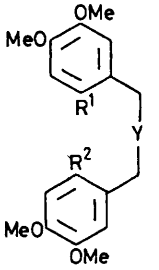
Thallium in Organic Synthesis. Synthesis of (±)-Ocoteine by Non-phenolic Coupling with Thallium Tris(trifluoroacetate) (TTFA)[1]

By EDWARD C. TAYLOR* and JUAN G. ANDRADE
(*Department of Chemistry, Princeton University, Princeton, New Jersey* 08540)
and ALEXANDER MCKILLOP
(*School of Chemical Sciences, University of East Anglia, Norwich* NR4 7TJ)

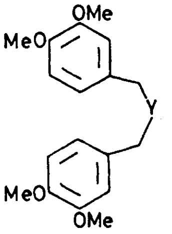
Summary (±)-Ocoteine (**8**), the acetoxy aporphine (**9**), and 5,7-dihydro-2,3,9,10-tetramethoxydibenzo[*c*,*e*]oxepin (**5**) have been synthesized by direct non-phenolic coupling with thallium tris(trifluoroacetate) (TTFA).

NON-PHENOLIC oxidative coupling reactions are currently receiving considerable attention.[2] We have recently described[3] 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.

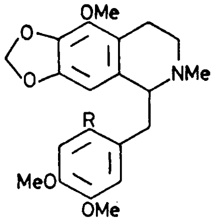
We report initial results on the successful realization of this objective. For example, the ether[4] (**2**) was smoothly coupled to 5,7-dihydro-2,3,9,10-tetramethoxydibenzo[*c*,*e*]-oxepin (**5**), 80%, m.p. 248·1 °C,[5] by stirring with 1·1 equiv. of TTFA in a mixture of MeCN and CCl_4 at −40 °C in the presence of a small amount of $BF_3{\cdot}Et_2O$. Attempts to obtain (**5**) by Ullmann coupling of (**3**) were reported to be unsuccessful.[4]



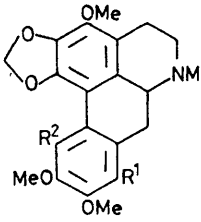
(**1**), $R^1 = R^2 = H, Y = CH_2$
(**2**), $R^1 = R^2 = H, Y = O$
(**3**), $R^1 = R^2 = Br, Y = O$



(**4**), $Y = CH_2$
(**5**), $Y = O$



(**6**), R = H
(**7**), $R = NH_2$



(**8**) $R^1 = R^2 = H$
(**9**) $R^1 = OCOMe, R^2 = H$
(**10**) $R^1 = H, R^2 = OCOMe$

Even more encouraging was the one-step conversion (46% yield), under the above conditions, of (**6**) into (±)-ocoteine (**8**) (we prefer the alternative name, thalicmine[6]), spectroscopic data of which were identical with those reported[7] [(**8**)·HCl, m.p. 259·5 °C[8]]. This direct non-phenolic coupling should be contrasted with the previously reported 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 × 3H, 3-OMe), 2·51 (s, 3H, NMe), 2·38 (s, 3H, ArOCOMe), and 3·25—2·2 (m, 7H, $3CH_2$ + 1CH)].[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 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.

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† This compound gave satisfactory microanalytical data.

‡ A possible analogy, however, is found in the conversion of magnesium or zinc porphyrins with TTFA into *meso*-trifluoroacetoxyporphyrins, 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) .

[1] For the preceeding 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.