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S. Morris Kupchan,* Om P. Dhingra, Chang-Kyu Kim, Venkataraman Kameswaran
Department of Chemistry, University of Virginia Charlottesville, Virginia 22901
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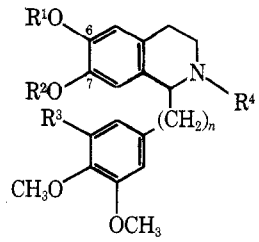
Efficient Intramolecular Monophenol Oxidative Coupling[1]

Summary: The remarkably efficient intramolecular oxidative couplings of monophenolic benzyltetrahydroisoquinolines **1a,b** to aporphines **4a,b** and of monophenolic phenethyltetrahydroisoquinolines **1c–g** to homoaporpines **4c–f,** spirodienones **2c–f,** and **6** are described.

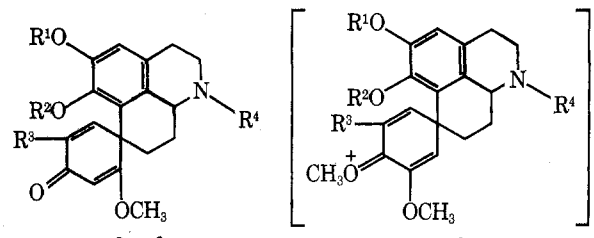
Sir: The important role played by diphenol oxidative coupling in the biosynthesis of alkaloids has been well documented and reviewed.[2] In general, laboratory attempts to effect intramolecular oxidative coupling of diphenols have suffered from low yields, mainly attributable to overoxidation. Recently, attention has been directed toward utilization of monophenolic substrates in an attempt to develop effective intramolecular oxidative coupling methods for use in alkaloid synthesis.[3–5] We report herewith the remarkable efficiency of the monophenol oxidative coupling method using VOF_3 for the syntheses of aporphines **4a,b,** homoproaporphines **2c–f,** homoaporphines **4c–f,** and homoproerythrinadienone **6.**

Treatment of a solution of (±)-*N*-trifluoroacetylnorcodamine (**1a**)[6,7] in CH_2Cl_2 with VOF_3 in trifluoroacetic acid (TFA)[8] at −10 °C for 10 min followed by aqueous workup gave (±)-*N*-trifluoroacetylwilsonirine[9] (**4a,** 70%, mp 196.5–197 °C) along with morphinandienone **5a**[10,11] (8%, mp 179.4–181.5 °C). Under the same conditions, oxidation of (±)-codamine (**1b**) gave a complex mixture of products from which only (±)-thalicmidine [**4b,** 38%, mp 191–193 °C dec (lit.[12] 190–192 °C)] was isolable. In contrast, an 80% overall yield of (±)-thalicmidine (**4b**) was obtained upon treatment of the borane complex[13] of **1b** with VOF_3–TFA (15 min at −10 °C) and subsequent removal of the blocking group by heating with anhydrous Na_2CO_3 in methanol under reflex. Morphinandienone **5b** could not be detected by thin layer chromatography in either of the latter experiments. The facile and high-yield conversions of **1a,b** to **4a,b** constitute the most efficient reported route to 1,2,9,10-tetrasubstituted aporphines.

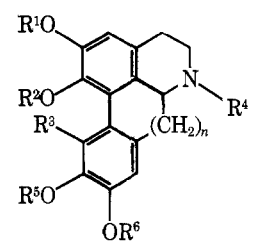
To evaluate the potential of the monophenol oxidative coupling method for the syntheses of homoaporphines and of homomorphinandienones such as the colchicine precursor *O*-methylandrocymbine,[14] 7-hydroxy-1-phenethyltetrahydroisoquinolines **1c–f** were prepared[7] and oxidized with VOF_3–TFA at −10 to −15 °C for 5–10 min. Thus the oxidation of **1c** yielded homoaporphine **4c**[15] (40%) along with homoproaporphine **2c** (18%, mp 192.5–193.5 °C), and **1d** gave homoproaporphine **2d** [42%, mp 200–201 °C dec (lit.[16] 200–202 °C)] along with homoaporphine **4d** [14%, mp 190–192 °C (lit.[17] 195–196 °C)]. Only one isomer of homoproaporphine **2c** or **2d** was obtained, in contrast to the diasteroisomeric mixture obtained by oxidation of diphenolic precursor **1d.**[15,16,18] Similarly, oxidation of **1e** yielded homoaporphine **4e** (46%, mp 161–162 °C) along with homoproaporphine **2e** (4%, mp 207–210 °C dec), and **1f** gave homoproaporphine **2f** [54%, mp



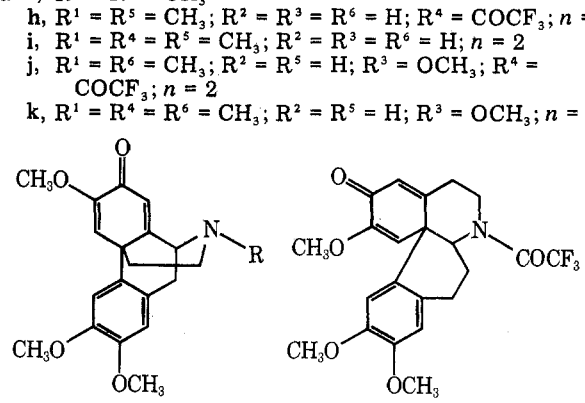
1a, $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = COCF_3$; $n = 1$
b, $R^1 = R^4 = CH_3$; $R^2 = R^3 = H$; $n = 1$
c, $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = COCF_3$; $n = 2$
d, $R^1 = R^4 = CH_3$; $R^2 = R^3 = H$; $n = 2$
e, $R^1 = CH_3$; $R^2 = H$; $R^3 = OCH_3$; $R^4 = COCF_3$; $n = 2$
f, $R^1 = R^4 = CH_3$; $R^2 = H$; $R^3 = OCH_3$; $n = 2$
g, $R^1 = R^3 = H$; $R^2 = CH_3$; $R^4 = COCF_3$; $n = 2$



2c–f **3c–f**



4a–f, $R^5 = R^6 = CH_3$
h, $R^1 = R^5 = CH_3$; $R^2 = R^3 = R^6 = H$; $R^4 = COCF_3$; $n = 2$
i, $R^1 = R^4 = R^5 = CH_3$; $R^2 = R^3 = R^6 = H$; $n = 2$
j, $R^1 = R^6 = CH_3$; $R^2 = R^5 = H$; $R^3 = OCH_3$; $R^4 = COCF_3$; $n = 2$
k, $R^1 = R^4 = R^6 = CH_3$; $R^2 = R^5 = H$; $R^3 = OCH_3$; $n = 2$



5a, R = $COCF_3$
b, R = CH_3 **6**

174–176 °C (lit.[16] 176–178 °C)] along with (±)-kreysigine [**4f,** 16%, mp 185–186 °C (lit.[16] 187–189 °C)]. No homomorphinandienone could be detected by thin layer chromatography in any of the above experiments. Homoproaporphines **2c, 2d, 2e,** and **2f** underwent smooth dienone–phenol rearrangements[16,19] upon treatment with BF_3–Et_2O in CH_2Cl_2 at room temperature[20] and afforded homoaporphines **4h** (93%, mp 167–168 °C), **4i** [70%, mp 241–242 °C dec (lit.[19] 241–242 °C)], **4j** (87%, mp 208–208.5 °C), and **4k** [(±)-multifloramine, 72%, mp 185–188 °C dec (lit.[16] 190–192 °C dec)], respectively. The formation of homoproaporphines **2c–f** and of homoaporphines **4c–f** in the oxidations of phenethyltetrahydroisoquinolines **1c–f,** and the demonstrated facile acid-catalyzed rearrangements of homoproaporphines **2c–f** to homoaporphines **4h–k** suggested that the formation of homoaporphines **4c–f** from monophenolic phenethyltetrahydroisoquinolines **1c–f** may proceed via homoproaporphine-type intermediates (**3c–f**)

and, in part, via direct coupling. Thus, the homoaporphines **4c–f** might be obtained in high yields if enough time were allowed for rearrangement of the corresponding homoproaporphine-type intermediates. Indeed, the phenethylisoquinolines[21] **1c, 1d,** and **1e** gave homoaporphines **4c** (77%), **4d** (60%), and **4e** (54%), respectively, upon treatment with VOF_3–TFA for 30–50 min.

Finally, 6-hydroxy-1-phenethyletetrahydroisoquinoline **1g** was subjected to the VOF_3–TFA oxidation (10 min at −10 °C) and homoproerythrinedienone **6**[15] was obtained in 98% yield.

The smooth intramolecular oxidative coupling reactions of monophenolic benzyl- and phenethyltetrahydroisoquinolines contrast remarkably with the results of most prior studies of oxidative cyclization of diphenolic precursors.[2] Further investigations are in progress to evaluate the potential of the monophenol oxidative coupling reactions for the synthesis of other alkaloids.

References and Notes

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(6) Benzyl- and phenethyltetrahydroisoquinolines **1a–g** were prepared by a standard method, i.e., condensation of benzyloxyphenethylamines and acids to the corresponding amides followed by Bischler–Napieralski cyclization, $NaBH_4$ reduction, N-acetylation or N-methylation, and subsequent debenzylation by hydrogenolysis.
(7) All new compounds were characterized by concordant analytical and spectral data. The structural formulas containing asymmetric atoms refer to racemic mixtures.
(8) In a typical oxidation 1 mmol of the substrate [0.05 M solution in methylene chloride containing 20% TFA–TFAA (20:1 by weight)] was treated with 2.5 molar equiv of VOF_3 [dissolved in a minimum volume of a 1:1 solution of ethyl acetate and TFA–TFAA (20:1 by weight)].
(9) Alkaline hydrolysis of **4a** and subsequent N-methylation (HCHO–$NaBH_4$) afforded (±)-thalicmidine[12] (**4b,** 80%).
(10) The structure of **5a** was confirmed by alkaline hydrolysis to the secondary amine, conversion of the secondary amine to the *N*-methyl dienols by treatment with HCHO–$NaBH_4$, and subsequent oxidation of the dienols to (±)-*O*-methylflavinantine[11] (**5b,** 65%).
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(13) The borane complex of **1b** was prepared[3] as an amorphous solid (99%) by treatment of **1b** in $CHCl_3$ with BH_3–THF and passage through a silica gel column using $CHCl_3$ as eluent.
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(20) Rearrangements of **2c–e** to **4h–j** were complete within an hour. However, conversion from **2f** to **4k** was very slow and required a much longer reaction time (overnight).
(21) The compound **1f** failed to give homoaporphine **4f** in high yield even after longer reaction time, probably owing to slow rearrangement[20] of homoproaporphine-type intermediate **3f.**

S. Morris Kupchan,* Om P. Dhingra, Chang-Kyu Kim
Department of Chemistry, University of Virginia
Charlottesville, Virginia 22901
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