ortho-Disubstituted *F*-Benzenes. II.[1] One-pot Syntheses of (*F*-Benzo)heterocyclic Compounds

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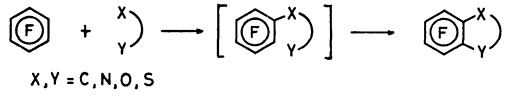
Convenient one-pot methods of converting *F*-benzene into substituted (*F*-benzo)furans, (*F*-benz)oxazole, -imidazolines, and -thiazoline are described. Ambident nucleophiles are generated *in situ* from ketone, amide, urea, thiourea, and their derivatives in the presence of sodium hydride. Enolate-anion nucleophiles are also generated *in situ* from silyl enol ethers in the presence of potassium fluoride in anhydrous DMF.

Research in our laboratories has been directed at the *ortho*-difunctionalization of simple, commercially available *F*-benzene.[2] This has led to the preparation of related (*F*-benzo)heterocyclic compounds, which were in most cases synthesized through laborious reaction sequences.[3] In a previous paper[1] we described the intramolecular cyclization of *ω*-functionalized *F*-anilide into some (*F*-benz)azacyclic compounds. Here we wish to report a convenient one-pot method for converting *F*-benzene into substituted (*F*-benzo)-furans, (*F*-benz)oxazole, -imidazolines, and -thiazoline by the use of such ambident nucleophiles as ketone, amide, urea, and their derivatives. Several preceding works with similar schemes have appeared in the literature.[4]

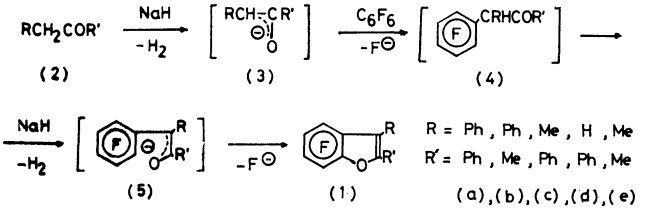


Scheme 1.

Results and Discussion

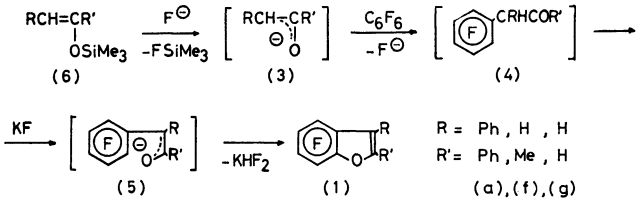
A range of (*F*-benzo)furans (**1**) were obtained by the reaction of *F*-benzene with the corresponding ketones (**2**). The reactions were carried out by adding the ketone to a mixture of *F*-benzene and two equivalents of sodium hydride in DMF.

The presence of four unequivalent fluorines in (**1a**) and (**1e**), based upon their ^{19}F-NMR spectra, and the regio-isomerism between (**1b**) and (**1c**) indicate the compounds (**1**) to have a benzofuran skeleton, which is compatible with their characteristic UV bands.



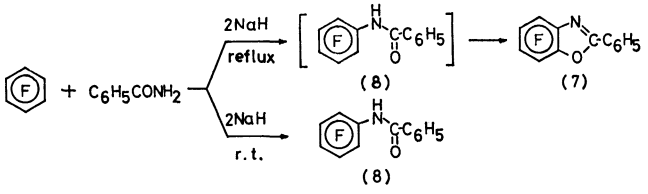
Scheme 2.

The reaction presumably proceeds in two steps *via* an intermediary (*F*-phenyl) ketone (**4**), as shown in Scheme 2. The presence of a phenyl group seems to give a higher yield than does a methyl group. One reason for this might be the resonance stabilization of the enolate anion forms, (**3**) and (**5**), resulting from the *α*- and *β*-phenyl groups, promoting the nucleophilic substitution of fluorine on the aromatic nucleus. Also, the steric bulkiness of a phenyl group, especially that adjacent to the ketone carbonyl, favors the intramolecular cyclization by hindering intermolecular aromatic substitution or aldol condensation. This presumption is compatible with the observation that the inverse addition of *F*-benzene to a mixture of ketone and sodium hydride afforded yields of less than 5% of the expected products (**1**) except for the 49% yield from phenyl benzyl ketone (**2a**). Sterically less hindered ketones would promote the aldol condensation or intermolecular aromatic substitution in basic media, thus consuming the starting ketones or intermediary (*F*-phenyl) ketones (**4**) prior to the intramolecular cyclization.



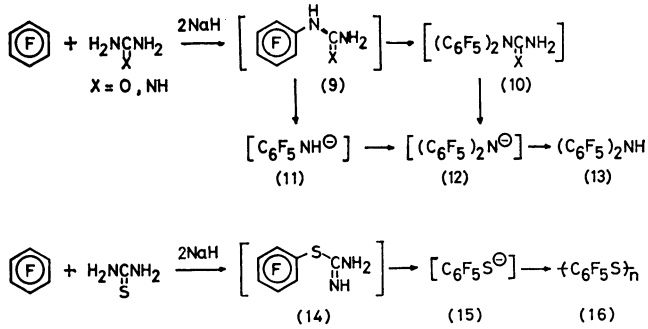
Scheme 3.

The generation of an enolate anion in neutral media can be achieved by the Si–O bond cleavage of silyl enol ethers in the presence of fluoride ions.[5] Also, one may expect that the protection of a ketone in the form of silyl enol ether suppresses the condensation reactions with the enolate. However, no satisfactory results have far been obtained except in the case of trimethylsilyl 1,2-diphenylvinyl ether (**6a**). The reactions using the trimethylsilyl enol ethers, (**6f**)[6] and (**6g**),[7] which were derived from acetone and tetrahydrofuran respectively, afforded none of the expected products (**1**), in which the intermolecular condensation or aromatic substitution of intermediary (*F*-phenyl) ketones (**4**) seemed to be preferred.



Scheme 4.

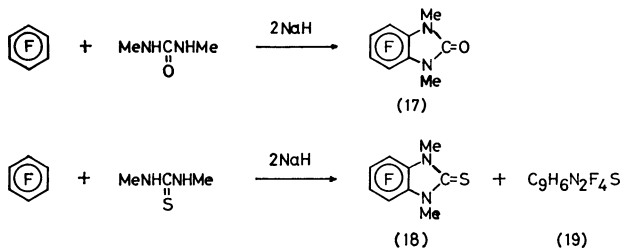
2-Phenyl-*F*-benzoxazole (**7**) was previously synthesized from *F*-aniline by way of benz-*F*-anilide (**8**).[1] The preparation of this compound was much simplified by the present one-pot reaction of *F*-benzene and benzamide under reflux. The reaction proceeds step-by-step *via* benz-*F*-anilide (**8**), and the intramolecular cyclization of the intermediary anilide required a higher temperature,[1] since the anilide (**8**) was isolated in an 80% yield when the reaction was carried out at room temperature.



Scheme 5.

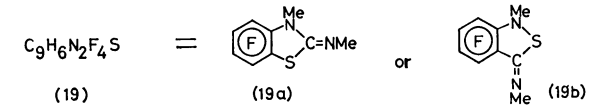
Urea, guanidine, and thiourea were also regarded as possible polyfunctional nucleophiles. The reactions with these nucleophiles, however, afforded no heterocyclic products; instead, di(*F*-phenyl)amine (**13**) was obtained from the former two and poly(thio-*F*-*p*-phenylene) (**16**) from the last one. The occurence of the above products indicates that the intermediary *F*-phenyl derivatives (**9**) and (**14**) cleave at the α–β bond prior to the intramolecular cyclization, thus liberating *F*-anilide anion (**11**) and *F*-benzothiolate anion (**15**) respectively, in the presence of an excess of hydride ions. The anions (**11**) and (**15**) afford the amine (**13**) and sulfide (**16**) respectively upon subsequent aromatic substitution. The intermediary *N*-carbamoyl-*F*-aniline (**9**), though not isolated, would be deprotonated at the α-amide in preference to the γ-amide. Such an α-amide anion favors the intermolecular nucleophilic aromatic substitution rather than the intramolecular cyclization, and in the presence of *F*-benzene it forms *N,N*-di(*F*-phenyl)urea (**10**), which then liberates the di(*F*-phenyl)amide anion (**12**) in the presence of an excess of sodium hydride. This may provide another possible route to di(*F*-phenyl)-amine.

The reaction with *N,N'*-dimethylurea gave 1,3-dimethyl(*F*-benz)imidazolin-2-one (**17**), where the active α-amide hydrogen of the intermediary *N*-carbamoyl-*F*-aniline is replaced with a methyl group;



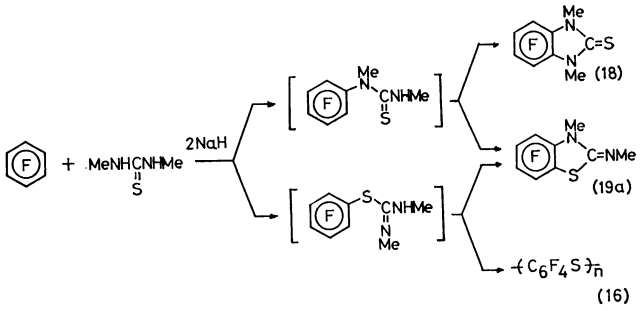
Scheme 6.

the only dissociable hydrogen of the intermediate is that of the γ-amide, and the α,β-bond cleavage seems to be suppressed. Increased steric hindrance by the methyl group would also favor the intramolecular cyclization.



Scheme 7.

The reaction with the *N,N'*-dimethylthiourea similarly afforded 1,3-dimethyl(*F*-benz)imidazoline-2-thione (**18**) and a comparable amount of poly(thio-*F*-*p*-phenylene) in addition to an isomeric product, $C_9H_6N_2F_4S$ (**19**). The ^{19}F-NMR and ^{1}H-NMR of the last product indicate the presence of four unequivalent aromatic fluorines and two unequivalent methyl groups on hetero atoms respectively, suggesting that the heterocyclic moiety has either thiazoline (**19a**) or isothiazoline (**19b**) structure. The rearrangement into the isothiazolidine structure seems less probable under the present reaction conditions. The results indicate that, in the reaction with *N,N'*-dimethylthiourea, the nucleophilic attacks by the amide and thiolate anions proceed competitively at the stage of the first aromatic substitution and/or the subsequent intramolecular cyclization.



Scheme 8.

Experimental

The melting points are uncorrected. The IR and UV spectra were obtained with JASCO IR A-1 and Hitachi 220 spectrophotometers respectively. The ^{1}H-NMR and ^{13}C-NMR chemical shifts were recorded on Hitachi R-24 and JEOL JNM FX 100 instruments respectively, against the internal TMS reference. The ^{19}F-NMR chemical shifts were recorded on Varian EM 390 and JEOL PS-100 instruments as positive values downfield from the internal *F*-benzene reference. The mass spectra were obtained with JEOL JMS-07 and Hitachi RMS-4 spectrometers.

*Preparation of (F-Benzo)furan Derivatives (**1a—e**).* *General Procedure Using Sodium Hydride*: A solution of a ketone (**2**) (10 mmol) in anhydrous DMF (5 ml) was added dropwise into a stirred mixture of *F*-benzene (10 mmol), sodium hydride (20 mmol), and anhydrous DMF (10 ml) over a 30-min period at room temperature and under a dry nitrogen atmosphere. The mixture was stirred at 80 °C for an additional 5 h and then poured into ether. The ethereal solution was washed with water, dried over sodium sulfate, and evaporated. The residue was fractionated by chromatography on a neutral

alumina column. The fraction eluted with hexane gave a (*F*-benzo)furan derivative (**1**), which was further purified by sublimation.

*2,3-Diphenyl-*F*-benzofuran (**1a**)*; Yield: 50%. White needles, mp 163.5—164.5 °C. ^{1}H-NMR ($CDCl_3$): 7.2—7.6 ppm (m, arom.). ^{19}F-NMR ($CHCl_3$): −1.8 (1F), 0.0 (1F), 1.2 (1F), 14.2 ppm (1F).[8] UV: λ_{max} (cyclohexane); 232 (log ε 4.34), 297 nm (4.40).[9] Found: C, 70.12; H, 2.83%; M$^+$, 342. Calcd for $C_{12}H_{10}F_4O$: C, 70.18; H, 2.95%, M, 342.

*2-Methyl-3-phenyl-*F*-benzofuran (**1b**)*; Yield: 29%. White needles, mp 86—87 °C. ^{1}H-NMR ($CDCl_3$): 2.45 (s, 3H, CH_3), 7.4—7.9 ppm (m, 5H, arom.). ^{19}F-NMR ($CHCl_3$): −2.1 (1F), −0.5 (2F), 15.2 ppm (1F).[8] UV: λ_{max} (cyclohexane); 246 nm (log ε 4.19).[9] Found: C, 64.47; H, 3.03%; M$^+$, 280. Calcd for $C_{15}H_8F_4O$: C, 64.29; H, 2.88%; M, 280.

*2-Phenyl-3-methyl-*F*-benzofuran (**1c**)*; Yield: 27%. White needles, mp 109.5—110.5 °C. ^{1}H-NMR ($CDCl_3$): 1.6 (s, 3H, CH_3), 7.3—7.5 ppm (m, 5H, arom.). ^{19}F-NMR ($CHCl_3$): −2.6 (1F), 0.5 (2F), 9.5 ppm (1F).[8] UV: λ_{max} (cyclohexane); 285 nm (log ε 4.40).[9] Found: C, 64.06; H, 3.10%; M$^+$, 280. Calcd for $C_{15}H_8F_4O$: C, 64.29; H, 2.88%; M, 280.

*2-Phenyl-(*F*-benzo)furan (**1d**)*; Yield: 49%. White needles, mp 112—114 °C (lit,[10] 114.5—115.5 °C). Found: C, 62.93; H, 2.23%; M$^+$, 266.

*2,3-Dimethyl-*F*-benzofuran (**1e**)*; Yield: 2.3%. White needles, mp 37.5—38.5 °C. ^{1}H-NMR ($CDCl_3$): 2.25 (s, 3H, CH_3), 2.35 ppm (s, 3H, CH_3). ^{19}F-NMR ($CHCl_3$): −3.5 (1F), −1.3 (1F), −0.5 (1F), 8.7 ppm (1F).[8] UV: λ_{max} (cyclohexane); 247 nm (log ε 4.11).[9] Found: C, 54.89; H, 2.76%; M$^+$, 218. Calcd for $C_{10}H_6F_4O$: C, 54.89; H, 2.77%; M, 218.

*General Procedure Using Trimethylsilyl Enol Ethers (**6**).*[6,7] A solution of a trimethylsilyl enol ether (**6**) (2.5 mmol) in anhydrous DMF (10 ml) was added, dropwise into a stirred mixture of *F*-benzene (2.5 mmol), anhydrous potassium fluoride (5 mmol), and anhydrous DMF (10 ml) over a 30-min period at room temperature and under a dry nitrogen atmosphere. The mixture was stirred at 80 °C for an additional 8 h and subsequently worked-up in a manner similar to that described above. **1a**; Yield: 49%. The reactions using trimethylsilyl isopropenyl ether (**6f**) and trimethylsilyl vinyl ether (**6g**), which had been prepared according to the literature,[6,7] afforded neither the expected (*F*-benzo)-furan (**1g**) nor 2-methyl derivative (**1f**).

Reactions of F*-Benzene with Benzamide. 2-Phenyl-*F*-benzoxazole (**7**)*: A solution of benzamide (1.21 g, 10 mmol) in anhydrous DMF (20 ml) was added dropwise into a stirred mixture of *F*-benzene (1.86 g, 10 mmol), sodium hydride (20 mmol) and anhydrous DMF (2.5 ml) over a 15-min period at room temperature and under a dry nitrogen atmosphere. The mixture was stirred at 80 °C for an additional 2 h, subsequently refluxed for an additional 3 h, and then poured into ether. The ethereal solution was washed with water, dried over sodium sulfate, and evaporated off. The residue was chromatographed on a silica gel column. The fraction eluted with hexane gave 2-phenyl-*F*-benzoxazole (**7**) (0.85 g, 32%). The product was indentified by comparison with an authentic specimen.[1]

*Benz-*F*-anilide (**8**)*: A solution of benzamide (2.42 g, 20 mmol) in anhydrous DMF (10 ml) was added dropwise into a stirred mixture of *F*-benzene (3.72 g, 20 mmol), sodium hydride (40 mmol), and anhydrous DMF (10 ml) over a 30-min period at room temperature and under a dry nitrogen atmosphere. The mixture was then stirred at room temperature for an additional 24 h and subsequently worked-up in a manner similar to that described above. The residue obtained after evaporation was recrystallized from benzene to give benz-*F*-anilide (**8**) (4.59 g, 80%). The product was identified by comparison with an authentic specimen.[1]

Reactions of F*-Benzene with Urea and Its Derivatives.*

Reaction with Urea: A solution of urea (0.50 g, 7.5 mmol) in anhydrous DMF (15 ml) was added dropwise into a stirred mixture of *F*-benzene (1.40 g, 7.5 mmol), sodium hydride (15 mmol), and anhydrous DMF (15 ml) over a 30-min period at room temperature and under a dry nitrogen atmosphere. The mixture was stirred at 80 °C for an additional 3 h and poured into ether. The ethereal solution was washed with water, dried over sodium surfate, and evaporated off. The residue was chromatographed on a silica gel column. The fraction eluted with hexane gave di(*F*-phenyl)amine (**13**) (0.73 g, 56%). The product was identified by comparison with an authentic specimen.[11]

Reaction with Guanidine: Di(*F*-phenyl)amine (**13**) was obtained in an 8% yield according to the above procedure by using guanidine in place of urea.

Reaction with Thiourea: A solution of thiourea (0.57 g, 7.5 mmol) in anhydrous DMF (15 ml) was added dropwise into a stirred mixture of *F*-benzene (1.40 g, 7.5 mmol), sodium hydride (15 mmol), and anhydrous DMF (15 ml) over a 30-min period at room temperature and under a dry nitrogen atmosphere. The mixture was stirred at 80 °C for an additional 3 h and then poured into a mixture of ether and water. The resulting precipitates were filtered off and washed with water and ether successively. Drying in a desiccator resulted in poly(thio-*F*-*p*-phenylene) (**16**) (1.21 g) as a pale yellow powder; mp>290 °C. The sulfur test using sodium tetracyanonitrosylferrate(III) was positive. The product was assigned by means of IR spectral comparison.[12]

Reaction with N,N′*-Dimethylurea.* A solution of *N,N′*-dimethylurea (1.93 g, 23 mmol) in anhydrous DMF (20 ml) was added dropwise into a stirred mixture of *F*-benzene (3.72 g, 20 mmol), sodium hydride (46 mmol), and anhydrous DMF (40 ml) over a 30-min period at room temperature and under a dry nitrogen atmosphere. The mixture was stirred at 80 °C for an additional 2 h and then poured into ether. The ethereal solution was washed with water, dried over sodium sulfate, and evaporated off. The residue was chromatographed on a neutral alumina column. The fraction eluted with hexane gave 1,3-dimethyl(*F*-benz)imidazolin-2-one (**17**) (0.86 g, 19%). Recrystallization from aqueous methanol afforded white needles; mp 104.5—105.5 °C. IR(KBr): 1710 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): 3.55 ppm (s). ^{19}F-NMR ($CHCl_3$): −6.6 (2F), −5.1 ppm(2F). ^{13}C-NMR ($CDCl_3$): 29.60 (CH_3), 154.23 ppm (C=O). UV: λ_{max} (EtOH); 209.5 (log ε 4.23), 224 (3.94), 277 nm (3.49). Found: C, 46.25; H, 2.59; N, 12.00; F, 29.7%; M$^+$, 234. Calcd for $C_9H_6N_2F_4O$: C, 46.17; H, 2.58; N, 11.96; F, 32.5%; M, 234.

Reaction with N,N′*-Dimethylthiourea.* A solution of *N,N′*-dimethylthiourea (1.04 g, 10 mmol) in anhydrous DMF (15 ml) was added dropwise into a stirred mixture of *F*-benzene (1.86 g, 10 mmol), sodium hydride (20 mmol), and anhydrous DMF (40 ml) over a 25-min period at room temperature and under a dry nitrogen atmosphere. The mixture was stirred at 80 °C for an additional 2 h, subsequently refluxed for an additional 3 h, and then poured into a mixture of ether and water. The resulting precipitates, poly(thio-*F*-*p*-phenylene) (**16**) (1.71 g), were filtered out, and the filtrate was extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate, and evaporated off. The residue was separated into two components by elution chromatography using hexane on a

silica-gel column.

An earlier fraction gave 1,3-dimethyl(*F*-benz)imidazoline-2-thione (**18**) (19%).[13] Recrystallization from ethanol afforded white needles; mp 123.5—124.5 °C. IR(KBr): 1160 cm^{-1} (C=S). ^{1}H-NMR ($CDCl_3$) 3.90 ppm (s). ^{19}F-NMR ($CDCl_3$): −2.2 (2F), −0.1 ppm (2F). ^{13}C-NMR ($CDCl_3$): 33.86 (CH_3), 172.90 ppm (C=S). UV: λ_{max} (EtOH); 218 (log ε 4.08), 248 (4.24), 302 nm (4.35). Found: C, 43.53; H, 2.53; N, 11.22; F, 30.7%; M^+, 250. Calcd for $C_9H_6N_2F_4S$: C, 43.20; H, 2.42; N, 11.20; F, 30.4%; M, 250. The sulfur test using sodium tetracyanonitrosylferrate(III) was positive.

A later fraction gave the isomeric product (**19**) (7%).[13] Sublimation afforded white needles; mp 80—81 °C. IR (KBr): 1670 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$): 3.10 (s, 3H, CH_3), 3.60 ppm (d, J=3Hz, 3H, CH_3). ^{19}F-NMR ($CHCl_3$): −5.8 (1F), 0.3 (1F), 2.7 (1F), 20.5 ppm (1F). ^{13}C-NMR ($CDCl_3$): 32.53 (d, J=0.34 Hz, CH_3), 40.93 (CH_3), 154.91 ppm (C=N). UV: λ_{max} (EtOH); 220 (log ε 4.41), 263 (3.80), 290 nm (3.44). Found: C, 42.94; H, 2.48; N, 11.12; F, 30.1%; M^+, 250. Calcd for $C_9H_6N_2F_4S$: C, 43.20; H, 2.42; N, 11.20; F, 30.4%; M, 250. The sulfur test using sodium tetracyanonitrosylferrate(III) was positive. The combined fractions eluted with hexane amounted to a total of 0.64 g.

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6) The trimethylsilyl enol ethers (**6**), except for trimethylsilyl vinyl ether (**6g**), were prepared according to the method reported by H. O. House, L. J. Czube, M. Gall, and H. D. Olmsted, *J. Org. Chem.*, **34**, 2324 (1969).

7) The trimethylsilyl vinyl ether (**6g**) was prepared according to the method reported by M. E. Jung and R. B. Blum, *Tetrahedron Lett.*, **1977**, 3791.

8) The chemical shifts were measured against the internal fluorobenzene reference; the values are given here after having been converted against an *F*-benzene reference, where the diference between the former reference and the latter one is regarded as 49.7 ppm.

9) An aryl substituent on the 2-position of the benzofuran structure[14] causes a bathochromic shift by 40—50 nm in the characteristic band of unsubstituted or 2-alkylbenzofuran near the 240-nm region.[15] A substituent at the 3-position, though, hardly affects the UV band.[16] Similarly the fluorine substituents on the fused aromatic ring in the present cases has little effect on their UV spectra.

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