. Complete details of the synthesis and spectral data will be published elsewhere in a full paper. All compounds gave satisfactory microanalyses (C, H, N ±0.4%) and spectral data (^{1}H and ^{13}C NMR, FTIR, MS). Yields given correspond to isolated pure compounds.