# Notes

## New Synthetic Route to Pheniramines via Hydroformylation of Functionalyzed Olefins

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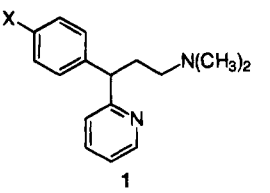
One of the most important class of antihistaminic agents is represented by pheniramines **1** (Figure 1).[1,2] Industrially, they are manufactured in racemic form by base-promoted reaction of phenylacetonitrile (or its *p*-chloro- and *p*-bromo derivatives) with 2-chloropyridine followed by alkylation of the resulting 2-pyridylphenylacetonitrile with 2-(dimethylamino)ethyl chloride and by removal of the cyano group.[3]

Alternatively, the appropriate benzyl chloride is used as alkylating agent of pyridine in the presence of copper to the corresponding α-benzylpyridines, which are in turn alkylated to pheniramines using 2-(dimethylamino)ethyl chloride in the presence of sodium amide.[3]

Brompheniramine (**1c**) (Dexbrompheniramine), which is commercialized mainly as pure dextrorotatory enantiomer (*S* configuration), is obtained, for example, by a resolution process using D-phenylsuccinic acid as the optically pure auxiliary.[4]

Owing to our interest in developing more efficient synthetic methods involving homogeneous catalysis to get pharmaceuticals,[5,6] we explored two new synthetic routes to pheniramines **1**,[7] using the rhodium-catalyzed hydroformylation of readily accessible olefinic substrates. The different strategies employed are depicted in Schemes 1 and 2.

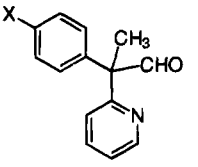
If the hydroformylation reaction of substrate **2** goes with good regiochemical control toward the formation of aldehyde **3**, a straightforward preparative pathway to pheniramines **1** would be opened, because these aldehydes can be easily converted by catalytic reductive amination[8,9] to the target products (Scheme 1).




**1**

**a**, X = H-; **b**, X = Cl-; **c**, X = Br-

**Figure 1.**




**4**

**a**, X = H-; **b**, X = Br-

**Figure 2.**

Unfortunately, the total yield of **3** obtained in a set of several hydroformylation experiments, carried out at 80–90 °C and 100 atm total pressure ($CO/H_2$ = 1:1) in benzene using various rhodium complexes as the catalytic precursors, was quite unsatisfactory, this catalytic reaction suffering from two main drawbacks: (i) the marked tendency of olefins **2** to undergo hydrogenation; (ii) the high regioselectivity promoted by the rhodium catalysts toward the formation of the more branched useless aldehydes **4** (Figure 2).

We have pointed out elsewhere the role played by the pyridine nitrogen in controlling the particular reactivity of this type of olefinic substrate **2** and in shifting the regioselectivity toward the production of the undesired isomeric aldehydes **4**.[10] The results obtained in the *oxo* reactions of olefins **2** can be summarized as follows: (1) only using $HRh(CO)(PPh_3)_3$ at 90 °C and 100 atm of an equimolecular mixture of $CO/H_2$ at 80/1 catalyst to substrate molar ratio, a chemoselectivity > 80% was obtained at 95% conversion; (2) the yields of linear aldehydes **3** were always <5% of the aldehydic products total yield; (3) benzene was the best solvent, more polar solvents like acetone, methylene chloride, and methanol being detrimental for the catalyst activity; (4) other rhodium complexes such as $Rh_4(CO)_{12}$, $(COD)Rh^+BPh_4^-$, $[RhCl(CO)_2]_2$ are much less active catalytic precursors; (5) other catalytic systems such as $Co_2(CO)_8$ and $(DPPB)PtCl_2/SnCl_2$ gave only hydrogenation products of the substrate.

The second synthetic approach to pheniramines **1** implies the construction of the pyridine ring from the aldehyde group introduced by hydroformylation in the framework of cinnamylamine **5** (Scheme 2). Reaction conditions and results obtained in some *oxo* experiments are summarized in Table 1.

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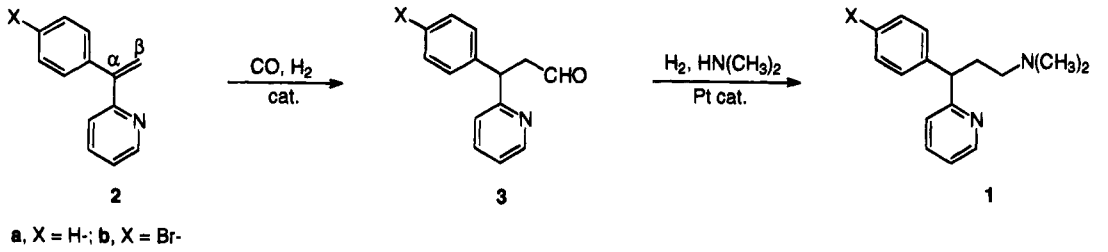
(1) Kleeman, A.; Engel, J. *Pharmaceutische Wirkstoffe;* George Thieme Verlag: Stuttgart, 1987.
(2) Elks, J.; Ganellin, G. R. *Dictionary of Drugs*; Chapman and Hall Ltd.: London, 1990.
(3) Kleeman, *A. Chem. Zeit.* **1977**, *9*, 389.
(4) Bayley, C. R.; Vaidya, N. A. *Chirality in Industry*; John Wiley & Sons: Chichester, 1992; p 71.
(5) Botteghi, C.; Paganelli, S.; Schionato, A.; Marchetti, M. *Chirality* **1991**, *3*, 355.
(6) Botteghi, C.; Del Ponte, G.; Marchetti, M. *J. Mol. Catal.* **1993**, *83*, L1.
(7) Marchetti, M.; Botteghi, C.; Paganelli, S.; Bigini, L.; Chelucci, G., Proceedings of *Xth FECHEM Conference on Organometallic Chemistry*, September 5–10, 1993, Crete, Greece; p P87.
(8) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis: Procedures and Commentary*; J. Wiley and Sons: New York, 1978; Chpt. 10.
(9) Klyuev, M. B.; Khidekel, M. L. *Russ. Chem. Rev.* **1980**, *49*, 14.
(10) Botteghi, C.; Paganelli, S.; Bigini, L.; Marchetti, M. *J. Mol. Catal.* **1994**, *93*, 279.

0022-3263/94/1959-7125$04.50/0 

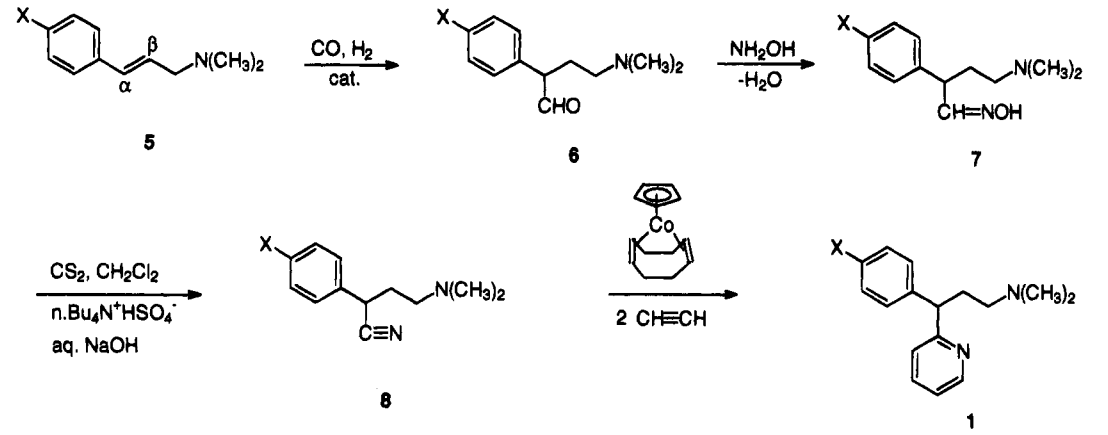
**Scheme 1**




2 3 1

a, X = H-; b, X = Br-

**Scheme 2**




5 6 7 8 1

a, X = H-; b, X = Cl-; c, X = Br-

**Table 1. Hydroformylation of *N,N*-Dimethylcinnamylamines 5 Catalyzed by Rhodium Complexes[a]**

| substrate | catalytic precursor | temp, °C | conv, % | hydrogenation yield, %[b] | hydroformylation yield, %[b] | α-isomer, % |
|---|---|---|---|---|---|---|
| **5a** | $HRh(CO)(PPh_3)_3$ | 80 | 99.2 | 8.1 | 91.1 | >99 |
| | $Rh_2O_3$ | 120 | 97.3[c] | 80.7 | 14.2 | >99 |
| | $(COD)Rh^+BPh_4^-$ | 120 | 96.2 | 80.9 | 15.3 | >99 |
| **5b** | $HRh(CO)(PPh_3)_3$ | 80 | 99.8 | 8.5 | 91.3 | 99 |
| | $Rh_2O_3$ | 120 | 98.7 | 92.3 | 6.4 | >99 |
| | $(COD)Rh^+BPh_4^-$ | 120 | 96.8 | 90.2 | 6.6 | >99 |
| **5c** | $HRh(CO)(PPh_3)_3$ | 80 | 99.0 | 7.5 | 91.5 | >99 |
| | $Rh_2O_3$ | 120 | 96.0 | 92.0 | 4.0 | >99 |
| | $(COD)Rh^+BPh_4^-$ | 120 | 94.2 | 86.7 | 7.5 | >99 |

[a] Substrate 6.2 mmol; benzene 10 mL; $P(CO) = P(H_2) = 50$ atm; reaction time 24 h; substrate to catalyst molar ratio 500:1. [b] Determined by GLC analyses. [c] 2.5% of high boiling byproducts were found; in the other experiments this amount was <1%.

The substrate hydrogenation becomes the main reaction when rhodium complexes not containing the triphenylphosphine ligand such as rhodium carbonyls (derived from anhydrous $Rh_2O_3$) or the zwitterionic complex $(COD)Rh^+BPh_4^-$ are used as the catalytic precursors. This fact is rather surprising taking into account that this latter complex showed to be an excellent catalyst for the hydroformylation of a wide range of olefins including substrates containing aromatic functions.[11] This points out the crucial role played by the phosphine ligand in the promoting the carbon monoxide insertion into rhodium–carbon bond of the intermediate σ-alkylrhodium complex and hence the formation of the aldehyde products.[12] Excellent regioselectivity was found when substrates **5** were subjected to the *oxo* reaction in the presence of various rhodium phosphine complexes. The pyridine moiety is then built cleanly in two steps (Scheme 2): (i) conversion of the aldehyde group of **6** into a cyano group, using $CS_2$ as the dehydrating agent of the intermediate aldoximes (85–90% yield);[13] (ii) cocyclotrimerization reaction of the dimethylamino nitriles **8** with acetylene catalyzed by ($\eta^5$-cyclopentadienyl)[*cis,cis*-(1,5-$\eta$)-cyclooctadienyl]cobalt.[14]

The overall yield of pheniramines **1** was about 70% based on compounds **5**. In conclusion, the rhodium-catalyzed hydroformylation of cinnamylamines **5** allows a new competitive synthetic route to pheniramines **1** to be performed.

## Experimental Section

**Materials.** $HRh(CO)(PPh_3)_3$ was prepared according to a well-known procedure.[15] The carbonyl complexes $Rh_4(CO)_{12}$ and $[RhCl(CO)_2]_2$ and $Co_2(CO)_8$ were Strem products. The zwitterionic complex $(COD)Rh^+BPh_4^-$ and $(DPPB)PtCl_2$ were prepared following previously described procedures.[16,17]

1-Phenyl-1-(2-pyridyl)ethene (**2a**) was prepared (80% overall yield) by Mannich reaction on 2-benzylpyridine with dimethylammonium chloride and paraformaldehyde followed by deamination using acetic anhydride and sodium acetate (reflux).[18] 1-(*p*-

(11) Amer, I.; Alper, H. *J. Am. Chem. Soc.* **1990**, *112*, 3674.
(12) Evans, D.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. A* **1968**, 3133.
(13) Shinozaki, H.; Imatzumi, M.; Tajima, M. *Chem. Lett.* **1983**, 929.
(14) Azzena, U.; Chelucci, G.; Delogu, G.; Gladiali, S.; Marchetti, M.; Soccolini, F.; Botteghi, C. *Gazz. Chim. Ital.* **1986**, *116*, 307.
(15) Ahmad, N.; Levison, J. J.; Robinson, S. D.; Uttley, M. F. *Inorg. Synth.* **1974**, *15*, 45.
(16) Schrock, R. R.; Osborn, J. A. *Inorg. Chem.* **1970**, *9*, 2339.
(17) Scrivanti, A.; Campostrini, R.; Carturan, G. *Inorg. Chim. Acta* **1988**, *142*, 187.
(18) Tramontini, M. *Synthesis* **1973**, 703.

Bromophenyl)-1-(2-pyridyl)ethene (**2b**) was prepared (27% overall yield) through dehydration of the corresponding tertiary carbinol deriving from the addition of the 2-lithiopyridine to *p*-bromoacetophenone.[19,20]

*N,N*-Dimethylcinnamylamine (**5a**) was obtained (89.3% yield) by reaction of cinnamyl bromide with *N,N*-dimethylamine as reported elsewhere;[21] *p*-chloro- (**5b**) and *p*-bromo-*N,N*-dimethylcinnamylamine (**5c**) were synthesized (61.0 and 65% yield, respectively) following a previously described procedure.[22]

Racemic pheniramine and its *p*-chloro and *p*-bromo derivatives were purchased as their maleate salts from Sigma Chemical Co.

Elemental analyses were performed using a Perkin Elmer Model 240C elemental analyzer. $^1$H NMR (300 MHz) spectra of $CDCl_3$ solutions were recorded using a Varian VXR 300s spectrometer.

**General Procedure for the Hydroformylation of Substrates 2a–c and 5a–c.** A mixture of the olefin (6.2 mmol) and rhodium complex (0.0121 mmol) in benzene (10 mL) was introduced in a 0.15 L stainless steel reaction vessel and pressurized to 100 atm with synthesis gas ($CO/H_2$ = 1:1). After 24 h at 80–120 °C (see Table 1) the reaction was completed. From the reaction mixture the aldehydes **3** and **4** were obtained by distillation under reduced pressure followed by purification using flash chromatography with 9:1 hexane/diethyl ether. The aldehydes **6** were isolated in satisfactory purity only by distillation under reduced pressure.

Compounds **3a,b**, **4a,b**, and **6a–c** gave satisfactory analytical data, and $^1$H NMR patterns were in agreement with their structures. **Compound 3a:** Anal. Calcd for $C_6H_5(C_5H_4N)$-$CHCH_2CHO$: C, 79.59; H, 6.21; N, 6.63. Found: C, 79.71; H, 6.30; N, 6.50. **Compound 4a:** Anal. Calcd for $C_6H_5(C_5H_4N)$-$C(CHO)CH_3$: C, 79.59; H, 6.21; N, 6.63. Found: C, 79.63; H, 6.24; N, 6.47. **Compound 3b:** Anal. Calcd for $C_6H_4Br(C_5H_4N)$-$CHCH_2CHO$: C, 57.95; H, 4.17; N, 4.83. Found: C, 58.05; H, 4.23; N, 4.66. **Compound 4b:** Anal. Calcd for $C_6H_4Br(C_5H_4N)$-$C(CHO)CH_3$: C, 57.95; H, 4.17; N, 4.83. Found: C, 57.98. **Compound 6a:** Anal. Calcd for $C_6H_5CH(CHO)CH_2CH_2N$-$(CH_3)_2$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.52; H, 9.09. Bp 60 °C/0.05 mmHg. **Compound 6b:** Anal. Calcd for $C_6H_4$-$ClCH(CHO)CH_2CH_2N(CH_3)_2$: C, 63.85; H, 7.15; N, 6.21. Found: C, 64.01; H, 7.28; N, 6.08. Bp 85 °C/0.05 mmHg. **Compound 6c:** Anal. Calcd for $C_6H_4BrCH(CHO)CH_{20}CH_2$-$N(CH_3)_2$: C, 53.35; H, 5.97; N, 5.18. Found: C, 53.80; H, 6.10; N, 4.90. Bp 115 °C/0.05 mmHg.

**General Procedure for the Conversion of Aldehydes 6a–c into Nitriles 8a–c.** Aldehydes **6a–c** were transformed into the corresponding aldoximes **7a–c** according to the experimental procedure described in the literature.[13] The yields are very high; the aldoximes were pure enough to be used as crude material.

To a solution of the crude aldoxime **7a** (3 g, 14.5 mmol), $Bu_4N^+HSO_4^-$ (4.9 mg, 0.0145 mmol), and $CS_2$ (1.3 g, 21.7 mmol) in 15 mL of methylene chloride was added dropwise 8 mL of 15% aqueous NaOH. The mixture was stirred for 0.5 h at room temperature, the organic layer was separated, and the aqueous phase was extracted with methylene chloride. The combined organic phase was dried ($Na_2SO_4$) and concentrated under reduced pressure. The resulting crude nitrile **8a** were purified by fractional distillation (2.6 g, 13.7 mmol, 95% yield).

Following the above described procedure **8b** and **8c** were obtained in 92 and 96% yield, respectively.

Compounds **8a–c** gave satisfactory analytical data and $^1$H NMR patterns were in agreement with their structures. **Compound 8a:** Anal. Calcd for $C_6H_5CH(CN)CH_2CH_2N(CH_3)_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.81; H, 8.63; N, 14.56. Bp 110 °C/0.1 mmHg; IR 2250 (s) cm$^{-1}$. **Compound 8b:** Anal. Calcd for $C_6H_4ClCH(CN)CH_2CH_2N(CH_3)_2$: C, 64.71; H, 6.79; N, 12.58. Found: C, 65.00; H, 6.84; N, 12.01. Bp 108 °C/0.05 mmHg; IR 2250 (s) cm$^{-1}$. **Compound 8c:** Anal. Calcd for $C_6H_4$-$BrCH(CN)CH_2CH_2N(CH_3)_2$: C, 53.95; H, 5.66; N, 10.48. Found: C, 54.17; H, 5.81; N, 9.86. Bp 120 °C/00.5 mmHg; IR 2252 (s) cm$^{-1}$.

**General Procedure for the Cocyclotrimerization Reaction of Nitriles 8a–c into Pheniramines 1a–c.** ($\eta^5$-Cyclopentadienyl)[(1,5-$\eta$)-cyclooctadienyl]cobalt (89.2 mg) was placed into a 0.15 l stainless steel pressure vessel. The reactor was sealed and evacuated to remove air, and a solution of **8a** (0.84 g, 4.46 mmol) in 45 mL of toluene was introduced by suction. The reactor was pressurized with acetylene at 14 atm and heated at 140 °C under stirring for 36 h. After cooling and gas release, the reaction mixture was worked up as previously described.[14] The expected pheniramine **1a** (0.91 g, 3.8 mmol) was obtained in 85% yield. Following the above described procedure, **1b** and **1c** were obtained in 75 and 70% yield, respectively. The chemical–physical properties of pheniramines **1a–c** obtained from nitriles **8a–c** were in perfect agreement with those of authentic samples.

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**Supplementary Material Available:** $^1$H NMR peak assignements and copies of the spectra of all compounds (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(19) Adamson, D. W.; Billinghurst, J. W. *J. Chem. Soc.* **1950**, 1039.
(20) Schubert, R.; Grützmacher, H. F. *J. Am. Chem. Soc.* **1980**, *102*, 5323.
(21) Young, W. G.; Webb, I. D.; Goering, H. L. *J. Am. Chem. Soc.* **1951**, *73*, 1076.
(22) Adamson, D. W.; Billinghurst, J. W.; Barret, P. A.; Jones, T. S. G. *J. Chem. Soc.* **1957**, 2315.