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Reinvestigation and Extension of the Aluminum Chloride Induced Reactions of Resorcinol and Hydroquinone with 3,6-Dichloropyridazine

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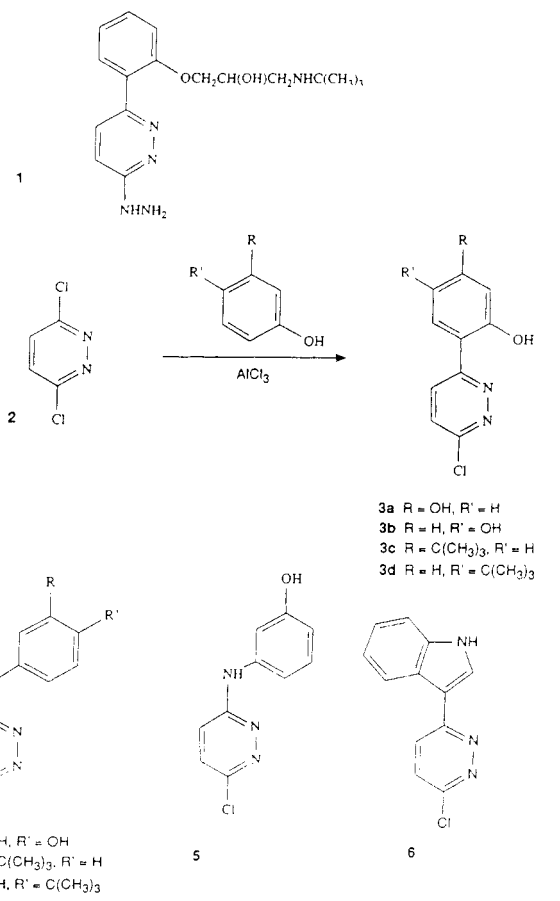
During a study of methods for the preparation of the combined β-blocker/vasodilator prizidilol (3-[2-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]-6-hydrazinopyridazine, **1**) and analogues, our interest was aroused by a report that reaction of 3,6-dichloropyridazine (**2**) with resorcinol and hydroquinone in the presence of aluminum chloride gave the 3-chloro-6-(2,4- and 2,5-dihydroxyphenyl)pyridazines, **3a** and **3b**, respectively.[1] This reaction proved to be successful with resorcinol and was used for the preparation of analogues of prizidilol with 4-alkoxy substituents in the phenyl ring.[2] Reaction of **2** with hydroquinone also proceeded as described; the product (mp 196–197 °C; lit.[1] mp 195–196 °C), however, was readily shown by ^{1}H NMR spectroscopy to be the ether **4a**, and not the arylated pyridazine **3b** as claimed.

Further study of the arylation reaction **2** → **3** has revealed that it is of very limited scope. Phenol, 3- and 4-chlorophenol, catechol, and a variety of anisole derivatives failed to react with **2**, while 3- and 4-*tert*-butylphenol gave the ethers **4b** and **4c** in 15 and 9% yield, respectively, together with only very small amounts (<2%) of products tentatively identified (MS, NMR) as the C-arylated pyridazines **3c** and **3d**. 3-Aminophenol gave the anilino product **5** in 45% yield. Clearly, successful arylation of **2** under the present conditions requires a relatively powerful aromatic nucleophile. In support of this hypothesis, reaction of **2** with indole gave the 3-indolyl derivative **6** in 30% yield. This latter compound was also prepared by reaction of **2** with indolylmagnesium bromide.

Extension of the resorcinol reaction to 3,4,6-trichloropyridazine (**7**) gave the expected 3,6-dichloro-4-(2,4-dihydroxyphenyl)pyridazine (**8**) in 63% yield, which is consistent with a general reinforcement of the normal reactivity of the 4-chloro substituent in **7**,[3] rather than a specific effect ortho to the ring nitrogen atoms. The position of substitution in **8** was confirmed by hydrogenolysis to give 4-(2,4-dihydroxyphenyl)pyridazine (**12**) and spectral comparison of **12** with the 3-isomer **13**, prepared similarly from **3a**. The isomers **9** (3.5%) and **10** (3.5%) were also isolated from the reaction of resorcinol with **7**, together with a trace amount of a highly fluorescent compound. This latter product was also produced when **8** was heated at its melting point and was identified as 3-chloro-7-hydroxybenzofuro[2,3-*c*]pyridazine (**11**). Compound **11**, which was readily prepared from **8** by treatment with potassium carbonate in acetone, is acidic (pK_a = 7.5) and shows fluorescein-like fluorescence in aqueous alkaline solution. The properties of **11**-$\nu_{C=O}$ at 1630 cm^{-1}, failure to give a typical phenolic color reaction with diazotized sulfanilic acid—appear to reflect the importance of the vinylogous amide tautomer **11a**.

In mechanistic terms, the above aluminum chloride induced arylation reactions almost certainly proceed by initial complexation of the aluminum chloride with the di- or trichloropyridazine, which would result in enhanced activation of the chlorine substituent to nucleophilic displacement.



Experimental Section

NMR spectra were recorded with a Bruker 250AE spectrometer; DMSO-d_6 was used as solvent unless otherwise stated; δ_H values are in ppm relative to TMS. Mass spectra were registered on AEI 902 or VG 70-70F instruments; relative abundances of the ions are given in parentheses. Melting points are uncorrected. Column chromatography was carried out with silica gel (Merck SG 60, 0.063–0.2 mm) and TLC analysis with precoated plates (Merck SG 60 F_{254}).

3-Chloro-6-(4-hydroxyphenoxy)pyridazine (4a). Reaction of **2** with hydroquinone in the presence of $AlCl_3$ as described by Stanovnik[1] gave a solid, mp 196–197 °C (lit.[1] mp 195–196 °C), identified as **4a**: NMR δ 6.8 (AA′, 2 H), 7.04 (BB′, 2 H), 7.48 (d, 1 H, J = 9.2 Hz), 7.90 (d, 1 H, J = 9.2 Hz), 9.5 (br s, 1 H) ppm.

Reaction of 3-*tert*-Butylphenol with 3,6-Dichloropyridazine. A stirred mixture of $AlCl_3$ (3.58 g, 27 mmol), 3-*tert*-butylphenol (4.55 g, 30 mmol), and **2** (4.0 g, 27 mmol) in nitrobenzene (40 mL) was heated at 120 °C for 4 h, cooled, and poured into ice–water (200 mL) containing HCl (10 mL). The residue left after stream distillation was extracted with EtOAc, and the extract was evaporated to give 4.22 g of an oil. Column

(1) Pollak, A.; Stanovnik, B.; Tisler, M. *J. Org. Chem.* **1966**, *31*, 4297–4298.
(2) Coates, W. J.; Roe, A. M.; Slater, R. A.; Taylor, E. M. British Patent 1,527,712 (to SK&F); *Chem. Abstr.* **1976**, *84*, 164819j.
(3) Aldous, D. L.; Castle, R. N. Halopyridazines. In *The Chemistry of Heterocyclic Compounds*; Castle, R. N., Ed.; Wiley: New York, 1973; Vol. 28.

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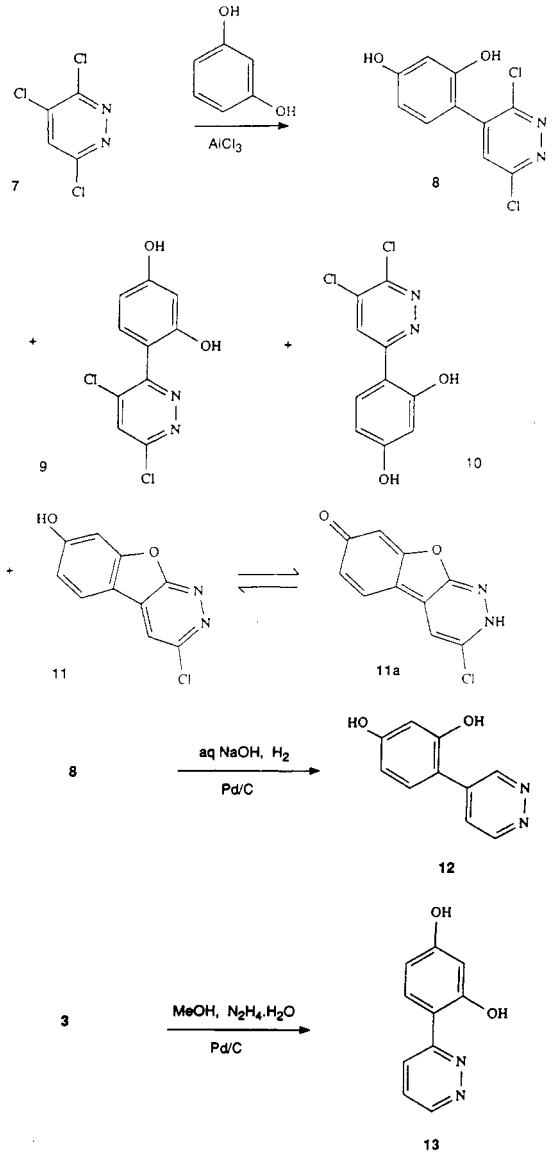

chromatography ($CHCl_3$) gave 0.13 g (1.8%) of a solid which after trituration with ether yielded 0.06 g (0.8%) of the less polar phenolic component. Recrystallization from cyclohexane afforded 3-(4-*tert*-butyl-2-hydroxyphenyl)-6-chloropyridazine (**3c**) as pale yellow needles, mp 151–152.5 °C: NMR δ 1.3 (s, 9 H), 7.05 (m, 2 H), 7.88 (d, 1 H, J = 8 Hz), 8.00 (d, 1 H, J = 9.8 Hz), 8.42 (d, 1 H, J = 9.8 Hz), 11.47 (s, 1 H) ppm; MS m/z 264 (10), 262 (29), 249 (17), 247 (51), 221 (49), 219 (100), 211 (4), 207 (4), 205 (4), 183 (4), 91 (41).

Anal. Calcd for $C_{14}H_{15}ClN_2O$: C, 64.00; H, 5.75; N, 10.66. Found: C, 64.14; H, 5.79; N, 10.61.

Further elution of the column gave 1.1 g (15%) of a solid, which after trituration with ether yielded 0.62 g (9%) of crude 3-(3-*tert*-butylphenoxy)-6-chloropyridazine (**4b**). Recrystallization from cyclohexane gave white needles of **4b**, mp 96.5–98 °C: NMR δ 1.29 (s, 9 H), 7.05 (m, 1 H), 7.24 (t, 1 H, J = 2 Hz), 7.31 (m, 1 H), 7.39 (m, 1 H), 7.55 (d, 1 H, J = 9.2 Hz), 7.94 (d, 1 H, J = 9.2 Hz) ppm; MS m/z 264 (6), 262 (19), 249 (29), 247 (77), 221 (4), 219 (10), 211 (21), 207 (15), 205 (29), 183 (19), 91 (100).

Anal. Calcd for $C_{14}H_{15}ClN_2O$: C, 64.00; H, 5.75; N, 10.66. Found: C, 64.60; H, 5.94; N, 10.61.

Reaction of 4-*tert*-Butylphenol with 3,6-Dichloropyridazine. In a similar procedure to that above, 4-*tert*-butylphenol (4.55 g) gave 3.1 g of crude product, chromatography of which yielded 1.07 g of a less polar component. Trituration with ether/petroleum ether (bp 60–80 °C) gave 0.32 g (4.5%) of 3-(4-*tert*-butylphenoxy)-6-chloropyridazine (**4c**). Recrystallization from cyclohexane gave **4c** as a white granular solid, mp 119–121 °C: NMR δ 1.31 (s, 9 H), 7.16 (dd, 2 H, J = 6.7 and 2 Hz), 7.47 (dd, 2 H, J = 6.7 and 2 Hz), 7.56 (d, 1 H, J = 9.2 Hz), 7.94 (d, 1 H, J = 9.2 Hz) ppm; MS m/z 264 (4), 262 (11), 249 (33), 247 (78), 221 (5), 219 (14), 211 (22), 207 (6), 205 (17), 183 (17), 149 (52), 91 (100).

Anal. Calcd for $C_{14}H_{15}ClN_2O$: C, 64.00; H, 5.75; N, 10.66. Found: C, 64.25; H, 5.90; N, 10.50.

The filtrate was allowed to evaporate, and the residue was washed with ether to give further **4c** as large plates, 0.3 g (4%), mp 120–121 °C, which were mechanically separated from 0.02 g (0.3%) of needles, mp 165–172 °C, tentatively identified as 3-(5-*tert*-butyl-2-hydroxyphenyl)-6-chloropyridazine (**3d**) containing about 20% of the ether **4c**: NMR ($CDCl_3$) δ 1.37 (s, 9 H), 7.06 (d, 1 H, J = 8.2 Hz), 7.47 (dd, 1 H, J = 8.2 and 2.2 Hz), 7.61 (d, 1 H, J = 2.2 Hz), 7.66 (d, 1 H, J = 9.2 Hz), 8.09 (d, 1 H, J = 9.2 Hz), 12.68 (s, 1 H) ppm. MS m/z 264 (12), 262 (32), 249 (71), 247 (100), 221 (26), 219 (50), 211 (26), 207 (12), 205 (15), 183 (21), 91 (82).

Further elution of the column gave 0.59 g (18%) of 6-chloro-2-(6-chloro-3-pyridazinyl)pyridazin-3(2*H*)-one,[4] mp 150–152 °C (lit.[5] mp 151–152 °C).

3-Chloro-6-(3-hydroxyanilino)pyridazine (5). A mixture of $AlCl_3$ (7.16 g, 53 mmol), 3-aminophenol (3.3 g, 30 mmol), and **2** (4.0 g, 27 mmol) in nitrobenzene (40 mL) was heated at 130 °C for 1.5 h then poured into ice–water (200 mL). The mixture was acidified (HCl), and the aqueous solution was washed with CH_2Cl_2, basified with K_2CO_3, and extracted with EtOAc. Evaporation of the extract gave 4.35 g of a solid which, digested with MeOH, yielded 2.7 g (45%) of **5**. Recrystallization from MeCN gave pale yellow prisms, mp 168–169 °C: NMR δ 6.40 (dq, 1 H, J = 8, 2.2, and 1.3 Hz), 7.03 (apparent dt, 1 H), 7.10 (apparent t, 1 H), 7.19 (d, 1 H, J = 9.3 Hz), 7.32 (apparent t, 1 H), 7.56 (d, 1 H, J = 9.3 Hz), 9.37 (s superimposed on br s, 2 H) ppm; MS m/z 223 (10), 222 (27), 221 (32), 220 (100), 206 (0.5), 204 (2), 194 (0.4), 192 (1), 186 (3), 185 (5), 158 (2), 157 (4).

Anal. Calcd for $C_{10}H_8ClN_3O$: C, 54.19; H, 3.64; N, 18.96. Found: C, 54.02; H, 3.60; N, 19.10.

3-Chloro-6-(3-indolyl)pyridazine (6). (a) $AlCl_3$ (5.92 g, 44 mmol) was added to a stirred mixture of **2** (6.0 g, 40 mmol) and indole (4.72 g, 40 mmol) in 1,2-dichloroethane[6] (60 mL); there was an exotherm from 21 to 35 °C. After 1.5 h the mixture was heated under reflux for 0.5 h. Addition of water to the cooled mixture gave 4.23 g (46%) of crude product, mp 248–254 °C, which was combined with a further 1.7 g (18%) obtained by EtOAc extraction of the filtrate. Recrystallization from ethanol gave 2.79 g (30%) of **6** as pale buff needles, mp 262–263 °C dec, identical with that prepared by the following method. (b) A solution of 1-indolylmagnesium iodide (from indole, 5.83 g, 50 mmol, and ethylmagnesium iodide) in ether (400 mL) was added during 1 h to a solution of **2** (7.45 g, 50 mmol) in ether (75 mL). After 64 h the mixture was heated under reflux for 5 h. Addition of 20% aqueous ammonium chloride (35 mL) to the cold mixture gave 4.25 g (37%) of a solid, mp 247–249 °C. Recrystallization from EtOH gave **6** as above: NMR δ 7.21 (m, 2 H), 7.5 (m, 1 H), 7.82 (d, 1 H, J = 9.1 Hz), 8.23 (d, 1 H, J = 9.1 Hz), 8.33 (d, 1 H, J = 2.6 Hz), 8.46 (m, 1 H), 11.85 (br s, 1 H) ppm; MS m/z 231 (11), 229 (32), 203 (3), 201 (9), 141 (100), 114 (47).

Anal. Calcd for $C_{12}H_8ClN_3$: C, 62.73; H, 3.51; N, 18.29. Found: C, 63.03; H, 3.33; N, 18.44.

Reaction of Resorcinol with 3,4,6-Trichloropyridazine (7). $AlCl_3$ (10.49 g, 78 mmol) was added to a stirred mixture of **7** (13.1 g, 71 mmol), resorcinol (7.85 g, 71 mmol), and 1,2-dichloroethane[6] (130 mL); there was an exotherm from 20 to 35 °C. After 1 h the mixture was heated under reflux for 0.75 h, cooled, and added to ice–water (400 mL) to give 17.46 g (95%) of crude product, mp ca. 180 °C. Soxhlet extraction of the solid using an azeotropic mixture of $CHCl_3$ (200 mL) and MeOH (15 mL) followed by distillation of the extract to a bp of 56 °C and filtration of the warm mixture gave 11.56 g (63%) of 3,6-dichloro-4-(2,4-di-

(4) 6-Chloro-2-(6-chloro-3-pyridazinyl)pyridazin-3(2*H*)-one is formed from **2** and its hydrolysis product 6-chloro-3(2*H*)-pyridazinone; see ref 5 and references therein.

(5) Coad, P.; Coad, R. A. *J. Org. Chem.* **1963**, *28*, 1919–1921.

(6) Halogenated hydrocarbons such as 1,2-dichloroethane and dichloromethane were found to be useful alternatives to the nitrobenzene solvent used in the original method of Stanovnik.[1]

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.

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New Zinc Difluorocarbenoid Reagent

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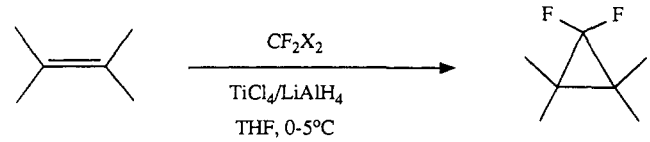
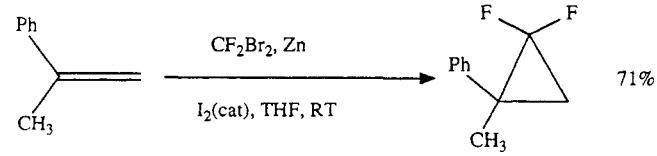
It was recently reported that good yields of *chlorofluorocarbene* adducts could be obtained from the reaction of $CFCl_3$ with reduced titanium in the presence of alkenes.[1,2] Unfortunately, the utilization of CF_2Cl_2, CF_2Br_2, or CF_2I_2 in this same reaction did not lead to generally good yields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

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