hydroxyphenyl)pyridazine (8), mp 190.5–192 °C dec. Recrystallization from MeCN gave 8 as pale yellow prisms, mp 195.5–197 °C dec: NMR δ 6.37 (dd, 1 H, J = 9.2 and 2 Hz), 6.44 (d, 1 H, J = 2 Hz), 7.09 (d, 1 H, J = 9.2 Hz), 7.98 (s, 1 H), 9.84 (br s, 1 H), 10.0 (br s, 1 H) ppm; MS m/z 260 (13), 258 (63), 256 (100), 222 (3), 220 (9), 193 (3), 158 (30), 129 (16).

Anal. Calcd for $C_{10}H_6Cl_2N_2O_2$: C, 46.72; H, 2.35; N, 10.90. Found: C, 46.61; H, 2.21; N, 10.79.

After removal of a further 2.1 g (11%) of crude 8 from the recrystallization liquors, evaporation gave 2.9 g of a solid which was combined with 0.3 g obtained by EtOAc extraction of the original aqueous filtrate. The solid (3.2 g) was digested with warm $CHCl_3$–MeOH, 25:1, leaving 0.4 g of insoluble residue. Column chromatography of the soluble material gave 0.64 g (3.5%) of the less polar component, which was recrystallized from MeOH to give 0.25 g (1.4%) of 3,4-dichloro-6-(2,4-dihydroxyphenyl)-pyridazine (10) as pale yellow platelets, mp 245 °C dec: NMR δ 6.4–6.5 (m, 2 H), 7.87 (m, 1 H), 8.65 (s, 1 H), 10.1 (s, 1 H), 11.65 (s, 1 H) ppm; MS m/z 260 (12), 258 (64), 256 (100), 223 (7), 221 (21), 195 (16), 193 (42).

Anal. Calcd for $C_{10}H_6Cl_2N_2O_2$: C, 46.72; H, 2.35; N, 10.90. Found: C, 46.55; H, 2.27; N, 10.89.

Further elution gave 0.63 g (3.5%) of the more polar isomer, which was recrystallized from acetone to give 0.33 g (2%) of 3,5-dichloro-6-(2,4-dihydroxyphenyl)pyridazine (9) as white granular crystals, mp 185–187 °C: NMR δ 6.36 (dd, 1 H, J = 8.3 and 2.2 Hz), 6.42 (d, 1 H, J = 2.2 Hz), 7.09 (d, 1 H, J = 8.3 Hz), 8.33 (s, 1 H), 9.72 (s, 1 H), 9.82 (s, 1 H) ppm; MS m/z 260 (4), 258 (19), 256 (30), 223 (35), 221 (100), 167 (6), 165 (17), 129 (7).

Anal. Calcd for $C_{10}H_6Cl_2N_2O_2$: C, 46.72; H, 2.35; N, 10.90. Found: C, 46.78; H, 2.26; N, 10.90.

4-(2,4-Dihydroxyphenyl)pyridazine (12). A solution of 8 (0.8 g, 3 mmol) in aqueous NaOH (0.5 g, 12 mmol in 40 mL) was shaken under H_2 (40 psi) with 10% Pd/C (0.1 g) until reaction was complete. Neutralization of the filtered solution gave 0.53 g (90%) of a solid mp 245–247 °C. Recrystallization from aqueous MeOH gave 12 as pale yellow needles, mp 248–249 °C: NMR δ 6.40 (dd, 1 H, J = 8.5 and 2.3 Hz), 6.48 (d, 1 H, J = 2.3 Hz), 7.37 (d, 1 H, J = 8.5 Hz), 7.82 (dd, 1 H, J = 5.5 and 2.4 Hz), 9.11 (dd, 1 H, J = 5.5 and 1.1 Hz), 9.44 (dd, 1 H, J = 2.3 and 1.1 Hz), 9.98 (br s, 2 H) ppm; MS m/z 188 (100), 160 (4), 134 (30), 131 (18), 105 (7), 103 (10), 77 (13).

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.59; H, 4.12; N, 15.15.

3-(2,4-Dihydroxyphenyl)pyridazine (13). Hydrogenolysis of 3a by the method of Stanovnik[1] gave 13, mp 265–269 °C (lit.[1] mp 274–275 °C): NMR δ 6.38 (d, 1 H, J = 2.4 Hz), 6.43 (dd, 1 H, J = 8.7 and 2.4 Hz), 7.81 (dd, 1 H, J = 4.8 and 9.0 Hz), 7.86 (d, 1 H, J = 9.0 Hz), 8.36 (dd, 1 H, J = 9.0 and 1.4 Hz), 9.08 (dd, 1 H, J = 4.8 and 1.4 Hz), 10.0 (br s, 1 H), 13.5 (br s, 1 H) ppm.

3-Chloro-7-hydroxybenzofuro[2,3-c]pyridazine (11). A stirred mixture of 8 (2.0 g, 7.8 mmol) and K_2CO_3 (1.2 g, 8.7 mmol) in acetone (50 mL) was heated under reflux for 18 h. After evaporation the residue was treated with water (50 mL), and the filtered solution was made pH 5–6 with AcOH to give 1.63 g (97%) of a solid. Recrystallization from aqueous DMF afforded 1.1 g (65%) of 11 as cream-colored microcrystals, which appeared to decompose above 270 °C but did not melt below 360 °C. TLC analysis indicated that this compound was a minor byproduct in the preparation of 8 and was also formed when 8 decomposed at its melting point. Compound 11 failed to give a colored reaction with alkaline diazotized sulfanilic acid, and its aqueous alkaline solutions displayed a marked green fluorescence in daylight: NMR δ 6.99 (dd, 1 H, J = 8.6 and 2.1 Hz), 7.14 (d, 1 H, J = 2.1 Hz), 8.10 (d, 1 H, J = 8.6 Hz), 8.47 (s, 1 H), 10.7 (v br s, 0.4 H) ppm; IR (Nujol mull) 3300–2300 (series bands), 1630 cm^{-1}; MS m/z 222 (33), 220 (100), 166 (7), 164 (2), 129 (55); UV (95% EtOH) λ_{max} (log ε) 332 (4.25), 389 (3.65), (basic 95% EtOH) 389 (4.47), (acidic 95% EtOH) 332 (4.32) nm; pK_a (25 °C) 7.5.

Anal. Calcd for $C_{10}H_5ClN_2O_2$: C, 54.44; H, 2.28; N, 12.70. Found: C, 54.46; H, 2.34; N, 12.71.

Acknowledgment. We thank our colleagues in the Physical Organic Chemistry Department of Smith Kline & French Research for providing microanalytical, spectral, and physical data.

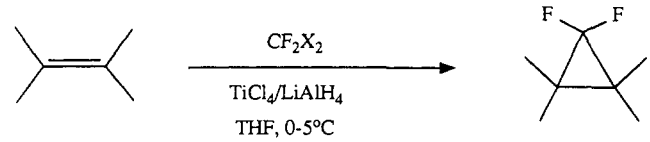
New Zinc Difluorocarbenoid Reagent

William R. Dolbier, Jr.,* Hanna Wojtowicz,† and Conrad R. Burkholder

Department of Chemistry, University of Florida, Gainesville, Florida 32611

Received March 29, 1990

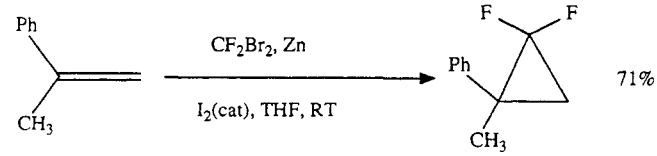
It was recently reported that good yields of *chlorofluorocarbene* adducts could be obtained from the reaction of $CFCl_3$ with reduced titanium in the presence of alkenes.[1,2] Unfortunately, the utilization of CF_2Cl_2, CF_2Br_2, or CF_2I_2 in this same reaction did not lead to generally good yields of the analogous difluorocarbene adducts (Table I).



Numerous methods of synthesizing *gem*-difluorocyclopropanes through the addition of difluorocarbene to olefins have been reported.[3] The yields of cyclopropanes, however, have been seen to be greatly dependent upon both the nucleophilicity of the olefin substrate and the nature of the carbene/carbenoid reagent. Two of the most effective methods we[4] and others have used for generation of difluorocarbene are Seyferth's phenyl(trifluoromethyl)mercury[5] and Burton's triphenyl(bromodifluoromethyl)phosphonium bromide[6] reagents. These reagents give excellent yields with relatively nucleophilic alkenes. However, phenyl(trifluoromethyl)mercury is both toxic and nontrivial to synthesize, while for optimum results Burton's reagent requires use of scrupulously dry solvents.

We have found that the thermolysis of hexafluoropropylene oxide[7] provided a more reactive difluorocarbene for use with nonnucleophilic alkenes. Unfortunately the high temperatures required (≥180 °C) for this thermal extrusion of CF_2: often precludes its use. There therefore has been a continued effort to find a simple and effective way of generating a "reactive" difluorocarbene reagent for use at more moderate temperatures.

We now report a new and useful difluorocarbene reagent, which is about equal in reactivity to the Seyferth and Burton reagents but has the advantage of being simply and cheaply prepared and needs no special, superanhydrous conditions. As such, it should prove to be the method of choice for synthesis of most difluorocyclopropane compounds.



In a reaction essentially analogous to the Simmons–Smith reaction,[8] difluorodibromomethane reacts with zinc in tetrahydrofuran at room temperature in the presence of an olefin to give difluorocyclopropanes in yields up to 96%. A total of 15 olefins have been utilized in this reaction, and Table II summarizes the results obtained. Most of the 1,1-difluorocyclopropanes that were prepared had been previously reported,[9–13] and they could be un-

† Permanent address: Instytut Chemii, Uniwersytet im. Adama Mickiewicza, Poznan, Poland.

0022-3263/90/1955-5420$02.50/0

Table I. Yields of Difluorocarbene Adducts in the Difluorodihalomethane/Reduced Titanium Reaction with Alkenes in THF[a]

alkene substrate	CF_2X_2	% yield
2,3-dimethyl-2-butene	CF_2Br_2	33
	CF_2Cl_2	3.5
	CF_2I_2	41
2-ethyl-1-butene	CF_2Br_2	3.2
2-methyl-2-butene	CF_2Br_2	traces
α-methylstyrene	CF_2I_2	16

[a] Procedure as in ref 2.

Table II. Yields and ^{19}F Nuclear Magnetic Resonance Data for the Reaction of Zinc Difluorocarbenoid with Various Alkenes[a]

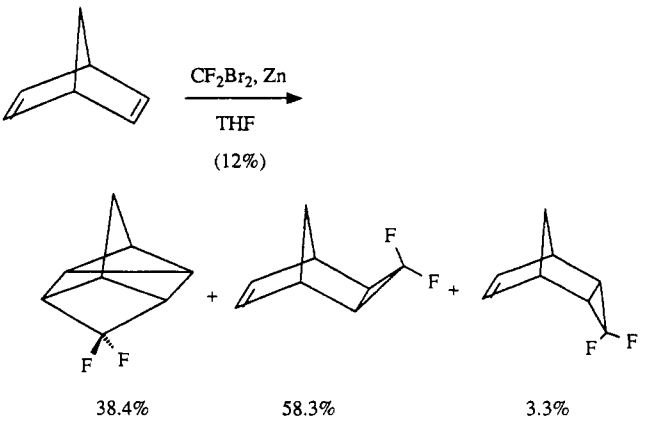
alkene substrate	% yield	φ, ppm ($CDCl_3$)	J_{FF}[b]	ref
2,3-dimethyl-2-butene	96	−148.6 (s)		9, 10
1-phenylcyclopentene	84	−127.1, −141.6 (dm)	155	
2-methyl-2-butene	72	−138.8, −150.8 (dm)	151	9, 11
α-methylstyrene	71	−132.8, −137.8 (dd)[b]	150	10, 11
2-ethyl-1-butene	40	−139.0 (m)		9
(*E*)-1-phenylpropene	29	−137.8, −138.9 (dd)[b]	153	
cyclopentadiene	21	−128.4, −154.7 (dm)	147	12
1,3-butadiene	17	−128.5, −141.6 (dd)[b]	156	11
styrene	15	−126.1, −142.9 (dm)	153	10
cis-2-butene	7	−127.4, −156.3 (dd)[b]	158	9, 11
trans-2-butene	4	−141.8 (br s)		9, 11
cyclohexene	7	−125.7 (dt)[b], −150.4	162.5	9, 13
1,4-cyclohexadiene	7	−127.7, −154.2 (dm)	155	
1-hexene	6	−128.2, −145.0 (dm)	156	

[a] All products were characterized by their ^{19}F NMR spectra. [b] When able to be measured, J_{FH}'s were found to be 12–14 Hz.

ambiguously identified by their characteristic ^{19}F NMR spectra. It should be noted that, in general, a 3-fold excess of carbene reagent was utilized in the reaction so as to conserve alkene.

The behavior of the reactive species derived from this zinc carbenoid reagent indicates that a "free" carbene is probably involved in the reaction. Certainly the reactivity profile of the reagent resembles those exhibited by most other difluorocarbene reagents.[14] In our case, when a 10-fold excess of each of 2,3-dimethyl-2-butene and α-methylstyrene was used in the reaction, the relative reactivity as derived directly from the ratio of cyclopropane products was found to be 3.5. This result can be compared with ratios obtained by Mitsch and Rodgers wherein 2,3-dimethyl-2-butene was found to be 3.71 times as reactive as 2-methyl-2-butene and 13.1 times as reactive as isobutylene in the CF_2 cyclopropanation reaction derived from the gas-phase photolysis of difluorodiazirine at 36 °C.[15]

Another indication of the normal behavior of our CF_2: reagent was the fact that its reaction with norbornadiene led to a relative degree of 1,4 versus 1,2 carbene addition that was similar to that observed by Jefford in his study wherein the CF_2 was derived from Burton's method[6] (i.e., decomposition of triphenyl(bromodifluoromethyl)-phosphonium bromide in triglyme).[16]



A number of alternative solvents were tried for the reaction with α-methylstyrene, with much poorer yields being observed in all cases: Et_2O (9%), CH_3CN (3%), DMF (9%), and dioxane (traces).

^{19}F NMR analyses of the reaction mixtures indicated that CF_3ZnBr (φ = −42.1 ppm) and $(CF_3)_2Zn$ (φ = −42.5 ppm) were formed in competition with the reactive carbenoid species.[17] Burton has reported such transformations from CF_2Br_2-derived organometallics before.[18] Under the reaction conditions, these species were not reversibly formed, and they were not reactive in the presence of alkenes. If the $CF_3ZnBr/(CF_3)_2Zn$ reagent was formed without alkene present, alkene added, and then the reagent decomposed by the addition of $TiCl_4$, one obtained difluorocyclopropane products with a similar reactivity pattern but with diminished yields: TME (67%), α-methylstyrene (32%), 2-ethyl-1-butene (traces only).[19,20]

Thus, the $CF_2Br_2/Zn/THF$ reagent has been demonstrated to offer significant advantages as a source of difluorocarbene. The good yields and simplicity of procedure should make this the method of choice for most difluorocyclopropane preparations where relatively reactive alkene precursors can be used.

Experimental Section

General Experimental Procedure. A 100-mL, three-necked flask was equipped with a magnetic stirrer, a thermometer, a rubber septum with an N_2 inlet needle, and an addition funnel with an outlet stopcock. (In the case of volatile alkene substrates, a dry ice condenser is also needed). After flushing with N_2, 10 mL of THF, 22.8 mmol of activated Zn, 7.6 mmol alkene, and a small crystal of I_2 were added. After the reaction vessel was placed in a water bath, 22.8 mmol of CF_2Br_2 in 10–15 mL of THF was added over a period of 1.5–2 h. The mixture was then stirred overnight. All Zn was consumed. An internal standard (hexafluorobenzene) was added directly to the mixture, and analysis

(1) Dolbier, W. R., Jr.; Burkholder, C. R. *Tetrahedron Lett.* **1988**, *29*, 6749.
(2) Dolbier, W. R., Jr.; Burkholder, C. R. *J. Org. Chem.* **1990**, *31*, 589.
(3) Burton, D. J.; Hahnfeld, J. L. *Fluorine Chemistry Reviews*; Tarrant, P., Ed.; Marcell Dekker, Inc.: New York, 1977; Vol. 8, pp 153–179.
(4) Dolbier, W. R., Jr. *Acc. Chem. Res.* **1981**, *14*, 195.
(5) Seyferth, D.; Hopper, S. P. *J. Org. Chem.* **1972**, *37*, 4070.
(6) Burton, D. J.; Naae, D. G. *J. Am. Chem. Soc.* **1973**, *95*, 8467.
(7) Mahler, W.; Resnick, P. R. *J. Fluorine Chem.* **1973**, *3*, 451. See also ref 3.
(8) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323.
(9) Wheaton, G. A.; Burton D. J. *J. Fluorine Chem.* **1977**, *9*, 25.
(10) Glemser, O. *Z. Naturforsch.* **1981**, *36b*, 1375.
(11) Kamel, M. *Chem. Ber.* **1976**, *109*, 2351.
(12) Dolbier, W. R., Jr.; Keaffaber, J. J.; Burkholder, C. R.; Pradhan, J., unpublished results.
(13) Seyferth, D.; Dertouzos, H. Suzuki, R.; Mui, J. Y.-P. *J. Org. Chem.* **1967**, *32*, 2980.
(14) Moss, R. A. *Carbenes*; Jones, M., Moss, R. A., Eds.; John Wiley and Sons: New York, 1973; Vol. 1, pp 153–304.
(15) Mitsch, R. A.; Rodgers, A. S. *Int. J. Chem. Kinet.* **1969**, *1*, 439.
(16) Jefford, C. W.; Mareda, J.; Gehret, J. C. E.; Kabengele, N.; Graham, W. D.; Burger, U. *J. Am. Chem. Soc.* **1976**, *98*, 2585.
(17) When I_2 is added, only the peak at φ = −42.1 ppm disappears with concomitant formation of CF_3I (φ = −7.0 ppm).
(18) Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 832.
(19) To a mixture of 15.2 mmol of preprepared reagent in THF were added 1.52 mmol of alkene and then 7.6 mmol of $TiCl_4$ at −20 °C.
(20) CF_3ZnI was first prepared by cocondensation of Zn atoms with CF_3I on a liquid N_2 surface: Klabunde, K. J.; Key, M. S.; Low, J. Y. F. *J. Am. Chem. Soc.* **1972**, *94*, 999.

and determination of yield of product were done by ^{19}F NMR spectroscopy.

6,6-Difluoro-1-phenylbicyclo[3.1.0]hexane. A 250-mL, three-necked, round-bottom flask was equipped with an N_2 inlet, a rubber septum, and a pressure-equalizing addition funnel with a nitrogen outlet. The system was flushed with N_2, and the apparatus was flame-dried. A stirring bar was added to the flask.

To the flask were added 50 mL of dry THF, 7.45 g (0.114 mol) of activated zinc dust, a small crystal of iodine, and 5.48 g (0.0380 mol) of 1-phenylcyclopentene.[21] To the stirred mixture was added a solution of 23.92 g (0.114 mol) of dibromodifluoromethane in 75 mL of anhydrous THF over a period of 3.5 h. The reaction was slightly exothermic. The zinc dust dissolved to give a clear, pale amber solution, which was stirred at ambient temperature overnight (20.5 h). To the reaction mixture was added 100 mg (0.5375 mmol) of hexafluorobenzene as internal standard, and the ^{19}F NMR spectrum was taken. Integration of the fluorine spectrum indicated the yield of the product to be 84%.

The reaction mixture was poured into 200 mL of 10% aqueous HCl containing 50 mL of crushed ice. The mixture was extracted three times with 50-mL portions of CH_2Cl_2. The combined organic extracts were washed with 50 mL of 10% aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4. The solution was concentrated by rotary evaporation at reduced pressure to give a clear, colorless liquid. Purification by fractional distillation at reduced pressure with a 15-cm Vigreux column gave 2.36 g (32%) of clear, colorless liquid product, bp 75 °C/1.0 mm. Analysis by GC (10 ft by 0.125 in. 20% QF-1 at 150 °C): IR (film) 3031, 2941, 2868, 1604 (w), 1500, 1452, 1433 (s), 1304, 1253, 1201 (s), 1149, 1119, 1060, 995 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22–7.34 (m, 5 H), 2.46 (m, 1 H), 2.06–2.20 (m, 4 H), 1.7–1.9 ppm (m, 2 H); ^{19}F NMR ($CDCl_3$, 282 MHz) ϕ −127.1 (dm, J_{FF} = 154.6 Hz, 1 F) and −141.6 ppm (dm, J_{FF} = 154.6 Hz, 1 F); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.9 (t, J_{CF} = 2.4 Hz, quat), 128.3 (s, CH), 128.2 (d, J_{CF} = 1.7 Hz, CH), 127.0 (s, CH), 116.5 (dd, J_{CF} = 280.2 and 306.4 Hz, CF_2), 42.9 (dd, J_{CF} = 8.6 and 12.5 Hz, quat), 34.3 (d, J_{CF} = 1.6 Hz, CH_2), 33.5 (dd, J_{CF} = 9.3 and 11.6 Hz, CH) 26.6 (s, CH_2), 24.1 (dd, J_{CF} = 1.4 and 10.2 Hz, CH_2); HRMS gave M^+ = 194.09011 ± 0.0006 (3.2 ppm), dev = −0.0006 (3.1 ppm); MS 194 (100), 143 (38), 129 (33), 115 (76), 91 (35), 77 (35), 51 (34).

Competition Experiment between α-Methylstyrene and 2,3-Dimethyl-2-butene. To a similarly equipped, 100-mL, round-bottom flask were added 2.5 mmol of zinc (165 mg), THF (20 mL), and 25 mmol each of olefins (2.96 g of α-methylstyrene and 2.10 g of 2,3-dimethyl-2-butene). The flask was placed in a water bath, and then a solution of 3.75 mmol of dibromodifluoromethane (787 mg) in THF (5 mL) was added during a period of 25 min. The reaction was not exothermic. The mixture was stirred overnight. Hexafluorobenzene (50 mg) was added to the mixture, and the products were analyzed by ^{19}F NMR spectroscopy for 1,1-difluoro-2,2,3,3-tetramethylcyclopropane (ϕ −148.6 ppm (s)) and for 1,1-difluoro-2-methyl-2-phenylcyclopropane (ϕ −132.8 (dd, J_{FF} = 150 Hz, J_{FH} = 13 Hz), −137.8 ppm (dd, J_{FF} = 150 Hz, J_{FH} = 12 Hz)). The yields of the products were 51.3% and 14.5%, respectively, with a ratio of 3.5.

Acknowledgment. The support of this research in part by the National Science Foundation is gratefully acknowledged.

(21) Garbisch, E. W., Jr. *J. Org. Chem.* **1961**, *26*, 4165.

Additions and Corrections

Vol. 55, 1990

Peter J. Garratt* and Andrew Tsotinis. Preparation and Reactions of Some (Trimethylsilyl)cyclopropenes. Synthesis of In–Out Tricyclic [*n*.3.2.0^{2,4}] Compounds, Potential Precursors to Cyclopropaparacyclophanes.

Page 84, column 2. The statement that the authors cited in ref 5 (Dent, B. R.; Halton, B.; Smith, A. M. F. *Aust. J. Chem.* **1986**, *39*, 1621) had prepared compound **5b** from compound 4 is incorrect. These workers prepared **5b** from compound 15, as we did. We thank Professor Halton for bringing this error to our attention.

Ernest L. Eliel* and Xu-Chang He. Highly Stereoselective Syntheses Involving *N*-Alkyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine Intermediates. 2.

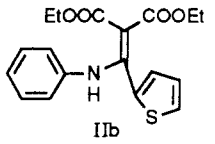
Page 2115, column 2, Scheme IV: 10% Pd/C should replace 1% Pd/C.

Page 2117, column 1, last line: 22.2 should replace 2.22.

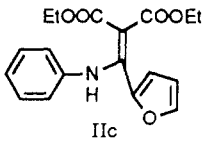
Page 2119, column 1, line 39: 2 mL should replace 2 mg.

Osmo E. O. Hormi,* Carita Peltonen, and Laila Heikkilä. 2-Aryl-4-quinolones and Fused Quinolines from β-Chloroarylidenemalonates and Related Chloro Esters.

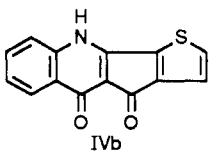
Page 2513, structures IIb, IIc, III, and IVb should be drawn as shown below.



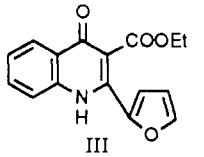
IIb



IIc



IVb



III