JOC Article

Polymer-Supported *O*-Alkylisoureas: Useful Reagents for the *O*-Alkylation of Carboxylic Acids

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Received May 5, 2004

Polymer-supported *O*-alkylisoureas were prepared by reaction of an alcohol with a polymer-supported carbodiimide under copper(II) catalysis. These reagents were used to transform carboxylic acids into the corresponding methyl, benzyl, allyl, and *p*-nitrobenzyl esters in a highly chemoselective manner in high yields and in very high purity after simple resin filtration and solvent evaporation. The reactions could be carried out using both conventional or microwave heating, with reaction times as short as 3−5 min in the latter case, without compromising yield, purity, or chemoselectivity. Unfortunately, the corresponding solid-supported *tert*-butyl isoureas could not be prepared.

Introduction

During the past few years, research on the preparation and use of polymer-supported reagents has received renewed interest.[1] The properties of these reagents (facilitated workup, reduced use of conventional purification techniques, ease of application to robotic equipment) make them ideal for the preparation of solution-phase libraries. Additionally, Ley and co-workers have demonstrated that polymer-supported reagents and scavengers can also be successfully employed for the total synthesis of complex natural products.[2] An impressive illustration in this respect was the synthesis of epothilone C, achieved in 29 overall steps (17 steps for the longest linear sequence), and which involved only one purification by flash chromatography, to eliminate an unwanted minor diastereoisomer, in the very last step.[2a] The usefulness of polymer-supported reagents was further illustrated by a successful application in which a library of histone deacetylase inhibitors was synthesized in four to five steps in a fully automated fashion.[3]

Polymer-assisted solution-phase protocols for ester formation are typically illustrated by the use of immobilized scavengers[4] or immobilized catalysts.[5] The use of solid-supported carbodiimides was reported only for the esterification of carboxylic acids with the reactive *N*-hydroxysuccinimide and perfluorophenol.[6] The use of polymer-supported sulfonyl chlorides and sulfonyl-3-nitro-1*H*-1,2,4-triazolide was reported for the esterification of carboxylic acids with alcohols in the presence of a base (*N*-methylimidazole).[7] The use of solid-supported alkylsulfonates as "alkylating resins" was only reported for the synthesis of secondary and tertiary amines, thioethers, and *N*-alkylimidazoles.[8]

It was not until 2001 that the first polymer-supported reagents capable of alkylating a carboxylic acid without requiring any other co-reagent appeared, when Bräse and Rademann independently described the efficient reaction of immobilized triazenes with carboxylic acids to give the corresponding ester products (Scheme 1a).[9] High yields and purities were obtained, and the reaction appeared to be highly chemoselective. These polymer-supported triazenes were initially developed by Bräse as "traceless" linkers for solid-phase organic chemistry (SPOS).[10] The

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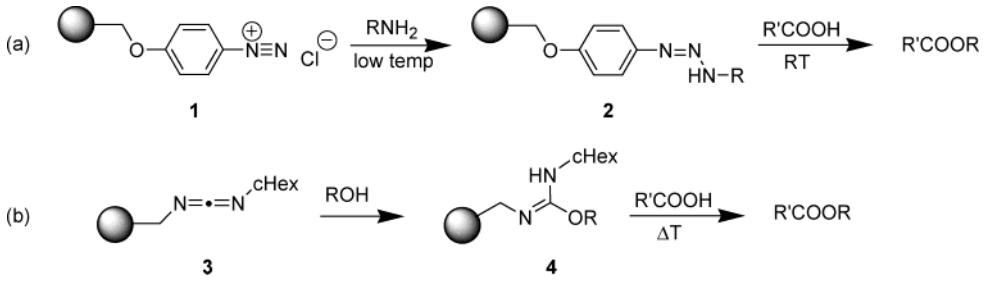
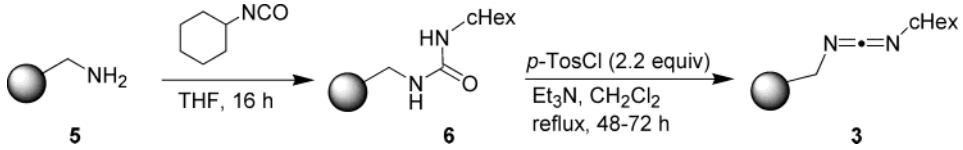
10.1021/jo049239e CCC: $27.50
Published on Web 08/05/2004

SCHEME 1. Solid-Supported Synthesis of Esters by (a) the Method of Bräse and Rademann and (b) Our Isourea-Mediated Method



SCHEME 2. Traditional Synthesis of Polymer-Supported Carbodiimide 3



solid-supported triazenes were synthesized from solid-supported diazonium salt by reaction with a primary amine.

Several triazene resins were prepared (including methyl, *n*-butyl, benzyl, and *tert*-butyl derivatives) starting from the appropriate amines. Although the reactions of most of these reagents with carboxylic acids gave the corresponding esters in high yields, *tert*-butyltriazene resin was not effective for the transformation of carboxylic acids into *tert*-butyl esters. More recently, an improved synthesis of polymer-supported triazenes was reported starting from unfunctionalized polystyrene resin, and the scope of this type of polymer-supported reagents for the esterification of carboxylic acids was further demonstrated.[9c]

Subsequently, we have reported an alternative approach toward esterification reactions using immobilized reagents based on solid-supported *O*-alkylisoureas **4** (Scheme 1b).[11] The isourea resins were synthesized from a solid-supported carbodiimide (Scheme 1b) by reaction with an alcohol. Subsequent reaction with a carboxylic acid gave the corresponding methyl, allyl, and benzyl esters in high yields and purities, and the process also displayed excellent chemoselectivity.

Both approaches displayed in Scheme 1 have the advantage that the alkylating resins **2** and **4** can be purified by washing before the carboxylic acid is added.

We report here a full account of the synthesis, optimization, and characterization of solid-supported isoureas (*O*-methyl, *O*-allyl, *O*-benzyl, *O*-*p*-nitrobenzyl, and *O*-2-(trimethylsilyl)ethyl) and their reaction with carboxylic acids, with both steps investigated under conventional thermal heating and under microwave heating conditions. A scavenging protocol is developed for potential parallel synthesis applications. We also report on an optimized procedure for the synthesis of polymer-supported carbodiimide **3**.

Results and Discussion

Synthesis of Polymer-Supported Carbodiimide 3. The synthesis of the polymer-supported *O*-alkylisourea reagents was achieved in one step from polymer-supported carbodiimide **3**. Though **3** is commercially available, and as such was successfully used for our purposes, in-house prepared solid-supported carbodiimide was mostly employed, as it could be easily obtained from the cheaper aminomethylpolystyrene resin **5**. In addition, it was noted that esterification reactions with polymer-supported isourea reagents derived from in-house prepared carbodiimide resin tended to give rise to products of higher purity, which was attributed to different gradations of impurity leaching.

The preparation of **3** (Scheme 2) has been described in the literature.[12] Aminomethylpolystyrene **5** was reacted with cyclohexyl isocyanate to form the resin-bound urea derivative **6**, which was subsequently converted to the corresponding carbodiimide **3**. On an industrial scale, the dehydration reaction is executed by using *p*-toluenesulfonyl chloride and triethylamine. However, as it was suspected that this particular method was associated with the generation of impurities, other dehydration methods were investigated.

Many methods are known for the dehydration of ureas to give carbodiimides (in the solution phase).[13] Surprisingly, many of these dehydration methods failed to achieve carbodiimide formation on the solid-support (Table 1). Good results were obtained with $Ph_3P{\cdot}Br_2$ and excess base, though the reaction was found not to be reproducible.

While these studies were in progress, the successful conversion of polymer-supported ureas to carbodiimides using dehydrating reagents such as the Burgess reagent

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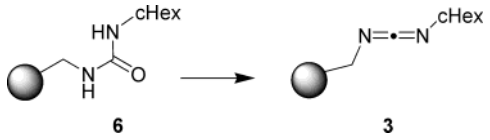
TABLE 1. Dehydration of Polymer-Supported Urea 6



6 3

dehydrating agent	base	carbodiimide formation
$SOCl_2$	Et_3N	no
$SOCl_2$	DBU	no
PBr_3	Et_3N	no
PBr_3	DBU	no
$(PhO)P(O)Cl_2$	Et_3N	no
$Ph_3P.Br_2$	Et_3N	yes
$CBr_4 + Ph_3P$	Et_3N	yes

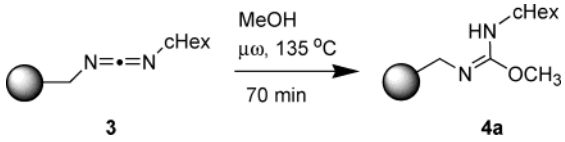
or with $CBr_4/Ph_3P/Et_3N$ was reported.[14] Though it was concluded that the best results were observed with the Burgess reagent, we decided against using this method as its cost was too high for large-scale preparations. Because no experimental details were provided (reagent equivalents, reaction times), it was decided to reinvestigate the CBr_4-mediated method, and it was found that the dehydration was successfully accomplished using 3 equiv of CBr_4 and Ph_3P and 9 equiv of Et_3N overnight in CH_2Cl_2.

It should be noted that repeated resin washings were required to remove all of the triphenylphosphine oxide byproduct.

Synthesis of the Polymer-Supported *O*-Alkylisoureas. Following the established procedure for the synthesis of *O*-alkylisoureas from carbodiimides and alcohols under CuCl catalysis,[15] the synthesis of the polymer-supported *O*-methylisourea was initially attempted in a similar fashion. However, these initial experiments were not successful, and it was decided to investigate a method, already described in 1899,[16] where *O*-alkylisoureas could be formed simply by heating a mixture of neat carbodiimide and an alcohol. Applied to the formation of polymer-supported *O*-methylisourea, this would require heating resin **3** in methanol as solvent. This was a major obstacle in transferring this method for our purposes, given the well-known inability of methanol to swell polystyrene-type resins without which no reaction could be expected within the beads. However, the polarity of a solvent decreases significantly at high temperature, and it was indeed demonstrated that methanol could be used as solvent for polystyrene-based solid-phase chemistry employing microwave induced heating.[17] In the event, it was found that heating resin **3** for 70 min at 135 °C under microwave irradiation (Scheme 3) resulted in complete conversion of the carbodiimide to *O*-methylisourea. The transformation was easily monitored by IR (Figure 1) through the disappearance of the carbodiimide band at 2117 cm^{-1} and the development of two characteristic isourea bands at 1663 and 1332 cm^{-1}. Purification of the obtained resin was easily achieved by filtration and two CH_2Cl_2 wash cycles.

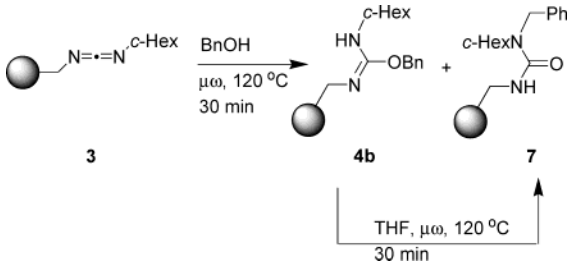
However, when resin **3** was heated with benzyl alcohol, the limitations of this preparation method became apparent. Although the carbodiimide band disappeared from the IR spectrum and the isourea band became visible, two strong bands were also present at 1640 and 1555 cm^{-1}, indicating the presence of a urea group. When the resin thus obtained was resubmitted to further heating in the absence of benzyl alcohol using THF as solvent, an increase of the urea bands at the expense of the isourea band was observed. Though this experiment indicated that a transformation of the *O*-benzylisourea to an immobilized urea species as shown in Scheme 4 was occurring, we did not observe a similar process when heating *N*,*N*′-diisopropyl-*O*-benzylisourea in a homogeneous solution in THF under otherwise identical conditions. The structure of **7** is suggested solely based on IR analysis.

SCHEME 3. Microwave-Assisted Synthesis of Polymer-Supported *O*-Methylisourea 4a



3 4a

SCHEME 4. Attempted Microwave-Assisted Synthesis of Polymer-Supported *O*-Benzylisourea 4b and Thermal-Induced Conversion of 4b to 7



3 4b 7

Hence, the formation of the solid-supported isourea reagent was reinvestigated under copper catalysis, with the aim of developing conditions at room temperature. Using copper(II) triflate as Lewis acid (50 mol %), which has a higher solubility compared to CuCl in organic solvents, stirring resin **3** in a 1:1 mixture of MeOH/THF overnight led to the formation of a resin whose IR did not show any carbodiimide band. However, the IR of the resin did not match that of **4a** previously prepared, nor was the resin efficient in effecting ester formation. The green color of the resin beads was indicative of the presence of significant quantities of copper catalyst still attached to the resin, which was confirmed by the fact that addition of the resin to a carboxylic acid solution resulted in a pale blue color. At this point we searched for a more effective procedure to remove the copper species from the resin. Simple solvent washings did not have any effect, nor washing with various primary/tertiary amines. However, when a solution of tetramethyl ethylenediamine (TMEDA) in CH_2Cl_2 was used, the mixture immediately became dark blue (Figure 2), evidencing formation of a Cu(II)−TMEDA complex.

After three washes, the diamine solution remained colorless (Figure 2), indicating that all copper species had been removed, and subsequent washings to remove any traces of TMEDA followed by drying gave a resin whose IR spectrum was identical to the authentic sample.

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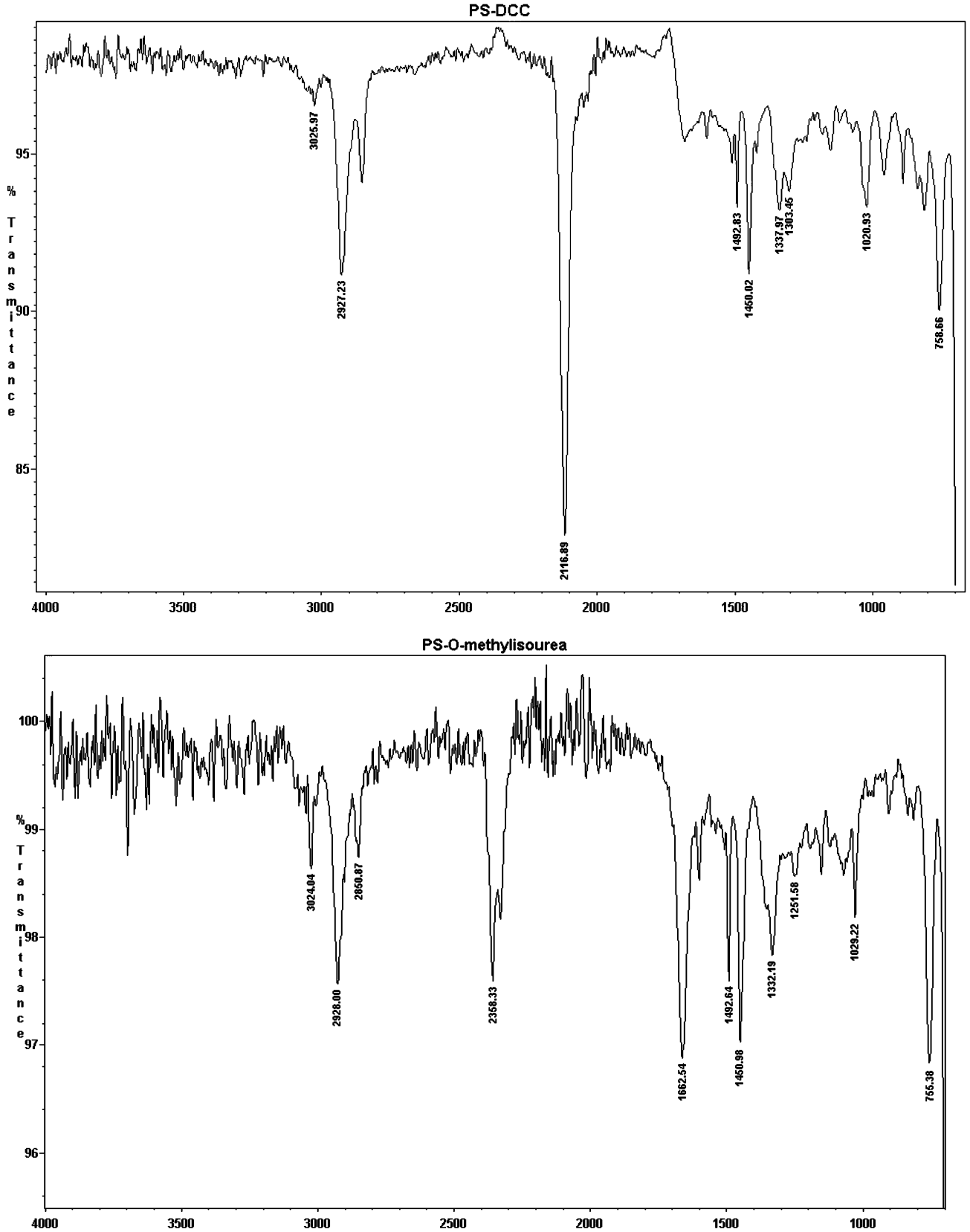


FIGURE 1. IR spectra of carbodiimide resin **3** (top) and isourea resin **4a** (bottom).

Although CuCl could be used to efficiently catalyze the isourea formation on solid-support instead of $Cu(OTf)_2$, the TMEDA-based washing procedure in this case failed to remove all the copper species from the resin.

With a suitable washing process established, we next optimized the reaction process. In the event, using only 7 mol % of $Cu(OTf)_2$ allowed the isourea transformation to be complete in 16 h at room temperature (Scheme 5).

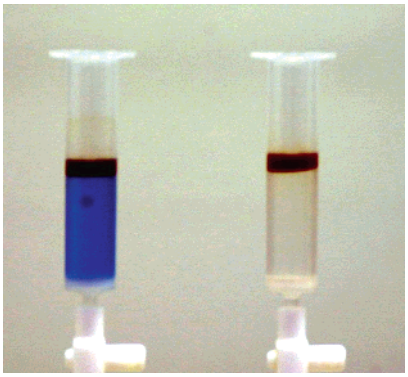
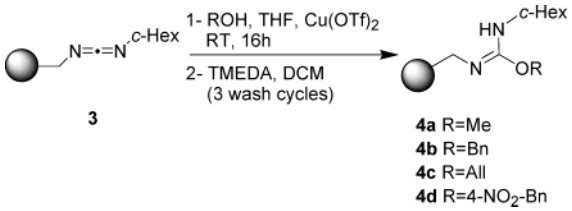
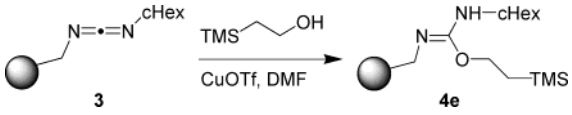


FIGURE 2. Effect of resin washing with TMEDA solutions in CH_2Cl_2: (left) first washing; (right) third washing. The resin is floating on top of the solvent.

SCHEME 5. Synthesis of Polymer-Supported *O*-Alkylisourea Catalyzed by Copper(II) Triflate



SCHEME 6. Synthesis of Polymer-Supported *O*-(Trimethylsilyl)ethylisourea Using Copper(I) Catalysis

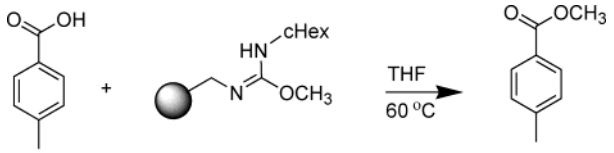


Using these low levels of catalyst, the IR spectra of the resin before washing with TMEDA revealed clear isourea bands, together with the peaks attributed to the isourea-copper complex. It appeared that TMEDA washings were still required to completely remove all copper species. This process was successfully applied for the preparation of the *O*-benzyl, *O*-allyl, *O*-4-nitrobenzyl (PNB) isoureas **4b**−**d**, as well as for *O*-methyl isourea **4a**. No urea band was visible for any of these isourea resins. Importantly, the preparation of the resins could now be carried out on large scale.

This procedure failed to form the corresponding 2-trimethylsilylethyl derivative **4e** (Scheme 6), where strong urea bands in the IR spectrum of the resulting resin were observed. MAS ^{1}H NMR and gel-phase ^{13}C NMR analysis evidenced almost complete absence of the TMS and of the ethyl groups. A possible explanation involves an E1 elimination catalyzed by the Lewis acid, which would be facilitated by the presence of the TMS group, forming ethylene and polymer-bound *N*-trimethylsilylurea. The resulting silicon−nitrogen bond could have been easily hydrolyzed during the subsequent resin washes. In the event, employing the milder Cu(I) triflate as catalyst gave satisfactory results for the preparation of **4e**.

Unfortunately, the solid-supported *tert*-butyl isourea could not be obtained using this process. Under all conditions tested, IR spectra displayed only urea bands and/or carbodiimide bands, and an isourea band was never observed when analyzed after various reaction times, which strongly indicated that immobilized *tert*-butyl isourea instantly decomposes. This observation was not expected, as it is possible to synthesize the corresponding *N*,*N*′-diisopropyl-*O*-*tert*-butyl isourea in the solution phase.

TABLE 2. Optimization of the Esterification Reaction



entry	*T* (°C)	time	equiv of **4a**	conversion
1	reflux	16 h	3	complete
2	rt	3 d	3	incomplete
3	reflux	16 h	1.2	incomplete
4	reflux	16 h	1.5	incomplete
5	reflux	16 h	1.8	incomplete
6	reflux	10 h	2	complete

Alkylation of Carboxylic Acids Using Polymer-Supported *O*-Alkylisoureas 4a−e. With a satisfactory large-scale procedure for the different polymer-supported *O*-alkylisoureas in hand, their reactivity toward carboxylic acids was investigated. As a model reaction, the conversion of 4-methylbenzoic acid **8** to the corresponding methyl ester **9** was chosen (Table 2). When **8** was treated with 3 equiv of **4a** in refluxing THF, complete conversion was achieved after overnight reaction. Importantly, a simple filtration followed by two resin washes with methanol and CH_2Cl_2 and finally evaporation of the solvents afforded very pure product as judged by NMR analysis. Further optimization was attempted with respect to reaction time, temperature and amount of resin. All experiments were conducted in THF as it represented a good compromise between ability to swell the resin, ability to solubilize carboxylic acid substrates and ease of removal after reaction.

The studies showed that the best conditions comprise refluxing in THF for 10 h with 2 equiv of resin. Nevertheless, to allow for slight differences of reactivity for different acids, in all further experiments 2 equiv of resin was used and the reactions were allowed to run for 16 h.

The full range of carboxylic acid substrates that were used in our investigations is displayed in Figure 3, and the results of the esterification reactions using the solid-supported isoureas are shown in Table 3. All reactions were worked-up as described above.

Simple carboxylic acids (entries 1−10) were alkylated in good yields and excellent purities using the immobilized isoureas **4a**−**d**. However, long-chain aliphatic acids (entries 9−10), while also yielding pure esters in high yield, required much longer reaction times. Presumably, this observation was due to increased hydrophobic interactions with the polystyrene-based resin, slowing down diffusion rates. In agreement with the corresponding reactions with *N*,*N*′-diisopropyl-*O*-alkylisoureas in homogeneous reaction media,[15] the esterifications using the polymer-supported version exhibited excellent chemoselectivity, even for the more reactive benzyl/allyl isoureas. Hence, mandelic acid (entries 11 and 12) and Boc-protected serine (entries 25−27) were cleanly alkylated

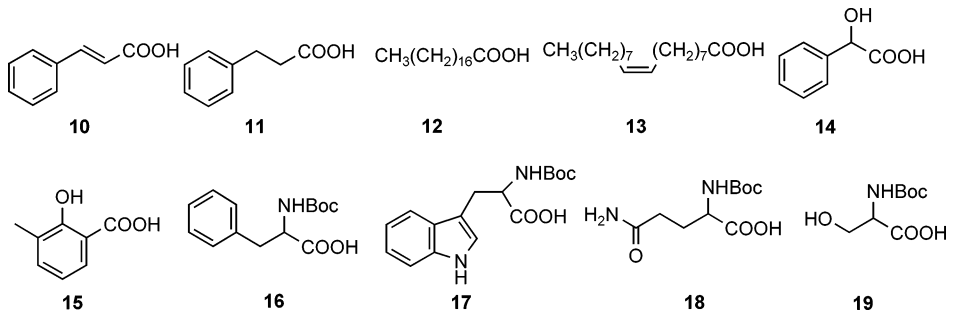
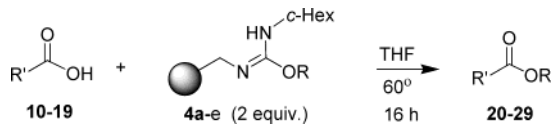


FIGURE 3. Substrates for the esterification reaction experiments.

TABLE 3. *O*-Alkylation of Carboxylic Acids Using Resins 4a−d



entry	acid	R	time (h)	ester	yield[a] (%) (purity (%))[b]
1	**10**	Me	16	**20a**	81 (>98)
2	**10**	Bn	16	**20b**	96 (>95)
3	**10**	All	16	**20c**	82 (>95)
4	**10**	PNB[c]	16	**20d**	94 (>95)
5	**11**	Me	16	**21a**	94 (>98)
6	**11**	Bn	16	**21b**	99 (>95)
7	**11**	All	16	**21c**	85 (>95)
8	**11**	PNB[c]	16	**21d**	94 (>95)
9	**12**	Me	40	**22a**	91 (>98)
10	**13**	Me	40	**23a**	88 (>98)
11	**14**	Me	16	**24a**	90 (>98)
12	**14**	PNB[c]	16	**24d**	92 (>95)
13	**15**	Me	16	**25a**	78 (93)
14	**15**	Bn	16	**25b**	96 (>95)
15	**15**	All	16	**25c**	90 (>95)
16	**15**	PNB[c]	16	**25d**	99 (>95)
17	**16**	Me	16	**26a**	74 (>98)
18	**17**	Me	16	**27a**	81 (>98)
19	**17**	Bn	16	**27b**	97 (>95)
20	**17**	All	16	**27c**	93 (>95)
21	**17**	PNB[c]	16	**27d**	98 (>95)
22	**18**	Me	16	**28a**	82 (>98)
23	**18**	Bn	16	**28b**	98 (>95)
24	**18**	All	16	**28c**	94 (>95)
25	**19**	Bn	16	**29b**	99 (>95)
26	**19**	All	16	**29c**	98 (>95)
27	**19**	PNB[c]	16	**29d**	99 (>95)

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] PNB = *p*-nitrobenzyl.

to give the corresponding ester with no detectable ether formation. When phenolic groups were present (entries 13−16), a small amount of dialkylation was observed when treated with *O*-methylisourea resin **4a** (entry 13), though the selectivity remained acceptable, and only about 3.5% of dialkylated product was formed (^{1}H NMR). Perhaps surprisingly, reaction of 3-methylsalicyclic acid **15** with the more reactive benzyl and allyl isoureas did not give the corresponding ether byproducts (entries 14−16). Boc-protected amino acids (entries 17−24) could also be cleanly transformed into the corresponding amino esters using all the isourea reagents. In contrast, the esterification was not successful with Fmoc-protected amino acids. When Fmoc-glycine was employed, no corresponding methyl ester could be observed. As dibenzofulvene was isolated from the reaction mixture, it was evident that isoureas were too basic for the Fmoc group to survive. Amides were also untouched with Boc-protected glutamine cleanly converted into the corresponding esters (entries 22−24).

Very importantly, all products were obtained in very good purity, as judged by ^{1}H and ^{13}C NMR after removal of the resin by filtration and evaporation of the reaction/wash solvents. A typical result is reproduced in Figure 4. The purity of the methyl esters was generally slightly higher than that of the other esters, which was attributed to the different preparation between the *O*-methyl isourea resin (135 °C) and the other resins (at room temperature). The high temperature presumably caused release of the resin impurities at that stage, which were then removed by washing the resin with CH_2Cl_2 to remove the traces of methanol (see above).

A concern for the reactions with the benzylic isoureas was that the isomerization to the corresponding urea as observed during their thermal preparation (see Scheme 4) could interfere with the ester formation reactions at the employed temperature. However, the excellent yields that were observed prove that the ester formation is a faster process.

For application in parallel synthesis, the methodology employed ideally should lead to high compound purity, regardless of the reactivity of the starting materials. Though most of the compounds in Table 3 indeed were obtained in high purity, the fatty acids proved to be slow reacting. To overcome such inherent reactivity differences, should an automated setup be employed using a set reaction time, a scavenging procedure[18] for this process using aminomethyl polystyrene was developed (Scheme 7).

Treatment of oleic acid **13** with isourea resin **4a** under typical conditions (16 h) gave a mixture of 70% ester and 30% unreacted oleic acid. When, after reaction, 4.5 equiv of basic scavenging resin was added, followed by a filtration and solvent evaporation step, a product of >98% purity was obtained.

Unfortunately, the reactions using the 2-trimethylsilyl isourea resin **4e** were not as successful. Even when up to 4 equiv of the resin was used for 4 days at 60 °C, low conversions (ca. 60%) were obtained. Most unsatisfactorily, the purity was very low even after employing the basic scavenging protocol described above. Surprisingly, a reaction at room temperature led to a higher conversion, but nevertheless gave a lower product purity.

(18) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874−4881.

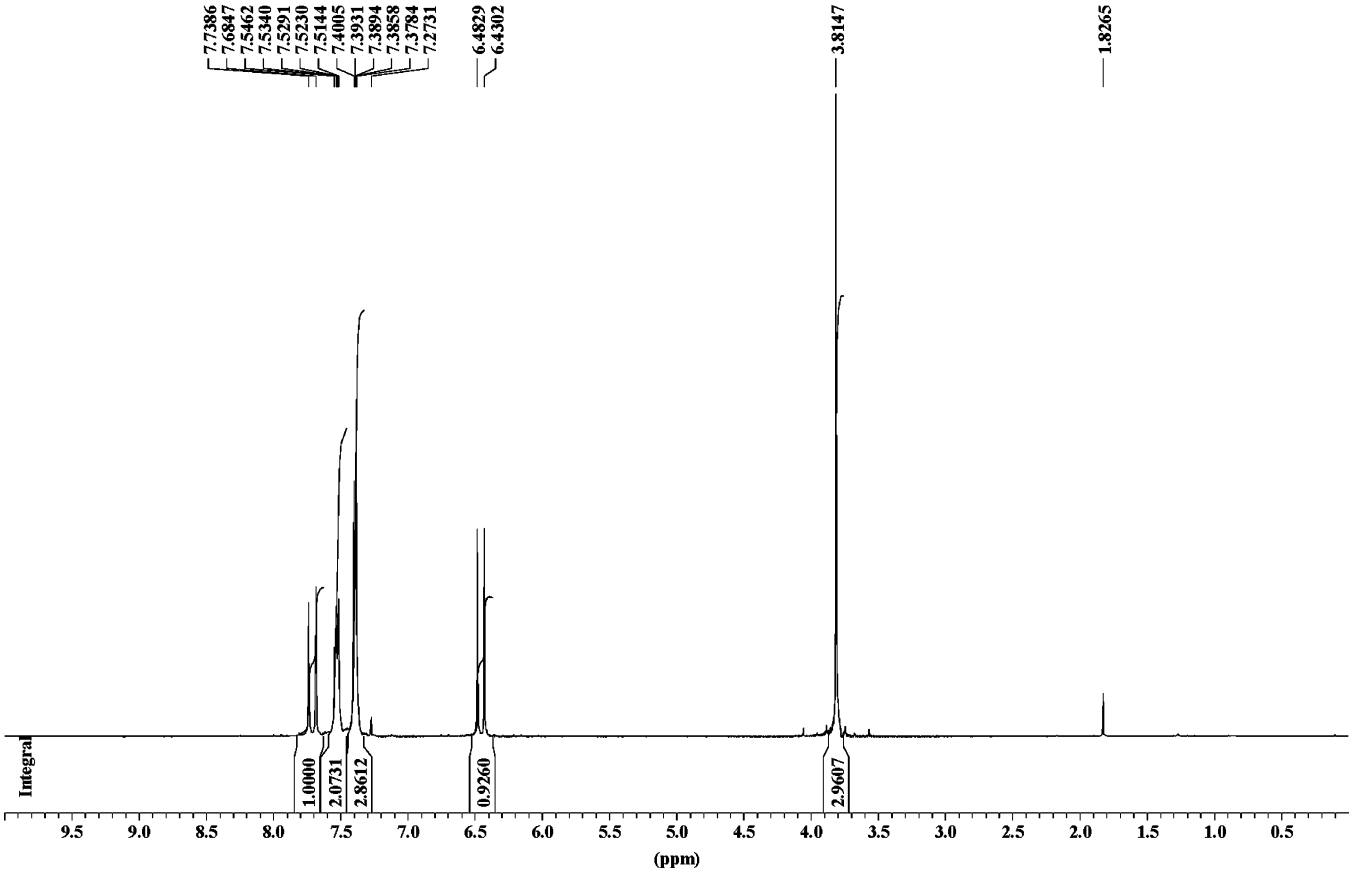
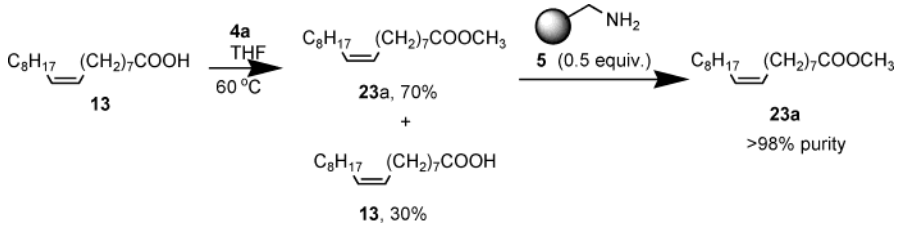


FIGURE 4. ^{1}H NMR spectrum of crude ester **20a**.

SCHEME 7. Use of a Basic Scavenger To Remove Unreacted Acid for Library Generation

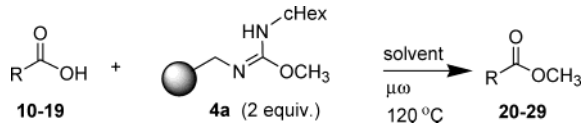


Considering the sensitivity of this resin toward elimination reactions (see above), it is perhaps not entirely surprising that complete conversions of the carboxylic acid into the TMS-ethyl ester could not be achieved, as elimination of the polymer-supported isourea to give ethylene would become increasingly competitive as the acid concentration decreases toward the end of the reaction.

Microwave-Assisted Esterification Reactions. Although the high yields and purities that were obtained should make the above-described methodology attractive for general use, the drawback is the long reaction time required for complete conversion. As we have demonstrated that the reaction between carboxylic acids and *N*,*N*′-diisopropyl-*O*-alkylisoureas is greatly accelerated when employing much higher temperatures under microwave irradiation,[11b] the use of this heating technique in conjunction with the isourea based resins was investigated.[19] Following the experiments described in the previous section, THF was initially used as solvent, for which a maximum temperature of 120 °C could be obtained in the microwave oven. However, more than 5 min was necessary to reach the maximum temperature (a time which is included in the overall heating time). Hence, it was decided to switch to acetonitrile which, having a larger tan δ value, is more efficient in converting microwave irradiation to heat[19c] and is also a good solvent for carboxylic acids. A temperature of 130 °C could be reached within 1 min. A comparison between the two conditions was made for solid-supported *O*-methylisourea reactions (Table 4). All reactions in THF were complete in 15 min, except for 3-phenylpropionic acid (entry 3) and for oleic acid (entry 5), which required 20 min reaction time and a slightly higher excess of resin. In contrast, reactions in acetonitrile were complete in merely 5 min, with the sole exception of oleic acid (8 min). Under the high-temperature conditions used, no significant degra-

(19) Reviews on microwave-assisted reactions: (a) Swamy, K. M. K.; Yeh, W.; Lin, M.; Sun, C. *Curr. Med. Chem.* **2003**, *10*, 2403−2423. (b) Blackwell, H. E. *Org. Biol. Chem.* **2003**, *1*, 1251−1255. (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

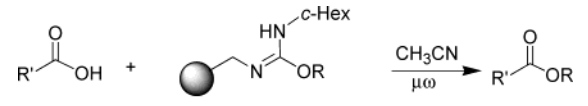
TABLE 4. Synthesis of Methyl Esters Using Resin 4a under Microwave Irradiation



entry	acid	solvent	time (min)	ester	yield[a] (%) (purity (%))[b]
1	**10**	THF	15	**20a**	86 (>98)
2	**10**	CH_3CN	5	**20a**	90 (>98)
3	**11**	THF	20	**21a**	79 (98)
4	**11**	CH_3CN	5	**21a**	83 (>98)
5	**13**	THF	20	**23a**	85 (>98)
6	**13**	CH_3CN	5	**23a**	96 (>98)
7	**14**	THF	15	**24a**	84 (>98)
8	**14**	CH_3CN	5	**24a**	76 (>98)
9	**15**	THF	15	**25a**	75 (98)
10	**15**	CH_3CN	5	**25a**	78 (89)
11	**16**	THF	15	**26a**	82 (>98)
12	**17**	THF	15	**27a**	92 (>98)
13	**17**	CH_3CN	5	**27a**	94 (>98)
14	**18**	THF	15	**28a**	75 (>98)

[a] Isolated yield. [b] Determined by ^1H NMR.

TABLE 5. Synthesis of Esters Using Resins 4a−d under Microwave Irradiation in Acetonitrile



entry	acid	R	*T* (°C)	time (min)	ester	yield[a] (%)
1	**10**	Bn	125	3	**20b**	96
2	**10**	PNB	130	5	**20d**	89
3	**14**	PNB	130	5	**24d**	98
4	**15**	Bn	125	3	**25b**	93
5	**15**	PNB	130	5	**25d**	97
6	**17**	Bn	125	3	**27b**	89
7	**17**	All	125	3	**27c**	93
8	**18**	All	125	3	**28c**	91
9	**19**	All	125	3	**29c**	94
10	**19**	PNB	130	5	**29d**	88

[a] Isolated yields. All products had >95% purity (NMR).

dation of the resin was observed. The chemoselectivity remained as excellent as in the experiments using conventional heating, and all products exhibited very high purities as evidenced from the NMR spectra (see the Supporting Information). The only instance in which the use of acetonitrile instead of THF proved to be detrimental to the purity of the product was when an acid bearing a phenolic group was employed (entries 9 vs 10): in this case, a higher level of dialkylation was observed in the reaction for which acetonitrile was used as solvent.

Nevertheless, acetonitrile was clearly a superior solvent than THF, and hence, it was used subsequently for the investigations using the other immobilized isoureas (Table 5). For the more reactive *O*-benzyl and *O*-allyl isoureas, all reactions were complete in just 3 min, while for the *p*-nitrobenzylisourea derivative 5 min at 130 °C were required. In contrast with the *O*-methylisourea resin, the reaction of 3-methylsalicylic acid led to the corresponding benzyl and PNB esters (entries 4 and 5) in very high purity, with very low levels of dialkylation. The results indicate that even at this temperature the possible isomerization to the urea products, as observed when using microwave irradiation (at similar temperatures) for the synthesis of solid-supported *O*-benzylisourea, is a slower process than the ester formation. In contrast, the negative results obtained with *O*-(trimethylsilylethyl)isourea resin in THF at 60 °C overnight were confirmed under microwave irradiation conditions. Only traces of the esterification products could be detected, signifying that in this case the elimination reaction is more favorable at these high temperatures.

Conclusions

We have demonstrated that it is possible to prepare a range of polymer-supported *O*-alkylisoureas in an easy, scalable manner from commercially available resins. Of the examples investigated, the only exception was the *tert*-butyl derivative, which proved to be too unstable and was never isolated. Polymer-supported *O*-methyl, *O*-benzyl, *O*-allyl, and *O*-*p*-nitrobenzyl isourea reagents efficiently convert carboxylic acids into esters in high yields and with excellent purities and chemoselectivities. Apart from resin filtration and solvent evaporation no further workup/purification is necessary. A scavenger protocol has also been developed to ensure that only products with high purities are obtained when less reactive substrates are employed. The potential of microwave-assisted chemistry for the use of the polymer-supported isoureas has also been demonstrated, leading to drastically reduced reaction times. The combination of the short reaction times achievable under microwave irradiation with the extremely simple workup procedure granted by the polymer-supported reagents is particularly advantageous, with the total time required to obtain the final product amounting to less than 1 h. Hence, the reported method should be attractive for both synthetic organic as well as for combinatorial synthesis applications.

Experimental Section

Synthesis of *N*-Cyclohexyl-*N*′-methylpolystyrene Urea 6. Aminomethyl polystyrene (5.00 g, 16 mmol) was swollen in anhydrous THF (40 mL) in a round-bottomed flask. Cyclohexyl isocyanate (10 mL, 80 mmol) was added in one portion under stirring. Gentle stirring was continued overnight, and then the reaction mixture was heated at reflux for 6 h. The resin was collected by filtration, washed with CH_2Cl_2, DMF, MeOH, and CH_2Cl_2, and dried overnight in a vacuum oven at 40 °C to give the title compound (6.85 g).

IR (neat): $\nu_{max}/(cm^{-1})$ 1627 (s), 1552 (s). ^{13}C NMR (75.47 MHz; $CDCl_3$) δ_C: 158.0; 48.8; 40.4; 33.8; 24.9.

Synthesis of *N*-Cyclohexyl-*N*′-methylpolystyrene Carbodiimide 3. *N*-Cyclohexyl-*N*′-methylpolystyrene urea **6** (2.00 g, 4.6 mmol) was swollen in CH_2Cl_2 (30 mL), and triphenylphosphine (3.46 g, 13.2 mmol) was added. The mixture was stirred for 10 min to allow complete dissolution of the triphenylphosphine, upon which CBr_4 (4.40 g, 13.2 mmol) was added, immediately followed by dropwise addition of Et_3N (6.0 mL, 43 mmol). The dark reaction mixture was gently stirred overnight, and then the resin was collected by filtration, washed with CH_2Cl_2, DMF, and CH_2Cl_2, and dried overnight in a vacuum-oven at 40 °C to give the title compound (1.82 g).

IR (neat): ν_{max}/(cm^{-1}) 2117 (s). ^{13}C NMR (75.47 MHz; $CDCl_3$) δ_C: 145.1; 55.6; 50.5; 34.8; 25.5; 24.5.

Synthesis of *O*-Methyl-*N*-cyclohexyl-*N′*-methylpolystyrene Isourea 4a under Microwave Irradiation. *N*-Cyclohexyl-*N′*-methylpolystyrenecarbodiimide **3** (500 mg, 0.900 mmol) was placed in a microwave vial. The vial was capped, and anhydrous methanol (3 mL) was added under nitrogen via a syringe. The vial was then heated under microwave irradiation at 135 °C for 70 min (internal pressure 9 bar). The resin was then collected by filtration, washed with CH_2Cl_2, and dried overnight in a vacuum oven at 40 °C to give the title compound (490 mg).

4a: IR(neat): ν_{max}/(cm^{-1}) 1655 (s); 1329 (s). ^{13}C NMR (75.47 MHz; $CDCl_3$) δ_C: 154.3; 53.0; 50.1; 34.2; 25.4; 24.8.

General Procedure for the Synthesis of *O*-Alkyl-*N*-cyclohexyl-*N′*-methylpolystyrene Isoureas 4a−d under Cu(OTf)$_2$ Catalysis. Polymer-supported carbodiimide **3** (2.00 g, 3.60 mmol) and $Cu(OTf)_2$ (50 mg, 0.14 mmol) were suspended in a mixture of anhydrous THF (6 mL) and the appropriate alcohol (15−99 mmol). The mixture was gently stirred at room temperature for 16 h, and then the resin was collected by filtration and washed with a 10% solution of TMEDA in CH_2Cl_2 until the washing solution remained colorless and then with DMF, MeOH, and CH_2Cl_2. The resin was dried at 40 °C under vacuum for 24 h to afford the title compound.

4b: IR(neat): ν_{max}/(cm^{-1}) 1656 (s), 1321 (s). ^{13}C NMR (75.47 MHz; $CDCl_3$) δ_C: 67.0; 55.6; 50.3; 34.8; 25.5; 24.5.

4c: IR (neat): ν_{max}/(cm^{-1}) 1656 (s), 1316 (s). ^{13}C NMR (75.47 MHz; $CDCl_3$) δ_C: 133.7; 115.9; 65.7; 55.4; 49.9; 34.5; 34.0; 25.2; 24.3.

4d: IR (neat): ν_{max}/(cm^{-1}) 1664 (s), 1340 (s), 1319 (s). ^{13}C NMR (75.47 MHz; $CDCl_3$) δ_C: 145.6; 123.2; 65.2; 50.1; 34.0; 24.5.

Synthesis of *O*-(2-Trimethylsilylethyl)-*N*-cyclohexyl-*N′*-methylpolystyrene Isourea 4e. Polymer-supported carbodiimide **3** (1.00 g, 1.80 mmol), 2-trimethylsilylethanol (2.00 mL, 14 mmol), and copper(I) triflate−toluene complex (2:1) (20 mg, 0.077 mmol) were suspended in DMF (10 mL). Stirring was continued overnight, and then the resin was collected by filtration, washed with a solution of TMEDA (10% in CH_2Cl_2), DMF, MeOH, and CH_2Cl_2, and dried for 40 h in a vacuum oven, giving the title compound (1.12 g).

IR (neat): ν_{max}/(cm^{-1}) 1654 (s), 1319 (s), 1245 (s), 832 (s). ^{13}C NMR (75.47 MHz; $CDCl_3$) δ_C: 63.2; 49.6; 33.8; 24.5; 17.2; −1.6.

General Procedure for Esterifications Using Solid-Supported *O*-Alkylisoureas with Conventional Heating. The carboxylic acid **10**−**19** (0.175 mmol) was dissolved in THF (2 mL), and the resulting solution was added to the isourea−resin (0.35 mmol) in a round-bottom flask. The mixture was heated at 60 °C under gentle stirring for the time indicated, and then the resin was removed by filtration and washed with MeOH and CH_2Cl_2. The combined filtrates were evaporated to afford the desired carboxylic ester. No purification was performed before NMR analysis.

Synthesis of Methyl Oleate 23 Using the Scavenger Protocol. Oleic acid **13** (44.5 mg, 0.175 mmol) was dissolved in THF (2 mL), and the resulting solution was added to the isourea−resin (200 mg, 0.35 mmol) in a round-bottom flask. The mixture was heated overnight at 60 °C under gentle stirring. Aminomethylpolystyrene (loading 0.8 mmol/g) was added in portions until TLC analysis showed complete disappearance of the oleic acid, for a total of 100 mg of resin added. The resins were removed by filtration and washed with MeOH and CH_2Cl_2. The combined filtrates were evaporated to afford methyl oleate **23** as a colorless oil (24.9 mg, 53%).

General Method for the Microwave-Assisted Synthesis of Methyl Esters Using Solid-Supported Isoureas. The carboxylic acid (0.175 mmol) was dissolved in THF or CH_3CN (2 mL), and the resulting solution was added to the resin (0.35 mmol) in a microwave vial. The vial was capped and heated under microwave irradiation for the time and at the temperature indicated, and then the resin was removed by filtration and washed with MeOH and CH_2Cl_2. The combined filtrates were evaporated to afford the desired carboxylic ester. No purification was performed before NMR analysis.

Acknowledgment. We acknowledge the supporting partners of the Southampton Combinatorial Centre of Excellence for financial support. The funding partners are Amersham Health and Amersham Biosciences, AstraZeneca, Evotec OAI Ltd., GlaxoSmithKline, Eli Lilly, Merck Biosciences Inc., Organon, Pfizer, and Roche. We thank Joan Street and Neil Wells for assistance with NMR, NovaBiochem for supplying resin **5**, and Personal Chemistry for the donation of a Smith Synthesizer. We wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury.[20]

Supporting Information Available: IR, MAS ^{1}H NMR, and gel-phase ^{13}C NMR spectra of all resins. ^{1}H and ^{13}C NMR spectra of all esters. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049239E

(20) The United Kingdom Database Service. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746−749.