

Thallium in Organic Synthesis. Synthesis of (\pm)-Ocoteine by Non-phenolic Coupling with Thallium Tris(trifluoroacetate) (TTFA)¹

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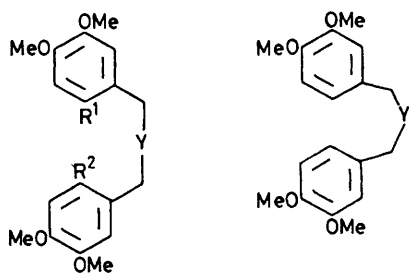
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Summary (\pm)-Ocoteine (**8**), the acetoxy aporphine (**9**), and 5,7-dihydro-2,3,9,10-tetramethoxydibenzo[*c,e*]oxepin (**5**) have been synthesized by direct non-phenolic coupling with thallium tris(trifluoroacetate) (TTFA).

NON-PHENOLIC oxidative coupling reactions are currently receiving considerable attention.² We have recently described³ a remarkably easy aryl coupling reaction leading to symmetrical biaryls using thallium tris(trifluoroacetate) (TTFA) as the coupling (oxidizing) reagent. Included among our examples was the intramolecular coupling of 1,3-(3,4-dimethoxyphenyl)propane (**1**) to give the corresponding bridged biphenyl (**4**) in 81% yield. If this oxidative coupling process could accommodate the presence of basic hetero atoms, a convenient and greatly simplified approach to a large number of intriguing heterocycles, including aporphine and homoaporphine alkaloids, would be in hand.

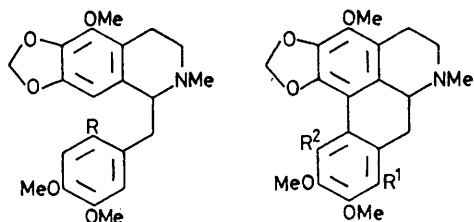
We report initial results on the successful realization of this objective. For example, the ether⁴ (**2**) was smoothly coupled to 5,7-dihydro-2,3,9,10-tetramethoxydibenzo[*c,e*]oxepin (**5**), 80%, m.p. 248.1 °C,⁵ by stirring with 1.1 equiv. of TTFA in a mixture of MeCN and CCl₄ at -40 °C in the presence of a small amount of BF₃·Et₂O. Attempts to obtain (**5**) by Ullmann coupling of (**3**) were reported to be unsuccessful.⁴

Even more encouraging was the one-step conversion (46% yield), under the above conditions, of (**6**) into (\pm)-ocoteine (**8**) (we prefer the alternative name, thalicmine⁶), spectroscopic data of which were identical with those reported⁷ [(**8**)·HCl, m.p. 259.5 °C⁸]. This direct non-phenolic coupling should be contrasted with the previously reported



- (1), R¹ = R² = H, Y = CH₂
 (2), R¹ = R² = H, Y = O
 (3), R¹ = R² = Br, Y = O

- (4), Y = CH₂
 (5), Y = O



- (6), R = H
 (7), R = NH₂

- (8) R¹ = R² = H
 (9) R¹ = OCOMe, R² = H
 (10) R¹ = H, R² = OCOMe

synthesis of (**8**) by Pschorr cyclization from the much less accessible precursor (**7**) (11% yield).⁷

Attempted coupling of (**6**) with thallium(III) acetate at 0 °C in the same solvent mixture surprisingly led to the

formation of the acetoxy aporphine (**9**) [(35%; m.p. 161–163 °C; λ_{\max} (EtOH) (log ϵ) 225 (4.49), 285 (4.22), 303 (4.1), and 311 (4.05) nm; ν (KBr) 1765 cm^{-1} ; δ (CDCl_3) 7.59 (s, 1H, ArH), 6.08, 5.92 (d, 2H, OCH_2O , J 1.8 Hz), 4.01, 3.91, 3.85 (3s, $3 \times 3\text{H}$, 3-OMe), 2.51 (s, 3H, NMe), 2.38 (s, 3H, ArOCOMe), and 3.25–2.2 (m, 7H, $3\text{CH}_2 + 1\text{CH}$)].^{9†} To our knowledge, this is the first example of direct aromatic acetoxylation with a thallium reagent,[‡] and of formal phenolic functionalization of the D ring of an aporphine alkaloid. The synthetic potential of this phenol synthesis remains to be explored.

† This compound gave satisfactory microanalytical data.

‡ A possible analogy, however, is found in the conversion of magnesium or zinc porphyrins with TTFA into *meso*-trifluoroacetoxy porphyrins, which also apparently proceeds by a radical process (G. H. Barnett, M. F. Hudson, S. W. McCombie, and K. M. Smith, *J.C.S. Perkin I*, 1973, 691).

This coupling reaction accommodates the presence of tertiary amines (without prior protection or deactivation), and oxygen, and thus should prove to be an exceptionally valuable procedure for natural product synthesis.

We thank the National Science Foundation for financial support.

(Received, 18th April 1977; Com. 365.)

¹ For the preceding paper on this series, see E. C. Taylor, C.-S. Chiang, and A. McKillop, *Tetrahedron Letters*, 1977, 1827.

² For a recent review on this subject, see S. Tobinga, *Bioorg. Chem.*, 1975, **4**, 110.

³ A. McKillop, A. G. Turrell, and E. C. Taylor, *J. Org. Chem.*, 1977, **42**, 764.

⁴ T. Kametani, K. Yamaki, and K. Ogasawara, *Yakugaku Zasshi*, 1969, **89**, 638.

⁵ R. Cromartie, J. Harley-Mason, and D. Wanningama, *J. Chem. Soc.*, 1958, 1982.

⁶ S. Yunusov and N. N. Progressov, *J. Gen. Chem. (U.S.S.R.)*, 1950, **20**, 1151.

⁷ T. Govindachari, B. Pai, and G. Shanmugasundaram, *Tetrahedron*, 1964, **20**, 2895.

⁸ K. Pulatova, Z. Ismailov, and S. Yunusov, *Khim. Prirod. Soedinenii*, 1966, **2**, 426.

⁹ The chemical shift of the C-11 proton at δ 7.59 excludes the isomeric structure (**10**): see M. Shamma and J. Moniot, *Experientia*, 1976, **32**, 282.