ORGANIC LETTERS

2003
Vol. 5, No. 6
853−856

Polymer-Supported *O*-Benzyl and *O*-Allylisoureas: Convenient Preparation and Use in Ester Synthesis from Carboxylic Acids

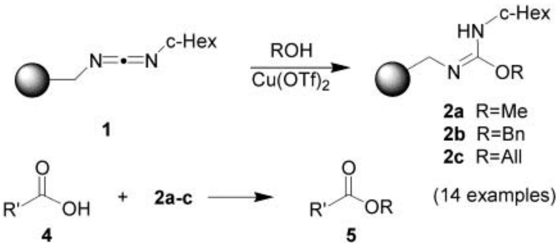
Stefano Crosignani,[†] Peter D. White,[‡] Rene Steinauer,[§] and Bruno Linclau*,[†]

Combinatorial Centre of Excellence, Chemistry Department, University of Southampton, Southampton, SO17 1BJ, United Kingdom, Novabiochem, Merck Biosciences Ltd., Padge Road, Beeston, NG9 2JR, United Kingdom, and Merck Biosciences AG, Weidenmattweg 4, CH-4448 Läufelfingen, Switzerland

bruno.linclau@soton.ac.uk

Received December 19, 2002

ABSTRACT



Polymer-supported *O*-methyl, *O*-benzyl, and *O*-allyl-isoureas were prepared by copper(II)-catalyzed reaction of polymer-supported carbodiimide with the corresponding alcohols. These polymer-supported reagents were successfully employed to convert a series of carboxylic acids to methyl, benzyl, or allyl esters, in good yields. The products were obtained with high purity (>95% by NMR) after a simple resin filtration–solvent evaporation sequence.

In the past decade, the availability of automated screening techniques has put a major emphasis on the number of compounds that can be produced per unit of time.

In this respect, the use of polymer-supported reagents has proven to be extremely useful, not least due to the successful combination of the advantages of both solution-phase and solid-phase chemistry. Many solid-supported reagents allow for a single filtration/evaporation sequence in order to isolate the desired product in good yield and purity.[1] The development of new immobilized reagents for which this simple workup protocol is sufficient is currently an important research area. Whereas the use of solid-supported reagents so far is mainly employed in parallel synthesis, recent reports convincingly proved their usefulness in traditional total synthesis applications.[2] Although a great variety of immobilized reagents have now been described, allowing for increasingly complex reaction processes to be accomplished, some basic transformations were overlooked for a long time. It took until 2001 before two groups independently described triazene-based resins as the first "alkylating resins" to achieve the conversion of carboxylic acids into the corresponding esters.[3] Reacting commercial solid-supported diazonium with

---

[†] University of Southampton.

[‡] Merck Biosciences Ltd.

[§] Merck Biosciences AG.

[1] (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem Soc., Perkin Trans. 1*, **2000**, *23*, 3815−4195. (b) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035−1074.

[2] (a) Baxendale, I. R.; Ley, S. V.; Piutti C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2194−2197. (b) Baxendale, I. R.; Lee, A. L.; Ley, S. V. *Synlett* **2001**, 1482−1484.

[3] (a) Pilot, C.; Dahmen, S.; Lauterwasser, F.; Bräse S. *Tetrahedron Lett.* **2001**, *42*, 9179−81. (b) Rademann, J.; Smerdka, J.; Jung, G.; Grosche, P.; Schmid, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 381−385.

10.1021/ol0275062 CCC: $25.00

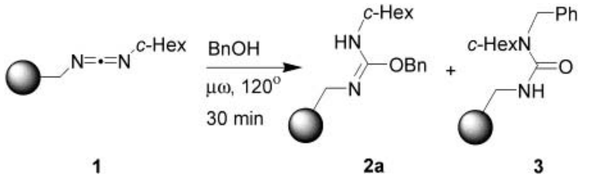
primary alkylamines at low temperatures formed immobilized triazenes, which were able to convert carboxylic acids into carboxylic esters. Subsequently, we have described that solid-supported *O*-methylisourea, readily synthesized from commercial carbodiimide resin and methanol, is an excellent reagent for the formation of methyl esters from carboxylic acids, with reaction times as short as 15 min when executed under microwave irradiation.[4]

In this communication, we report our results regarding the O-benzylation and O-allylation of carboxylic acids using the corresponding solid-supported isoureas under both thermal and microwave-assisted reaction conditions. In addition, we disclose an improved, more practical synthesis of solid-supported isoureas.

We have reported the preparation of solid-supported *O*-methylisourea by heating polymer-supported carbodiimide **1** under microwave irradiation in methanol as a solvent. No other reagents were used, obviating the need for any subsequent resin washing operations. Following this successful preparation, we attempted to synthesize *O*-benzyl and *O*-allyl isoureas in a similar way.

Hence, solid-supported carbodiimide resin **1** (Scheme 1)[5] was suspended in benzyl alcohol and heated under microwave irradiation until disappearance of the strong carbodiimide IR absorption band (2119 cm^{-1}). However, from the IR spectra, it was apparent that apart from the expected isourea absorption bands (1654 and 1329 cm^{-1}), another strong absorption was present, indicating a urea group (1640 and 1555 cm^{-1}). When *O*-methylisourea was prepared in this way, no urea band was observed. The formation of the urea bands could be explained by a rearrangement of **2a** to the corresponding immobilized *N*-benzyl urea **3**. Resubjecting this resin to the same conditions led to an increase in the proportion of urea compared to the isourea bands. Although we have no direct proof of the exact structure of the urea byproduct, there is solution-phase precedent for similar rearrangements of isoureas to the corresponding N-substituted urea products.[6]

Scheme 1. Microwave-Assisted Synthesis of *O*-Benzylisourea

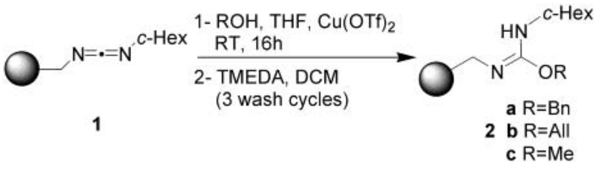


Although the urea byproduct would not interfere in the ester formation reaction, the result is a decrease in isourea loading, and an alternative preparation was desirable. In addition, the procedure using microwave irradiation is only possible on a small scale (0.5 g), and a modified preparation suitable for larger scale production of isourea resins was required.

The formation of isoureas is known to be easily accomplished by reaction of a carbodiimide and an alcohol under CuCl catalysis,[7] a process that is possible at room temperature. As we reasoned that the rearrangement was accelerated at high temperature, a low-temperature process could prove to be successful.

We selected copper(II) triflate as the catalyst, not only because of its greater solubility in THF and easy handling and stability but also because, in our experience, it is superior to CuCl in its activity for isourea formation. Hence, carbodiimide resin **1** was treated with benzyl alcohol (9 equiv) in THF and a catalytic amount (7 mol %) of Cu(OTf)$_2$ (Scheme 2). Gratifyingly, we observed no detectable trace of urea formation by IR, while the carbodiimide band completely disappeared.[8] Identical results were obtained using allyl alcohol as a reagent.

Scheme 2. Copper-Catalyzed Synthesis of *O*-Alkylisoureas



To remove the copper species after reaction, the resin was subjected to solvent washings. Unfortunately, we were not able to fully eliminate the copper species by repeated wash cycles with a variety of solvents. The failure to remove the catalyst represented a concern because ester formation using isourea resins that still were contaminated with copper salts did not proceed to completion. However, a mixture (10% v/v) of *N*,*N*′-tetramethylethylenediamine (TMEDA) in dichloromethane (DCM) as a washing solvent resulted in complete removal of the copper catalyst, through diamine complexation to the copper species. As the copper−diamine complex has an intense deep blue color, visual monitoring of the washing operation is very straightforward. It is worth noting that monoamine species were not able to effect complete removal of the copper catalyst. While amine hydrochloride salts and amino acids are known to react with isoureas to form quaternary ammonium salts,[9] neutral amines do not react with isoureas. We have observed no degradation

---

[4] (a) Crosignani, S.; White P. D.; Linclau, B. *Org. Lett.* **2002**, *6*, 1035−1037. (b) Crosignani, S.; White P. D.; Linclau, B. *Org. Lett.* **2002**, *6*, 2961−2963.

[5] We have used both commercial carbodiimide resin (loading 1.8 mmol/g) and resin prepared “in-house” from aminomethyl polystyrene resin (loading 3.2 mmol/g) in two steps: reaction with cyclohexylisocyanate in THF (Weinshenker, N. M.; Shen, C. M.; Wong, J. Y. *Org. Synth.* **1977**, *56*, 95−99), followed by dehydration (PPh$_3$, CBr$_4$, TEA, DCM, 16 h; Lange, U. E. W. *Tetrahedron Lett.* **2002**, *43*, 6857−6860).

[6] Tsuboi, S.; Stromguist, P.; Overman, L. E. *Tetrahedron Lett.* **1976**, *17*, 1144−1148.

[7] Mathias, L. J. *Synthesis* **1979**, 561−576.

[8] Use of the copper catalyst (7 mol %) under microwave irradiation accelerates the formation of both the desired isourea **2a** and the urea byproduct: after 5 min at 100 °C, the IR spectrum shows a complete disappearance of the carbodiimide absorption band, while both isourea and urea bands are present. After 30 min at 120 °C, only the urea bands are visible.

[9] Musich J. A.; Rapoport H. *J. Org. Chem.* **1977**, *42*, 139−141.

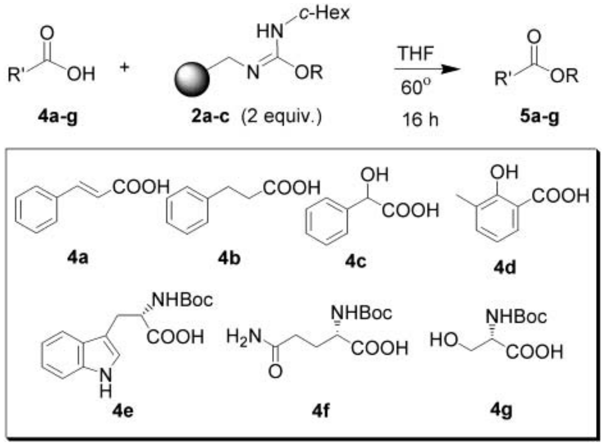
of **2** after prolonged treatment with the diamine solution, even in the presence of Cu(OTf)$_2$.

The formation of solid-supported *O*-methylisourea was also possible using this methodology. The copper-catalyzed isourea formation is superior compared to the thermal method, not only because of the absence of rearranged urea products but also because upscaling is easier, as the microwave oven is no longer required. Another benefit is that the alcohol substrate is used not as the reaction solvent but as a solution in THF, which considerably extends the scope in terms of possible alcohol starting materials. Currently, 9 equiv of benzyl or allyl alcohol is used. Unfortunately, all attempts to prepare polymer-supported *O*-*tert*-butylisourea using *tert*-butyl alcohol as a reagent have failed so far. From IR analysis, it appeared that no isourea bands were visible at all, with only the carbodiimide and urea bands being observed at any point during the reaction.

With an efficient preparation method of the *O*-benzyl and *O*-allylisoureas in hand, we next turned to the formation of benzyl and allyl esters from the corresponding carboxylic acids.

Esterification of a series of carboxylic acids (Table 1) using **2a**,**b** went smoothly using 2 equiv of reagent (based on the resin loading, calculated assuming 100% conversion in each preparation step). As we had observed previously for polymer-supported *O*-methylisourea **2c**,[4] the chemoselectivity of these isourea reagents is excellent, which demonstrates their utility for the protection of polyfunctional molecules. Both alcohols (entries 6, 12, and 14) and phenols (entries 3 and 9) were unreactive under the reaction conditions even by the more reactive benzyl isourea. Boc-protected amines (entries 4−6 and 10−12) proved to be stable under these conditions. Finally, primary amides were also not touched (entries 5 and 11).

Table 1. Synthesis of Carboxylic Esters Using **2a**−**c**



entry	acid	R	yield[a]	purity[b]	entry	acid	R	yield[a]	purity[b]
1	**4a**	Bn	96%	>95%	8	**4b**	All	85%	>95%
2	**4b**	Bn	99%	>95%	9	**4d**	All	90%	>95%
3	**4d**	Bn	96%	>95%	10	**4e**	All	93%	>95%
4	**4e**	Bn	97%	>95%	11	**4f**	All	94%	>95%
5	**4f**	Bn	98%	>95%	12	**4g**	All	98%	>95%
6	**4g**	Bn	99%	>95%	13	**4a**	Me	83%	>95%
7	**4a**	All	82%	>95%	14	**4c**	Me	85%	>95%

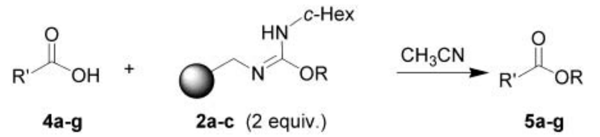
[a] Isolated yield. [b] Determined by ^{1}H and ^{13}C NMR.

No other reagent is needed for the reaction, and as both the urea byproduct and any excess isourea remain immobilized on the polystyrene beads, a simple filtration of the resin followed by two washings with DCM and evaporation of the solvent affords the product: all the isolated yields are good to excellent, and all the products were obtained in excellent purity.[10]

We also performed some esterification reactions with the solid-supported *O*-methylisourea **2c**, prepared via the Cu(II)-catalyzed procedure (entries 13−14), and the results show that the method of reagent preparation does not play a significant role with regard to yield and purity of the methyl ester products.

The use of microwave irradiation is becoming a common technique for obtaining increased rates of reactions on the solid phase, which otherwise suffer from slower kinetics.[11] In a previous communication,[4b] we demonstrated that the time needed for the esterification of carboxylic acids using *O*-alkylisoureas can be significantly reduced by performing the reaction under microwave irradiation. When using polymer-supported reagent **2c**, most reactions were complete in just 15 min at a temperature of 125 °C, using THF as a solvent. However, due to its low polarity, THF does not absorb microwave irradiation efficiently. When reactions are performed on rather dilute solutions, as is the case when polymer-supported reagents are employed, this results in a relatively slow increase in the reaction temperature and also limits the maximum temperature achievable.[12] To further reduce the reaction time of our esterification reactions, we decided to use acetonitrile as a solvent. Due to its higher polarity, higher reaction temperatures can be achieved in a shorter time under microwave irradiation. The results of the microwave-assisted experiments are listed in Table 2.

Table 2. Microwave-Assisted Synthesis of Carboxylic Esters Using **2a**−**c** in Acetonitrile as a Solvent



entry	acid	R	temp (°C)	time (min)	yield[a]	purity[b]
1	**4a**	Bn	125	3	96%	>95%
2	**4d**	Bn	125	3	93%	>95%
3	**4e**	Bn	125	3	89%	>95%
4	**4e**	All	125	3	93%	>95%
5	**4f**	All	125	3	91%	>95%
6	**4g**	All	125	3	94%	>95%
7	**4a**	Me	130	5	90%	>95%
8	**4e**	Me	130	5	94%	>95%

[a] Isolated yield. [b] Determined by ^{1}H and ^{13}C NMR.

Using the more reactive immobilized *O*-benzyl and *O*-allyl isoureas led to the completion of all reactions in 3 min. While we cannot exclude that rearrangement to the corresponding *N*-benzyl or *N*-allyl urea products as shown in Scheme 1 is not occurring at the high reaction temperature, the excellent isolated yields suggest that the ester formation is a faster process. With solid-supported *O*-methylisourea, the reaction required 5 min at a slightly higher temperature, compared to 15 min when THF is used as the reaction solvent. No loss in chemoselectivity is observed compared to the standard thermal heating. As reactions using solid-supported substrates or reagents are known for requiring longer reaction times, these results clearly illustrate the usefulness of microwave irradiation for reactions on the solid phase and demonstrate that very short reaction times are feasible. The combination of these short reaction times with the extremely simple workup procedure is particularly advantageous, with the total time required to obtain the final product being less than 1 h.

In conclusion, a simple, inexpensive, and easy to scale-up preparation of polymer-supported *O*-alkylisoureas has been described. Using this method, we have prepared three polymer-supported reagents capable of converting functionalized carboxylic acids to the corresponding esters. The groups that can be introduced are among the most used protecting groups for carboxylic acids. The esterification reactions can be performed either with conventional heating or under microwave irradiation. In both cases, several functional groups can be present in the substrate without affecting the reaction. Most importantly, all products are obtained in high purity after a simple resin filtration/solvent evaporation protocol.

Acknowledgment. The authors acknowledge the supporting partners of the Southampton Combinatorial Centre of Excellence for financial support. The funding partners are Amersham Health and Amersham Biosciences, AstraZeneca, GlaxoSmithKline, Eli Lilly, Merck Biosciences Ltd., Organon, Pfizer, and Roche. The authors thank Joan Street and Neil Wells for assistance with NMR and Personal Chemistry for the donation of a Smith Synthesizer.

Supporting Information Available: IR spectra and experimental procedures for the preparation of resins **2a**−**c** and **1** and ^{1}H and ^{13}C NMR spectra of compounds **5a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0275062

---

(10) When commercial carbodiimide **1** was used as a starting material, the products obtained after the esterification reactions were contaminated by unknown products. The authors believe that the harsh conditions employed in the commercial preparation of **1** are responsible for this, and that the use of a mild dehydration step to obtain carbodiimide **1** is essential for obtaining polymer-supported isoureas that do not suffer from leaching.

(11) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95−105.

(12) In our experience, using 0.175 mmol of carboxylic acid and 2 mL of THF, the maximum temperature achievable is around 130 °C.