10 mmol) in H_2O (100 mL) was added bromine (510 μL, 10 mmol) in one portion. After ca. 7 min, when the yellow color of bromine disappeared, (*S*)-L-cysteine (1.21 g, 10 mmol) was added to the solution. The resulting mixture was kept in the ice–water bath for 2 h and then passed through a column (2.0 × 10 cm) of Dowex 50W (H^+ form, equilibrated with H_2O). The components in the mixture were eluted with 1 M HCl and fractions of 100 mL were collected and analyzed by TLC. Fractions 2–5 that contained 2-*S*-cysteinylhistidine (1) were combined, and the solvent was removed to dryness in a rotary evaporator. The residue was applied on a column (2.0 × 6.5 cm) of Dowex 50W (equilibrated with 2 M HCl) and eluted with 2 M HCl (20 mL/fraction). Fractions 3–8 that contained **1** were evaporated to afford the 3 HCl salt of **1** (1.04 g). The amino acid was further purified in the free form by two crystallizations from H_2O (adjusted to pH 6 with pyridine–EtOH: colorless crystals (540 mg, 19% yield); mp >280 °C; $[\alpha]_D$ +147° (5 mg/mL, 1 M HCl); UV (0.1 M HCl) λ_{max} (ϵ) 253 nm (7610), 219 (5270); ^1H NMR (2 M DCl–D_2O) δ 3.52 (2 H, d, J = 7 Hz, Ar CH_2), 3.86 (2 H, d, J = 5 Hz, SCH_2), 4.52 (1 H, t, J = 7 Hz, CH), 4.60 (1 H, t, J = 5 Hz, CH), 7.59 (1 H, s, Ar H); amino acid analysis, 362 min (γ-aminobutyric acid; 356 min). Anal. Calcd for $C_9H_{14}N_4O_4S{\cdot}0.5H_2O$: C, 38.16; H, 5.34; N, 19.78; S, 11.32. Found: C, 38.31; H, 5.22; N, 19.75; S, 11.29.

Preparation of 2-Mercapto-(*S*)-histidine (2) by HI Hydrolysis of 2-*S*-Cysteinylhistidine (1). A mixture of 2-*S*-cysteinylhistidine (**1**; 300 mg, 0.106 mmol) and red P (1.5 g) in 57% HI (10 mL) was heated under reflux. After 16 h when the reaction completed by 98% (by amino acid analysis), the mixture was evaporated to dryness at 70 °C, and the residue, taken up in H_2O, was passed through a column (2.0 × 7.5 cm) of Dowex 50W (H^+ form, equilibrated with H_2O). The components in the mixture were eluted with H_2O (50 mL) and then with 1 M HCl. The first 100 mL of the HCl eluate that contained alanine and 2-mercaptohistidine (**2**) was evaporated to dryness, and the residue was applied on a column (2.0 × 23 cm) of Dowex 50W (equilibrated with 0.15 M HCl; 20-mL fractions being collected and analyzed by UV and TLC). Fractions 24–33 and 30–39 contained alanine and **2**, respectively. Evaporation of fractions 24–30 and 31–39 afforded the HCl salt of alanine (130 mg) and 2HCl salt of **2** (209 mg). Further purification of **2** as the free amino acid was achieved by crystallization from H_2O (adjusted to pH 6 with pyridine)–EtOH in the presence of dithiothreitol: colorless crystals (126 mg, 62% yield); mp >280 °C; $[\alpha]_D$ −9.8° (5 mg/mL, 1 M HCl); UV (0.1 M HCl) λ_{max} (ϵ) 257 nm (16300); ^1H NMR (2 M DCl–D_2O) δ 3.35 (2 H, d, J = 7 Hz, CH_2), 4.47 (1 H, t, J = 7 Hz, CH), 7.02 (1 H, s, Ar H); amino acid analysis, 104 min (aspartic acid, 96 min). Anal. Calcd for $C_6H_9N_3O_2S$: C, 38.49; H, 4.85; N, 22.44; S, 17.13. Found: C, 38.13; H, 4.88; N, 22.00; S, 16.85. A commercial sample of **2**: $[\alpha]_D$ −10.6° (5 mg/mL, 1 M HCl) (lit. $[\alpha]_D$ −9.5°);[10] UV (0.1 M HCl) λ_{max} (ϵ) 257 nm (16000).

Free (*RS*)-alanine (51 mg, 54% yield) was obtained by crystallization from H_2O (adjusted to pH 6 with pyridine)–EtOH: $[\alpha]_D$ 0.0° (5 mg/mL, 1 M HCl).

Preparation of 2-Mercapto-(*S*)-histidine (2) by a Direct Method. To a stirred, ice-cooled solution of (*S*)-histidine·HCl·H_2O (1.05 g, 5 mmol) in H_2O (50 mL) was added bromine (255 μL, 5 mmol) in one portion. After ca. 7 min, $Na_2S{\cdot}9H_2O$ (1.20 g, 5 mmol) was added to the solution. The resulting mixture was kept in the ice–water bath for 2 h and then passed through a column (2.0 × 7.5 cm) of Dowex 50W (H^+ form, equilibrated with H_2O). The components in the mixture were eluted with H_2O (50 mL) and then with 1 M HCl. The first 50 mL of the HCl eluate that contained 2-mercaptohistidine (**2**) was evaporated to dryness, and the residue was applied on a column (2.0 × 20 cm) of Dowex 50W (equilibrated with 0.2 M HCl) and eluted with 0.2 M HCl (20 mL/fraction). Fractions 22–28 that contained **2** were evaporated to afford the 2HCl salt (197 mg). The amino acid was purified in the free form as described above: colorless crystals (108 mg, 12% yield); mp >280 °C; $[\alpha]_D$ −10.6° (5 mg/mL, 1 M HCl) λ_{max} (ϵ) 257 nm (17200). Found: C, 38.17; H, 4.91; N, 21.97; S, 16.82.

Preparation of 5-Bromo-(*S*)-histidine. To a stirred, ice-cooled solution of (*S*)-L-histidine methyl ester hydrochloride (1.03 g, 5 mmol) in H_2O (50 mL) was added bromine (305 μL, 6 mmol). After the disappearance of the yellow color, 6 M HCl (10 mL) was added and the mixture refluxed for 1 h to cleave the ester bond. The resulting dark violet solution was evaporated to dryness, and the residue was applied on a column (2.0 × 23 cm) of Dowex 50W (equilibrated with 1 M HCl) and eluted with 1 M HCl (20 mL/fraction). Fractions 30–54 that contained 5-bromohistidine were evaporated to afford the 2HCl salt (672 mg). The amino acid was purified in the free form by crystallization from H_2O (adjusted to pH 6 with pyridine)–acetone: colorless crystals (460 mg, 39% yield); mp 238 °C dec; $[\alpha]_D$ +11.1° (10 mg/mL, 1 M HCl); UV (0.1 M HCl) λ_{max} (ϵ) 220 nm (4970); ^1H NMR (2 M DCl–D_2O) δ 3.51 (2 H, d, J = 7 Hz, CH_2), 4.51 (1 H, t, J = 7 Hz, CH), 8.86 (1 H, s, Ar H); amino acid analysis, 356 min (γ-aminobutyric acid, 356 min). Anal. Calcd for $C_6H_8N_3O_2Br$: C, 30.79; H, 3.45; N, 17.96; Br, 34.14. Found: C, 31.13; H, 3.84; N, 17.96; Br, 34.03.

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Registry No. 1, 77504-36-0; **2**, 2002-22-4; **2**·2HCl, 97589-45-2; **4a**, 97486-07-2; (*S*)-L-histidine hydrochloride, 1007-42-7; (*R*)-L-cysteine, 52-90-4; (*S*)-L-histidine methyl ester hydrochloride, 22888-60-4; 5-bromo-(*S*)-histidine, 97486-06-1.

Electrophilic Benzylation and Nitration of 2,6-Dimethylanisole, 2,6-Dimethylphenol, and 2,6-Diisopropylphenol. Isomer Distribution and Mechanistic Considerations

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Aromatic benzylation reactions are among the most thoroughly investigated reactions in Friedel–Crafts chemistry both from the view point of synthetic usefulness and mechanistic importance.[1]

Olah and co-workers[2] reported a detailed investigation of electrophilic benzylation of benzene and toluene using a variety of Friedel–Crafts catalysts and discussed mechanistic aspects. Predomiment ortho–para substitution of toluene was observed. Similar studies were subsequently also carried out on anisole.[3]

Recently, Miller et al.[4] studied the benzylation of 2,6-dimethylphenol (2,6-DMP) and 2,6-dimethylanisole (2,6-DMA) with benzyl chloride using $ZnCl_2$ catalyst or with benzyl alcohol catalyzed by H_2SO_4. Predominent "meta" substitution was observed in reaction of 2,6-DMA (68–74% 3-substitution), whereas 2,6-DMP gave 38–41% of the 3-benzyl isomer. During the course of the study by Miller et al.[4] several possible mechanisms including intermolecular benzyl transfer (rearrangement), rearrangement within the σ-complex and ortho benzylation (ipso attack) followed by rearrangement could be excluded. But some evidence was presented to support partial intervention of a mechanism in which O-benzylation occurs followed by intermolecular benzyl shift. It was, however, concluded that the product of meta benzylation arises by direct attack.[4] Similar results were obtained on alkylation of 2,6-DMP with allyl alcohol using H_2SO_4 as catalyst or with allyl halides using $ZnCl_2$.[5]

An interesting kinetic study by Cerfontain et al.[6] on the aprotic (SO_3) and protic (H_2SO_4) sulfonation of several

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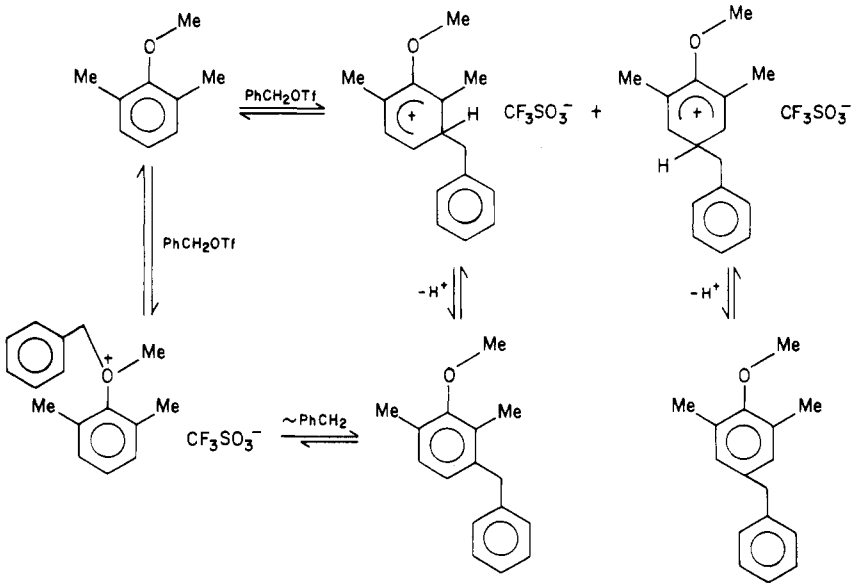
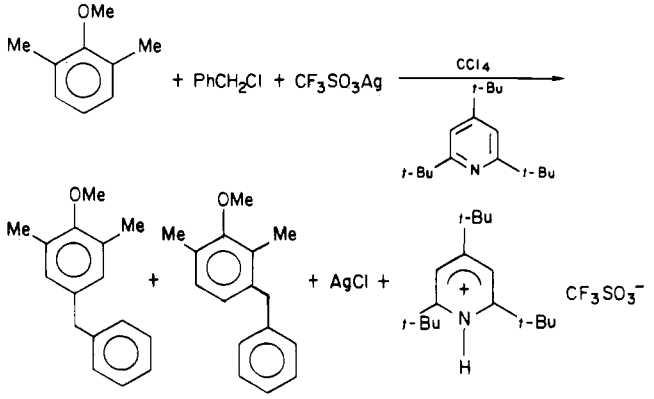
Scheme I



2,6-disubstituted phenols including 2,6-DMA and 2,6-DMP has shown that in excess substrate initial O-sulfonation occurs followed by O-desulfonation/C-sulfonation, whereas the reverse (e.g., O-sulfonation/C-sulfonation/O-desulfonation) was found in excess SO_3. The relative ratio of 3-/4-substitution was found to be strongly dependent on H_2SO_4 concentration.

We describe herein a study of alkylation of 2,6-DMA, 2,6-DMP, and 2,6-DIP using the mild benzylating reagent benzyl triflate $PhCH_2O_3SCF_3$[7] formed in situ by reaction of benzyl chloride and silver triflate in CCl_4 solvent in the presence of excess aromatic substrate. Benzyl triflate reacts readily with the substrates to form both 3- and 4-benzyl derivatives. In order to assure that isomer distributions are not affected by subsequent isomerization under our conditions, in control experiments 1 equiv of 2,4,6-tri-*tert*-butylpyridine (2,4,6-TBP) was added as a proton trap to the reaction. No change of isomer distribution was observed. In these reactions 61.5%, 33%, and 18% of the 3-benzyl isomer and 38.5%, 67%, and 82% of the 4-isomer were formed from 2,6-DMA, 2,6-DMP, and 2,6-DIP, respectively. In the latter case the isopropyl groups can cause increased steric hindrance in the adjacent positions, which leads to a decrease in the amount of the 3-isomer. Benzyl triflate benzylation of the parent anisole, on the other hand, gave only 1.6% meta substitution together with 31.1% ortho and 67.3% para substitution.



In a control experiment when 2,6-DMA was allowed to react with benzyl chloride in the presence of AgCl in dry CCl_4 under the reaction condition used for benzylation with benzyl triflate, only a trace of benzylated products was obtained. When the reaction was allowed to continue overnight at room temperature a ca. 1% yield of benzylated products was obtained. The isomer distribution in the silver ion catalyzed benzylation of 2,6-DMA was 56% 3-isomer and 34% 4-isomer, confirming that the observed isomer distributions are not affected by the presence of AgCl formed in the reaction.

We also carried out the nitration of 2,6-DMA and 2,6-DIP with nitronium tetrafluoroborate. When 2,6-DMA was nitrated with $NO_2^+BF_4^-$ in nitromethane, 20% 3-nitro and 80% 4-nitro isomers were obtained. Similar nitration in methylene chloride gave 25% 3-nitro and 75% 4-nitro isomers. As the solubility of the nitronium salt is limited in these solvents, the difference in isomer distributions is not considered to be significant. The nitration of 2,6-DIP gave more complicated reaction mixtures (probably also involving dealkylation). The isomer distribution of the intact nitrated products was 18% 3-nitro and 82% 4-nitro isomers.

Whereas the observed isomer distribution for the nitration of 2,6-DMA is considered to be a typical example, reflecting competing ortho–para-directing effects of the methoxy and the hydroxy group with alkyl substituents, benzylation of 2,6-DMA must involve an additional mechanism that contributes to the overall formation of the meta benzyl derivative. The magnitude of meta substitution for benzylation of 2,6-DMA appears to be too high to be explained simply in terms of steric inhibition to resonance,[8] e.g., a decrease in overlap between the π-system and the oxygen lone pair, destabilizing the σ-complex

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leading to 4-substitution.

In order to obtain more mechanistic information we protonated 2,6-DMP, 4-benzyl-2,6-DMP, 2,6-DMA, and 4-benzyl-2,6-DMA in $FSO_3H + SbF_5$ (1:1)/SO_2ClF at low temperature. The ^{13}C NMR spectra clearly showed that whereas 2,6-DMP and 4-benzyl-2,6-DMP are C-protonated to form the corresponding benzenium ions, $\delta_{^{13}C\,(methylene)}$ 39.2 and 52, respectively, 2,6-DMA and 4-benzyl-2,6-DMA are O-protonated, $\Delta\delta_{^{13}C\,(OMe)}$ 13.5 and 12.35, respectively, and no arenium ion is formed. 2,6-DMA was previously shown by Brouwer et al.[9] to be O-protonated by ^1H NMR using $HF + BF_3$ at -100 °C.

Similarly, whereas low-temperature methylation of 2,6-DMA with $MeF/SbF_5/SO_2$ gave exclusively (^{13}C NMR) O-methylation, $\Delta\delta_{^{13}C\,(OMe)}$ 24.5, with 2,6-DMP the C-methylated species was observed as major species, $\delta_{^{13}C\,(methylene)}$ 58.2. The corresponding oxonium ion was also detected as a minor species, $\delta_{^{13}C\,(OMe)}$ 60.5.

For 2,6-DMA, the presence of a methyl group on oxygen is, therefore, sufficient to render the oxygen more accessible for protonation (methylation) than 2,6-DMP. Our control experiments suggest that competing O-benzylation, especially for 2,6-DMA for which a higher percentage of meta substitution is actually observed, is taking place, thus contributing to the overall percentage of meta substitution (see Scheme I).

Since the extent of intermolecular benzyl transfer was found to be only of minor significance in Miller's control experiments with 2,6-DMP, it has to be assumed that benzyl shift occurs preferentially through an intramolecular process involving a five-membered ring transition state.

Experimental Section

The aromatic substrates and benzyl chloride were commercially available samples of highest purity and used without further purification. Rigorously dried CCl_4 was used as solvent. Silver triflate was prepared from Ag_2CO_3 and triflic acid. Nitronium tetrafluoroborate was prepared and used as reported previously.[10]

Whereas 4-benzyl-2,6-DMP was synthesized according to the literature from 4-benzoyl-2,6-DMP by Clemenson reduction,[11] 4-benzyl-2,6-DMA was prepared by reduction of the 4-benzoyl-2,6-DMA using Et_3SiH/TFA reagent.[12]

GLC analyses were performed on a Varian Model 3700 gas chromatograph equipped with a 50-m capillary column (OV 101) and an online automatic integrator.

For 2,6-DMA and 2,6-DIP isomer distributions were also determined by NMR as previously described.[5]

^{13}C NMR spectra were recorded on a Varian FT-80 instrument equipped with a variable temperature probe.

General Procedure for Benzylation Reactions. To the aromatic compound (10 mmol) diluted in 15 mL of CCl_4 was added silver triflate (1.05 g, 4.08 mmol) and 2,4,6-TMP (1.02 g, 4.1 mmol) under dry nitrogen with good stirring at room temperature. Subsequently, benzyl chloride (0.515 g, 4.08 mmol) was dropwise added, whereupon AgCl was immediately precipitated. After continued stirring for 40 min at room temperature, the reaction mixture was filtered and was analyzed by GLC.

General Procedure for Nitration Reactions. To the aromatic compound (5 mmol) in 25 mL of solvent at 5-10 °C was added a slurry of 0.015 mol of $NO_2^+BF_4^-$ in 20 mL of the same solvent. After being vigorously stirred, the samples were quenched with water, separated, extracted with ether, washed with Na_2CO_3 solution, dried over $MgSO_4$, and analyzed by GLC.

Preparation of the Ions. For protonation studies, a cold slurry of the aromatic compound (50 mg) in SO_2ClF was added to Magic Acid (1 mL) in SO_2ClF (1 mL) at dry ice/acetone temperature with efficient vortex mixing.

For methylation reactions, methyl fluoride was slowly bubbled through a cold solution of SbF_5 in excess SO_2 until homogeneous. A proton-decoupled ^{13}C NMR spectrum of the resulting solution confirmed the formation of $MeSO_2^+SbF_6^-$ [$\delta_{^{13}C}$ 72.9 (s)], together with some uncomplexed MeF [$\delta_{^{13}C}$ 72.3 (d, J_{C-F} = 151 Hz)]. To this solution was added a cold solution of the aromatic compound (50-60 mg) in SO_2 with efficient vortex mixing.

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Registry No. $PhCH_2O_3CSF_3$, 17674-16-7; nitronium tetrafluoroborate, 13826-86-3; 2,6-DMA, 1004-66-6; 2,6-DMP, 576-26-1; 2,6-DIP, 2078-54-8; 3-benzyl-2,6-DMA, 69804-73-5; 4-benzyl-2,6-DMA, 61259-78-7; 3-benzyl-2,6-DMP, 31040-78-5; 4-benzyl-2,6-DMP, 41772-31-0; 3-benzyl-2,6-DIP, 97674-51-6; 4-benzyl-2,6-DIP, 61563-91-5; 3-nitro-2,6-DMA, 50536-74-8; 4-nitro-2,6-DMA, 14804-39-8; 3-nitro-2,6-DIP, 97674-52-7; 4-nitro-2,6-DIP, 1576-14-3; anisole, 100-66-3; *o*-benzylanisole, 883-90-9; *m*-benzylanisole, 23450-27-3; *p*-benzylanisole, 834-14-0.

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Synthesis of Novel Pyrazoles Containing Perfluoroalkyl Groups by Reactions of Perfluoro-2-methylpent-2-ene and Hydrazones

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In our studies of heterocyclic compounds from perfluoroolefins, we previously reported the synthesis of pyrazolium aminimine containing perfluoroalkyl groups from perfluoro-2-methylpent-2-ene (1) and 1,1-dimethylhydrazine.[1] In this note, we describe the synthesis of some novel pyrazoles containing perfluoroalkyl groups from 1 and hydrazones 2.

Perfluoro-2-methylpent-2-ene (1) reacted readily with hydrazone 2 (**a**; R = H; **b**; R = CH_3) in the presence of base such as sodium carbonate in THF at 0 °C to give the azines **3a,b** in 35% yield. Without base, this reaction proceeded to 3 in lower yield (Scheme I).

Spectral data of **3a,b** (Experimental Section) indicate the presence of both hexafluoroisopropyl and pentafluoroethyl groups. This reaction is assumed to proceed via nucleophilic attack of 2 on 1, followed by elimination of hydrogen fluoride and proton shift as suggested in the reaction of amine.[2]

Azine **3a** was readily and cleanly converted to pyrazole **4a** by heating with a mixture of sodium carbonate and cesium fluoride in dioxane at 100 °C. In the case of **3b** (R = CH_3), a mixture of **4b** and **4c** was obtained in 6:1 molar ratio (calculated from ^1H NMR). These cyclization to **4a,b** can be understood by fluoride attack on intermediate I followed by the steps shown in Scheme I (route a). From the fact that **4b** could not be dehydrofluorinated to **4c** in the corresponding reaction conditions, another cyclization mode leading to **4c** can be induced. The basicity

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