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Polymer-Supported *O*-Methylisourea: A New Reagent for the *O*-Methylation of Carboxylic Acids

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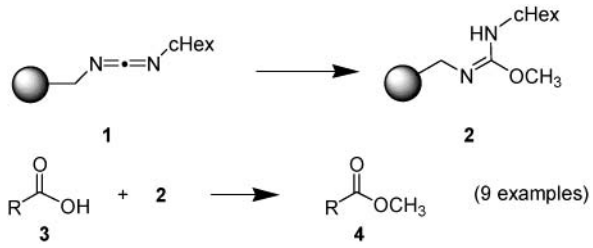
ABSTRACT



A solid-supported *O*-methylisourea reagent has been prepared in one step starting from commercially available solid-supported carbodiimide. The isourea reagent has been successfully used for the preparation of methyl esters from the corresponding carboxylic acids. The crude products obtained after resin filtration and solvent evaporation are generally obtained in >98% purity.

The alkylation of a carboxylic acid to the corresponding methyl ester is a fundamental transformation in organic chemistry.[1] However, the use of typical methylating agents such as methyl iodide, diazomethane, and dimethyl sulfate is severely compromised due to their toxic and/or carcinogenic properties. In addition, the use of diazomethane is not recommended because of its explosive nature. A low-toxicity alternative is the use of *O*-methylisourea, which has been known as a suitable alkylating agent for 50 years.[2] The mild reactivity of *O*-methylisourea allows for selective ester formation of heavily functionalized substrates and has been used in the final stages of complex natural products synthesis.[3] The main drawback of this methylating agent is the formation of a urea byproduct, requiring a potentially difficult purification step. The need for alternative protocols that avoid troublesome purifications is particularly important for applications in solution-phase combinatorial chemistry.

An elegant solution for clean methyl ester formation which avoids the use of toxic or explosive reagents and/or difficult workup procedures was reported by Rademann,[4] in which a solid-supported triazene was used to effect the transformation. The main drawback of this method is the preparation of the triazene resin, which required four steps from Merrifield resin.

In this Letter, we wish to report the first preparation of a solid-supported *O*-methylisourea in one step from a commercial resin and its successful use as a methylating agent for carboxylic acids. The products are obtained by a simple filtration/solvent evaporation procedure, which makes this

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(1) Otera, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2044−2045.
(2) For a review on the use of *O*-alkyl isoureas see Mathias, L. J. *Synthesis* **1979**, 561−76.
(3) (a) Hugger, U.; Sharpless, K. B. *Tetrahedron Lett.* **1995**, *36*, 6603−6606. (b) Biftu, T.; Acton, J. J.; Berger, G. D.; Bergstrom, J. D.; Dufresne, C.; Kurtz, M. M.; Marquis, R. W.; Parsons, W. H.; Rew, D. R.; Wilson, K. E. *J. Med. Chem.* **1994**, *37*, 421−424.
(4) Rademann, J.; Smerdka, J.; Jung, G.; Grosche, P.; Schmid, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 381−385.

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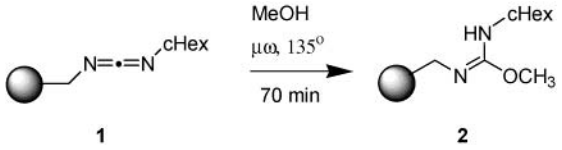
method suitable for automated solution-phase parallel synthesis purposes.

O-Alkylisoureas are usually prepared through the reaction of a carbodiimide and an alcohol under copper(I) catalysis.[2] However, preliminary experiments to prepare resin **2** using this strategy were not satisfactory. As it was suggested in the older literature that the transformation could be performed at high temperatures without added catalyst,[5] we decided to investigate the thermal synthesis of the solid-supported isourea **2**. It is known that reactions at high temperatures can be efficiently carried out under microwave irradiation.[6] Indeed, we found that irradiation of commercially available carbodiimide resin **1**[7] in dry methanol in a focused microwave oven for 70 min resulted in complete conversion to the *O*-methylisourea **2** (Scheme 1).[8] Completion of the

Scheme 1. Microwave-Assisted Synthesis of **2**



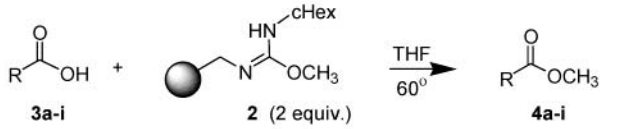
1 **2**

reaction can be easily detected using IR, by monitoring the disappearance of the strong carbodiimide band at 2119 cm^{-1} and the development of two characteristic bands at 1654 and 1329 cm^{-1}.

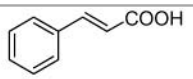
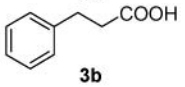
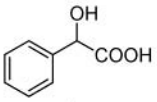
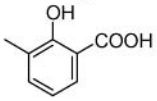
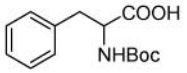
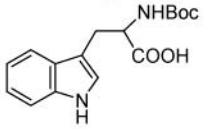
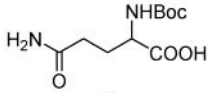
This clean transformation does not require any catalyst or reagent other than methanol, and the workup simply consists of removing the methanol through filtration followed by oven-drying to afford the desired *O*-methylisourea resin. It is worth noting that although methanol is a poor solvent for swelling polystyrene based resins, at these high temperatures (135 °C) the increased resin swelling allows reaction at all available sites.[9]

We subsequently investigated the usefulness of resin **2** as a methylating agent for carboxylic acids. Preliminary experiments showed that 2 equiv of resin **2** is sufficient to drive the ester formation reaction to completion in a reasonable time. Reactions at room temperature proceeded very sluggishly and did not reach completion even after 3 days. Reactions at 60 °C, however, were complete overnight.[10] We have monitored the reactions by TLC or HPLC. The results are summarized in Table 1.

Table 1. Synthesis of Carboxylic Esters Using **2**



3a-i **2** (2 equiv.) **4a-i**

entry	acid	time (h)	yield[a]	purity[b]
1	 **3a**	16	81%	>98%
2	 **3b**	16	94%	>98%
3	$CH_3(CH_2)_{16}COOH$ **3c**	40	91%	>98%
4	C_7H_{15} $(CH_2)_6COOH$ **3d**	40	88%	>98%
5	 **3e**	16	90%	>98%
6	 **3f**	16	78%	93%[c]
7	 **3g**	16	74%	>98%
8	 **3h**	16	81%	>98%
9	 **3i**	16	82%	>98%

[a] Isolated yield. [b] Determined by ^1H NMR. [c] 3.5% of **3f** and 3.5% of dimethylated product could be detected.

Simple carboxylic acids (entries 1−4) are alkylated in good yields and excellent purities. The reaction requires longer times with long-chain aliphatic acids (compare entries 3−4 with entry 2). Hydroxy acids (entry 5) are also cleanly alkylated to give the corresponding hydroxy ester. No alkylation of the alcohol moiety has been detected. When phenolic groups are present (entry 6), a small amount of dialkylation is observed. However, the selectivity remains very good, and only about 3.5% of dialkylated product is formed. Boc-protected amino acids (entries 7 to 9) can also be cleanly transformed in the corresponding amino esters. In contrast, we found that Fmoc groups are cleaved under the reaction conditions. Amides are untouched as exemplified

(5) Dains, F. B. *J. Am. Chem. Soc.* **1899**, *21*, 136−192.

(6) (a) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (b) Stadler, A.; Kappe, C. O. *Eur. J. Org. Chem.* **2001**, 919−925.

(7) *N*-Cyclohexylcarbodiimide-*N*′-methylpolystyrene HL **1** was provided by Novabiochem (loading 1.80 mmol/g). Alternatively, it can be prepared using the method described in Weinshenker, N. M.; Shen, C. M.; Wong, J. Y. *Org. Synth.* **1977**, *56*, 95−99.

(8) The reaction is performed in a Smith Synthesizer, at a temperature of 135 °C and a pressure of 9 bar.

(9) The phenomenon has been attributed to a decreased solvent polarity at higher temperatures: Westman, J. *Org. Lett.* **2001**, *3*, 3745−3747.

(10) **Typical experimental procedure:** carboxylic acid **3** (0.175 mmol) is dissolved in 2 mL of THF. The solution is added to resin **2** (200 mg, 0.35 mmol). The mixture is heated at 60 °C with gentle stirring overnight; then the resin is filtered and washed with MeOH (3 × 2 mL) and DCM (3 × 3 mL). The solvent is then evaporated under reduced pressure to give the desired product.

by the clean conversion of Boc-protected glutamine into the corresponding methyl ester (entry 9).

In all cases except entry 6, no side products were observed and the products obtained were of >98% purity by NMR after simple resin filtration and solvent evaporation.

It is worth noting that if a small amount of starting material remains, it can be easily removed by using a scavenger resin[11] (e.g., dimethylaminomethylpolystyrene). The scavenger could be added directly into the reaction mixture before the filtration. To test this strategy, stearic acid **3c** was reacted with **2** (2 equiv) overnight. Analysis revealed that ca. 30% of starting material was still present. However, treatment of the reaction mixture with aminomethylpolystyrene resin (100 mg) led to the desired methyl ester in >98% purity.

In conclusion, we report (1) a facile one-step synthesis of a solid-supported methylating agent and (2) the successful methylation of carboxylic acids in high yield and purity. Carboxylic acids can be selectively methylated in the presence of alcohol, phenol, and amide functional groups. Both the reaction conditions for preparing the solid-supported reagent and the actual esterification reaction are extremely simple, with no reagents employed other than methanol and the carboxylic acid substrate, respectively. Apart from resin filtration and solvent evaporation, no further purification is required. Hence the reported procedure should be very useful for automated parallel synthesis, as well as traditional organic synthesis applications.

The synthesis of several other polymer-supported isoureas derived from coupling of different alcohols to resin **1** is in progress, as well as studies on the regeneration of resin **1**.

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Supporting Information Available: IR spectra of resins **1** and **2** and ^{1}H and ^{13}C NMR spectra of compounds **4a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) 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.