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A ROMPGEL-Supported *N*-Hydroxysuccinimide: A Host of Acylations with Minimal Purification

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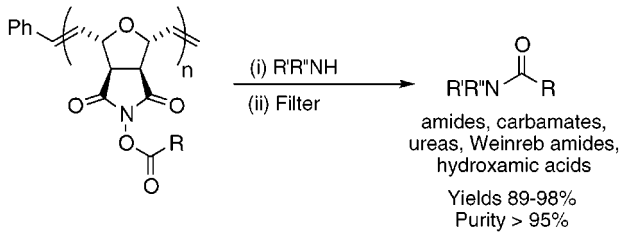
ABSTRACT



A novel *N*-hydroxysuccinimide ring-opening metathesis polymer is described as a recyclable supported acyl transfer reagent. Amides, carbamates, ureas, Weinreb amides, and hydroxamic acids are all obtained in excellent yields and purities from amines with minimal purification.

Polymer-supported reagents for organic synthesis are currently enjoying a renewed popularity with the emergence of combinatorial chemistry.[1,2] The current trend for automation in synthesis is driving the need for the speed of production and the ease of handling of large numbers of discrete compounds, together with a need for a wide range of possible synthetic transformations. Supported reagents are allowing the integration of well-established solution-phase chemistry (along with the myriad analytical techniques available) with automation through the use of robotics.

Supported reagents can be used either catalytically or used in excess, driving reactions to completion, and both spent and unreacted reagent are removed by simple filtration. Supported reagents seem to offer advantages over methods which rely on separation by physical or chemical properties (automated chromatography, aqueous[3] or fluorous-phase[4] workup, acid/base-tagged reagents[5]) since in the context of a diverse library, these properties are frequently nongeneral.

Most polymer-supported reagents to date have used cross-linked polystyrene as the insoluble support due to its commercial availability. With polystyrene, since all synthetic modifications are invariably carried out post-polymerization, the quality of the resin is an important consideration, since monitoring reactions on-resin is not straightforward and purification is generally not possible. We find an alternative

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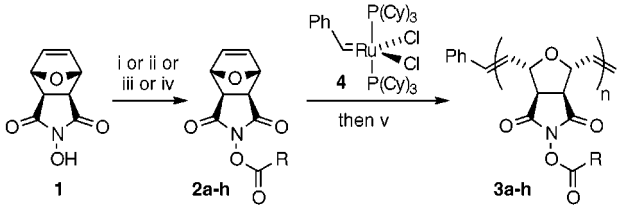
method in the use of ring-opening metathesis polymers (ROMP). Monomer units containing all the desired functionality for the reagent and a strained alkene are synthesized in solution and are then polymerized using the Grubbs' functional group tolerant ruthenium benzylidene catalyst **4**.[6] The ROM-polymers thus produced (we term these functionalized polymers ROMPGELs[7]) are of excellent quality and quantitative[8] loading. We now report that acyl derivatives of an *N*-hydroxysuccinimide ROMPGEL act as versatile, recyclable, activated ester equivalents for the formation of amides (including Weinreb amides[9]), carbamates, hydroxamic acids, and ureas from a range of acids and amines.[10]

Activated esters derived from *N*-hydroxysuccinimide find widespread use as acylating agents, especially for activated amino acids, as reagents for the introduction of carbamate protecting groups and a range of radio-labeling, staining, and cross-linking reagents for biological systems.[11] Normally, the *N*-hydroxysuccinimide byproduct is removed by precipitation and/or chromatography. A water-soluble analogue, *N*-hydroxysulfosuccinimide,[12] allows for the removal of the byproduct and excess reagent by aqueous extraction. Alternatively, there are several resins that can be used, copoly(ethylene-*N*-hydroxymaleimide),[13] copoly(styrene-*N*-hydroxymaleimide),[14] and most recently polystyrene-supported *N*-hydroxysuccinimide,[15] along with a number of other acyl transfer polymers including polymer-supported *o*-nitrophenol,[16] *p*-(hydroxyphenyl)sulfone,[17] hydroxybenzotriazole,[18] supported aminopyridinium-acyl complexes,[19] hydroxytriazine,[20] and a range of mixed anhydrides.[21] An ideal resin should possess the properties of mechanical stability, good site accessibility, high reactivity, good selectivity, and high loading. We find that the ROMPGEL support fulfills all of these criteria combined with ease of synthesis and versatility of use.

Acylation of *exo*-*N*-hydroxy-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide **1** could be achieved with either acid chlorides (**5a**,**b**, NEt_3, CH_2Cl_2), carboxylic acids (**5c**−**e**, DIC, CH_2Cl_2), alkyl chloroformates (**5f**,**g**, NEt_3, CH_2Cl_2), or isocyanates (**5h**, CH_2Cl_2) to give the desired activated ester monomers **2a**−**h** in excellent yields. Polymerization was carried out using the Grubbs catalyst **4** (1.5 mol %, CH_2Cl_2), terminating the reaction with ethyl vinyl ether. The ROMPGELs **3a**−**h** were insoluble, high-loading (between 2.1 and 3.8 mmol g^{-1}) polymers which became slightly swollen in a range of organic solvents (Scheme 1).[22]

Scheme 1. Synthesis of ROMPGEL Activated Esters



Reagents: (i) R^1COCl, NEt_3, CH_2Cl_2; (ii) R^2CO_2H, DIC, CH_2Cl_2; (iii) R^3OCOCl, NEt_3, CH_2Cl_2; (iv) R^4NCO, CH_2Cl_2; (v) $EtOCH{=}CH_2$.

Chromatographic separation of monomers **2c**−**e** from *N*,*N*′-diisopropylurea was not possible due to similar chromatographic polarities; however, ROM-polymerization of the crude mixtures gave a quantitiative yield of the ROMPGEL and the contaminant urea could easily be removed by washing the polymer with CH_2Cl_2−MeOH (9:1).

Reaction of a slight excess of ROMPGEL **3** (1.2 equiv.) with a range of amines **6** (Figure 1), filtration, and evapora-

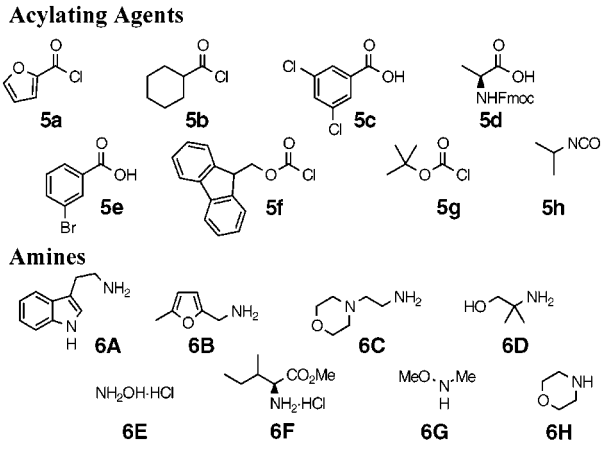


Figure 1. Acyl and amine units.

(6) Benzylidenebis(tricyclohexylphosphine)dichlororuthenium **4** is commercially available from Fluka.

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tion of the solvent gave the desired products **7** in excellent isolated yields and purities (Table 1). The ROMPGELs **3**

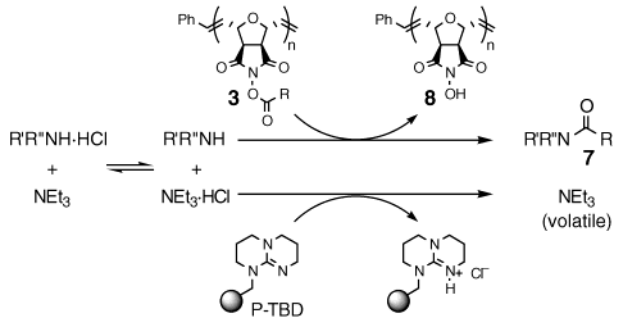
Table 1. Acylation of a Range of Amines Using ROMPGELs **3a**−**h**. Isolated Yields of Products **7** Are Quoted. All Componds Were >95% Pure by GCMS

	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**
6A	95	90	97	95	*a*	*a*	*a*	91
6B	97	93	97	95	95	97	95	98
6C	97	97	98	93	96	93	89	92
6D	89	90	80[b]	*a*	*a*	*a*	*a*	*a*
6E	91	90	96	*a*	*a*	*a*	*a*	*a*
6F	96	*a*	98	*a*	*a*	*a*	*a*	*a*
6G	95	93	98	*a*	*a*	*a*	*a*	*a*
6H	95	98	96	*a*	*a*	*a*	*a*	*a*

[a] The reaction was not run. [b] Product contaminated with 20% of the *N*,*O*-bis-acylated compound.

were selective for amines over alcohols, except when a reactive acyl group (**3c**) was used. Also, amine hydrochloride salts could be used directly in the reaction with the addition of either solid KOH (**6E**) or triethylamine as a proton shuttle and a polystyrene-supported guanidine base, P-TBD,[23] as a proton sink (**6F**) (Scheme 2).

Scheme 2. Acylation of Amines Using ROMPGEL **3**

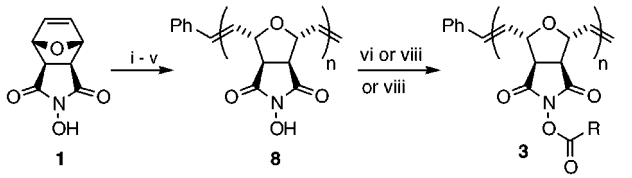


Excess triethylamine was removed along with the solvent by evaporation. Therefore, amino acid ester hydrochloride salts (e.g., **6F**) could be used directly. There was no observable racemization of the amino acid when used as the acylating agent or as the amine component.

Acylation of the *N*-hydroxysuccinimide monomer **1** prior to ROM-polymerization generates a polymer which is very useful for the bulk acylation of a range of amines. We also checked whether the *N*-hydroxysuccinimide functionalized polymer could be acylated post-polymerization.

Oxanorbornene monomer **1** does not undergo ROM-polymerization, presumably due to its low solubility. Hence, compound **1** was silylated (TBSCl, imidazole, CH_2Cl_2) and the monomer polymerized as before. Desilylation (NEt_3·3HF, then Me_3SiOMe)[24] gave the supported *N*-hydroxysuccinimide ROMPGEL **8** (5.5 mmol g^{-1} loading) in quantitative yield (Scheme 3).

Scheme 3. Divergent Synthesis of ROMPGEL Esters **3**



Reagents: (i) TBSCl, imidazole, 99%; (ii) $(PCy_3)_2Cl_2Ru$=CHPh (**4**), CH_2Cl_2; (iii) EtOCH=CH_2; (iv) NEt_3·3HF, THF; (v) $MeOSiMe_3$; (vi) R^1COCl, NEt_3, CH_2Cl_2; (vii) R^2CO_2H, DIC, CH_2Cl_2; (viii) R^4NCO, CH_2Cl_2.

ROMPGEL **8** could be acylated (RCOCl, NEt_3, CH_2Cl_2 or RCO_2H, DIC, CH_2Cl_2) or converted to the carbamate (RNCO, CH_2Cl_2) as previously discussed.

Again, treatment of an excess of ROMPGELs **3** (1.2 equiv) with an amine **6** gave the desired products **7** (amide or urea) in good yield and excellent purity.[25]

Finally, all the *N*-hydroxysuccinimide polymers (either ROMPGELs **3** or **8**) recovered from acylation reactions could be recycled. Remaining acyl groups were removed (NH_3, MeOH, THF), and the recovered ROMPGEL **8** could be reused with no loss of activity.[26]

In conclusion, we have demonstrated the use of a novel support for the acylation of amines with minimal purification. The bulk ROMPGELs produced by polymerization of monomers **2** are suitable when multigram quantities of acylated compounds are needed. Acylation of the *N*-hydroxy ROMPGEL **8** becomes the method of choice when diverse libraries of compounds are needed. Furthermore, the polymers can be recycled and reused without any loss of yield or purity of the final product. Further applications of ROMPGELs will be reported in due course.

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(22) The ROMPGELs **3** obtained were sometimes soluble in dichloromethane or ethyl acetate depending the nature of the acyl substituent. In these cases, copolymerisaztion of the monomers **2** with norbornadiene (5 mol %) yielded an insoluble polymer.

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(24) NEt_3·3HF complex was the reagent of choice since all byproducts were liquids. Desilylation with tetrabutylammonium fluoride (TBAF) gave a crystalline polymer, presumably due to ammonium salts trapped in the resin, which led to poorer yields in subsequent acylation reactions.

(25) Amides **7cB**, **7cC**, **7dB**, **7dC**, **7eC**, **7eC**, and urea **7hA** were synthesized in 79−97% yield and in greater than 95% purity by GCMS.

(26) ROMPGEL **3c** (1.2 equiv) was treated with amine **6A** to give amide **7cA** (97% yield), hydrolyzed to ROMPGEL **8**, reacylated with acid chloride **5a**, and used to make amide **7aA** (95% yield, >95% purity). No cross contamination was observed.

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Supporting Information Available: General procedures for the synthesis and use of ROMPGELs **3** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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