Table I

$RCO_2H + CH_2(X)(Y) \xrightarrow[\text{in DMF}]{(EtO)_2P(O)CN,\ Et_3N^a} RCOCH(X)(Y)$

R	X	Y	yield,[b] %	mp,[c] °C
Ph	CN	CO_2Et	93.4 (83)[d]	39.5–40[d]
Ph	NO_2	H	85.5 (73)[e]	106–108[e]
Ph	CN	CN	92.8 (88)[f]	129[f]
			(87)[g]	
Ph	CO_2Et	CO_2Et	96.8[h]	(183–184)[j]
			(68–75)[i]	
Ph	NC	Tos	80.7 (65)[k]	139–141[k]
$Ph(CH_2)_2$	CN	CO_2Et	98.4	(209–211)
n-C_5H_{11}	CN	CO_2Et	97.2	(101–102)
$CH_3CO(CH_2)_2$	CN	CO_2Et	93.4	(168–170)
$CH_3CO(CH_2)_2$	CN	CO_2Bu^t	quant	(163–164)
$CH_3C(CH_2)_2$ (O O)	CO_2Et	CO_2Et	58.1[l]	(134–136)
$PhCH_2CH(NHCOOCH_2Ph)$-	CN	CO_2Et	87.8	146–148[m]
$CH_3CH(OH)CH(NHCOOCH_2Ph)$-	CN	CO_2Et	63.8	128–130[n]

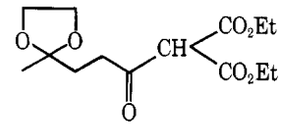
[a] Unless otherwise stated, the reactions were carried out as described in the text. [b] Yields by the reported procedures are in parentheses. [c] Melting points of copper salts are in parentheses. [d] Benzoyl cyanide was used: lit.[8] mp 41 °C. [e] Benzoyl cyanide was used: lit.[9] mp 105–106 °C. [f] Benzoyl cyanide was used: lit.[8] mp 129–130 °C. [g] Benzazide was used.[10] [h] Sodium hydride was used in place of triethylamine. [i] The mixed anhydride from benzoic acid and ethyl chlorocarbonate was used.[12] [j] Lit. mp 182 °C: D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957). [k] Benzoyl chloride was used. The isolated product was 5-phenyl-4-tosyloxazole. Lit. mp 142–143 °C: A. M. van Leusen, B. F. Hoogenboom, and H. Siderius, *Tetrahedron Lett.*, 2369 (1972). [l] Sodium hydride (2 equiv) and 1,5-diazabicyclo[5.4.0]undec-5-ene (2 equiv) were used in place of triethylamine. [m] $[\alpha]^{23}_D$ +37.1° (*c* 0.9, benzene). [n] $[\alpha]^{23}_D$ +38.2° (*c* 0.99, chloroform).

diazabicyclo[5.4.0]undec-5-ene, sodium hydride, or potassium carbonate can be used with similar efficiency. Three equivalents of the base are indispensable, because 2 equiv are used for the activation of both the carboxylic acid and the active methylene compound and 1 equiv for the salt formation of the acylated product.

The scope of the new C-acylation procedure is shown in Table I.[14] Benzoic acid efficiently coupled with various active methylene compounds, e.g., ethyl cyanoacetate, nitromethane, malononitrile, diethyl malonate, and tosylmethyl isocyanide. In the case of benzoylation of diethyl malonate, the use of sodium hydride in place of triethylamine gave a better result. Compared with the known method using activated forms of benzoic acid, the present method is more convenient to perform and gives benzoylated products in much higher yields under mild reaction conditions, as shown in Table I.

3-Phenylpropionic acid and hexanoic acid caused no trouble to couple with ethyl cyanoacetate. Levulinic acid which contains γ-keto function smoothly reacted with cyanoacetates to give the corresponding C-acylated products in excellent yields. The ethylene ketal derivative of levulinic acid also coupled with diethyl malonate to yield the C-acylated product **1**, which was easily converted to the 1,4-diketone[15] **2** by the successive treatment with (i) allyl iodide in the presence of tetra-*n*-butylammonium hydroxide,[16] (ii) sodium chloride in hot wet dimethyl sulfoxide,[17] and (iii) methanolic hydrogen chloride.

Another interesting example of the C-acylation is the coupling of ethyl cyanoacetate with two N-protected derivatives



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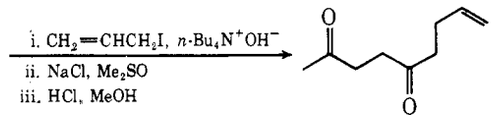

2

of α-amino acids, i.e., *N*-benzyloxycarbonyl-L-phenylalanine and -L-threonine, since the optical activities of the starting acids were retained in the products.

This direct C-acylation procedure in a single operation using DEPC appears to be quite general, may be used for many substrates containing various functions, and offers advantages over many existing methods.

Acknowledgment. We wish to thank Emeritus Professor S. Yamada and Professor K. Koga of University of Tokyo for their interests and discussions.

References and Notes

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(13) The real activated species of the C-acylation will be acyl phosphates and/or acyl cyanides. See ref 3.
(14) All new compounds were fully characterized by NMR and IR spectral means and elemental composition. Known compounds were identified by comparing their physical data (melting points, IR and NMR spectra) with reported ones.
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Takayuki Shioiri,* Yasumasa Hamada
Faculty of Pharmaceutical Sciences
Nagoya City University, 3-1, Tanabe-dori
Mizuho-ku, Nagoya 467, Japan
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Thallium in Organic Synthesis. 52. Oxidations of 3-(Alkoxyaryl)propionic Acids by Thallium(III) Trifluoroacetate: Synthesis of Dihydrocoumarins, Spirocyclohexadienone Lactones, and *p*-Benzoquinones[1,2]

Summary: Dihydrocoumarins, spirocyclohexadienone lactones, and *p*-benzoquinones are formed via intramolecular capture of radical cation intermediates generated from 3-(alkoxyaryl)propionic acids by oxidation with TTFA.

Sir: The products obtained from the reactions of aromatic compounds with thallium(III) trifluoroacetate (TTFA) depend on the oxidation potentials of the aromatic substrates. Arylthallium bis(trifluoro)acetates, the products of overall

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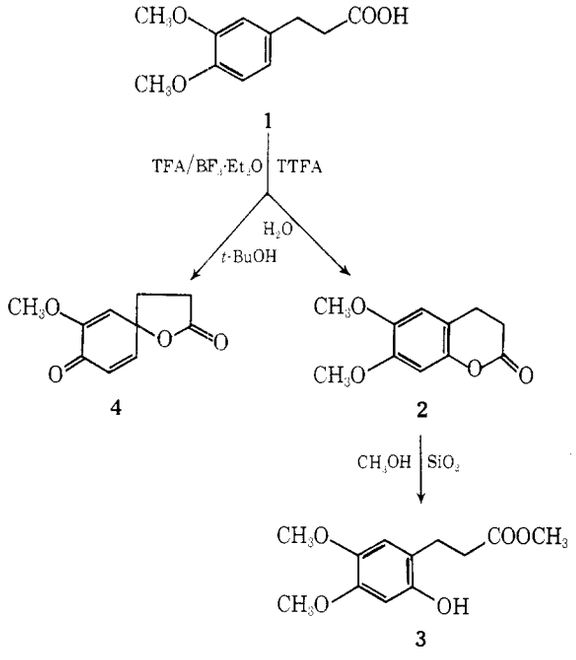
electrophilic aromatic thallation, are obtained from aromatic compounds with relatively high oxidation potentials (benzene, alkylbenzenes, halobenzenes, etc.), while biaryls, the products of overall dehydrodimerization, are obtained from aromatic compounds with lower oxidation potentials (polyalkoxybenzenes, naphthalenes, etc.). Mechanistically, biaryl formation is believed to involve electron transfer from the aromatic substrate to Tl(III), reaction of the resulting aryl radical cation with another molecule of the aromatic compound, and oxidative aromatization of the intermediate thus produced.[3]

The synthetic potential of nucleophilic aromatic substitution via radical cation intermediates is a topic of considerable current interest,[4] and we have recently demonstrated the utility of TTFA-induced *intra*molecular oxidative coupling of aromatic substrates to biaryls via radical cations for the synthesis of aporphine[5] and homoaporphine alkaloids.[6] We now demonstrate that radical cations can be trapped intramolecularly by a suitably positioned carboxyl group, and that this reaction has synthetic utility for the preparation of dihydrocoumarins, spirocyclohexadienone lactones, and *p*-benzoquinones.[7]

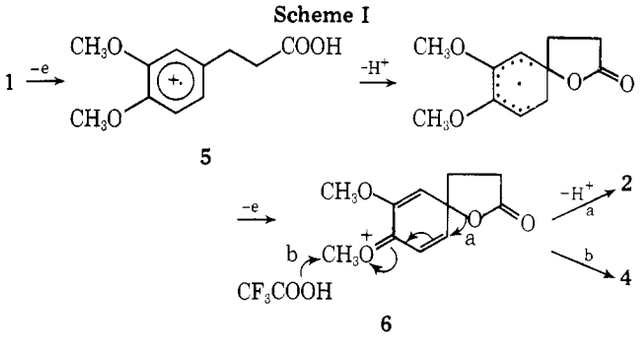
Reaction of 3-(3,4-dimethoxyphenyl)propionic acid (**1**) (1 mmol) with 1 equiv of TTFA in TFA (30 mL) containing boron trifluoride etherate (1 mL) was instantaneous at 0 °C. The reaction mixture was therefore quenched *immediately*[12] with water (50 mL); chloroform extraction followed by chromatography of the crude product on silica using chloroform–methanol (9:1) as eluent gave methyl 3-(2-hydroxy-4,5-dimethoxyphenyl)propionate (**3**) in 20% yield. Standard control experiments established that formation of the methyl



ester in the above sequence of operations occurred during chromatography. Quenching of the oxidation medium with methanol led directly to the ester **3**, while the use of *tert*-butyl alcohol gave a 3:1 mixture (57% yield) of the dihydrocoumarin **2** and the spirocyclohexadienone lactone **4**.[13,14]

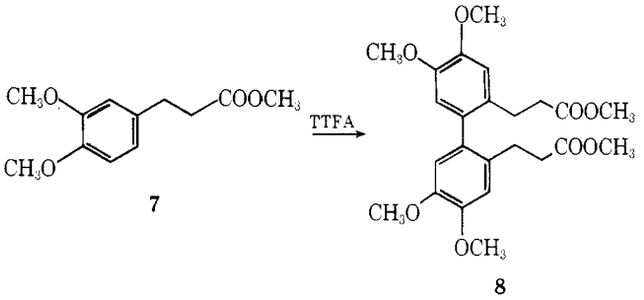
We suggest that formation of products **2–4** in these reactions is most easily explained on the basis of the ECE mechanism[15] outlined in Scheme I. Thus, one-electron oxidation of **1** by TTFA gives the radical cation **5**, intramolecular reaction of which with the carboxyl group gives **6**;[16] dienone–phenol type rearrangement of **6** leads to the dihydrocoumarin **2** (path a), which is either obtained as such on quenching of the reaction mixture with *tert*-butyl alcohol or is converted to the ester **3** when chloroform–methanol/silica is used. For-

Scheme I

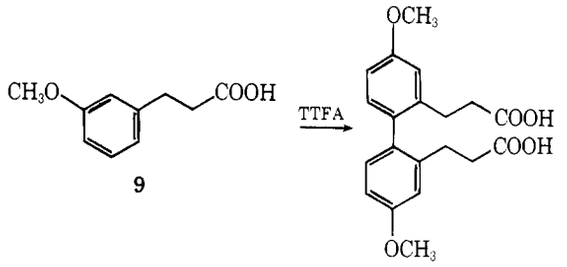


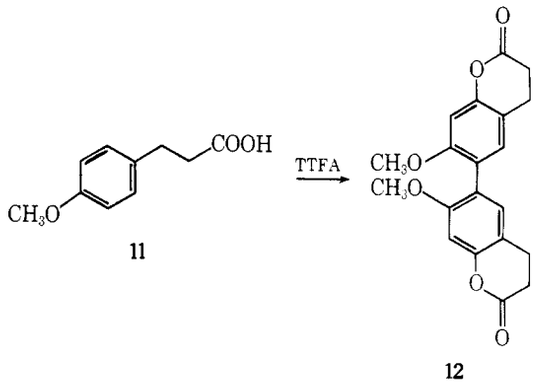
mation of the spirocyclohexadienone lactone **4** presumably arises via nucleophilic attack at the $CH_3O^+=$ methyl group by TFA (path b).

Evidence in support of the mechanism outlined in Scheme I comes from the following observations. (1) Oxidation of the methyl ester **7** with TTFA gave the biaryl **8** in 58% yield. In-



tramolecular trapping of the radical cation is clearly impossible in this case, and hence intermolecular coupling occurs. (2) Oxidation of 3-(3-methoxyphenyl)propionic acid (**9**) did not give any products of the type **2–4**, but only the biaryl **10** (56%). In this instance there is no mesomeric stabilization of

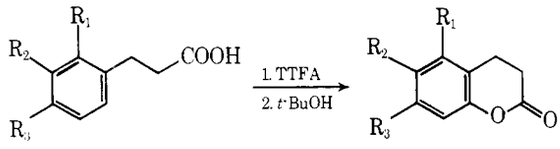




the reactive intermediates by the methoxy group, and intermolecular coupling is again the preferred pathway. (3) Oxidation of 3-(4-methoxyphenyl)propionic acid (**11**), on the other hand, resulted both in dihydrocoumarin formation and in biaryl coupling to give **12** in 24% yield.

The fate of the radical cations generated from 3-(3-alkoxyaryl)propionic acids thus appears to depend on the position

of the alkoxy substituent(s) relative to the carboxyethyl group. Substrates without a *p*-alkoxy group undergo oxidative dimerization to biaryls, whereas those with a *p*-alkoxy group[17] give dihydrocoumarins and lesser amounts of spirocyclohexadienone lactones.[18] In agreement with these conclusions, oxidation of the acids **13** with TTFA followed by quenching with *tert*-butyl alcohol gave the dihydrocoumarins **14**.

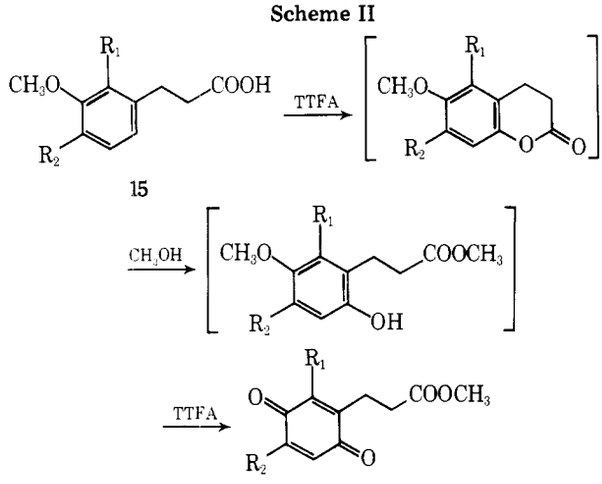


13 **14**

a, $R_1 = H$; $R_2 = R_3 = OCH_2O$, 21%
b, $R_1 = R_2 = R_3 = OCH_3$, 53%

Moreover, use of methanol to quench the reaction mixture resulted in acid-catalyzed esterification and formation of a methyl 3-(2-hydroxyaryl)propionate; consequently, given that there is an alkoxy group para to the newly introduced hydroxy group and that excess TTFA is available, it is possible to effect a second, different type of oxidation.[19] Thus, treatment of the acids **15** with 2 equiv of TTFA and quenching of the reaction mixture with methanol gave the *p*-benzoquinones **16** directly (Scheme II).

Scheme II



a, $R_1 = H$; $R_2 = OCH_3$, 73%
b, $R_1 = R_2 = OCH_3$, 61%

These results clearly demonstrate that aromatic radical cations can be trapped intramolecularly by a suitably situated carboxyl group. They illustrate, moreover, that a substantial degree of control is possible over the nature of the products obtained from such intramolecular trapping reactions by variation in substrate structure, amount of oxidant employed, and the isolation procedure used. Further studies are in progress to extend and exploit these novel oxidations.

References and Notes

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(7) Phenolic oxidative coupling of *p*-hydroxyarylpropionic acids to spirodienone lactones (and hence to dihydrocoumarins by rearrangement) is known,[8-11] but the only reported example of a nonphenolic oxidative coupling of this type appears to be that of Scott,[11] who employed NBS in $NaOAc/CH_3CN$ solution and obtained dibrominated products by a pathway which almost certainly does not involve radical cation intermediates.
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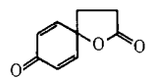
(13) Satisfactory microanalytical and spectroscopic data were obtained for all new compounds.
(14) Rearrangement of spirocylohexadienone lactones derived from *p*-hydroxyarylpropionic acids requires heating with mineral acid, often under extremely vigorous conditions. By contrast, rearrangement of **6** to **2** (see Scheme I) under our conditions occurs almost instantaneously at room temperature.
(15) J. H. P. Utley in "Essays in Chemistry", Vol. 6, J. N. Bradley, R. D. Gillard, and R. F. Hudson, Eds., Academic Press, London, 1977, p 83.
(16) It is possible that the low yield oxidative coupling of *p*-hydroxyphenylpropionic acid to the spirocyclohexadienone lactone i with peracetic acid, lead



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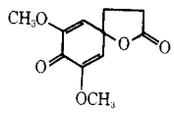
tetraacetate in methanol, or by electrolysis occurs via a radical cation intermediate, but this mechanistic pathway has apparently not been considered previously for this conversion [J. S. Davies, C. H. Hassall, and J. A. Schofield, *J. Chem. Soc.*, 3126 (1964)].
(17) Oxidation of 3-(2-methoxyphenyl)propionic acid failed to give any products of the type **2–4**; starting material was recovered (~50%), and the material balance was comprised of dark-colored, resinous matter.
(18) 3-(3,4,5-Trimethoxyphenyl)propionic acid was converted almost exclusively to the spirodienone ii (37%). Trace amounts of 2,6-dimethoxy-*p*-benzo-



ii

quinone were also obtained, but no dihydrocoumarin was isolated, presumably since dienone–phenol rearrangement is considerably slower than dealkylation (cf. path b, Scheme I). Facile and selective demethylation of the 2-methoxy group of 1,2,3-trimethoxyarenes has been observed previously with both acid [A. Brossi, J. van Burick, and S. Teitel, *Helv. Chim. Acta*, **51**, 1965 (1968); A. Brossi and S. Teitel, *Org. Prep. Proced.*, **1**, 171 (1969)] and TTFA [A. S. Kende and P. S. Rutledge, *Synth. Commun.*, **8**, 245 (1978)].
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(20) On leave of absence from the University of Orange Free State, Bloemfontein, South Africa; financial assistance from the CSIR, Pretoria, is gratefully acknowledged.

Edward C. Taylor,* Juan G. Andrade
Gerhardus J. H. Rall[20]
Department of Chemistry, Princeton University
Princeton, New Jersey 08540

Alexander McKillop
School of Chemical Sciences
University of East Anglia
Norwich NR4 7TJ, England

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