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A Novel Formamidine Linker for Use in Solid-Phase Synthesis

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Abstract: A variety of amidines have been evaluated as linkers for solid-supported synthesis. As a demonstration of its utility, an amidine linker was used to prepare a set of compounds involving amine exchange, oxidation, reduction and ether formation reactions. These compounds were successfully cleaved from the support to generate α-substituted, secondary amine derivatives, which were thoroughly characterized by spectroscopic methods.
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The field of solid phase synthesis has experienced a rapid expansion of creative ideas and methodologies over the last several years, due primarily to its application and utility in the field of combinatorial chemistry.[1-4] The solid-supported synthesis of organic compounds requires specially designed linkers which can withstand the relatively harsh conditions employed in many organic syntheses. Most currently available solid supports were originally developed for peptide synthesis, and therefore employ relatively labile carboxylic acid based linkers, which typically generate acids or amides upon cleavage. An increasing emphasis has therefore been placed on the development of straightforward, generally applicable methods for coupling a wider variety of starting materials onto solid supports via suitable linkers.

Relatively few linkers suitable for the release of amine derivatives from a solid support have been described. Two reports have employed carbamates as linkers, which can be cleaved under acidic or basic conditions.[5,6] An allyl carbamate linker, which could be cleaved by palladium-catalyzed allyl transfer, has also been described.[7] Although useful for some synthetic reactions, these linkers possess limitations. For example, the presence of a labile hydrogen atom on the carbamate moiety can potentially interfere with certain chemical reactions, such as carbanion formation and alkylation.

The formamidine group has been used in a variety of applications, including its use as a protective group,[8,9] as a bioisostere for amides[10-12] and as an "activator" of the α-position of amines for deprotonation and alkylation.[13-15] In view of the versatility of the reactions involving formamidines, we have developed methods for the synthesis of solid-supported amidines for evaluation as linkers which have been used to make a deuterated amino-ether, starting from (±)-α-(methylaminomethyl)benzyl alcohol. We envisioned the use of the amidine to connect the compound of interest to the solid support at the secondary amine functionality, and thus protect it from modification. The synthetic route for the preparation of amidine-derivatized supports is outlined in Figure 1.

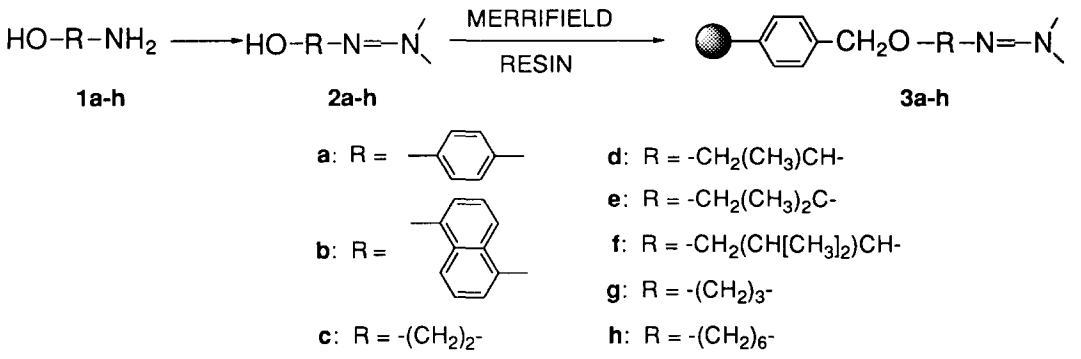

Figure 1. Synthesis of Solid-Supported Amidine Linkers

Reaction of a range of amino-alcohols (**1a-h**) with dimethylformamide dimethyl acetal produced the corresponding amidines (**2a-h**), which were reacted with chloromethyl polystyrene (Merrifield) resin to produce the solid-supported amidines (**3a-h**). The presence of the amidine on the support can be confirmed by FT-IR, since the amidine group gave a prominent new peak at about 1650 cm^{-1}. Gel-phase ^{13}C NMR showed a loss of the chloromethyl signal at δ 46, and the signal from the newly generated benzyl ether carbon was observed about δ 72. Unreacted chloromethyl polystyrene could potentially react with an amine during the subsequent amine exchange reaction to form a benzylamine derivative, which would give a signal about δ 63; thus, the absence of a signal in this region may indicate complete incorporation of the linker.

N'-(p-hydroxyphenyl)-*N,N*-dimethylformamidine (**2a**) was found to be the most satisfactory linker for the particular amines we wished to study. Some specific advantages included the ease of interpretation of the ^{13}C NMR spectra of various amine-linked derivatives, production of amine exchange products of higher purity, and its resistance to strong acids and bases. Although an *N,N*-dimethylformamidino-polystyrene derivative can be generated without the use of a linker using the appropriate amine-derived support, such as polystyrene A NH_2, aminomethyl polystyrene, TentaGel S NH_2 or benzylhydrylamine polystyrene, these supports possessed similar disadvantages as were evident with the aliphatic linkers **3c**, **g** and **h**, such as the difficulty of finding suitable conditions for clean metalation and alkylation. As shown by Kolb and Barth, a methylene hydrogen of the alpha-position to the imine nitrogen of the amidine group is known to be susceptible to deprotonation.[9]

Synthesis of a deuterated amino-ether using the selected linker **2a** is shown in Figure 2. A solution of (±)-α-(methylaminomethyl)benzyl alcohol (**4**) in toluene was heated at reflux overnight in the presence of **3a** and amine exchange gave the desired amidine **5**, as determined by gel-phase ^{13}C NMR and FT-IR. Attempts to oxidize the alcohol with chromium-based oxidizing agents produced resins which were contaminated with chromium salts. Oxidation with a sulfur trioxide/pyridine complex provided a convenient method for the formation of the carbonyl derivative **6**. A peak at 1707 cm^{-1} in the FT-IR spectrum confirmed the presence of the ketone functionality. Reduction of the carbonyl group with [^2H]-$NaBH_4$ gave **7**,

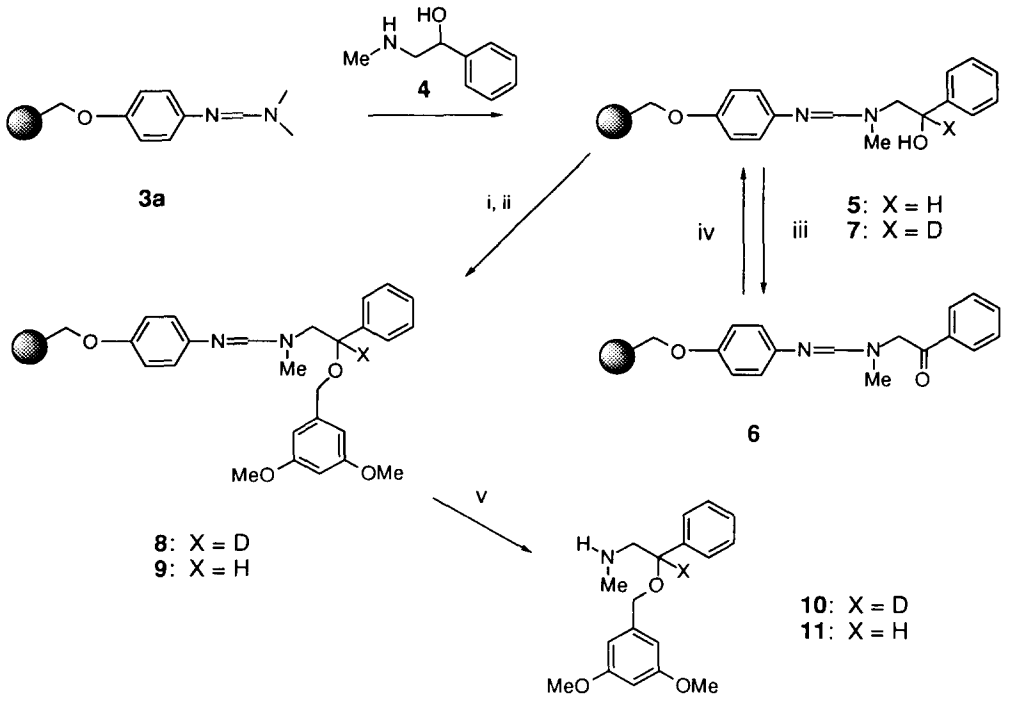

Figure 2. Synthesis of an Amino-Ether Using the Amidine-Derivatized Support **3a**. (i) NaH, (ii) 3,5-dimethoxybenzyl chloride, (iii) SO_3/pyridine, (iv) $NaBH_4$ or $NaBD_4$, (v) hydrazine/acetic acid.

a material with similar spectroscopic properties to **5**, with an additional peak at 2119 cm^{-1} attributable to the C-D bond.

Both the non-deuterated derivative **5** and the corresponding deuterated compound **7** were independently reacted with 3,5-dimethoxybenzyl chloride, under conditions similar to those for amidine-to-support coupling, to generate the corresponding benzyloxy derivatives **9** and **8** respectively, and FT-IR analysis showed the loss of the hydroxyl peak in both cases. The final products **10** and **11** were obtained by heating the benzyloxy-derivatized resins in an ethanolic solution of hydrazine/acetic acid. Extended exposure over several days resulted in the production of more polar degradation products. Other reagents could also be used to cleave the formamidine, such as lithium aluminum hydride, KOH in MeOH or $ZnCl_2$ in EtOH. Confirmation of the structures was obtained from both proton and ^{13}C NMR of the purified materials, and mass spectral analysis showed the deuterium incorporation of **8** to be approximately 93%.

In conclusion, we have found that the formamidine group is a useful addition to the arsenal of linkers which have utility in solid-supported synthesis. It possesses excellent chemical resistance to a variety of harsh reaction conditions, such as alkylation, as well as oxidation and reduction. The formamidine linkage to the solid support can be readily cleaved under relatively mild conditions to generate the desired amine derivatives.

General Procedure for Dimethylformamidino-polystyrene derivatives (3a-h)

A solution of the amino-alcohol (**1a-h**, 183.2 mmol, 1 equiv.) and DMF dimethyl acetal (32.9 mL, 29.5 g, 247.6 mmol, 1.4 equiv.) in methanol (200 mL) was heated to 45°C with stirring under nitrogen for 3 h, or until completion as indicated by TLC. The reaction was cooled to room temperature and the product was either isolated via filtration or evaporated to dryness to give **2a-h** in quantitative yield. The linker (**2a-h**, 37.39 mmol, 1.5 equiv.) in anhydrous THF (200 mL) and acetonitrile (40 mL) was treated with sodium hydride (1.15 g, 47.9 mmol, 1.9 equiv.) and 15-crown-5 (110 μL, 0.554 mmol) and stirred at room temperature under nitrogen for 1 h. Merrifield resin (20.49 g, 25.41 mmol, 1 equiv.) was added, and the heterogeneous mixture was heated at reflux overnight. The reaction was cooled to room temperature and the resin was isolated by filtration and washed extensively with water, methanol and CH_2Cl_2. Vacuum drying overnight gave **3a-h**. Yields were calculated based on elemental nitrogen analysis, and generally were in the region of 80-95%.

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