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Preparation of a novel polystyrene-based urea resin

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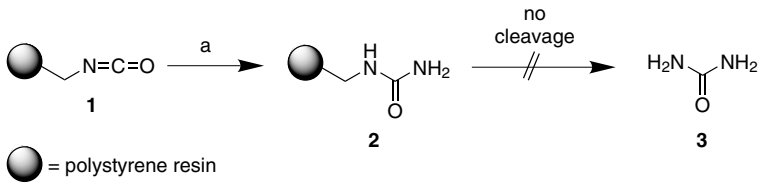
Abstract—A urea-functionalized polystyrene-resin with a Rink linker was prepared by adaptation of a solution-phase synthesis to solid-phase chemistry. Thereby, a resin-bound acylurea was formed by reacting a Rink-amide resin with trichloroacetyl isocyanate, followed by the thermal removal of the trichloroacetyl group and thus generating the unsubstituted solid-supported urea.

Solid-phase organic synthesis (SPOS) has revolutionized organic synthesis in the past decade. Successful solid-phase chemistry requires careful selection of the solid support, the linker technology and the solvents employed. During our efforts toward the solid-phase synthesis of nitrogen-containing heterocycles, there was a pressing need for a resin-bound unsubstituted urea. Ureas have been important reagents and building blocks in numerous syntheses of mono- and bicyclic azaheterocycles,[1] for example, 2-azetidinones,[2] 3,1-benzoxazin-4-ones,[3] barbituric acids,[4] and hydantoins.[5] Herein, we describe the preparation of a polystyrene (PS)-based urea resin as a valuable material to be used in SPOS.

A methylthiourea PS-resin and methyliso(thio)cyanate PS-resins are commercially available as nucleophilic and electrophilic scavengers, respectively. Bräse and Dahmen described some resin-bound ureas, all of them being terminally substituted.[6] To the best of our knowledge, there are no reports on the existence of a terminally unsubstituted urea moiety. Such a resin could easily be synthesized, when starting from the mentioned methylisocyanate resin and treating it with gaseous ammonia (Scheme 1). We performed the reaction control via IR spectroscopy by observing the disappearance of the NCO signal at 2250 cm^{-1}. However, the concept of these scavenger resins includes that they should permanently catch excess electrophilic (e.g., bromomethylcarbonyl compounds[7]) or nucleophilic reagents (e.g., amines[8]) in solution reactions, and are therefore not designed to release the formed products. Thus, neither urea **3** could be released from the resin **2**, nor any products that might be generated from **2** by SPOS.

It was our primary objective to provide a resin containing a urea moiety connected to a suitable linker for cleavage of intermediates and products. We therefore chose the frequently used Rink linker, which is easy-to-handle, stable under non-acidic conditions and moderately priced. In order to explore this strategy, a solution synthesis applicable to the polymer support was developed. Mimicking the Rink amide backbone, the benzhydryl group was selected. The idea was to prepare a *N*-acyl-*N*′-benzhydrylurea, where the acyl functionality should be cleaved by nucleophilic attack in the following step. Benzhydrylamine **4** was reacted with



Scheme 1. Reagents and conditions: (a) excess gaseous ammonia, dry dichloromethane, 1 h, rt.

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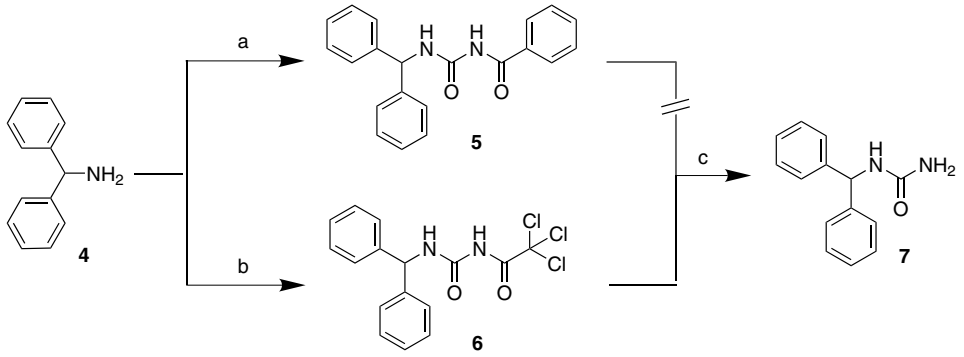


Scheme 2. Reagents and conditions: (a) PhCONCO (1.5 equiv), dry THF, 24 h, rt; (b) CCl_3CONCO (1.5 equiv), dry THF, 24 h, rt; (c) MeOH, 16 h, reflux.

benzoyl- and trichloroacetyl isocyanate in dry THF for 24 h at room temperature (Scheme 2). Heating the product **6** in methanol[9] for 16 h generated the desired benzhydrylurea **7**[10] in 63% yield after purification by column chromatography,[14] whereas *N*-benzhydryl-*N*′-benzoylurea **5** did not react similarly. It could be concluded that the benzoyl compound **5** would require much stronger conditions to form **7**.

With a sound solution-phase strategy in hand, we now extended our methodology to polymer supported synthesis. Fmoc-protected Rink-amide resin **8** (Scheme 3) was deprotected with 20% piperidine in DMF and washed. Fmoc removal was indicated by a positive TNBS- (trinitrobenzol sulfonic acid) or Kaiser test. The resin **9** was reacted with trichloroacetyl isocyanate as described above for the solution reaction to generate the resin-bound trichloroacetylurea **10**. The TNBS and Kaiser test performed after the washing procedure were negative if the reaction was complete. For reaction control, the product could then be cleaved from the solid support under standard TFA conditions. Best yields resulted when 5% TFA in dichloromethane was applied, in comparison to 10% or 20% TFA. After evaporation of the solvent, trichloroacetylurea **12** was obtained in good yield (72%)[11] and excellent purity (96%).[12]

Evidence for structure **12** was obtained from ^1H and ^{13}C NMR spectroscopy.[14] The ^1H spectrum of **12** displayed three different NH signals at 7.28, 7.52 and 10.99 ppm. As known from the literature data,[13] the first two signals, belonging to the NH_2 group, nearly coalesce, due to the formation of an intramolecular hydrogen bond in **12** (Fig. 1).

To obtain the urea resin **11** (Scheme 3), the trichloroacetyl group had to be removed. This could be managed by refluxing the resin **10** for 48 h in a mixture of equal portions of methanol and dioxane containing 0.1% water. In contrast to the solution reaction, the addition of dioxane as a solvent, which causes good swelling of the PS-resin, was necessary when applying that method to solid phase. Indeed, urea itself was finally detached from the resin **11**. The solid (yield of crude product: 94%)[11] was identified as urea **3** (purity: 56%)[15] and the structure was confirmed by means of ^1H, ^{13}C NMR and EIMS.[14]

In summary, an urea-functionalized PS-resin with a Rink linker was prepared by adaptation of a solution-phase synthesis to solid phase. Thereby, trichloroacetyl isocyanate was used to generate a resin-bound acylurea,

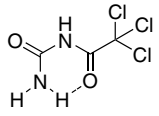
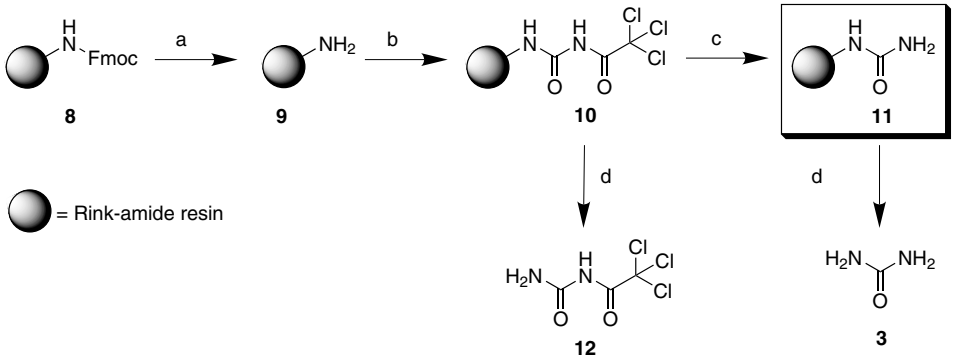


Figure 1.



Scheme 3. Reagents and conditions: (a) 20% piperidine/DMF, 1 h, rt; (b) CCl_3CONCO (10 equiv), dry THF, 24 h, rt; (c) MeOH/dioxane (1:1), 48 h, 67 °C; (d) 5% TFA/dichloromethane, 2 h, rt.

from which the desired resin-bound urea could be generated by simple heating in methanol/dioxane. Investigations are in progress to utilize this resin in our studies toward the solid-phase synthesis of certain small organic molecules. In general, the urea resin promises to be a versatile starting material for various SPOSs.

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11. Calculated on the basis of the initial loading of the Rink-amide resin.
12. Determined by RP18-HPLC on the basis of relative areas, eluent acetonitrile:water = 24:76 as described in: Eichelbaum, M.; Sonntag, B.; Von Unruh, G. *Arch. Toxicol.* **1978**, *41*, 187–193.
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14. Following are ^{1}H NMR, ^{13}C NMR, MS spectral and other analytical data of compounds:
Compound **5**: white, crystalline solid; mp 202–203 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.12 (d, 1H, J = 7.55 Hz, CH), 7.25–7.99 (m, 15H, Ph), 9.58 (d, 1H, J = 7.55 Hz, CHN*H*), 10.88 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 57.18 (CH), 126.89, 127.39, 128.35, 128.63, 128.86, 132.52, 133.03, 142.33 (Ph), 152.86 (NHCONH), 168.98 (CO). EIMS (*m*/*z*, 70 eV): 330 (M^+, 40), 182 ($Ph_2C{=}NH_2^+$, 100).
Compound **6**: white, crystalline solid; mp 110–115 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.01 (d, 1H, J = 7.65 Hz, CH), 7.25–7.38 (m, 10H, Ph), 8.53 (d, 1H, J = 7.60 Hz, CHN*H*), 11.10 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 57.56 (CH), 92.32 (CCl_3), 127.45 (C-4′, C-4″), 127.04, 128.78 (CH–Ph), 141.88 (C-1′, C-1″), 150.47 (NHCONH), 160.60 (CO). EIMS (*m*/*z*, 70 eV): 370 (M^+, 4), 208 ($Ph_2C{=}N{-}CO^+$, 100).
Compound **7**: white, crystalline solid; mp 128–131 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.52 (s, 2H, NH_2), 5.86 (d, 1H, J = 8.51 Hz, CH), 6.93 (d, 1H, J = 8.51 Hz, CHN*H*), 7.19–7.34 (m, 10H, Ph); ^{13}C NMR (125 MHz, DMSO-d_6) δ 56.87 (CH), 126.81 (C-4′, C-4″), 127.08, 128.44 (CH–Ph), 143.88 (C-1′, C-1″), 157.89 (CO). EIMS (*m*/*z*, 70 eV): 226 (M^+, 100), 182 ($Ph_2C{=}NH_2^+$, 82).
Compound **12**: white, crystalline solid; mp 152–153 °C, lit.[16] mp 150 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.28 (s, 1H, NH_2), 7.52 (s, 1H, NH_2), 10.99 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 92.39 (CCl_3), 152.25 (NHCONH), 161.19 (CO). EIMS (*m*/*z*, 70 eV): 205 (MH^+, 2) 87 ($MH^+ - CCl_3$, 100).
Compound **3**: brownish solid; mp 110–113 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.79 (s, br, 4H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.00 (CO). EIMS (*m*/*z*, 70 eV): 60 (M^+, 100).
15. Determined by RP18-HPLC on the basis of a calibration curve obtained from four different concentration of urea, eluent water:acetonitrile = 95:5, λ = 210 nm, flow: 1 mL/min.
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