Solid-Phase Synthesis of Isoxazoles and Isoxazolines: En Route to a New Class of Ionophores

Eric J. Kantorowski and Mark J. Kurth*

Department of Chemistry, University of California, Davis, California 95616

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Solid-phase organic synthesis (SPOS) was employed in the construction of isoxazole and/or isoxazoline polyheterocyclic systems. The [3 + 2] cycloaddition reactions of nitrile oxides, generated from the corresponding primary nitro compounds, with resin-bound alkynes or alkenes were highly efficient both chemically and with regard to purification. A parallel solution-phase synthesis was carried out which compared the synthetic efficiency in both media. SPOS of isoxazole/isoxazoline **11**, employing a functionalized polystyrene resin, was found to be more efficient than the solution-phase approach. Three other oligoisoxazoles were prepared with average yields per step being 82, 84, and 89%.

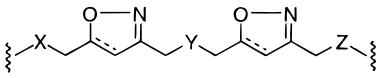
Introduction

Nitrogen-containing ring systems have been widely used as ligands in organometallic chemistry and their role as "tunable" ligands, as well as their application as cryptands, cannot be overstated.[1,2] An important class of nitrogen-containing heterocycles includes both the oxazole and oxazoline ring systems. The latter can be readily prepared by condensation of a carboxylic acid and an amino alcohol.[3] This coupled with the availability of chiral 1,2-amino alcohols allows access to a host of asymmetric ligands which have been utilized in asymmetric catalysis.[4]

The isoxazole and isoxazoline ring systems have been less extensively used in ligand design. The construction of these heterocycles is typically accomplished by [3 + 2] cycloaddition of a nitrile oxide to an alkyne or alkene, respectively.[5] The 1,3-dipole intermediate is usually generated *in situ* from the corresponding primary nitro compound[6] or hydroximoyl chloride.[7]

Interest in ionophoric compounds[8] coupled with our recent work in the area of isoxazoline and isoxazole preparation on solid-support[9] has led us to investigate the preparation of these as polyheterocyclic systems. In this report we disclose preliminary studies targeting construction of potentially tunable ionophores which may find application as polymer-bound or polymer-free ligands. The impetus for such chelating polymers derives from the interest in developing methods for ion-specific analysis/removal of metals from aqueous environments.[10]

Herein, we report our design of polymers incorporating repeating isoxazole and/or isoxazoline heterocycles separated by a variable spacer group (X, Y, Z). With a potentially-iterative sequence for the preparation of these compounds, it seemed tactically efficient to append the developing chain to a polymer-support. Solid-phase organic synthesis (SPOS) of heterocycles derived from 1,3-dipole/dipolarophile coupling has been achieved with high efficiency in both linear syntheses and library preparation.[11] Alcohol-protected 2-nitroethanol seemed an ideal 1,3-dipole precursor as the latent alcohol could be used for further chemical elaboration post-cycloaddition. In this way, the spacer groups between the heterocyclic moieties could be easily augmented to incorporate additional functionality which should lend itself to fine-tuning the properties of these compounds.



Results and Discussion

The strategy reported here was to affix an alkynyl alcohol to a polymer support via a benzoyl ester. The ester linkage was considered to be stable under the conditions we anticipated utilizing, and the substrate could then be liberated from the resin by transesterification with $NaOCH_3$ in THF. Additionally, we chose to run a parallel solution-phase synthesis of one targeted compound where, to mimic the polymer-bound substrate to an approximate degree, the benzoyl ester was chosen

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(1) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721−2085.

(2) (a) Gokel, G. *Crown Ethers and Cryptands*; The Royal Society of Chemistry: Cambridge, England, 1991. (b) Zhang, X. X.; Bordunov, A. V.; Izatt, R. M.; Bradshaw, J. S. *NATO ASI Ser., Ser. C* **1996**, *485 (Physical Supramolecular Chemistry)*, 413−431. (c) Chand, D. K.; Ghosh, P.; Shukla, R.; Sengupta, S.; Das, G.; Bandyopadhyay, P.; Bharadwaj, P. K. *Proc. - Indian Acad. Sci., Chem. Sci.* **1996**, *108*, 229−233. (d) Khopkar, S. M.; Gandhi, M. N. *J. Sci. Ind. Res.* **1996**, *55*, 139−155.

(3) (a) Meyers, A. I.; Temple, D. L.; Nolen, R. L.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2778−2783. (b) Wehrmeister, H. L. *J. Org. Chem.* **1961**, *26*, 3821−3824.

(4) (a) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786−787. (b) Nishibayashi, Y.; Segawa, K.; Takada, H.; Ohe, K.; Uemura, S. *Chem. Commun.* **1996**, 847−848. (c) Nishibayashi, Y.; Segawa, K.; Ohe, K.; Uemura, S. *Organomet.* **1995**, *14*, 5486−5487. (d) Nishiyama, H.; Yamaguchi, S.; Park, S.-B.; Itoh, K. *Tetrahedron: Asymmetry* **1993**, *4*, 143−150.

(5) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410−416. Caramella, P.; Grunanger, P. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.

(6) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339−5342.

(7) Christl, M.; Huisgen, R. *Chem. Ber.* **1973**, *106*, 3345−3367.

(8) For example, see: (a) Shih, J. S. *J. Chin. Chem. Soc. (Taipei)* **1994**, *41*, 309−314. (b) Moss, R. E.; Sutherland, I. O. *Anal. Proc. (London)* **1988**, *25*, 272−274. (c) Schneider, H. J.; Blatter, T.; Eliseev, A.; Ruediger, V.; Raevsky, O. A. *Pure Appl. Chem.* **1993**, *65*, 2329−2334. (d) Ungaro, R.; Arduini, A.; Casnati, A.; Pochini, A.; Ugozzoli, F. *Pure Appl. Chem.* **1996**, *68*, 1213−1218.

(9) (a) Kurth, M. J.; Randall, L. A. A.; Takenouchi, K. *J. Org. Chem.* **1996**, *61*, 8755−8761. (b) Lorsbach, B. A.; Miller, R. B.; Kurth, M. J. *J. Org. Chem.* **1996**, *61*, 8716−8717.

(10) (a) Morishima, Y.; Sato, T; Kamachi, M. *Macromolecules* **1996**, *29*, 1633−1637. (b) Saxena, R.; Singh, A. K.; Sambi, S. S. *Anal. Chim.* **1994**, *295*, 199−204. (c) Tomida, T.; Inoue, T.; Tsuchiya, K; Masuda, S. *Ind. Eng. Chem. Res.* **1994**, *33*, 904−906.

(11) Kantorowski, E. J.; Kurth, M. J. *Mol. Diversity* **1997**, *2*, 207−216.

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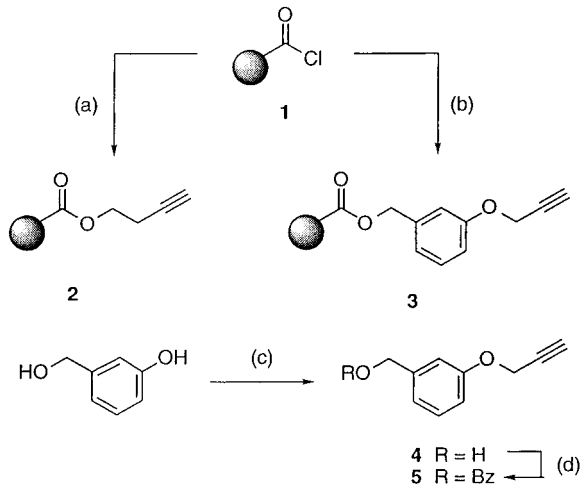
Scheme 1[a]



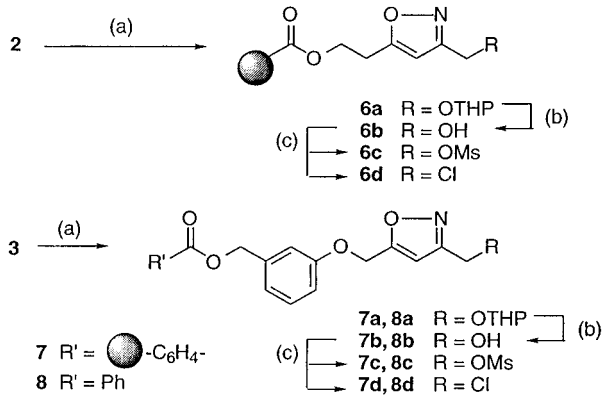
[a] Reagents: (a) 3-Butyn-1-ol, Et_3N, CH_2Cl_2; (b) **4**, Et_3N, CH_2Cl_2; (c) $HC{\equiv}CCH_2Br$, NaOH, H_2O; (d) PhCOCl, Et_3N, CH_2Cl_2.

to protect the alcohol (i.e., solution-phase **5** *vs* solid-phase **3**). This solution synthesis would serve several purposes: (i) make possible comparisons with the IR spectra for the corresponding resin-bound material, (ii) make possible direct comparisons of the ^{1}H- and ^{13}C-NMR spectra of the liberated material (i.e. ®$C_6H_4CO_2R \rightarrow$ ROH and BzOR $\rightarrow$ ROH),[12] and (iii) establish which approach was more efficient.

Alkynyl esters **2** and **3** were readily prepared from polymer-bound benzoyl chloride[13,14a,b] (**1**) and the corresponding alkynols (Scheme 1). Pyridine was initially used as solvent, but extended reaction times (8 d at 23 °C or 3 d at 60 °C) were required. Methylene chloride proved to be superior in these reactions as the esterification is complete after 10−12 h at ambient temperature. Thus, 3-butynol was added to **1** (swollen in CH_2Cl_2) along with triethylamine to yield **2**.[15] Alkyne **3** was prepared in a similar manner using alkynol **4** which is readily accessible by propargylation of 3-hydroxybenzyl alcohol in aqueous NaOH. The progress of these reactions can be followed by IR spectroscopy, wherein the disappearance of the acid chloride carbonyl stretch at 1760 cm^{-1} is accompanied by appearance of an ester carbonyl stretch at 1720 cm^{-1}.

Polymer-bound alkynes **2** and **3** were reacted with the tetrahydropyranyl ether of 2-nitroethanol[16] in refluxing benzene in the presence of PhNCO along with a catalytic amount of Et_3N. The intermediate nitrile oxide (THPO$CH_2C{\equiv}N^+O^-$) underwent [3 + 2] cycloaddition

Scheme 2[a]



[a] Reagents: (a) $O_2NCH_2CH_2OTHP$, PhNCO, PhH; (b) PPTS, THF, EtOH, reflux; (c) MsCl, Et_3N, CH_2Cl_2.

with these tethered alkynes to provide isoxazoles **6a** and **7a** (Scheme 2). Loss of the ≡C−H stretch (3297 cm^{-1} for **2** and 3291 cm^{-1} for **3**) in the IR spectrum (KBr) indicated these reactions were complete after 30 h. When the same cycloaddition was performed in solution on **5**, the resulting cycloadduct was difficult to isolate due to the ubiquitous nature of the 1,3-diphenyl urea byproduct. This urea's moderate solubility in organic solvents and low solubility in water made extraction troublesome and made chromatography difficult for larger reaction scales. *Alternatively, polymer-bound cycloaddition reactions boast a simplified workup and isolation as this urea is easily removed with several washings of the polymer beads.* A commonly used justification for employing SPOS is the ability to overwhelm the substrate with a large excess of reagent to drive the reaction to completion. This is generally performed without regard for the large quantity (usually 5 to 10 equiv) of reagent or reagent byproducts that necessarily remain as filtration and subsequent washing of the polymer obviate the need for chromatographic separation of the product. In contrast, addition of a large reagent excess to the solution-phase approach severely retards product isolation.

Deprotection of the THP ether (**6a**, **7a**) was effected using PPTS in refluxing THF/H_2O (14:1).[17] No sign of ester hydrolysis is observed under these conditions. Alcohols **6b** and **7b** are easily discernible in their IR spectra by appearance of a broad OH absorbance at 3426 cm^{-1}. The spectra are also partially simplified between 1250 and 950 cm^{-1} due to loss of the tetrahydropyranyl moiety. In an attempt to simplify purification of crude isoxazole **8a**[18] (solution-phase analogue), it was thought that removal of the THP group might allow for recrystallization or at least generate disparate R_f values (product *vs* contaminating diphenyl urea) to expedite chromatography. However, THP deprotection or, as was also discovered, removal of the benzoyl group was problematic when any significant amount of diphenyl urea was present. Deprotection of the ether proceeded smoothly when the urea content was less than 10% (determined by ^{1}H-NMR), by employing Dowex 50W-X8 polymer-bound acid as the acid catalyst.[19] Alcohol **8b** was isolated in 65% overall yield from starting alkyne **5**.

(12) The resin is represented by the symbol ® in the text or as a ball in the schemes.

(13) (a) Fyles, T. M.; Leznoff, C. C. *Can. J. Chem.* **1976**, *54*, 935−942. (b) Fyles, T. M.; Leznoff, C. C.; Weatherson, J. *Can. J. Chem.* **1978**, *56*, 1031−1041.

(14) (a) The solid support used was a 2% divinyl benzene cross-linked/polystyrene copolymer which was lithiated, exposed to CO_2, and acidified. Two batches of this polymer were made, and their loading capacities were determined by titration. The polymer indicated for compound **2** (and all subsequent compounds) was determined to have a loading of 2.01 mmol/g; compound **3** (and all subsequent compounds) had a loading of 1.50 mmol/g. This material was refluxed in $SOCl_2$ to generate the benzoyl chloride. See reference 9a for a detailed preparation. (b) After determination of initial loading, the loading for each polymer was assumed to be constant throughout the synthesis.

(15) A typical workup of the polymer reactions consisted of washing with THF, THF/H_2O (1:1), CH_2Cl_2, THF, and Et_2O (ea. 2 × 10 mL) and then overnight drying in a vacuum desiccator.

(16) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366−372.

(17) PPTS or TsOH in refluxing THF/EtOH are ineffective even after 40 h.

(18) A further point of consternation was that compound **8a** had near-identical R_f values with diphenyl urea for all solvent systems investigated.

(19) Beier, R.; Mundy, B. P. *Synth. Commum.* **1979**, *9*, 271−273.

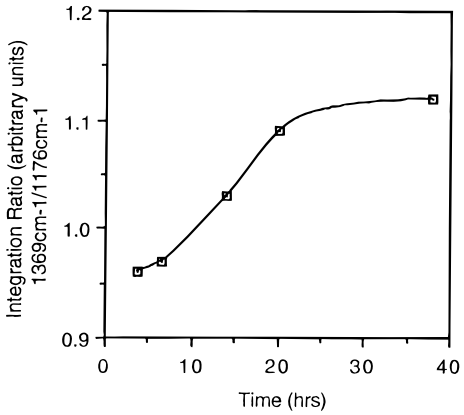
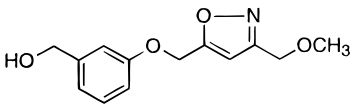


Figure 1. Progress of mesylation of **6b** by FTIR analysis. The developing absorbance at 1369 cm^{-1} (S=O) was compared against a static peak at 1176 cm^{-1}.

With the alcohol unmasked, the substrate was now poised for elaboration to a number of heteroatom-based isoxazole spacers. Our choice was to explore the use of interspersing nitrogen which could (i) offer the ability to make branched isoxazole/isoxazoline oligomers and (ii) in itself act as a chelating locus. Hence, preparation of the mesylate followed by *N*-alkylation of a primary or secondary amine was the evolution planned for these compounds.[20] Solid-phase alcohol mesylation (**6b** → **6c**) proved to be slow at ambient temperature, and refluxing the reaction (CH_2Cl_2) had a negligible effect on the rate. The progress of the reaction was followed by comparing the relative intensities of IR absorbances at 1369 cm^{-1} (S=O stretch) against what was considered a static absorbance at 1176 cm^{-1} (Figure 1). The reaction was deemed complete after 40 h.

The solution-phase analogue of the mesylation reaction (**8b** → **8c**) revealed a limitation in analyzing the extent of the polymer-bound reaction by IR spectroscopy. It was found that mesylate **8c** was the minor product; the major product isolated in this solution reaction was chloride **8d** as was indicated by a 16-proton integration in the ^{1}H-NMR spectrum and a positive Beilstein test. The chloride/mesylate product ratio was 3.8:1 (as determined by ^{1}H-NMR analysis of the crude product mixture). Liberation of the crude mesylation product from the resin by transesterification using $NaOCH_3$ in THF provided methyl ether **21** which presumably can arise from either the mesylate or the chloride. The Cl/OMs product ratio from the solid-phase reaction was therefore not easily ascertained.

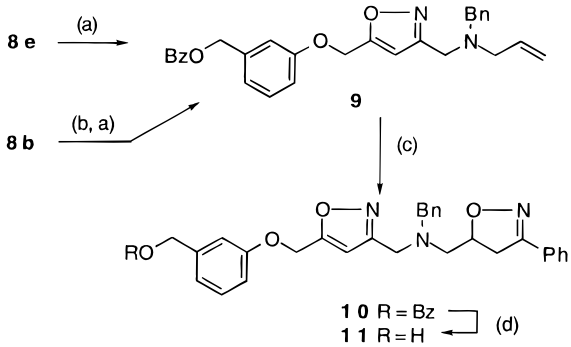


21

Not surprisingly, chloride **8d** proved to be a poor alkylating agent for *N*-benzyl-*N*-allylamine or *N*-allylaniline.[21] Use of catalytic amounts tetrabutylammonium iodide (TBAI) to generate the more reactive iodide *in situ*

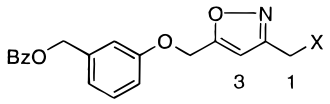
(20) Deprotonation/propargylation of the alcohol which could lead to ether-linked heterocycles tended to cause autocleavage of the ester from the resin. Some initial attempts to incorporate sulfide-linked heterocycles by mesylation followed by alkylation of allylmercaptan led to cleavage of the ester linkage.

Scheme 3[a]



[a] Reagents: (a) $BnHNCH_2CH{=}CH_2$, THF, K_2CO_3; (b) Ph_3P, NBS, CH_2Cl_2; (c) $PhCH_2NO_2$, PhNCO, PhH; (d) $NaOCH_3$, THF.

Table 1. Chemical Shift Values for Intermediates in the Solution-Phase Preparation of Tertiary Amine 9



X	δ H_1 (ppm)	δ H_3 (ppm)	δ C_1 (ppm)
OH	4.74	6.40	–
Cl	4.56	6.45	35.41
Br	4.39	6.44	20.31
I	4.27	6.39	−10.93
OMs	5.27	6.51	–
NBn(C_3H_5)	3.59 or 3.65[a]	6.35	–

[a] One singlet is from the methylene on the benzyl group; actual assignment not made.

was ineffective in a variety of solvents.[22] In solution, sodium iodide with **8d** in refluxing DMF provided only a small amount of product after 2 d. Thus, the solution-phase iodide **8e** was prepared by Finkelstein conversion which was rapid and quantitative. This material smoothly alkylated benzylallyl amine in THF with K_2CO_3 to afford the desired tertiary amine **9** in excellent yield (Scheme 3). In a separate preparation, starting alcohol **8b** was converted to the bromide **8f** using NBS and triphenylphosphine in CH_2Cl_2.[23] This bromide similarly provided amine **9** after approximately twice the reaction time required for the iodide. The chemical shifts of the methylene protons (CH_2X) and the isoxazole ring proton were useful in tracking these transformations (Table 1). The isoxazoline ring was appended to **9** under standard conditions which afforded **10**. Removal of the benzoyl ester ($NaOCH_3$, THF) gave **11** in 35% overall yield starting from alkynol **4**.

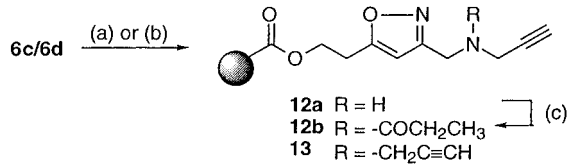
Surprisingly, the mesylated/chlorinated polymers (**6c**/**6d** and **7c**/**7d**) displayed a higher reactivity toward amine alkylation (Scheme 4). When reacted in THF with either a primary or secondary amine containing an *N*-propargyl group in THF, evidence for a ≡C−H stretch was seen in the FTIR spectrum within 1 h. This absorbance increased to a maximum within 12−14 h. On the basis of these results, we speculate that either (i) the mesylate

(21) (a) Clinton, R. O.; Salvador, U. J.; Laskowski, S. C. *J. Am. Chem. Soc.* **1949**, *71*, 3366−3370. (b) Gibson, M. S. The Introduction of the Amino Group. In *The Chemistry of the Amino Group*; Patai, P., Ed.; Wiley: New York, 1968; pp 45−52. (c) Spialter, L.; Pappalardo, J. A. *The Acyclic Aliphatic Tertiary Amines*; Macmillan Co.: New York, 1985.

(22) THF, EtOH, PhH, and PhMe were ineffective solvents for this reaction.

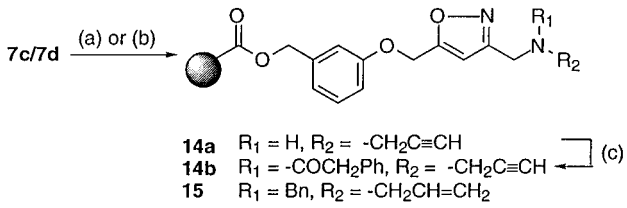
(23) Torrado, A; Imperiali, B. *J. Org. Chem.* **1996**, *61*, 8940−48.

Scheme 4[a]



[a] Reagents: (a) $H_2NCH_2C{\equiv}CH$, THF; (b) $HN(CH_2C{\equiv}CH)_2$, THF; (c) CH_3CH_2COCl, Et_3N, CH_2Cl_2.

Scheme 5[a]



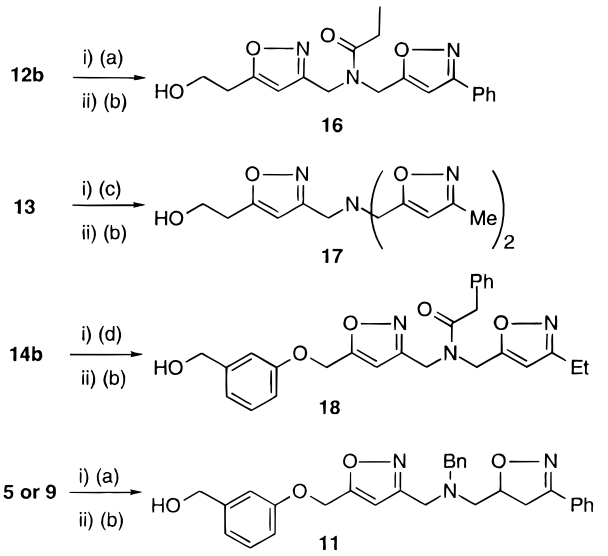
[a] Reagents: (a) $H_2NCH_2C{\equiv}CH$, THF; (b) $BnNHCH_2CH{=}CH_2$, THF; (c) $PhCH_2COCl$, Et_3N, CH_2Cl_2.

is the major product for the polymer-supported reaction or (ii) the microenvironment of the resin provides some additional stabilization for the alkylation which is not realized in solution. We side with the former explanation on the grounds that (i) the S_N2 alkylation is Type II and a toluene-like environment does not assist in this regard, (ii) although generally not intense, the C−Cl stretch in IR is not evident, and (iii) intense absorbances typical of the S═O group are present in the reaction of **6b** or **7b** with MsCl/Et_3N. Alkylation of *N*-benzyl-*N*-allylamine with **7c**/**7d** was difficult to monitor as the C═C offered no strong absorbances with which to track the reaction (Scheme 5). Hence, this reaction was run for 14 h and presumed to be complete. In the case of secondary amine products **12a** and **14a**, the amide was prepared using the corresponding acid chloride in CH_2Cl_2 with Et_3N. Amide formation was rapid (7 h) as was evidenced by the appearance of absorbances at 1663 cm^{-1} and 1655 cm^{-1} for compounds **12b** and **14b**, respectively.

These four alkene or alkyne polymer-bound isoxazoles were then subjected to a second 1,3-dipolar cycloaddition with a "chain-terminating" nitrile oxide (derived from RCH_2NO_2) and subsequently cleaved from the resin with $NaOCH_3$ in THF (Scheme 6). In each case, the overall yields were good to excellent. Diisoxazoles **16** and **18**, each requiring eight synthetic steps beginning from resin **1**, were prepared in 39.4% (89.0% average yield per step) and 20.1% (81.8% average yield per step), respectively. Triisoxazole **17** was obtained in 30.3% overall yield (7 steps, 84.3% average yield) from resin **1**. Figure 2 shows the ^{1}H-NMR spectrum of diisoxazole **16** which, due to the possibility of two amide rotomers, displays two sets of resonance signals. The two rotomers are present in a ratio of 43:57.

At several stages in solid-phase synthesis of **11** (from **3**), we chose to liberate the polymer-bound products and compare the efficiency against the solution-phase chemistry (**5** → **11**). In these comparisons, synthetic efficiencies were based on the starting alkynol **4** (Table 2). The solution-phase approach delivered **11** in 35% overall yield (seven steps) via the bromide intermediate **8f**. When the route incorporating iodide **8e** was used, a 36% yield was realized (eight steps). Application of SPOS to constructing **11** resulted in an overall yield of 43% (seven steps, 88.6% average yield per step). It should be noted that

Scheme 6[a]



[a] Reagents: (a) $PhCH_2NO_2$, PhNCO; (b) $NaOCH_3$, THF; (c) $EtNO_2$, PhNCO; (d) *n*-$PrNO_2$, PhNCO.

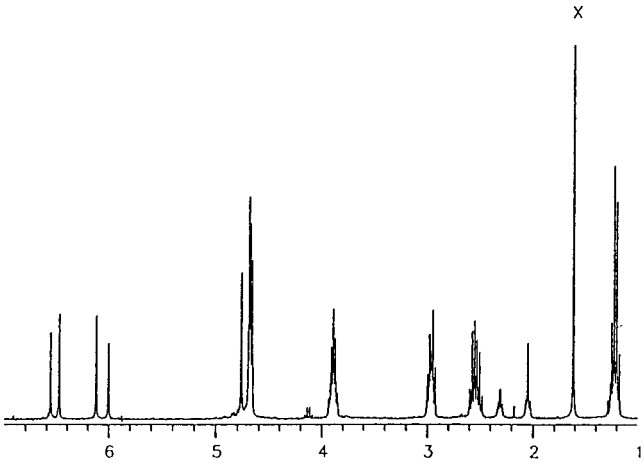
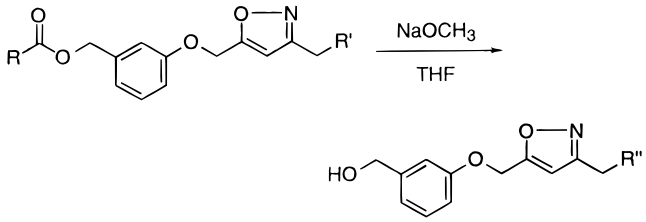


Figure 2. ^{1}H-NMR spectrum (1 to 7 ppm) of **16**.

Table 2. Comparison Between Solution-Phase and Solid-Phase Efficiency



R					yield (%)[a]		no. of
®	Ph	R′	R″	cmpd	polym	soln	steps
7a	**8a**	OTHP	OTHP	**20**	85	66	3
7c/7d	**8c/8d**	OMs/Cl	OCH_3	**21**	54	48	5
15	**9**	N(Bn)(allyl)	N(Bn)(allyl)	**22**	43	40	6[b]
						41	7[c]
19	**10**	N(Bn)(isox)	N(Bn)(isox)	**11**	43	35	7[b]
						36	8[c]

[a] Yields were calculated with the esterification step (i.e. **1** → **3** or benzoylation of **4**) being the first step. [b] This is via bromide **8f**. [c] This is via iodide **8e**.

in the case of liberation of alcohols **22** and **11** that the yield remains the same (i.e. 43%). This does not necessarily imply that the [3 + 2] cycloaddition which generates the polymer-bound isoxazoline **19** is quantitative,

but rather that liberation of the alcohol ($NaOCH_3$/THF) may have varying degrees of efficiency. On the assumption that the transesterification step was efficient, however, then it may be reasonable to project that the isoxazoline formation on the polymer-bound alkene was more efficient than the solution-phase version (i.e. **9** → **10** *vs* **15** → **19**). We believe the solid support accelerated and improved the cycloaddition reactions and avoided chloride formation in the mesylation step.

Experimental Section

General Procedures. Polystyrene/2%-divinylbenzene (200−400 mesh) was purchased from Acros Organics and used as received. Solvents were purified as follows: tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl; methylene chloride (CH_2Cl_2) was distilled from CaH_2; benzene was distilled from potassium. All reactions, unless otherwise stated, were conducted under an inert atmosphere (N_2 or Ar). Infrared spectra were determined on a Galaxy 3000 Series Mattson FTIR. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 and 75 MHz, respectively, and chemical shifts are reported in ppm downfield from internal tetramethylsilane. Thin layer chromatography (TLC) was performed on silica gel plates, and components were visualized by UV light, iodine, or by heating the plates after treatment with a phosphomolybdic acid reagent (1:1 in EtOH). CC, RC, and PC refer to column, radial, and planar chromatography on silica gel, respectively. For CC and RC the eluent indicated refers to the starting mixture of stepwise elution. Elemental analyses were performed at the MidWest Microlab, Indianapolis, IN.

General Procedure for Analysis of Polymer Reaction Progression/Workups. A small sample (10 mg) of polymer was collected, filtered, and washed with THF, THF/H_2O (1:1), CH_2Cl_2, THF, Et_2O (2 × 1 mL each). FTIR spectroscopy was used to analyze the extent of the reaction (KBr). When a reaction was judged complete, it was filtered and washed as described above. The polymer was then dried in a vacuum desiccator overnight.

Polymer-Bound 3-Butynyl Benzoate 2. 3-Butyn-1-ol (5.8 mL, 76.6 mmol) was added to polymer-bound benzoyl chloride[9a] (5.2 g, 2.01 mmol/g) which was swollen in CH_2Cl_2 (150 mL). Triethylamine (2.7 mL, 19.4 mmol) was added, and the reaction was stirred until the IR indicated the reaction was complete (10−12 h). The polymer was filtered, washed, and dried overnight in a vacuum desiccator. FTIR (KBr) 3297 (≡C−H), 1720 (C═O) cm^{-1}.

Polymer-Bound Benzoate 3. Prepared by the same method as **2**. FTIR (KBr) 3291 (≡C−H), 1718 (C═O) cm^{-1}.

3-(2-Propynyloxy)benzenemethanol (4).[24] 3-Hydroxybenzyl alcohol (8.67 g, 70 mmol) was added to aqueous NaOH (150 mL, 1.5 M) producing a homogeneous orange solution. Propargyl bromide (11.0 mL, 74 mmol) was added, and the reaction was stirred for 24 h. The biphasic reaction was extracted with Et_2O (3 × 50 mL), and the combined organics were washed with 1.5 M NaOH (2 × 50 mL) and brine (2 × 75 mL) and dried ($MgSO_4$). Removal of solvent provided an orange oil which, after passing through a short silica column, afforded alkynol **4** as a colorless liquid (10.77 g, 95%). FTIR (thin film) 3356, 3289, 2121 cm^{-1}. ^1H NMR δ 2.51 (t, 1H, J = 2.4 Hz), 2.72 (br s, 1H), 4.60 (d, 2H, J = 4.4 Hz), 4.64 (d, 2H, J = 2.4 Hz), 6.84−6.95 (m, 3H), 7.22 (m, 1H).

General Procedure for [3 + 2] Cycloaddition Reactions on Polymer-Bound Alkynes or Alkenes. The polymer (1−10 g) was swollen in benzene (10−100 mL) along with the nitro compound (1.4−5.0 equiv) and phenyl isocyanate (3.0−10.7 equiv). A catalytic amount of Et_3N was added (5−10 drops from a pipette), and the reaction was stirred at room temperature. Within 20 min, precipitated diphenylurea was observed, and the reaction was then heated at reflux overnight (20−30 h). Samples of the polymer were taken and analyzed by FTIR to determine the progress of the reaction. When the reaction was judged complete, the polymer was filtered and subsequently washed with THF, THF/H_2O, CH_2Cl_2, THF, Et_2O. The polymer was dried in a vacuum desiccator overnight. **6a**: FTIR (KBr) 1718, 1118 cm^{-1}. **7a**: FTIR (KBr) 1718, 1114 cm^{-1}.

Polymer-Bound Isoxazole/Alcohol 6b. Pyridinium *p*-toluenesulfonate (0.84 g, 3.36 mmol) was added to polymer-bound alkyne **6a** (2.65 g, 2.01 mmol/g[14b]) swollen in THF/H_2O (325 mL, 14:1 THF:H_2O). After 12 h the reaction was filtered, washed in the usual manner and dried in a vacuum desiccator. **6b**: FTIR (KBr) 3426, 1720 cm^{-1}.

Polymer-Bound Isoxazole/Alcohol 7b. In similar fashion to **2** → **6b**, **3** delivers **7b**: FTIR (KBr) 3426, 1716 cm^{-1}.

Polymer-Bound Mesylate/Chloride 6c/6d. To a 0 °C suspension of polymer-bound alcohol **6b** (1.79 g, 2.01 mmol/g) in CH_2Cl_2 (175 mL) were added methanesulfonyl chloride (1.35 mL, 17.44 mmol) and triethylamine (2.68 mL, 19.23 mmol). The cold bath was removed, and the reaction was stirred at room temperature for 40 h. The reaction was filtered, washed in the usual manner and dried in a vacuum desiccator. **6c**/**6d**: FTIR (KBr) 1719, 1369 cm^{-1}.

Polymer-Bound Mesylate/Chloride 7c/7d. In similar fashion to **6b** → **6c**/**6d**, **7b** delivers **7c**/**7d**: FTIR (KBr) 1716, 1371 cm^{-1}.

Polymer-Bound Amine 12a. To polymer-bound mesylate/chloride **6c**/**6d** (0.83 g, 2.01 mmol/g) in THF (40 mL) was added propargylamine (1.10 mL, 16.01 mmol). After stirring at room temperature for 14 h, the reaction was filtered, washed in the usual manner, and dried in a vacuum desiccator. FTIR (KBr) 3292, 1717 cm^{-1}.

Polymer-Bound Amine 13. In similar fashion to **6c**/**6d** → **12a**, **6c**/**6d** with dipropargylamine delivers **13**: FTIR (KBr) 3296, 1718 cm^{-1}.

Polymer-Bound Amine 14a. In similar fashion to **6c**/**6d** → **12a**, **7c**/**7d** with propargylamine delivers **14a**: FTIR (KBr) 3295, 1717 cm^{-1}.

Polymer-Bound Amine 15. In similar fashion to **6c**/**6d** → **12a**, **7c**/**7d** with *N*-benzyl-*N*-allylamine delivers **15**: FTIR (KBr) 1717 cm^{-1}.

Polymer-Bound Amide 12b. To a 0 °C suspension of **12a** (0.27 g, 2.01 mmol/g) in CH_2Cl_2 (25 mL) were added propionyl chloride (0.24 mL, 2.76 mmol) and triethylamine (0.40 mL, 2.86 mmol). After stirring 7 h at room temperature, the reaction mixture was filtered, washed in the usual manner, and dried in a vacuum desiccator. FTIR (KBr) 1720, 1663 cm^{-1}.

Polymer-Bound Amide 14b. In similar fashion to **12a** → **12b**, **14a** with phenylacetyl chloride delivers **14b**: FTIR (KBr) 1718, 1655 cm^{-1}.

3-(2-Propynyloxy)benzenemethyl Benzoate (5). To a 0 °C solution of **4** (8.2 g, 50.6 mmol) and benzoyl chloride (7.8 g, 55.5 mmol) in CH_2Cl_2 (100 mL) were added Et_3N (7.73 g, 76.4 mmol) and DMAP (0.31 g, 2.54 mmol). The reaction was stirred for 1.5 h at 0 °C and then poured into crushed ice (150 g). When the ice had melted, the organic layer was removed and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with water and brine (2 × 150 mL each), dried (Na_2SO_4), filtered, and rotoevaporated. CC (10% EtOAc in hexanes) provided 12.5 g of the ester (93%). FTIR (thin film) 3288, 2121, 1720 cm^{-1}. ^1H NMR δ 2.51 (t, 1H, J = 2.5 Hz), 4.70 (d, 2H, J = 2.5 Hz), 5.34 (s, 2H), 6.90−8.25 (m, 9H).

Isoxazole 8a. Alkyne **5** (7.11 g, 26.7 mmol), tetrahydropyranyl-2-nitroethanol (5.19 g, 29.6 mmol), and PhNCO (7.0 mL, 64.4 mmol) in PhH (150 mL) were treated with a catalytic amount of Et_3N (5−10 drops from a pipette). After 15 min a precipitate formed. The reaction was stirred at rt for 12 h and then at reflux for 6 h. The reaction was filtered, washed with benzene, and concentrated. The resulting red oil was purified by CC (15% EtOAc in hexanes) to afford **8a** contaminated with diphenyl urea (73%, yield determined by ^1H NMR). This material was used without further purification. ^1H NMR δ 1.50−1.86 (m, 6H), 3.54 (m, 1H), 3.86 (m, 1H), 4.61 (d, 1H, J = 12.9 Hz),4.72 (t, 1H, J = 3.2 Hz), 4.77 (d, 1H, J = 12.9 Hz), 5.16 (s, 2H), 5.34 (s, 2H), 6.42 (s, 1H), 6.91−8.09 (m, 9H).

(24) Miura, M.; Gabel, D.; Oenbrink, G.; Fairchild, R. *Tetrahedron Lett.* **1990**, *31*, 2247−50.

Alcohol 8b. Dowex 50W-X8 resin (2 g) was added to a solution of **8a** (2.20 g, 5.2 mmol) in CH_3OH (25 mL). After stirring at room temperature for 2 h, the reaction was filtered and concentrated. RC (20% EtOAc in hexanes) gave **8b** as a white solid (1.69 g, 96%). FTIR (KBr) 3431, 1718, 1282, 711 cm^{-1}. ^1H NMR δ 4.74 (s, 2H), 5.16 (s, 2H), 5.33 (s, 2H), 6.40 (s, 1H), 6.90−8.08 (m, 9H). ^{13}C NMR δ 56.96, 61.27, 66.27, 102.24, 114.42, 114.49, 121.46, 128.40, 129.68, 129.87, 129.93, 133.12, 137.91, 157.86, 163.61, 166.37, 168.17.

Chloride 8d. To a 0 °C solution of alcohol **8b** (1.90 g, 5.6 mmol) and methanesulfonyl chloride (1.38 g, 12.0 mmol) in CH_2Cl_2 (40 mL) was added Et_3N (2.20 mL, 15.8 mmol). The reaction was stirred for 12 h at 0 °C and then poured onto crushed ice (100 g) and stirred until the ice had melted. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organics were washed with 2% Na_2CO_3 (1 × 50 mL), water (2 × 50 mL), and brine (2 × 50 mL), and dried (Na_2SO_4). After filtration and rotoevaporation, the material was passed through a short silica plug to provide 1.58 g (79%) of chloride **8d** as a beige solid which was used without further purification. FTIR (KBr) 1716, 1272, 713 cm^{-1}. ^1H NMR δ 4.56 (s, 2H), 5.16 (s, 2H), 5.34 (s, 2H), 6.45 (s, 1H), 6.90−8.05 (m, 9H). ^{13}C NMR δ 35.41, 61.17, 66.19, 103.02, 114.29, 114.41, 121.51, 128.37, 129.64, 129.87, 129.90, 133.09, 137.94, 157.80, 160.88, 166.27, 168.75.

Iodide 8e. Chloride **8d** (296 mg, 0.79 mmol) and NaI (290 mg, 2.04 mmol) were dissolved in acetone (12 mL) and stirred for 12 h at rt. The solvent was removed by rotoevaporation, and the remaining solid was diluted with Et_2O (10 mL) and $NaHSO_3$ (10 mL). The white insoluble solid that remained was collected by filtration and found to be pure **8e** (356 mg, quantitative). Mp 105.0−106.0 °C. FTIR (KBr) 1714, 1705, 1271, 709 cm^{-1}. ^1H NMR δ 4.27 (s, 2H), 5.13 (s, 2H), 5.34 (s, 2H), 6.39 (s, 1H), 6.90−8.10 (m, 9H). ^{13}C NMR δ −10.93, 61.26, 66.24, 103.75, 114.34, 114.46, 121.52, 128.41, 129.69, 129.88, 133.12, 134.83, 137.95, 157.85, 162.00, 166.31, 168.51. Anal. Calcd for $C_{19}H_{16}NO_4I$: C, 50.80; H, 3.59; N, 3.12. Found: C, 50.78; H, 3.55; N, 3.12.

Bromide 8f. Following the procedure of Imperiali,[23] NBS (216 mg, 1.21 mmol) was added in one portion to a 0 °C solution of alcohol **8b** (392 mg, 1.10 mmol) and Ph_3P (431 mg, 1.64 mmol) in CH_2Cl_2 (20 mL). The reaction was stirred at rt for 6 h and then concentrated and subjected directly to CC (30% EtOAc in hexanes). Removal of the solvents afforded **8f** (382 mg, 86%) as a beige solid. Mp 90.5−91.5 °C. FTIR (KBr) 1715, 1705, 1273, 709 cm^{-1}. ^1H NMR δ 4.39 (s, 2H), 5.15 (s, 2H), 5.34 (s, 2H), 6.44 (s, 1H), 6.90−8.09 (m, 9H). ^{13}C NMR δ 20.31, 61.21, 66.21, 103.47, 114.31, 114.42, 121.52, 128.39, 129.66, 129.89, 129.91, 133.10, 137.95, 157.81, 166.15, 167.15, 168.71. Anal. Calcd for $C_{19}H_{16}NO_4Br$: C, 56.73; H, 4.01; N, 3.48. Found: C, 56.37; H, 3.89; N, 3.41.

***N*-(Phenylmethyl)-*N*-(2-Propenyl)amine.** Benzaldehyde (10.7 mL, 10.53) was added to neat allylamine (6.05 g, 10.59 mmol).[25] The exothermic reaction was cooled by means of an ice/water bath (10−20 °C). After 2 h the biphasic reaction was separated and the aqueous portion extracted with CH_2Cl_2 (2 × 10 mL). The combined organic portions were dried (Na_2SO_4), filtered, concentrated, and dissolved in 100 mL of CH_3OH. The solution was cooled to −30 °C and $NaBH_4$ (4.22 g, 111.5 mmol) was added in portions.[26] Once the gas evolution had subsided the reaction was allowed to stir at 0 °C for 1.5 h. The reaction was diluted with CH_2Cl_2 (100 mL), poured onto crushed ice (350 g), and stirred until the ice had melted. The organic layer was removed and the aqueous portion extracted with CH_2Cl_2 (2 × 75 mL). The combined organics were washed with water and brine (2 × 150 each), dried (Na_2SO_4), filtered, and concentrated to give a colorless liquid. Distillation (66.0 °C/2.0 torr) gave the pure secondary amine (14.5 g, 90%). FTIR (thin film) 3313, 1643, 1495, 1453 cm^{-1}. ^1H NMR δ 1.38 (br, 1H), 3.27 (ddd, 2H, J = 1.3, 1.4, 3.1 Hz), 3.78 (s, 2H), 5.15 (m, 2H), 5.93 (m, 1H), 7.21−7.35 (m, 5H). ^{13}C NMR δ 51.57, 53.05, 115.72, 126.70, 127.95, 128.17, 136.64, 140.11.

Tertiary Amine 9. *N*-Benzyl-*N*-allylamine (72 mg, 0.49 mmol) was added to a mixture of iodide **8e** (134 mg, 0.30 mmol) and K_2CO_3 (58 mg) in THF (12 mL) at rt. When the reaction was judged complete (TLC, approximately 12 h) it was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organics were washed with water and brine (2 × 50 mL each), dried (Na_2SO_4), filtered, and rotoevaporated. RC (20% EtOAc in hexanes) provided pure **9** as a colorless, highly viscous oil (116 mg, 83%). Under similar conditions, bromide **8f** provided **9** in 75% yield. FTIR (thin film) 1719, 1601, 1270, 1251, 1110, 713. ^1H NMR δ 3.09 (d, 2H, J = 6.3), 3.59 (s, 2H), 3.65 (s, 2H), 5.13 (s, 2H), 5.26 (m, 2H), 5.33 (s, 2H), 5.86 (ddd, 1H, J = 6.3, 6.3, 13.7 Hz), 6.36 (s, 1H), 6.91−8.08 (m, 14H). ^{13}C NMR δ 48.00, 56.48, 57.60, 61.32, 66.19, 103.48, 114.26, 114.50, 118.07, 121.31, 127.02, 128.22, 128.33, 128.77, 129.62, 129.76, 129.90, 133.02, 135.10, 137.83, 138.54, 157.93, 162.36, 166.23, 167.45.

Isoxazole/Isoxazoline 10. Alkene **9** (205 mg, 0.44 mmol), PhNCO (142 mg, 1.19 mmol), and phenylnitromethane (80 mg, 0.58 mmol) were dissolved in benzene (30 mL). A catalytic amount (5−10 drops from a pipette) of Et_3N was added and within 20 min precipitated diphenylurea was observed. The reaction was stirred at rt for 10−12 h at which time it was refluxed if starting material was still present. The precipitate was filtered and washed with benzene, and the filtrate was concentrated. The yellow oil was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were washed with water and brine (2 × 50 mL each), dried (Na_2SO_4), and rotoevaporated. RC (20% EtOAc in hexanes) affords pure **10** (222 mg, 86%) as a highly viscous oil. FTIR (thin film) 1718, 1450, 1270, 1110 cm^{-1}. ^1H NMR δ 2.77 (d, 2H, J = 5.3 Hz), 3.02 (dd, 1H, J = 7.58, 16.6 Hz), 3.20 (dd, 1H, J = 11.0, 16.6 Hz), 3.69 (s, 2H), 3.81 (s, 2H), 4.83 (m, 1H), 5.08 (s, 2H), 5.31 (s, 2H), 6.31 (s, 1H), 6.90−8.07 (m, 19H). ^{13}C NMR δ 38.23, 49.63, 56.40, 59.19, 61.25, 66.17, 80.19, 103.6, 104.38, 114.21, 114.48, 121.30, 126.55, 127.21, 128.28, 128.33, 128.58, 128.97, 129.47, 129.60, 129.75, 129.93, 133.02, 137.82, 138.44, 156.57, 157.89, 161.97, 166.21, 167.59.

General Procedure for Transesterification of Compounds 8a, 8b, 8c/8d, 9, and 10. A sodium methoxide solution (5−10 equiv, 25 wt % in CH_3OH, Aldrich) was added to the ester (0.1−0.5 mmol) which was dissolved in THF (3 mL). When the reaction was judged complete (TLC, typically 15−45 min) it was quenched with NH_4Cl (2mL), diluted with water (3 mL), and extracted with CH_2Cl_2 (3 × 3 mL). The organics were washed with water and brine (2 × 5 mL each), dried (Na_2SO_4), filtered, and rotoevaporated. RC or PC provided the pure alcohol.

General Procedure for Liberation of Polymer-Bound Compounds. The polymer was swollen in THF for 30 min followed by addition of $NaOCH_3$ (5−10 equiv, 25 wt % in CH_3OH, Aldrich). After stirring at room temperature for 4 h the reaction was quenched with saturated NH_4Cl and allowed to stir for an additional 1.5 h. The resin was removed by filtration and subsequently washed with CH_2Cl_2 and H_2O. The filtrate was extracted with CH_2Cl_2 (4 × 5 mL), washed with brine (2 × 10mL), dried (Na_2SO_4), and filtered, and the solvent was removed. The crude material was then purified by RC or PC.

Isoxazole 20. Transesterification of **8a** provided alcohol **20** as an oil (97%). Similarly, transesterification of **7a** (110 mg, 1.50 mmol/g) provided alcohol **20** (44.8 mg, 85% from **1**). FTIR (thin film) 3428, 1603, 1451, 1259, 1037 cm^{-1}. ^1H NMR δ 1.50−1.86 (m, 6H), 2.63 (br s, 1H), 3.52 (m, 1H), 3.85 (m, 1H), 4.58 (d, 1H, J = 12.9 Hz), 4.63 (s, 2H), 4.69 (t, 1H, J = 3.2 Hz), 4.75 (d, 1H, J = 12.9 Hz), 5.12 (s, 2H), 6.40 (s, 1H), 6.83−7.28 (m, 4H). ^{13}C NMR δ 19.02, 25.15, 30.18, 60.16, 61.13, 62.12, 64.62, 98.23, 102.83, 112.93, 113.71, 120.03, 129.58, 142.94, 157.88, 161.58, 167.99.

Isoxazole 21. Transesterification of **8c**/**8d** provided alcohol **21** as a colorless liquid (93%). Similarly, transesterification of **7c**/**7d** (102 mg, 1.50 mmol/g) provided alcohol **21** (15.4 mg, 54.2% from **1**). FTIR (thin film) 3404, 1258, 1104 cm^{-1}. ^1H

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NMR δ 2.40 (br s, 1H), 3.37 (s, 3H), 4.50 (s, 2H), 4.65 (s, 2H), 5.14 (s, 2H), 6.38 (s, 1H), 6.84−6.98 (m, 3H), 7.24−7.30 (m, 1H). ^{13}C NMR δ 58.51, 61.19, 64.79, 65.58, 102.54, 113.03, 113.82, 120.13, 129.69, 142.89, 157.93, 161.41, 168.24.

Isoxazole 22. Transesterification of **9** affords **22** as a colorless, highly viscous oil (96%). Similarly, transesterification of **15** (147 mg, 1.50 mmol/g) affords **22** (34.5 mg, 42.9% from **1**). FTIR (thin film) 3400, 1450, 1258, 698 cm^{-1}. ^{1}H NMR δ 2.16 (br s, 1H), 3.09 (d, 2H, J = 6.3 Hz), 3.58 (s, 2H), 3.65 (s, 2H), 4.64 (s, 2H), 5.11 (s, 2H), 5.20 (m, 2H), 5.86 (m, 1H), 6.35 (s, 1H), 6.84−7.31 (m, 9H). ^{13}C NMR δ 48.02, 56.50, 57.62, 61.31, 64.80, 103.46, 113.07, 113.88, 118.20, 120.08, 127.07, 128.25, 128.83, 129.66, 135.02, 138.46, 142.87, 157.98, 162.36, 167.67.

Isoxazole/Isoxazoline 11. Transesterification of **10** affords **11** as a colorless, highly viscous oil (97%). Similarly, transesterification of polymer-bound isoxazoline **19** (114 mg, 1.50 mmol/g) also provides alcohol **11** (35.2 mg, 42.5% from **1**). FTIR (thin film) 3405, 1447, 1358, 1258, 692 cm^{-1}. ^{1}H NMR δ 2.08 (br s, 1H), 2.77 (d, 2H, J = 5.3 Hz), 3.01 (dd, 1H, J = 7.6, 16.6 Hz), 3.21 (dd, 1H, J = 10.5, 16.6 Hz), 3.70 (s, 2H), 3.81 (s, 2H), 4.65 (s, 2H), 4.82 (m, 1H), 5.09 (s, 2H), 6.31 (s, 1H), 6.82−7.61 (m, 14H). ^{13}C NMR δ 38.31, 49.69, 56.50, 59.29, 61.27, 64.83, 80.19, 103.62, 113.02, 113.94, 120.09, 126.61, 127.29, 128.34, 128.65, 129.02, 129.43, 129.66, 130.03, 138.47, 142.92, 156.70, 157.92, 162.03, 167.83.

Diisoxazole 16. Transesterification of resin **12b′** (**12b** + PhC≡N$^+$—O$^-$ → **12b′**) (97 mg, 2.01 mmol/g) provided, after PC (70% EtOAc in hexanes), diisoxazole **16** (27.2 mg, 39.4% overall yield from **1**) as a viscous oil. FTIR (thin film) 3419, 3124 (w), 1656, 1602, 1470, 1442, 1212, 1056 cm^{-1}. ^{1}H NMR (two amide rotomers) δ 1.19 (t, 0.43H, J = 7.3 Hz), 1.21 (t, 0.57H, J = 7.3 Hz), 2.04 (t, 0.57H, J = 5.8 Hz, disappears w/D_2O), 2.30 (t, 0.43H, J = 5.8 Hz, disappears w/D_2O), 2.35 (br s, 0.43H), 2.50 (q, 0.43H, J = 7.3 Hz), 2.55 (q, 0.57H, J = 7.3 Hz), 2.94 (t, 0.57H, J = 6.1 Hz), 2.97 (t, 0.43H, J = 5.9 Hz), 3.87 (t, 0.57H, J = 6.1 Hz), 3.89 (t, 0.43H, J = 5.9 Hz), 4.65 (s, 0.43H), 4.67 (s, 0.57H), 4.68 (s, 0.57H), 4.75 (s, 0.43H), 6.00 (s, 0.43H), 6.10 (s, 0.57H), 6.47 (s, 0.57H), 6.54 (s, 0.43H), 7.45 (m, 3), 7.76 (m, 2H). ^{13}C NMR δ (two amide rotomers) 9.13, 9.20, 26.36, 26.45, 26.51, 30.37, 41.14, 41.41, 43.31, 44.10, 59.87, 59.94, 100.93, 101.19, 101.66, 102.02, 126.75, 126.81, 128.31, 128.64, 128.90, 129.00, 130.11, 130.33, 159.85, 160.26, 162.60, 162.72, 167.86, 168.78, 171.34, 171.42, 173.79, 173.96.

Diisoxazole 18. Transesterification of resin **14b′** (**14b** + EtC≡N$^+$—O$^-$ → **14b′**) (106 mg, 1.50 mmol/g) provided, after PC (70% EtOAc in hexanes), diisoxazole **18** (14.8 mg, 20.1% overall yield from **1**) as a viscous oil. FTIR (thin film) 3419, 3128 (w), 1654, 1604, 1455, 1257, 1156, 1042, 1107 cm^{-1}. ^{1}H NMR (two amide rotomers) δ 1.23 (m, 3H), 2.10, (br s, 1H), 2.62 (m, 2H), 3.81 (s, 0.4H), 3.85 (s, 0.6H), 4.53 (s, 1.2H), 4.58 (s, 0.8H), 4.63 (s, 1.2H), 4.64 (s, 0.8H), 4.66 (s, 1.2H), 4.67 (s, 0.8H), 5.09 (s, 2H), 5.81 (s, 0.4H), 5.89 (s, 0.6H), 6.03 (s, 0.4H), 6.32 (s, 0.6H), 6.83−6.99 (m, 3H), 7.20−7.32 (m, 6H). ^{13}C NMR (two amide rotomers) δ 12.48, 12.51, 19.43, 40.67, 40.93, 40.99, 41.24, 43.39, 44.07, 61.13, 61.19, 64.75, 64.80, 64.84, 101.87, 102.53, 102.78, 103.41, 112.75, 112.90, 112.94, 113.96, 120.19, 120.25, 127.15, 127.18, 128.73, 128.84, 128.87, 129.72, 129.76, 133.98, 143.00, 143.13, 157.83, 157.91, 158.41, 158.75, 159.72, 159.99, 165.35, 165.42, 166.53, 167.38, 168.51, 169.28, 171.11, 171.31.

Triisoxazole 17. Transesterification of resin **13′** (**13** + MeC≡N$^+$—O$^-$ → **13′**) (67 mg, 2.01 mmol/g) provided, after PC (60% EtOAc in hexanes), triisoxazole **17** (13.5 mg, 30.3% overall yield from **1**) as a viscous oil. FTIR (thin film) 3400, 3125 (w), 1603, 1419 cm^{-1}. ^{1}H NMR δ 2.29 (s, 6H), 3.01 (t, 2H, J = 6.2), 3.05 (br s, 1H), 3.74 (s, 2H), 3.82 (s, 4H), 3.95 (t, 2H, J = 6.2), 6.10 (s, 2H), 6.18 (s, 1H). ^{13}C NMR δ 11.37, 30.35, 48.64, 48.72, 59.93, 104.46, 104.69, 159.87, 161.11, 168.28, 171.08.

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Supporting Information Available: ^{1}H NMR spectra for compounds **4**, **8a**, **8b**, **8d**, **8e**, **8f**, **9**, **10**, **11**, **16**, **17**, **18**, **20**, **21**, and **22**, ^{13}C NMR spectra for compounds **8b**, **8d**, **8e**, **8f**, **9**, **10**, **11**, **16**, **17**, **18**, **20**, **21**, and **22**, and FT-IR spectra for compounds **8b**, **8e**, **8f**, **9**, **10**, **11**, **16**, **17**, **18**, **20**, **21**, and **22** (40 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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