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Solid-Phase Synthesis of Novel Amino-Ether Derivatives

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Abstract: Three amino-ether derivatives have been prepared by a solid-phase synthesis using a novel amidine-based linker. The sequence of reactions involved a) amine exchange of a solid-supported dimethylformamidine with a secondary amine, b) α-alkylation of the solid-supported formamidine with an aromatic aldehyde, c) alkylation of the newly generated hydroxyl group with a benzylic halide, and d) cleavage of the formamidine linkage to the solid support.

The level of interest in combinatorial chemistry as a tool for the rapid discovery and evaluation of new compounds of potential biological, therapeutic or other material value has greatly increased over the last few years.[1-2] Advances in this area have spawned an ever increasing demand for novel methodologies for the synthesis of organic compounds on solid supports. We have recently described the use of an amidine linker which can be cleaved under relatively mild conditions to generate secondary amine-containing derivatives.[3] This type of linker has been further exploited in the present work by the synthesis of a series of ether-substituted amino compounds. Based on the methodologies reported herein, a combinatorial library of compounds can be generated using a standard parallel synthesis approach or divide-and-pool methodology.[4]

Results and Discussion

General Strategy.

The general reaction sequence for the solid-phase synthesis of the amino-ether compounds is outlined in Figure 1. The solid-supported dimethyl formamidine **1**[3] was treated with a set of secondary amines by an amine exchange reaction, to give solid-supported amidines of structure **2**. The success and yields of these reactions were monitored by ^{13}C NMR, FT-IR, and increase in mass of the supports produced. The second step in the synthesis involved alkylation of the anion generated from the solid-supported amidines **2** with an aromatic aldehyde, to give the α-substituted hydroxy compound **3**. A similar alkylation has been extensively studied in solution phase by Meyers and his colleagues,[5-8] including studies regarding the regioselectivity of anion formation and asymmetric carbon-carbon bond formation. The solid-supported α-alkylation reaction was investigated since no solid-phase method has

been previously described. The appearance of a strong, broad peak at about 3350 cm^{-1} in the FT-IR spectrum confirmed the formation of the hydroxyl group, and peaks at other regions confirmed the addition of the corresponding adducts.

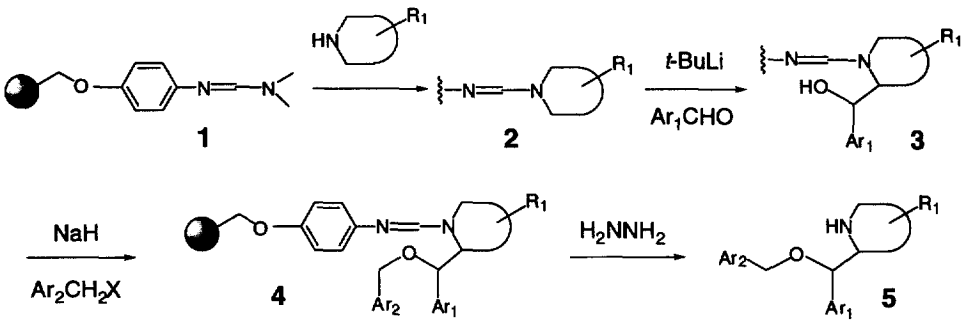

Figure 1. Reaction sequence for the solid-supported synthesis of amino-ether derivatives

The resulting hydroxyl group of **3** was alkylated through a Williamson reaction with a benzylic halide to generate an ether of type **4**. IR analysis showed loss of the hydroxyl peak and confirmation of the desired adduct. The final step involved cleavage of the amidine bond of the linker to yield the desired amino-ether **5** as a mixture of two diastereomers. Cleavage could be accomplished using either aqueous hydrazine/acetic acid or alternatively with lithium aluminum hydride. This sequence of chemical reactions was investigated by the initial synthesis of three individual compounds, shown in Figure 2. Yields for the three derivatives were formed in about 60% starting from the amidine **2**. This procedure can be used to generate a combinatorial library.

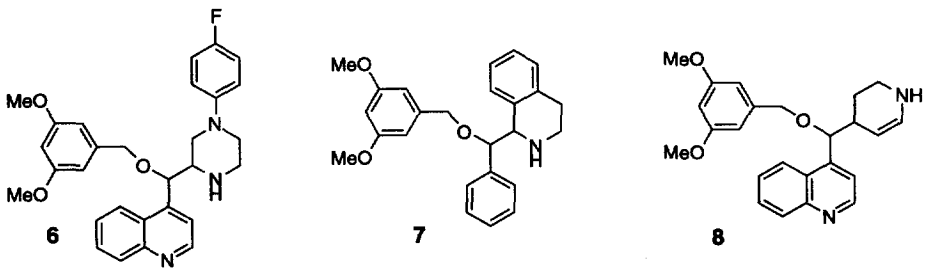

Figure 2. Structures of three compounds prepared.

Experimental Section

General. Unless otherwise stated, ^{13}C NMR spectra of all resins were obtained in C_6D_6 on a Varian Unity Plus 500 MHz instrument by the gel-phase technique. Electrospray mass spectra were obtained on an API I Perkin Elmer SCIEX spectrometer from Mass Consortium Corporation, San Diego, CA. HPLC

was carried out on a DeltaPak C_4 reversed phase column (3.9 x 150 mm, Waters) using 0.1% aqueous trifluoroacetic acid (solvent A) in acetonitrile (ACN, solvent B) as the eluant; gradient = 5-100% B over 30 min. Merrifield resin (100-200 mesh, 2% cross-linked) was purchased from Rapp Polymere, Tübingen, Germany. The hydrazine solution consisted of anhydrous hydrazine (1 mL, 32 mmol) and glacial acetic acid (0.69 mL, 12 mmol) in absolute ethanol (40 mL).

Synthesis of Solid-Supported Formamidines 2a-c.

The solid-supported dimethylformamidine **1**[3] (5 g) was heated with a solution of the individual secondary amine in toluene under nitrogen, in the presence of ammonium sulfate (approx. 30 mg) as catalyst, for 18 h under reflux. The beads were washed thoroughly with water, MeOH and CH_2Cl_2, and dried to give the solid supported amidines **2a-c**. The efficiency of amine exchange reaction was estimated from the increase in mass of the resin.

2a: Secondary amine, 1,2,3,6-Tetrahydropyridine: Loading (mmol/g), 0.72, Yield, 76%; ^{13}C NMR (C_6D_6) δ 155.5, 151.9 (NCHN), 146.4, 128 (resin), 124.7 (CH=), 122.2, 115.8, 70.5 ($PhCH_2O$), 53.1 (NCH_2), 50.1 (NCH_2), 41.0 (resin), 26.7; FT-IR (KBr) ν 1633 (NCHN), 1619 (C=C) cm^{-1}.

2b: Secondary amine, 1,2,3,4-Tetrahydroisoquinoline: Loading (mmol/g), 0.69, Yield, 84%; ^{13}C NMR (C_6D_6) δ 155.6, 151.5 (NCHN), 146.5, 134.5, 133.6, 128 (resin), 126.5, 122.3, 115.8, 70.6 ($PhCH_2O$), 45.5 (NCH_2), 40.9 (resin), 29.8 (CH_2Ph); FT-IR (KBr) ν 1639 (NCHN) cm^{-1}.

2c: Secondary amine, 1-(4-Fluorophenyl)piperazine: Loading (mmol/g), 0.79, Yield, 80%; ^{13}C NMR (C_6D_6) δ 157.2 (d, CF), 156.9, 151.3 (NCHN), 148.3 (C-N), 146.1, 128 (resin), 126.1, 122.2, 118.9 (CH), 115.8, 70.5 ($PhCH_2O$), 50.2 (NCH_2), 41.0 (resin); FT-IR (KBr) ν 1640 (NCHN) cm^{-1}.

Synthesis of 6-8.

The solid-supported amidine **2c** (431 mg, 0.79 mmol/g, 0.34 mmol) was swollen by gentle stirring in anhydrous THF (5 mL) under nitrogen for 15 min, then cooled to -70°C. *tert*-Butyllithium in pentane (1.7 M, 1.3 mL) was added, and the mixture was maintained at -20°C for 1 h with gentle stirring under nitrogen. The mixture was again cooled to -70°C and a solution of 4-quinolinecarboxaldehyde (460 mg, 2.93 mmol) in anhydrous THF (1.5 mL) was added. The reaction was stirred overnight and allowed to warm to room temperature. Water (0.5 mL) was added and gentle stirring was continued for 10 min to quench the reaction. The resin was collected by filtration, washed thoroughly with water, MeOH and CH_2Cl_2 (approx. 20 mL of each), and dried *in vacuo* overnight to give 508 mg of the alkylated resin **3** (R_1 = 1-(4-fluorophenyl)piperazinyl, Ar_1 = 4-quinolinyl, 192 mg); FT-IR (KBr) ν 3411 (OH), 1599 (N=C-N) cm^{-1}.

A portion of this resin (467 mg, 0.31 mmol) was stirred in anhydrous THF (7 mL) and ACN (1.5 mL) in the presence of sodium hydride (65 mg, 2.58 mmol) and 15-crown-5 (1 drop) at room temperature for 1 h. 3,5-Dimethoxybenzyl chloride (503 mg, 2.67 mmol) was added, and the reaction was gently stirred overnight at reflux. The resin was collected by filtration, thoroughly washed with water, MeOH and CH_2Cl_2 (25 mL of each), and dried *in vacuo* overnight to give 486 mg the alkylated resin **4** (R_1 = 1-(4-fluorophenyl)piperazinyl, Ar_1 = 4-quinolinyl, Ar_2 = 3,5-dimethoxyphenyl); FT-IR (KBr) ν 1599 (N=C-N), 1504 (O-CH_3) cm^{-1}. A portion of the resulting resin (222 mg, 0.06 mmol) was swelled in anhydrous THF (1 mL) and treated with a solution of hydrazine/acetic acid solution (1 mL) at 60°C overnight with stirring under nitrogen. The resin was removed by filtration, washed with water, MeOH and CH_2Cl_2 (25 mL of each). The filtrate and washings were combined, evaporated to dryness, dissolved in CH_2Cl_2 and washed with aqueous sodium bicarbonate, followed by saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and evaporated to dryness to give crude **6** (50 mg). A portion was HPLC purified for analysis.

^1H NMR ($CDCl_3$) δ 9.23 (d, 0.7 H), 8.94 (d, 0.3 H), 8.44 (d, 0.7 H), 8.42 (d, 0.3 H), 8.34 (d, 0.3 H), 8.20 (d, 0.3 H), 8.11 (d, 0.7 H), 7.98 (t, 0.3 H), 7.95 (d, 0.7 H), 7.86 (t, 0.3 H), 7.77 (t, 0.7 H), 7.19 (t, 0.7 H), 6.89 (m, 1.4 H), 6.74 (m, 1.4 H), 6.64 (d, 0.6 H), 6.56 (s, 0.6 H), 6.51 (s, 0.3 H), 6.47 (m, 0.6 H), 6.46 (s, 1.4 H), 6.40 (s, 0.7 H), 4.62 (d, 1 H), 4.58 (d, 1 H), 3.80 (s, 0.9 H, OCH_3), 3.78 (s, 2.1 H, OCH_3), 3.40 (m, 1 H, CH-O), 3.30 (m, 3 H, NCH_2); ^{13}C NMR ($CDCl_3$) δ 165.5, 162.2, 161.0, 157.4, 154.1, 151.2, 147.7, 144.5, 138.7, 133.9, 130.1, 129.3, 125.9, 123.9, 122.9, 120.3, 119.0, 117.3, 116.4, 106.0, 100.0, 71.3, 70.5, 55.4 (OCH_3), 53.4, 47.1 (NCH_2), 43.4 ($HNCH_2$); HPLC t_R =

15.7 and 15.9 min for the two diastereomers in a 2:1 ratio; UV (THF/ACN) λmax 215, 237 nm; Electrospray MS (positive ion mode): *m/z* 488 (MH^+), calcd for $C_{29}H_{30}N_3O_3F$ (M) 487.

The procedure described above was followed for the synthesis of **7**, using the solid-supported amidine **2b** (465 mg, 0.69 mmol/g, 0.321 mmol) with benzaldehyde (0.30 mL, 313 mg, 2.95 mmol) as the alkylating agent to yield 532 mg of the hydroxy resins. A portion of this resin (466 mg, 0.28 mmol) was reacted with 3,5-dimethoxybenzyl chloride (503 mg, 2.67 mmol) as the ether-forming agent to yield 509 mg amino-ether resin. Hydrazinolysis of a portion of this resin (240 mg, 0.24 mmol) as described for **6** gave crude **7** (37 mg). A portion was HPLC purified for analysis; t_R = 16.3 and 16.6 min for the two diastereomers in a 2:1 ratio.

^1H NMR ($CDCl_3$) δ 7.48-6.98 (m, 9 H), 6.39 (s, 0.8 H), 6.38 (s, 1.2 H), 6.36 (s, 0.4 H) 6.35 (s, 0.6 H), 5.10 (d, 0.4 H), 4.83 (d, 0.4 H), 4.68 (d, 0.6 H), 4.63 (d, 0.4 H), 4.42 (d, 0.6 H), 4.35 (d, 0.6 H), 4.23 (d, 0.6 H), 4.22 (0.4 H), 3.72 (s, 6 H), 3.21-3.01 (m, 2 H), 2.86-2.61 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 161.8, 142.2, 142.0, 130-126, 105.2, 99.7, 84.2, 71.8, 59.5, 55.3, 40.2, 29.7.

A similar method was used to prepare **8**, using **2a** (452 mg, 0.72 mmol/g, 0.33 mmol), *tert*-butyllithium in pentane (1.7 M, 1.3 mL), and 4-quinolinecarboxaldehyde (460 mg, 2.93 mmol) to yield 527 mg of the hydroxy resin. A portion (487 mg, 0.30 mmol) was reacted with 3,5-dimethoxybenzyl chloride (503 mg, 2.67 mmol) to yield 524 mg of the amino-ether resin. Hydrazinolysis of a portion of this resin (223 mg, 0.10 mmol) as described for **6** gave crude **8** as a brownish solid (35 mg), of which a portion was HPLC purified for analysis. Alkylation did not occur at the 2-position, but at the less sterically hindered 4-position, consistent with the observations made by Meyers et al.[8]

^1H NMR ($CDCl_3$) δ 8.96 (d, 1 H), 8.20 (d, 1 H), 7.77 (t, 1 H), 7.59 (t, 1 H), 6.82 (d, 1 H, CH=), 6.65 (d, 1 H, CH=), 6.59 (d, 1 H), 6.55 (d, 1 H), 6.42 (s, 2 H), 6.40 (s, 1 H), 4.47 (d, 1 H, $PhCH_2$), 4.20 (d, 1 H, $PhCH_2$), 3.81 (s, 6 H, OCH_3), 3.78 (m, 2 H), 2.28 (m, 1 H), 2.05 (m, 1 H), 1.58 (m, 1 H), 1.41 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 161.2 (C-OMe), 150.3, 148.9, 140.2, 130.8, 129.6, 126.9, 123.5, 116.6, 116.3, 105.9, 105.4, 104.7, 100.0, 99.8, 71.4, 71.0, 55.6 (OCH_3), 53.6 (OCH_3 minor isomer), 36.9 ($NHCH_2$), 29.9 (CH), 26.1 (CH_2); HPLC: t_R = 11.6 min; UV (THF/ACN) λmax 215, 237 nm; Electrospray MS: *m/z* 391 (MH^+), calcd for $C_{24}H_{26}N_2O_3$ (M) 390.

Conclusions

We have successfully developed a solid-phase synthesis of ether-derived amino compounds using a novel formamidine linker, and have demonstrated that the procedure is suitable for the synthesis of single compounds, with the potential for libraries of larger numbers of compounds. One attractive feature of this approach is that the products do not possess any residual functionality derived from the linker to the solid support. The key reaction step, involving α-alkylation of a series of solid-supported formamidines, employed chemistry previously developed by Meyers et al. for solution phase, which, with some modifications, was shown to be compatible for solid-phase synthesis. Further development of the solid-phase synthesis and those derivatives using this methodology is in progress.

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