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One-Pot Synthesis of Pharmacologically Active Secondary and Tertiary 1-(3,3-Diarylpropyl)amines via Rhodium-Catalysed Hydroaminomethylation of 1,1-Diarylethenes

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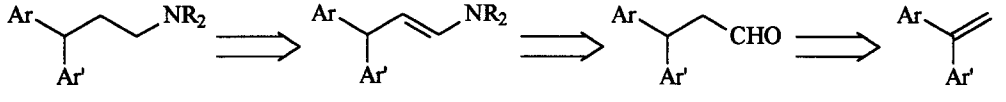
Abstract

Pharmacologically active secondary and tertiary 1-(3,3-diarylpropyl)amines **1** are prepared in high yields and chemoselectivity by the reaction of 1,1-diarylethenes **4**, primary or secondary amines **5**, carbon monoxide and hydrogen in presence of $[Rh(cod)Cl]_2/PBu_3$ as catalyst via a one-pot hydroformylation - amine condensation - reduction sequence.

Keywords: Hydroaminomethylation, Rhodium catalysis, Amines, Pharmaceutics, Carbonylation.

Numerous secondary and tertiary 1-(3,3-diarylpropyl)amines **1** possess pharmacological activity and are commercially obtainable therapeutic agents. Usually they are prepared via three or more step procedures not involving transition metal catalysis.[1] According to a retrosynthetic analysis these substrates should be more easily accessible via a hydroformylation - reductive amination sequence leading to an overall hydroaminomethylation of the starting alkene **4**.



1 **2** **3** **4**

Scheme 1.

Following this reaction pathway Botteghi et al. recently reported convenient stepwise syntheses of the 1-(3,3-diarylpropyl)amines fenpiprane **(1a)**, diisopromine **(1b)** and tolpropamine **(1c)** starting from simple 1,1-diarylethenes **4a,b**.[2]

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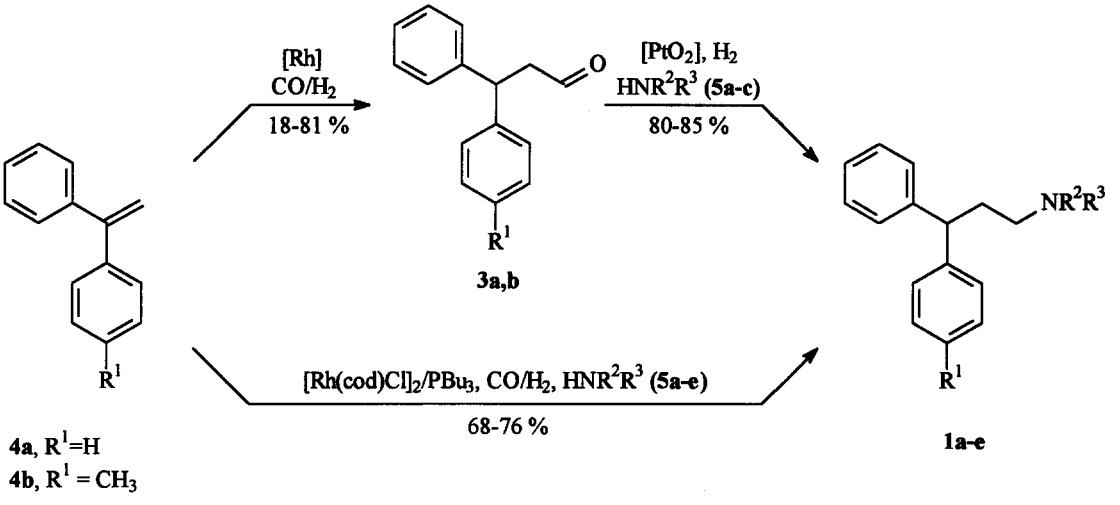
These substrates undergo selective rhodium(I) - catalysed hydroformylation (18-81 %) to the corresponding 3,3-diarylpropanals **(3a,b)**, which are converted in 80-85 % to the pharmaceutical agents **1a-c** by platinum catalysed reductive amination in the second step (scheme 2).[2a]



Scheme 2. Two-step[2a] and one-pot synthesis of 1-(3,3-diarylpropyl)amines **1a-e**

Reported attempts to carry out a one-pot hydroaminomethylation of 1,1-diphenylethene **(4a)** with piperidine **(5a)**, carbon monoxide and water gave only 20 % of the desired fenpiprane **(1a)**. Due to substrate hydrogenation 1,1-diphenylethane was isolated as the major product. Obviously the amines present modify the rhodium carbonyl catalyst towards a preferred substrate hydrogenation.[2,3] This drawback can only be circumvented if the amine is injected into the pressurised reaction vessel after completion of the hydroformylation step.[2a]

Following our own efforts in synthetic applications of the one-pot hydroaminomethylation[4] we selected the synthesis of 1-(3,3-diarylpropyl)amines **1** for a search for catalytically active systems and conditions in order to achieve a more convenient and efficient one-pot conversion starting from 1,1-diarylethenes **4** (scheme 2).

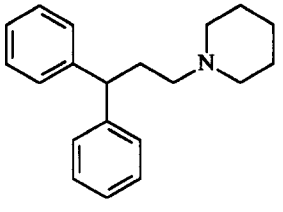
Using $[Rh(cod)Cl]_2$ (1 mol % Rh or lower) as catalyst precursor in the synthesis of fenpiprane **(1a)** from 1,1-diphenylethene **(4a)**, piperidine **(5a)**, carbon monoxide and hydrogen leads to direct hydroaminomethylation only with comparably low rates and selectivities (10 %) due to excessive hydrogenation (88 %). Substrate hydrogenation, however, is effectively suppressed if alkyl phosphine ligands such as PBu_3 are added. Depending on the PBu_3/catalyst ratio fenpiprane **(1a)** is obtainable in up to 72 % yields (entry 1, table 1). The best results are achieved with a

$PBu_3/[Rh(cod)Cl]_2$ ratio of 16/1 (1 mol % Rh) whereas lower phosphine/Rh ratios lead to lower selectivities.

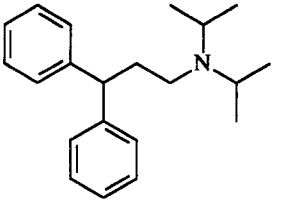
Table 1. One-pot hydroaminomethylation of **4a,b** to the therapeutic agents **1a-e**.

entry	olefin	amine	$P(Bu_3)$/[Rh] -ratio	conversion [%]	hydrogenation [%]	yield (1a-e) [%]
1	**4a**	piperidine (**5a**)	16/1	91	19	72 (**1a**)
2	**4a**	diisopropylamine (**5b**)	16/1	100	24	76 (**1b**)
3	**4b**	dimethylamine (**5c**)	16/1	88	12	70 (**1c**)
4	**4a**	hexamethylenimine (**5d**)	16/1	87	17	70 (**1d**)
5	**4a**	1-phenylethylamine (**5e**)	8/1	85	17	68 (**1e**)

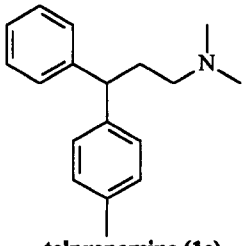
Using this procedure the spasmolytics and choleretics diisopromine **(1b)** and prozapine **(1d)** are obtained in good yields, if diisopropylamine (**5b**, entry 2) or hexamethylenimine (**5d**, entry 4), respectively, are added. The conversion of **4b** with dimethylamine, carbon monoxide and hydrogen in presence of $[Rh(cod]Cl]_2/PBu_3$ as catalyst gives the antihistaminic and antipuritic tolpropamine **(1c)** in comparably good yields (entry 3). Under similar reaction conditions with 1-phenylethylamine **(5e)** the coronardilator fendilline **(1e)** is obtainable in 68 % yield if a 8/1-$PBu_3/[Rh(cod)Cl]_2$-ratio is established (entry 5). With further increase of the phosphine ligand/Rh ratio (e.g. 32/1) the catalytically active system looses activity and the hydroaminomethylation rate slows down drastically. Here in low yields the corresponding imine is formed as the main by-product resulting from incomplete hydroaminomethylation.



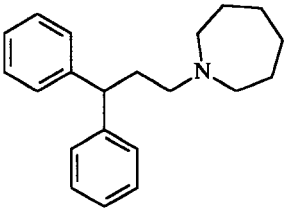
fenpiprane (1a)
(spasmolytic / antiallergic)



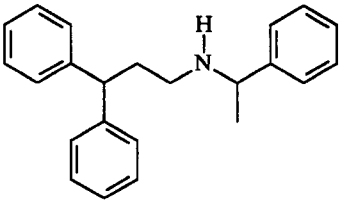
diisopromine (1b)
(spasmolytic / choleretic)



tolpropamine (1c)
(antihistaminic / antipuritic)



prozapine (1d)
(spasmolytic / choleretic)



fendilline (1e)
(coronardilatic)

Scheme 3. Pharmacologically active secondary and tertiary 1-(3,3-diarylpropyl)amines **1**[1,2]

In conclusion we have shown that the hydroaminomethylation with $[Rh(cod)Cl]_2/PBu_3$ as catalyst is an efficient method to transform 1,1-diarylethenes directly into pharmaceutically active secondary or tertiary amines. With this catalyst the enhanced tendency of 1,1-diarylethenes towards hydrogenation can effectively be suppressed. All olefins used in the reaction undergo selective one-pot hydroaminomethylation in high yields. Further investigations towards an extension of the synthetic potential of this reaction are in current progress.

EXPERIMENTAL

NMR spectra were recorded on Bruker spectrometers DPX 300 and DRX 400 using TMS as internal standard. IR spectra were obtained with a Nicolet Impact 400D, mass spectra on a Finnigan CA 5 and elementary analysis with a Leco CHNS-932. Column chromatography was carried out with aluminum oxide N (act. I) from ICN Biomedicals, Eschwege, by using MTBE (methyl *tert*-butyl ether)/PE (petroleum ether, bp 30-60 °C) mixtures as eluent. Gas chromatography was carried out on a Carlo Erba GC-4160 with 25 m or on a Fisons GC-8130 with 30 m CP sil-5 capillaries. GC-MS and GC-IR spectra were obtained by using comparable capillaries and a Finnigan MAT 8320 (MS) or a Bruker IFS 48 (IR), respectively. The $[Rh(cod)Cl]_2$ catalyst was prepared according to literature procedures.[5] Pressure reactions have been carried out in autoclaves (type A, 250 ml, PTFE-insert) from Berghof, Eningen, Germany.

General procedure for the hydroaminomethylation of the 1,1-diarylethenes 4a,b

A mixture of the olefin (7.2 mmol), the corresponding primary or secondary amine (7.2 mmol), $[Rh(cod)Cl]_2$ (1 mol % Rh) and a defined amount of tri-butylphosphine (PBu_3) (see table 1) in 10 ml anhydrous dioxane was heated for 3 d, at 120°C in an autoclave under 90 bar carbon monoxide and 20 bar hydrogen (p_{total} = 110 bar) pressure. The residue was dissolved in Et_2O and filtered through neutral alumina. Product mixtures were separated by column chromatography on neutral alumina using a mixture of MTBE/PE as eluent or by Kugelrohr distillation.

Fenpiprane, 1-(3,3-Diphenylpropyl)piperidine (1a).[1a-i,2] Obtained from 1,1-diphenylethene **(4a)** and piperidine **(5a)** in 71 % yield (entry 1, table 1). The spectroscopical data are identical to those in the literature.

Diisopromine, N-(3,3-Diphenylpropyl)-N,N-diisopropylamine (1b).[1a,j-m,2] Obtained from 1,1-diphenylethene **(4a)** and diisopropylamine **(5b)** in 76 % yield (entry 2, table 1). The spectroscopical data are identical to those in the literature.

Tolpropamine, N,N-Dimethyl-N-[3-(4-methylphenyl)-3-phenylpropyl]amine (1c).[1a,g,i,j,n,2] Obtained from 1-phenyl-1-(p-tolyl)ethene **(4b)** and dimethylamine **(5c)** in 70 % yield (entry 3, table 1). The spectroscopical data are identical to those in the literature.

Prozapine, 1-(3,3-Diphenylpropyl)azepane (1d).[1j,n-p] Obtained from 1,1-diphenylethene **(4a)** and hexamethylenimine **(5d)** in 70 % yield (entry 4, table 1). ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 1.57 (br s, 8 H, 4 x CH_2), 2.20 (~q, J = 7.7 Hz, 2 H, CH_2), 2.39 (t, ^{3}J = 7.7 Hz, 2 H, NCH_2), 2.56 (t, ^{3}J = 5.1 Hz, 4 H, 2 x NCH_2), 4.01 (t, ^{3}J = 7.7 Hz, 1 H, CH), 7.13 (m, 2 H, 2 x PhH), 7.23 (~d, J = 4.0 Hz, 8 H, 8 x PhH). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 26.8 (2 x CH_2), 28.0 (2 x CH_2), 33.4 (CH_2), 48.8 (CH), 55.3 (2 x NCH_2), 56.2 (NCH_2), 125.8 (2 x PhH), 127.7 (4 x PhH), 128.2 (4 x PhH), 144.9 (2 x Cq). GC-MS (EI, 70 eV): m/z (%) = 293 (M^+, 15), 165 (3), 112 (100), 58 (25). IR (NaCl/film) $\tilde{\nu}$ = 3083 w, 3060 w, 3036 m, 2926 s, 2856 m, 2810 m, 2774 m, 1599 w, 1493 m, 1450 m, 1359 w, 700 cm^{-1} s.

Fendilline, N-(3,3-Diphenylpropyl)-N-(1-phenylethyl)amine (1e).[1j,q-v] Obtained from 1,1-diphenyl-ethene **(4a)** and *S*-1-phenylethylamine **(5e)** in 68 % yield (entry 5, table 1). ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 1.28 (d, ^{3}J = 6.6 Hz, 3 H, CH_3), 2.20 (m, 2 H, CH_2), 2.44 (m, 2 H, NCH_2), 3.66 (q, ^{3}J = 6.6 Hz, 1 H, NCH), 3.96 (t, ^{3}J = 7.8 Hz, 1 H, CH), 7.23 (m, 15 H, 15 x PhH). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 24.2 (CH_3), 35.9 (CH_2), 45.9 (NCH_2), 48.9 (CH), 58.0 (NCH), 126.0 (2 x PhH), 126.4 (2 x PhH), 126.7 (PhH), 127.7 (4 x PhH), 128.25 (2 x PhH), 128.30 (4 x PhH). 144.6 (Cq), 144.9 (2 x Cq). GC-MS (EI, 70 eV): m/z (%) = 315 (M^+, 36), 300 (14), 251 (8), 207 (8), 181 (10), 165 (26), 147 (8), 134 (14), 120 (28), 105 (100), 91 (42), 71 (40), 51 (26). IR (NaCl/film) $\tilde{\nu}$ = 3304 w, 3083 w, 3060 m, 3026 s, 2961 s, 2929 s, 2863 m, 1599 w, 1493 s, 1450 s, 1377 w, 1369 w, 700 cm^{-1} vs.

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