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Electrolysis as an Efficient Key Step in the Homogeneous Polymer-Supported Synthesis of *N*-Substituted Pyrroles

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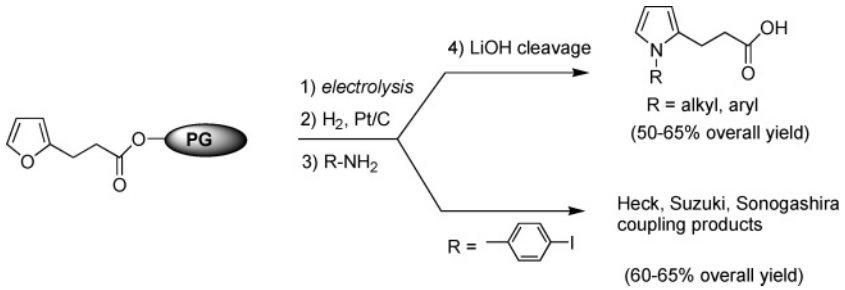
ABSTRACT



An efficient and general route to the soluble polymer-assisted synthesis of a set of 14 different *N*-substituted pyrroles using dendritic polyglycerol as a high-loading support is presented. The transformation of furan to the key intermediate 2,5-dialkoxytetrahydrofuran was performed by electrochemical oxidation followed by catalytic hydrogenation with Pt/C in high yield. Both reactions required heterogeneous reagents which can be conveniently used with polyglycerol as a soluble support.

Polymer-supported synthesis has become a valuable tool for the synthesis of libraries of compounds with potential interest for applications in life sciences, catalysis, and material sciences. Solid-phase organic synthesis (SPOS) using insoluble solid supports such as polystyrene resins takes advantage of the simple removal of excess or consumed reagents by a simple filtration workup operation.[1] On the other hand slow reaction kinetics and the intrinsic difficulty to monitor reaction progress are factors which limit the use of SPOS in certain applications. Due to the heterogeneous nature of the solid support in which more than 99% of the substrate molecules are located in the interior of a bead, no direct contact of these molecules with heterogeneous reagents is possible, which imposes a severe limitation for the use of such useful synthetic operations, such as catalytic hydrogenation or electroorganic synthesis.[2] Recently, we reported the successful electrochemical oxidation of furans on solid phase, in which a redox catalyst serves as an electron shuttle between electrode and support.[3] Having a method for the solid-phase synthesis of 2,5-dialkoxydihydrofurans in hand, we aimed at the synthesis of the pharmacologically interest-

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(1) Reviews: (a) Früchtel, J. S.; Jung, G. *Angew. Chem.* **1996**, *108*, 19−46; *Angew. Chem., Int. Ed.* **1996**, *35*, 17−42. (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527−4554. (c) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643−5678. (d) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1999**, *54*, 15385−15443. (e) Zaragoza Dörwald, F. *Organic Synthesis on Solid Phase*, 2nd ed.; Wiley-VCH: Weinheim, 2002.

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ing class of *N*-substituted pyrroles[4] by condensation of primary amines with 2,5-dialkoxytetrahydrofurans, which would require the hydrogenation of the olefinic double bond of a solid-phase bound substrate. Here, we faced a methodological problem which we could not solve even by the attempted use of diimide reduction as a homogeneous reduction method for the corresponding substrate molecule.[5] Obviously, the use of an insoluble polymer support represented a dead end street for the planned synthetic strategy, and we turned to soluble polymers, such as polyglycerol **1**, as an alternative support.[2]

Soluble polymeric supports enable the use of homogeneous reaction conditions and standard analytical techniques for reaction monitoring.[6,7] Recently, we introduced hyperbranched polyglycerol (**1**) as an inexpensive support to parallel library synthesis, offering the advantages of high loading capacity and facile monitoring of the reaction progress (Figure 1).[8]

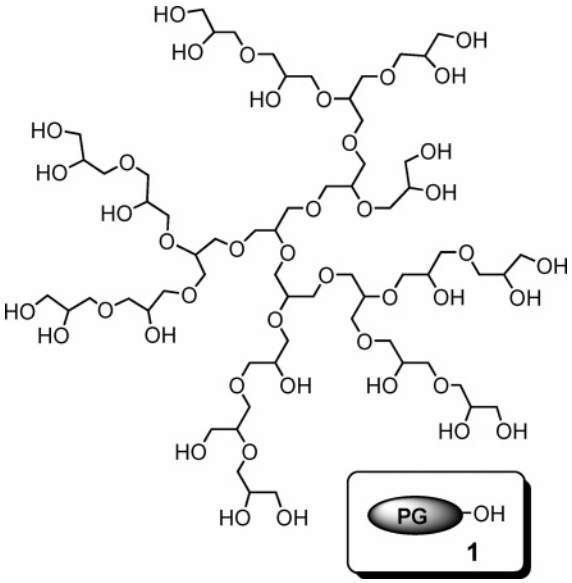
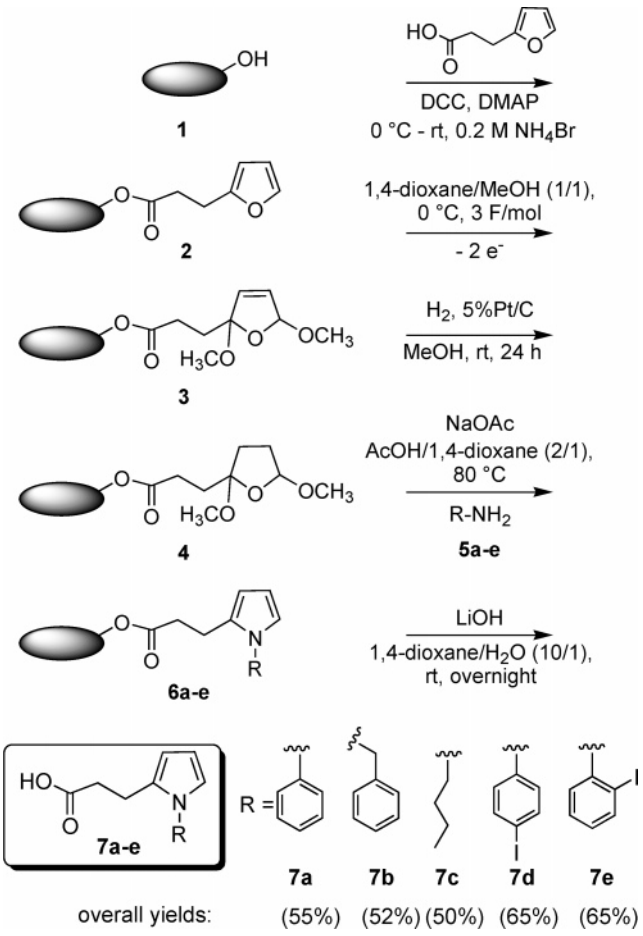


Figure 1. Hyperbranched polyglycerol (**1**): the depicted polymer structure represents only one possible isomer and a small part of the polyglycerol (M_n = 8000 g/mol) scaffold.

2-Furanpropanoic acid was attached to polyglycerol (**1**) using a DCC-mediated esterification protocol which we had developed recently (Scheme 1).[8c] After removal of the urea

Scheme 1. Synthesis of *N*-Substituted Pyrroles Using **1** as a Soluble Support



side product via dialysis, the loading of ester **2** was calculated to be 6.5 mmol/g (see the Supporting Information). For the oxidation of the furan substrate, it was planned to use the electrochemical method of Clauson−Kaas.[9] Due to the modification with a hydrophobic residue at its tentacle termini, the polyglycerol ester **2** was not soluble in MeOH anymore, and for the subsequent electrolysis an electrolyte of 0.2 M NH_4Br in 1,4-dioxane/MeOH (1:1) was chosen instead, for which 1,4-dioxane served as a cosolvent. Electrolysis was performed in an undivided beaker type cell using carbon electrodes and a current density of 0.015 A/cm^2. After consumption of 3 F/mol, NMR analysis revealed that **2** had been converted smoothly and quantitatively into 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglycerol ester (**3**). Gratifyingly, due to the clean conversion and the polar properties of the electrolyte, a simple extractive workup allowed the isolation of **3** without requiring further purification by dialysis. The crucial hydrogenation step,[10] which had

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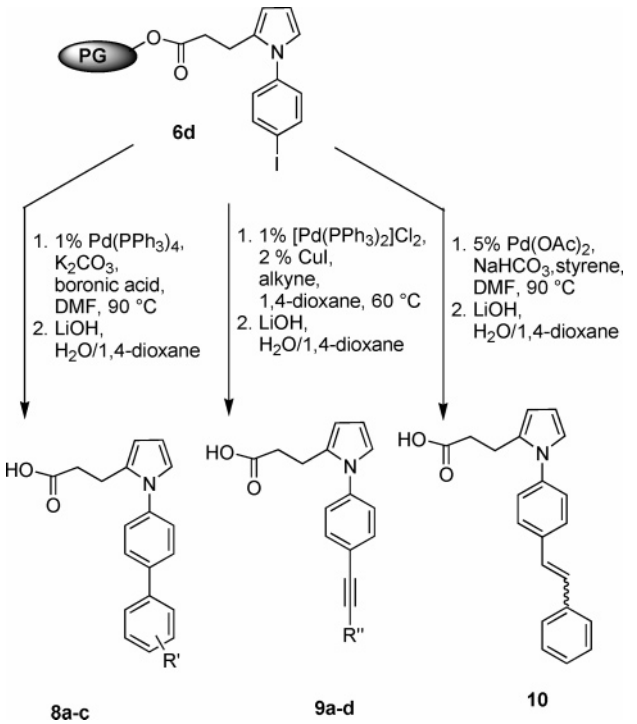
previously failed using insoluble polymer resins, turned out to be facile when using polyglycerol as a homogeneous support. Whereas Pd/C as a hydrogenation catalyst delivered unsatisfying results in various solvents, hydrogenation with Pt/C in MeOH enabled the clean conversion of **3** into 2,5-dimethoxytetrahydrofuran derivative **4**. Due to the heterogeneous nature of the reagents, a simple filtration through a bed of Celite gave product **4** in pure form.

Having established a robust and scalable synthetic route to key intermediate **4**, we investigated the formation of pyrrole derivatives **6a**−**e** by in situ hydrolytic release of the latent carbonyl moieties and concomitant Paal−Knorr-type condensation with amines **5a**−**e**.[11] Using model reactions in solution, we identified Jefford's conditions with R-NH_2/AcOH/NaOAc (1/1/1) in MeOH at 80 °C as useful for our purposes.[12] Unfortunately, when applying these reaction conditions for the condensation of polygycerol-supported substrate **4** and aniline (**5a**) as a model substrate, we observed not only the desired product **6a** but also significant amounts of the corresponding methyl ester product which resulted from a transesterification side reaction. Slight modification of the reaction conditions by using R-NH_2/NaOAc (2/1) in AcOH/1,4-dioxane (2/1) as the solvent system cleanly led to the pyrrole condensation product **6a**, which was subjected to purification via dialysis.[8a] Product **7a** was cleaved off the polymer via saponification in the presence of LiOH in 1,4-dioxane/H_2O (10/1) and was isolated after purification by column chromatography in respectable 55% overall yield (starting from **2**). The reaction sequence proved to be general for any type of primary amines or anilines **5a**−**e** delivering *N*-substituted pyrrole propionic acids **7a**−**e** in 50−65% overall yield (Scheme 1).

While condensation of the key intermediate **4** with a variety of amines has already allowed the flexible synthesis of a diverse array of *N*-substituted pyrroles, the diversity of the compound set could be increased when appropriately substituted intermediates were subjected to further modification. Exemplifying this strategy, we performed a series of Pd-catalyzed cross-coupling reactions with *N*-(4-iodophenyl)-2-pyrrolpropanoic acid polyglycerol ester **6d** (Scheme 2).[8b,13] Suzuki reaction with $Pd(PPh_3)_4$ as a catalyst and K_2CO_3 as base produced *N*-biphenyl derivatives **8a**−**c** in good overall yield. Similarily, Sonogashira reaction with [$Pd(PPh_3)_2Cl_2$] and Heck reaction using Jeffery's conditions[14] delivered the corresponding coupling products **9a**−**d** and **10** in good overall yields 60−65% (Scheme 2, Figure 2). These modification reactions considerably contribute to the overall diversity of the prepared compound set and highlight the flexibility of our synthetic approach, which exploits the ready accessibility of a variety of primary amines as building blocks.

Scheme 2. Diversification via Pd-Catalyzed Cross-Coupling Reactions



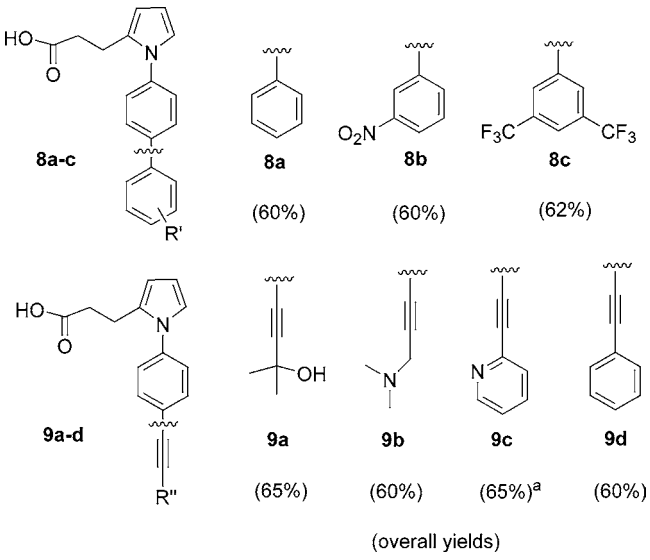


Figure 2. Reaction products of diversification through Pd-catalyzed cross-coupling reactions. [a]Contains an impurity.

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In conclusion, we have demonstrated that hyperbranched polyglycerol **1** is an excellent soluble support for the synthesis of a diverse array of compounds using multistep synthesis. In particular, polyglycerol offers the advantage of (i) facile monitoring of reaction progress, which (ii) significantly accelerates the optimization process of reaction conditions, and (iii) due to its homogeneous nature allows the use of heterogeneous reagents. This allowed us to use a combination of reagents (electrolysis and catalytic hydrogenation) which could not be used in the presence of an insoluble polystyrene resin as support.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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