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A New Linker for Anchoring/Masking Primary Amines on Solid Support

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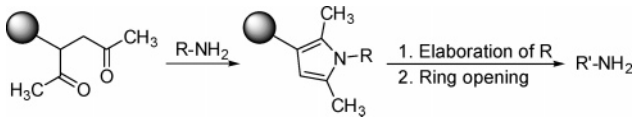
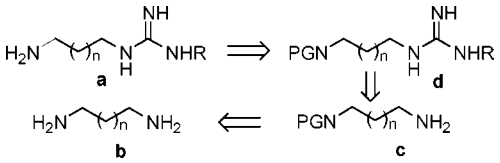
ABSTRACT



A polymer-supported diketone was synthesized and used to fully protect/mask primary amines by the formation of a pyrrole ring. Various reactions can be performed on this system which then can be cleaved with full restoration of the amine functionality. The resin can also be recycled at least once without loss of purity of the final compound.

Because of its basicity and hydrogen-bonding properties, the guanidine moiety is an important functional group in many biologically active compounds of natural or synthetic origin.[1] Accordingly, methodologies for the parallel synthesis of guanidine derivatives have attracted much attention from both academia and industry.[2] In the course of our ongoing efforts directed toward the preparation of analogues of agmatine of type **a**[3] (Scheme 1) starting from the appropriate diamine **b**,

Scheme 1. Retrosynthetic Analysis of Target Compounds **a**



we became aware of the importance of having a protecting group (PG) which could totally mask one amino moiety (**c**), thus allowing further elaboration of the molecule (**d**).

The following characteristics were key to the necessary amino-protecting group: (a) nonionizable; (b) nonnucleophilic; (c) stable in the presence of strong bases; (d) stable to strong reducing agents.

We focused our attention on 2,5-dimethylpyrrole which was first described by Bruekelman[4] as a versatile primary amine protecting group, compatible with a range of transformations commonly employed in synthetic organic chemistry. 2,5-Dimethylpyrrole is readily installed by treatment of an amine with 2,5-hexanedione in the presence of an acidic catalyst and can be cleaved by treatment with hydroxylamine hydrochloride.[5]

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During the course of our investigations, we became interested in developing an efficient solid phase approach that could help us to avoid the tedious and troublesome purification procedures which usually accompany the chemistry of polyamines. However, because of the heterogeneous nature of organic reactions occurring at the interface of polymeric support and solution, working on solid-phase often requires a long reaction time or results in incomplete conversion of starting materials. It has been demonstrated[6] that microwave dielectric heating can be used to speed up organic reactions carried out on solid polymeric supports. The combination of solid support as a medium for chemical synthesis with microwave heating offers several advantages over conventional techniques. Rapid and elevated heating of reaction mixtures can induce the completion of chemical transformations in minutes while several hours or days may be required for the same chemistry under conventional conditions; moreover, microwave-accelerated chemistry often delivers products of higher purity when compared to conventional heating techniques, since it permits decreasing the time of exposure of chemicals to high temperatures and hence lessens their thermal degradation.

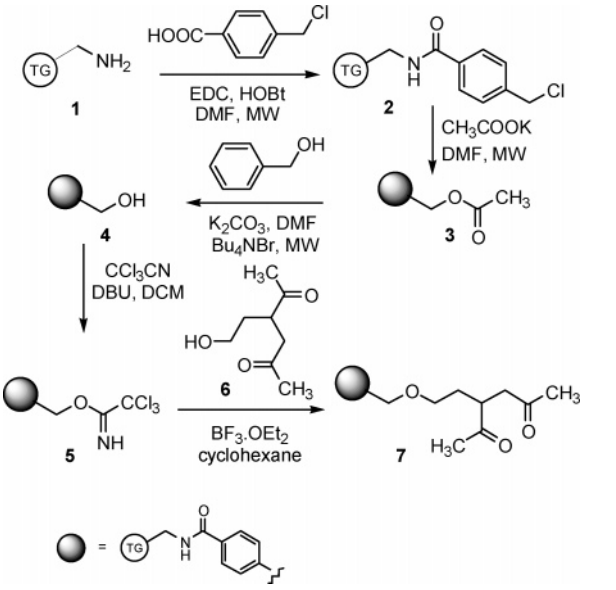
Taking advantage of the aforementioned techniques, we explored the possibility of using 2,5-dimethylpyrrole to completely protect/mask amino groups on the solid phase using an approach that could be easily adapted for parallel synthesis and extended to the preparation of a small library of guanidines.

To the best of our knowledge, there have been no reports about the use of 2,5-dimethylpyrrole as an amine protecting group in solid-phase synthesis, despite its well-documented use in solution.

TentaGel S-NH_2 (TG), a standard type of resin used for peptide synthesis, solid-phase organic synthesis, and combinatorial chemistry, was chosen as the solid support since it swells well even in aqueous solvent; moreover, as the reaction occurs at the end of poly(ethylene glycol) (PEG) spacer and there is no cross-linking between them, the access of reagents to the reaction site is easier than with polystyrene resin (PS), and hence, the reaction rate on TG is usually higher than on PS.

We decided to anchor the linker to the solid support by the formation of a benzyl ether,[7] a functionality which is usually compatible with the conditions required by a variety of synthetically useful transformations, particularly basic conditions. Resin **1** (Scheme 2) was acylated with 4-chloromethylbenzoic acid in the presence of EDC/HOBt, and the complete transformation of **1** into **2** was confirmed by a negative colorimetric Kaiser test,[8] which is specific for the

Scheme 2. Anchoring of the Linker to the Solid Support



detection of primary amino groups. The chloromethyl polymer **2**, treated with CH_3COOK, gave **3** which, by transesterification with benzyl alcohol in the presence of Bu_4NBr, afforded the alcohol **4** which represents the key intermediate for the activation of the polymer in the form of trichloracetimidate (TCA). The presence of the OH group on the resin was visualized with a colorimetric test.[9] The whole sequence, starting from the commercially available polymer **1** to the alcohol **4** could be performed in only 30 min by the use of MW irradiation.

The TCA derivative **5** (appearance of a strong C═N stretching band at 1664 cm^{-1} in the IR spectrum) was obtained by reacting a suspension of resin **4** in CH_2Cl_2 with trichloroacetonitrile in the presence of DBU.[7] The complete conversion of the polymer-bound benzyloxy group to benzyl trichloroacetimidate was shown by treating **5** with AcCl/Et_3N: no AcO absorption band was observed in the IR spectrum of the product. Polymer **5** was finally used for *O*-benzylation of the alcohol **6**, prepared according to the literature,[10] in the presence of $BF_3{\cdot}OEt_2$: the reaction was monitored by IR spectroscopy, observing the disappearance of the band of the C═N stretching and the appearance of the carbonyl band of the diketone **7** at 1713 cm^{-1}.

To prove its ability to react with amines, **7** was first treated with *p*-anisidine in the presence of catalytic amount of pyridine hydrochloride in refluxing dioxane[11] (Scheme 3). The formation of the polymer-bound pyrrole derivative **8** proved to be complete after two cycles of reaction as shown by IR analysis.

This result was further confirmed by opening of the pyrrole ring using hydroxylamine hydrochloride and Et_3N in a

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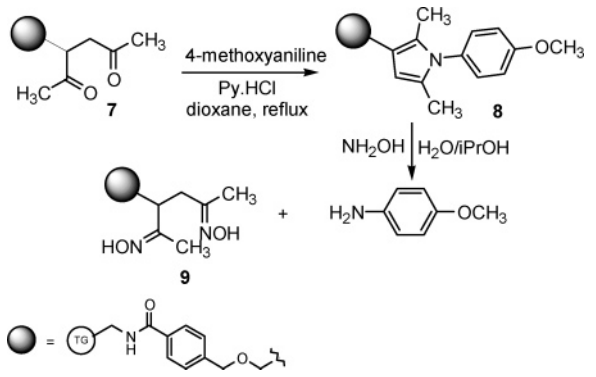
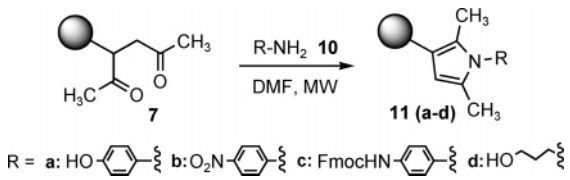
Scheme 3. Protection and Deprotection of *p*-Anisidine by the Use of Polymer-Bound Linker **7**



refluxing H_2O/^{i}PrOH mixture. After washing of the resin **9** and alkalinization of the filtrate, *p*-anisidine was obtained in pure form and quantitative yield, demonstrating that along the whole solid-phase sequence the loading of each intermediate had been quantitative. Alternatively, the formation of the pyrrole ring was successfully achieved under microwave irradiation[12] using a few drops of DMF as solvent and an excess of amine. With this approach, the solid-supported 2,5-dimethylpyrrole was obtained in only 5 min, thus confirming the importance of microwaves in speeding the reaction rate on solid phase.

To further probe the scope of the reaction and to evaluate the possibility of its general use for the synthesis of our target compounds, **7** was then reacted with a series of structurally different amines **10** (Scheme 4), and the corresponding products **11a**−**d** were further chemically elaborated.

Scheme 4. Protection of Structurally Different Amines by the Use of Linker **7**

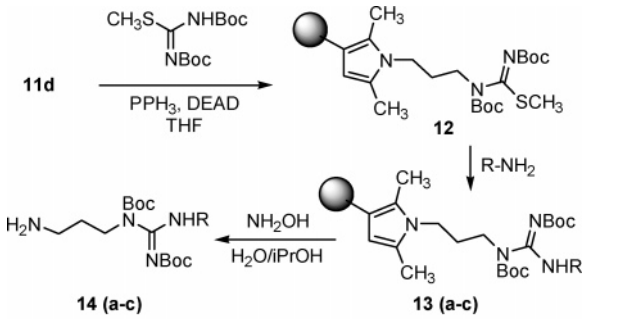


In fact, alkylation of **11a** according to Mitsunobu conditions (MeOH, PPh_3, DEAD) gave the corresponding methyl ether, which, after cleavage of the pyrrole ring (NH_2OH·HCl/Et_3N), afforded 4-methoxyaniline in 70% yield.

The nitro group of**11b** was first reduced in the presence of $Cu(acac)_2$ and $NaBH_4$ in EtOH/DMF,[13] and the NH_2 moiety thus obtained was acylated with benzoic acid in the presence of DIC and catalytic amounts of DMAP. After cleavage, *N*-(4-aminophenyl)benzamide was obtained in 30% yield. The same compound was obtained in a more satisfactory 80% yield by deprotection of **11c** (25% pyperidine/DMF) and subsequent acylation. This result prompted us to investigate more deeply the cyclization reaction of polymer **7** with 4-nitroaniline. It was easy to demonstrate, by simple cleavage of **11b** under standard conditions to give 4-nitroaniline (35% yield), that the low yield in the benzamide formation was essentially due to the scarce nucleophilicity of 4-nitroaniline, leading to incomplete formation of **11b**.

Next, we investigated the possibility of preparing compounds having a guanidine core by using the approach we had set up on solid phase. Polymer **11d** (Scheme 5) was

Scheme 5. Synthesis of Di-Boc-Protected Guanidines **14a**−**c**



reacted under Mitsunobu conditions (PPh_3, DEAD, THF) with di-Boc-protected *S*-methylisothiourea, and the formation of **12** was confirmed by a colorimetric test. The polymer-bound *S*-methylisothiourea **12** was then divided into three portions which were reacted in parallel, in a Büchi Syncore Reactor synthesizer, with benzylamine, 3,4-dichlorobenzylamine, and 4-methoxybenzylamine respectively (CH_3CN, 45 °C, overnight), to give the corresponding solid-supported guanidines **13a**−**c**. Cleavage under standard conditions led to the Boc-protected guanidines **14a**−**c** in 55%, 60%, and 65% yield, respectively. The satisfactory results thus obtained confirmed the usefulness of our linker for the preparation, on solid phase, of the afored mentioned compounds and our initial idea of adapting this methodology to the synthesis of a small library of compounds by means of parallel synthesis.

Even better results were obtained starting from polymer **11c** (Scheme 6) which was first deprotected[14] to give the amine **15** and then reacted with cyclohexyl isothiocyanate or phenyl isothiocyanate in CH_2Cl_2. The corresponding thioureas **16a** and **16b** were first alkylated with Mukaiyama's reagent (the reaction was repeated three times in order to avoid the recovering of unreacted thiourea)[15] and then treated with (±)-1-(1-naphthyl)ethylamine and 4-methoxybenzylamine to afford the solid supported guanidines **17a** and **17b**. Opening of the pyrrole ring under the usual conditions gave compounds **18a** and **18b** in an excellent 90% yield.

The opening of 2,5-dimethylpyrrole with NH_2OH·HCl and Et_3N is known to proceed through the formation of a

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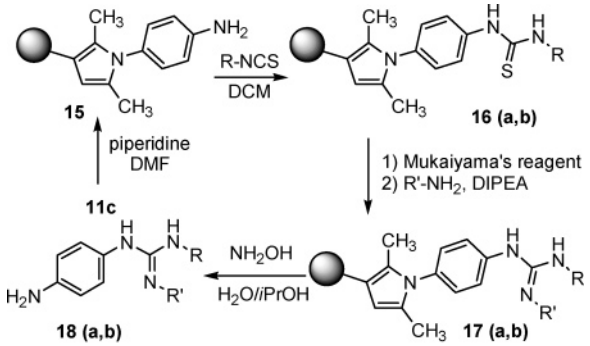
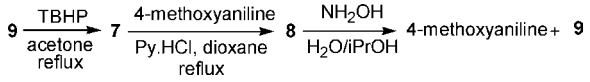
Scheme 6. Synthesis of Guanidines **18a,b**



dioxime.[16] The formation of oximes represents a largely used approach for the protection of ketones and aldehydes and several methods are known for the conversion of dioximes into the corresponding carbonyl compounds. We thought, therefore, to use polymer **9** (Scheme 7), obtained as a side

Scheme 7. Regeneration and Recycling of Polymer **7**



product from the pyrrole opening reaction, to regenerate the diketonic resin **7**. Since most of the methods known for the conversion of oximes to carbonyl compounds[17] are not compatible with the solid phase, we focused our attention on *tert*-butyl hydroperoxide (TBHP)[18] as the oxidizing agent because of the possibility to work in mild reaction conditions without the formation of precipitates that are difficult to remove from the solid support. Thus, TBHP was added to a suspension of **9** in acetone, and the reaction mixture was refluxed for 24 h. The formation of **7** was confirmed by IR analysis. Cyclization of **7** with 4-methoxyaniline to provide **8** and subsequent ring opening of **8** gave 4-methoxyaniline in 90% yield. A further cycle of oxidation, cyclization, and ring opening resulted in a loss of purity of the recovered amine (50%, determined by GC), thus indicating the possibility to use the same resin not more then twice.

In summary, it has been demonstrated that polymer-bound diketone **7** reacts smoothly with primary amines giving a pyrrole system, which in turn can be easily opened to release in solution the original amine in a pure form and high yield. For this reason, 2,5-dimethylpyrrole can be considered a good protecting group for protecting/masking terminal amines on the solid phase, a crucial point in the synthesis of guanidine compounds of type **a**. Resin **7** can also be recycled at least once without loss of purity of the final compound. The possibility to extend this methodology to the synthesis of small libraries of compounds by means of parallel synthesis has been also ascertained.

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Supporting Information Available: Experimental procedures and characterization for compounds **2**−**5**, **7**, **8**, **11**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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