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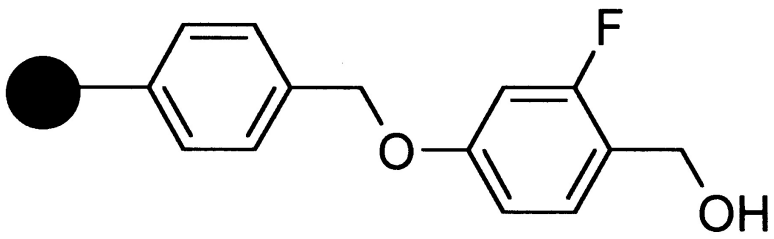

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Synthesis of a New Fluoro-Wang Resin for Solid-Phase Reaction Monitoring by ^{19}F NMR Spectroscopy

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A new fluoro-Wang resin is presented which facilitates solid-phase reaction monitoring using ^{19}F NMR. The resin is easily synthesized and amenable to scale-up. The method described herein compliments single-bead FT-IR and ^{13}C NMR techniques. This method allows monitoring of solid-phase reactions even if the resin bound intermediate is unstable to the cleavage conditions. In addition, this is a useful tool to study reaction kinetics on the solid phase.

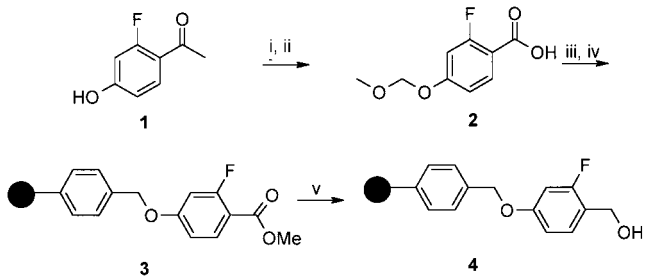
Solid-phase organic synthesis has emerged as a powerful tool for the synthesis of chemical libraries.[1] A major drawback to solid-phase chemistry is the difficulty to directly monitor a desired chemical reaction on resin. Standard analytical techniques for reaction optimization are available once the reaction product is cleaved from the solid support. However, the typically harsh conditions necessary to remove the reaction product from the solid support may introduce impurities and undesired side products, thus not revealing a true indication of the reaction that is being monitored. Both IR and NMR analytical techniques[2,3] have been used to directly monitor the progress of a reaction on the solid phase.

In this report we present 4-(methanol)-3-fluorophenoxy-methyl-copolystyrene-1%-divinylbenzene resin, a new fluoro-Wang resin. This resin facilitates monitoring the progress of a solid-phase reaction using ^{19}F NMR. The advantages of using ^{19}F NMR to monitor a solid-phase reaction include high sensitivity, wide spectral dispersion, and simple spectra (one line per nonequivalent F).[4] This is a nondestructive technique applied after washing the resin in the usual manner of workup. Nonfluorinated solvents are transparent to the technique, thus eliminating a rigorous drying procedure.

The fluoro-Wang resin is efficiently synthesized and amenable to large-scale synthesis (Scheme 1). MOM protection of the phenolic oxygen in **1**, followed by oxidation, gives the acid **2**. Deprotection under acid conditions in the presence of methanol, followed by alkylation of Merrifield resin, gives **3**. LAH reduction of **3** gives the fluoro-Wang resin **4**.

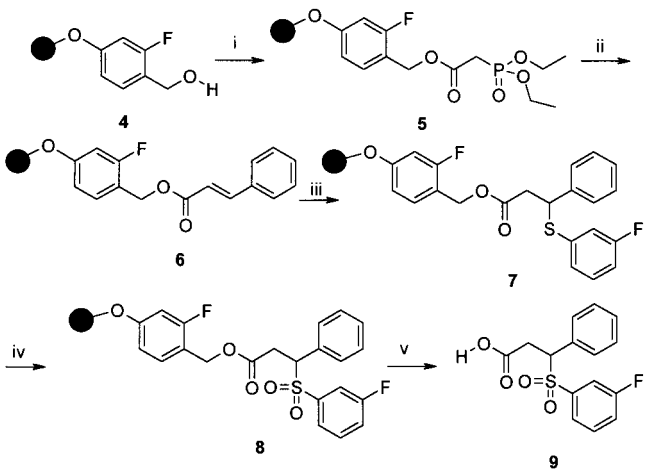
A study of a multistep reaction sequence demonstrates the utility of the fluoro-Wang as a tool to facilitate on-resin analysis (Scheme 2). Thus, diethylphosphonoacetic acid was loaded to the fluoro-Wang resin, followed by reaction with benzaldehyde to give resin bound acrylate **6**. Treatment of **6** with 3-fluoro-phenylthiol under basic conditions gave the sulfide **7**. Oxidation with mCPBA gave **8**. Treatment of the resin **8** with TFA yielded **9**.[5] ^{19}F NMR was used to monitor the progress of the reaction, and where appropriate, resin intermediates were cleaved and confirmed by standard methods.

Scheme 1[a]



[a] Key: (i) MOM-Cl, NaH, THF, rt to 80 °C, 1 h, 93%; (ii) NaOCl, H_2O, dioxane, 70 °C, 15 h, 99%; (iii) MeOH, HCl, reflux, 12 h, 100%; (iv) Merrifield resin, Cs_2CO_3, DMF, 80 °C, 12 h; (v) LAH, THF, 25 °C, 2 h.

Scheme 2[a]



[a] Key: (i) diethylphosphonoacetic acid, 2,6-dichlorobenzoyl chloride, anhydrous pyridine, DMF, 25 °C, 8 h; (ii) lithium bis(trimethylsilyl)amide, THF, 0−25 °C, 60 min, then filter under argon, add benzaldehyde (4 equiv), 60% cyclohexane in THF 25 °C, 24 h; (iii) 3-fluoro-phenylthiol, DMF, DBU (cat.), 65 °C, 12 h; (iv) mCPBA, dioxane, 25 °C, 12 h; (v) 30% TFA in CH_2Cl_2, 25 °C, 1 h.

Using resin **3** (Scheme 1) as a baseline, the ^{19}F NMR spectra shows a singlet at −106 ppm, corresponding to the fluorine on the aromatic ring of the linker. Reduction to the

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alcohol under LAH conditions provides the fluoro-Wang resin **4**. The fluorine signal shifts to −118 ppm and the signal at −106 ppm completely disappears, confirming completion of the reaction. Loading diethylphosphonoacetic acid to **4** provides the phosphonate loaded resin **5**. The fluorine signal shifts from −118 ppm to −116 ppm. To explore the use of this technique as a means to monitor the rate of conversion of resin **4** to resin **5**, six samples of resin were examined at various time points in the reaction. The first time point was taken immediately after the reagents were mixed together with resin **4**. Surprisingly, the reaction appears to have proceeded about 50% to completion. After 1 min it is apparent that the signal at −116 ppm is increasing and the signal at −118 ppm is decreasing in height. The height ratio of the signals is about 60:40. The ratio of the signals is about 80:20 after 5 min, with the signal at −116 ppm increasing in size. After 10 min, the ratio of the signals is about 95:5, and almost all of the starting material represented by the signal at −118 ppm is converted to product signal at −116 ppm. This was surprising to us since we wrongly assumed the reaction to proceed slowly, over a 3−6 h period. This experiment clearly shows that this particular reaction is complete in 30 min or less.

The next reaction in this sequence was the Horner−Emmons condensation of **5** to **6** (Scheme 2). The fluorine signal did not show any significant shift at this point. This evidently defines the distance limit from the fluorine on the linker of six carbon atoms, where a shift in the ^{19}F NMR signal is no longer apparent. Resin **6** was then treated with 3-fluoro-phenyl thiol (Scheme 2). The ^{19}F NMR spectra now shows two signals for resin **7**: one at −116 ppm for the fluoro-Wang linker fluorine atom, and another at −112 ppm for the 3-fluoro-phenyl moiety. Note that the Michael reaction is not easily monitored by the ^{19}F NMR technique, but it may be followed easily by FT-IR due to the shift in the carbonyl stretch from about 1710 cm^{-1} to 1730 cm^{-1}.[5] However, oxidation of the polymeric sulfide **7** to the polymeric sulfone **8** may be monitored using this ^{19}F NMR technique. The ^{19}F NMR spectra of **8** shows two signals: one at −116 ppm corresponding to the fluoro-Wang linker fluorine atom and another at −111 ppm. The shift from −112 ppm to −111 ppm confirms the completion of the oxidation of sufide **7** whose signal at −112 ppm disappears, and a new signal for sulfone **8** appears at −111 ppm. To confirm the results of the ^{19}F NMR, the resin bound products were cleaved from the resin and characterized by standard methods.

In summary, this new fluoro-Wang resin facilitates solid-phase reaction monitoring using ^{19}F NMR. The resin is easily obtained and provides a useful tool to monitor loading and other chemical transformations on the solid phase. This method compliments other useful analytical methods such as single-bead FT-IR and ^{13}C NMR for directly observing the progress of solid phase reactions. This method should facilitate analysis of solid-phase reactions, particularly if the resin bound intermediate is unstable to the cleavage conditions. This new resin should also facilitate the study of reaction kinetics and aid in the transfer of chemistry optimized on loose resin to IRORI microkans.

Experimental Section

General Procedures. ^{19}F NMR spectra were obtained on an NMR spectrometer operating at an ^{19}F frequency of 470.2 MHz. The ^{1}H nanoprobe was tuned to ^{19}F frequency. Typical spectral width was 100 000 Hz, and the chemical shifts were referenced relative to $CFCl_3$ using the transmitter frequency. The spectra were acquired using a nanoprobe in which the sample was oriented at the magic angle (54.7°) and was spun at a rate of 1000−1500 Hz. The samples were prepared by swelling 1−2 mg of resin with about 40 μL of deuterated dimethylformamide (DMF). ^{1}H NMR spectra were recorded in 5 mm tubes on a 300 MHz spectrometer in $CDCl_3$ unless otherwise stated. FT-IR were recorded at 4 cm^{-1} resolution on a spectrometer interfaced to an InspectIR attenuated total reflectance microscope with Si sampling optics. Solvents used were EM Science of OmniSolv distilled grade unless specified otherwise. The following abbreviations are used: DCM = dichloromethane, DMF = dimethylformamide, THF = tetrahydrofuran.

2-Fluoro-4-methoxymethoxybenzoic Acid. (2). To a suspension of sodium hydride (6.05 g, 151.2 mmol, 60 wt % in oil) in dry THF (150 mL) under an inert atmosphere (nitrogen) was slowly added 2-fluoro-4-hydroxyacetophenone (23.3 g, 151.2 mmol) in dry THF (150 mL). The solution was heated to reflux for 1 h. The solution was then cooled to room temperature, and chloromethyl methyl ether (12.0 mL, 144 mmol) in dry THF (50 mL) was added dropwise over 15 min. The solution was refluxed for 1 h. The solution was poured into water (500 mL) and extracted with ether (3 × 150 mL). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give a brown liquid. 2-Fluoro-4-methoxymethoxyacetophenone was obtained as a colorless liquid (27.8 g, 93%) after column chromatography (silica; hexane:ethyl acetate, 5:1, v/v). ^{1}H NMR δ 7.82 (1H, t, J = 8.7 Hz), 6.72−6.82 (2H, m), 5.17 (2H, s), 3.44 (3H, s), 2.54 (3H, s); ^{13}C NMR δ 194.71, 194.66, 165.56, 162.72, 162.56, 162.18, 131.86, 119.74, 119.57, 112.66, 104.28, 103.91, 94.56, 56.62, 31.49, 31.39; MS m/z = 198 [M$^+$]. To a solution of 2-fluoro-4-methoxymethoxyacetophenone (20.0 g, 101 mmol) in dioxane (100 mL) was added sodium hypochlorite solution (200 mL, 10−13%). The solution was heated at 70 °C for 5 h. After this time a further amount of sodium hypochlorite solution (100 mL, 10−13%) was added, and heating continued overnight. The solution was cooled and extracted with ether (2 × 200 mL). The aqueous layer was acidified (concentrated HCl; pH = 2−3) and extracted with ether (3 × 200 mL). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give **2** as an off-white solid (19.9 g, 99%). ^{1}H NMR δ 7.85 (1H, t, J = 8.8 Hz), 6.70−6.79 (2H, m), 5.12 (2H, s), 3.38 (3H, s); ^{13}C NMR δ 205.33, 167.19, 167.14, 166.52, 163.84, 163.68, 163.09, 134.66, 113.08, 113.02, 105.51, 105.16, 95.50, 56.65; MS m/z = 200 [M$^+$].

4-(Methylformate)-3-fluorophenoxymethyl-copoly(styrene-1% divinylbenzene) Resin (3). To a solution of 2-fluoro-4-methoxymethoxybenzoic acid **(2)** (19.9 g, 100 mmol) in methanol (200 mL) was added concentrated hydrochloric acid solution (0.5 mL, catalytic). The solution was heated at reflux overnight. The solution was evaporated

in vacuo to give methyl-2-fluoro-4-hydroxybenzoate as an off-white solid (16.9 g, 100%). ^{1}H NMR (CD_3OD) δ 7.78 (1H, t, J = 8.7 Hz), 6.63 (1H, dd, J = 2.1, 8.5 Hz), 6.52 (1H, dd, J = 2.3, 12.9 Hz), 3.83 (3H, s); ^{13}C NMR (CD_3OD) δ 205.58, 167.65, 167.60, 167.03, 166.79, 166.46, 166.38, 165.19, 165.09, 165.03, 164.93, 163.61, 163.36, 134.96, 134.61, 112.48, 110.78, 104.34, 104.30, 52.34; MS m/z = 170 [M^+], 139 [$M - OMe)^+$]. To a suspension of Merrifield resin (5.0 g, 8.9 mmol, loading 1.78 mmol/g) and cesium carbonate (30.0 g, 89 mmol) in dry DMF (80 mL) was added methyl-2-fluoro-4-hydroxybenzoate (7.57 g, 44.5 mmol) in dry DMF (40 mL). The suspension was mechanically stirred at 80 °C overnight. The mixture was cooled, filtered, and washed with DMF (×3), THF, 1 N HCl (3:1, ×3), THF:H_2O (3:1, ×3), THF (×3), and MeOH (×3). The resin was dried in vacuo overnight to give 6.2 g of resin **3**. ^{19}F NMR ($CDCl_3$) δ −106 ppm; IR (C═O) 1717 cm^{-1}. Elemental analysis: % F = 2.35, which corresponds to a loading of 1.24 mmol/g.

4-(Hydroxymethyl)-3-fluorophenoxymethyl)-copoly(styrene-1% divinylbenzene) Resin (4). The resin **3** (6.2 g, 7.7 mmol, loading 1.24 mmol/g) was swelled in dry THF (30 mL) with gentle agitation for 15 min. To the suspension was added lithium aluminum hydride solution (44.5 mL, 44.5 mmol, 1.0 M solution in THF). The resin was agitated for 2 h. The mixture was filtered and washed with THF (×3), THF: H_2O (3:1, ×3), MeOH (×3), THF (×3), and CH_2Cl_2 (×3). The resin was dried in vacuo overnight. ^{19}F NMR (DMF) δ −118 ppm; IR (C═O) 1717 cm^{-1} disappears. Elemental analysis: % F = 2.03, which corresponds to a loading of 1.1 mmol/g.

4-*O*-(Benzyldiethylphosphonoacetate)-3-fluorophenoxymethylcopoly(styrene-1%-divinylbenzene) Resin (5). Fluorinated Wang resin (2.0 g, 2.1 mmol, loading 1.1 mmol/g) was swelled in dry DMF (40 mL) with gentle agitation for 10 min. To the suspension were added in succession diethylphosphonoacetic acid (2.09 g, 10.7 mmol), anhydrous pyridine (1.7 g, 21.4 mmol), and 2,6-dichlorobenzoyl chloride (2.2 g, 10.7 mmol) at room temperature. The mixture was stirred at ambient temperature for 12 h, during which time the reaction mixture turned a red color. The resin was then filtered and washed with DMF (3 × 50 mL), DMF:H_2O (1:1, 3 × 50 mL), THF:H_2O (1:1, 3 × 50 mL), THF (3 × 50 mL), MeOH (3 × 50 mL), DCM (3 × 50 mL), and Et_2O (3 × 50 mL). The resin was dried in vacuo overnight. ^{19}F NMR (DMF) δ −116 ppm; IR (C═O) 1747 cm^{-1}.

3-Phenyl-acrylic Acid 3-Fluorophenoxymethylcopoly-(styrene-1%-divinylbenzene) Resin (6). Resin **5** (500 mg, 0.53 mmol) was swelled in dry THF (10 mL) for 15 min at room temperature and then cooled under nitrogen to 0 °C for 15 min. LiHMDS (1 M in THF, 1.34 mL, 1.34 mmol) was added, and the reaction mixture was brought to room temperature over 30 min. The reaction was filtered under an inert nitrogen atmosphere, and then cyclohexane (10 mL) was added to the reaction vessel followed by the addition of benzaldehyde (136 mg, 1.28 mmol) in 1 mL of THF. The mixture was shaken for 12 h on an orbital shaker under nitrogen. The resin was filtered, washed with DMF (2 × 20 mL), THF (2 × 20 mL), THF: H_2O (1:1, 2 × 20 mL), MeOH (2 × 20 mL), DCM (2 × 20 mL), and Et_2O (2 × 20 mL), and dried in vacuo overnight. ^{19}F NMR (DMF) δ −116 ppm.

A resin sample (50 mg) was cleaved with 50% TFA in DCM (2 mL) for 1 h at room temperature and washed with the cleavage solution (3 × 1 mL). The washes were combined and evaporated in vacuo to afford 7.8 mg (99% yield) of 3-phenyl-acrylic acid. MS (ESI) m/z = 148 [M + H]$^+$; LC area (UV_{220})= 95%; ^{1}H NMR (CD_3OD) δ 7.66 (d, 1H, J = 16.0 Hz), 7.38−7.59 (m, 5H), 6.47 (d, 1H, J = 16.0 Hz).

3-(3-Fluoro-phenylsulfanyl)-3-phenyl-propionic Acid 3-Fluorophenoxymethylcopoly(styrene-1%-divinylbenzene) Resin (7). Resin **6** (500 mg, 0.53 mmol) was swelled in dry DMF (10 mL) for 15 min. To the suspension were added 3-fluorothiophenol (684 mg, 5.35 mmol) and DBU (0.08 mL, 0.535 mmol). The resin was agitated for 12 h at 65 °C under nitrogen. The resin was filtered and washed with DMF (2 × 20 mL), THF:H_2O (1:1, 2 × 20 mL), THF (2 × 20 mL), MeOH (2 × 20 mL), DCM (2 × 20 mL), and Et_2O (2 × 20 mL) and dried in vacuo overnight. ^{19}F NMR (DMF) δ −112 ppm and −116 ppm.

A resin sample (50 mg) was cleaved with 50% TFA in DCM (2 mL) for 1 h at room temperature and washed with the cleavage solution (3 × 1 mL). The washes were combined and evaporated in vacuo to afford 10.1 mg (98% yield) of 3-(3-fluoro-phenylsulfanyl)-3-phenyl-propionic acid. MS (ESI) m/z = 276 [M + H]$^+$; LC area (ELS) = 98%; ^{1}H NMR (CD_3OD) δ 6.91−7.58 (m, 9H), 4.69 (t, 1H, J = 7.7 Hz), 2.90 (d, 2H, J = 7.7 Hz).

3-(3-Fluoro-benzenesulfonyl)-3-phenyl-propionic Acid 3-Fluorophenoxymethylcopoly(styrene-1%-divinylbenzene) Resin (8). Resin **7** (200 mg, 0.21 mmol) was swelled in dioxane (10 mL) for 15 min and then was treated with mCPBA (369 mg, 2.1 mmol). The resin was agitated for 12 h at ambient temperature under nitrogen. The resin was filtered, washed with DMF (2 × 20 mL), THF: H_2O (1:1, 2 × 20 mL), THF (2 × 20 mL), MeOH (2 × 20 mL), DCM (2 × 20 mL), and Et_2O (2 × 20 mL), and dried in vacuo overnight. ^{19}F NMR (DMF) δ −111 ppm and −116 ppm.

3-(3-Fluoro-benzenesulfonyl)-3-phenyl-propionic Acid (9). A sample of resin **8** (50 mg) was cleaved with 50% TFA in DCM (2 mL) for 1 h at room temperature and washed with the cleavage solution (3 × 1 mL). The washes were combined and evaporated in vacuo to afford 16.3 mg (99% yield) of **9**. MS (ESI) m/z = 308 [M + H]$^+$; LC area (ELS) = 85%; ^{1}H NMR (CD_3OD) δ 7.16−7.64 (m, 9H), 4.79 (1H, q, J = 9.9 Hz), 3.36 (1H, dd, J = 16.4, 4.8 Hz), 3.11 (1H, dd, J = 16.4, 9.9 Hz).

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Supporting Information Available. ^{19}F NMR spectra of **3**, **4**, conversion of **4** to **5**, **5**, **6**, **7**, and **8** and ^{1}H NMR spectra of 2-fluoro-4-methoxymethoxyacetophenone, 2-fluoro-4-methoxymethoxybenzoic acid (**2**), and methyl-2-fluoro-4-hydroxybenzoate are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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