ORGANIC LETTERS

2002
Vol. 4, No. 17
2961−2963

Microwave-Accelerated *O*-Alkylation of Carboxylic Acids with *O*-Alkylisoureas

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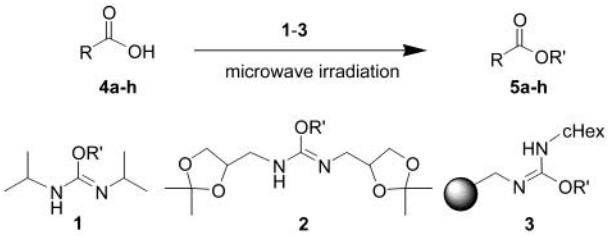
Received June 14, 2002

ABSTRACT

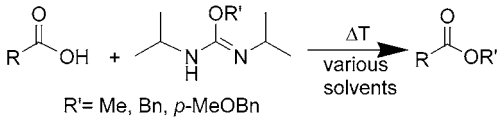


Microwave-assisted *O*-alkylations of several carboxylic acids have been performed with three different *O*-alkylisoureas. All reactions are significantly faster compared to conventionally heated reactions, while retaining high chemoselectivity. The combination of microwave technology with the use of the solid-supported isourea 3 enables the synthetic chemist to obtain the pure methyl esters starting from the corresponding acids in less than an hour.

In recent years, the use of microwave irradiation to accelerate chemical reactions has become increasingly popular.[1] Although there is still some debate over the mode of action of microwave-assisted chemistry, the most recent observations suggest that the high temperatures that can be quickly achieved in such systems are responsible for the acceleration of chemical reactions.[2] The use of modern focused microwave systems offers a number of advantages over traditional household microwave ovens: the temperature inside the reaction vessel can be constantly monitored, and the presence of a single mode cavity prevents the formation of overheated spots. Also, these systems can operate at high pressures, so it is possible to achieve very high temperatures with low-boiling solvents.

O-Alkylisoureas have been reported as convenient reagents for the esterification of functionalized carboxylic acids (Scheme 1).[3] *O*-Alkylisoureas are less reactive, and as a consequence less toxic, than other alkylating species. This, however, slows the *O*-alkylation of carboxylic acids, meaning prolonged reaction times and/or use of higher temperatures are required.

Scheme 1. Esterification Reactions with *O*-Alkylisoureas



Hence we were interested in investigating whether microwave irradiation could lead to an improved process for

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10.1021/ol0263705 CCC: $22.00
Published on Web 07/31/2002

ester formations, especially regarding reaction time.[4] In this Letter, we wish to communicate our preliminary results in this field.

The microwave-assisted esterification reactions of a range of carboxylic acids **4a**−**h** (Figure 1) with *O*-alkylisoureas

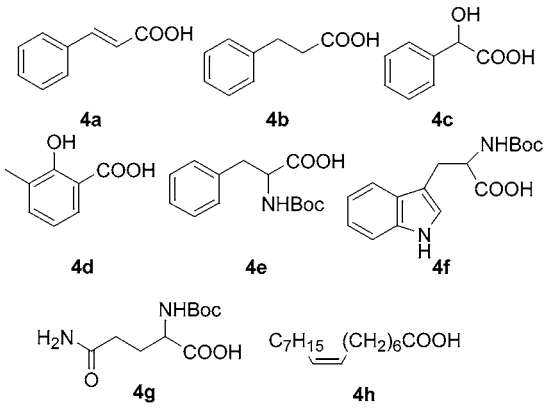
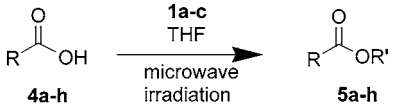


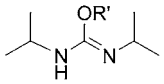
Figure 1. Carboxylic acid substrates for the esterifications.

1a−**c** are listed in Table 1.[5,6] In all examples, excellent yields were obtained after 5 min. This constitutes a dramatic reduction in reaction time compared with the conventional thermal process.[7] For example, esterifications of **4c** and **4d** with **1a** with conventional heating have been reported to require respectively 3 and 4 h at 60 °C.[8] Several esterifications with isourea **1b** were reported to be complete in 1 h (in benzene at 80 °C),[9] while esterifications with **1c** typically are performed at moderate temperatures (room temperature to 40 °C) for 18−72 h.[10]

As reported in the literature,[3a] when using the *tert*-butyl derivative **1c**, it is necessary to use a larger excess of reagent to drive the reaction to completion due to the tendency of this reagent to form isobutene via an E1-type side reaction. In our experience, the formation of this gaseous byproduct in the sealed system has proved not to be a problem. When

Table 1. Synthesis of Carboxylic Esters with Soluble *O*-alkylisoureas **1a**−**c**





1a R'=Me
1b R'=Bn
1c R'=*t*Bu

entry	isourea/ equiv	acid	*T* (°C)	time (min)	yield[a] (%)
1	**1a**/1.1	**4a**	130	5	94
2	**1a**/1.1	**4c**	130	5	81
3	**1a**/1.1	**4d**	130	5	89
4	**1a**/1.1	**4f**	130	5	92
5	**1a**/1.1	**4g**	130	5	87
6	**1b**/1.3	**4a**	130	5	90
7	**1b**/1.3	**4d**	130	5	83
8	**1b**/1.3	**4f**	130	5	94
9	**1c**/4.5	**4a**	120	5	85
10	**1c**/4.5	**4c**	120	5	75
11	**1c**/4.5	**4f**	120	5	87

[a] Isolated yield after column chromatography.

performing the reaction on a 1.0-mmol scale, only 1.8 bar of overpressure was observed. Nonetheless, some caution should be exercised when scaling-up this process with isourea **1c**.

The acceleration of the reaction was not detrimental to the chemoselectivity of the reagent: aliphatic alcohols and phenols are not alkylated, and Boc-protected amino acids are cleanly transformed in the corresponding protected amino esters. Primary amides are also not touched in these conditions.

However, despite the observed reduction in reaction time, the overall time necessary for the experimenter to obtain the final product in pure form is not reduced substantially, as the urea byproduct is not readily removed. Although the reaction is very clean and the bulk of the urea byproduct precipitates out in most appropriate reaction solvents (THF, DCM), chromatography is eventually necessary to separate the desired ester from traces of urea byproduct as well as from the excess of *O*-alkylisourea reagent **1**. To fully exploit the gain in reaction time for the ester formation, we decided to investigate phase-tagged isourea derivatives. The facilitated removal of urea byproducts from the reaction mixture is a well-established methodology originally developed for peptide couplings. The use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), which leads to the formation of a water-soluble urea byproduct, is the best known example.[11] Unfortunately, it is reported that water-soluble EDC fails to form *O*-alkylisoureas when reacted with alcohols.[12] The synthesis of an *O*-alkylisourea reagent containing a different phase label was reported by Rapoport et al.[12] This reagent was reported to have similar reactivity

(4) Traditional ester formation between carboxylic acids and alcohols with silica gel as the acid source has been successfully accelerated under microwave conditions. See: Lami, L.; Casal, B.; Cuandra, L.; Merino, J.; Alvarez, A.; Ruiz-Hitzky, E. *Green Chem.* **1999**, *1*, 199−204.

(5) A typical procedure is as follows: a microwave vial is charged with the carboxylic acid **4** (1.0 mmol) and *O*-alkylisourea **1** followed by addition of THF (2 mL). The vial is heated at the reported temperature in a Smith Synthesizer for 5 min. The white solid is filtered off and the solvent evaporated under vacuum. The residue is then further purified by column chromatography.

(6) We recommend avoiding the use of lower boiling alcohols such as methanol as solvents for this reaction. In one case, the use of such solvents led to a large increase of the pressure inside the vial, which can be potentially hazardous.

(7) Since the microwave reaction conditions involve a higher reaction temperature and a sealed tube, no direct comparison with the conventional thermal process can be made regarding the reaction rate. See ref 2a for a thorough discussion of thermal vs microwave effect.

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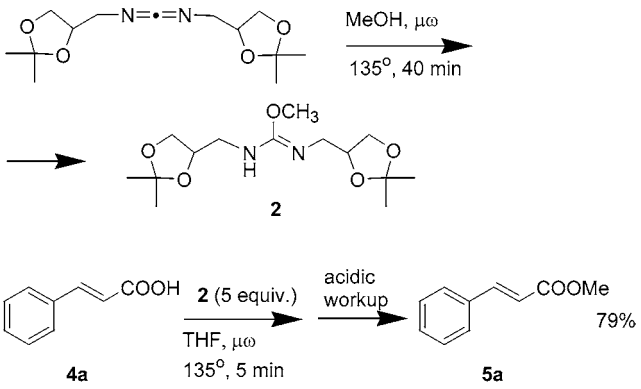
as **1**, but it has the advantage of being readily removed, along with the corresponding urea byproduct, with a simple acidic workup.

However, in our hands reproducible or satisfactory results could not be obtained when isourea **2** was used for microwave-assisted ester formation reactions. We attributed the problem to our inability to obtain pure samples of **2**. Hence it was decided to modify the synthesis of this reagent (Scheme 2): isourea **2** was prepared by microwave irradiation of a solution of the corresponding carbodiimide, which is commercially available, in dry methanol. After removal of the solvent under vacuum, the crude product was immediately used to perform the alkylation. This approach avoids the use of a copper catalyst, which considerably facilitates the isolation of **2**. With use of isourea **2** prepared via this procedure, esterification, which was complete within 5 min, followed by an acidic aqueous workup as described by Rapoport yielded pure compound **5a** in good yield (Scheme 2).

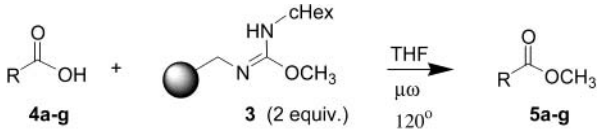
Scheme 2. Esterification Reactions with *O*-Alkylisourea **2**



Nevertheless, while the required acidic workup is compatible with standard peptide synthesis, it does restrict the scope with respect to substrate substitution for the esterification reaction. In addition, 5 equiv of reagent are needed to drive the reaction to completion.

The use of solid-supported *O*-methylisourea allows for a simple purification protocol, leading to pure methyl esters.[13] However, overnight reflux in THF is required for complete reactions. Hence, microwave irradiation of reactions with this solid-supported reagent would be an important test case. In the event, with 2 equiv of resin, most esterifications were completed in 15 min.[14] The exceptions were **4b**, which required a slightly longer reaction time, and **4h**, which required the use of 2.5 equiv of resin for 20 min. Under the conditions used, we have not observed any significant degradation of the resin. All the functional groups that were unreactive toward the reagent with conventional heating were not touched either in the microwave-accelerated reactions.

Table 2. Synthesis of Carboxylic Esters with Resin **3**



entry	acid	time (min)	yield[a] (%)	purity[b] (%)
1	**4a**	15	86	>98
2	**4b**	20	79	98
3	**4c**	15	84	>98
4	**4d**	15	75	98
5	**4e**	15	82	>98
6	**4f**	15	92	>98
7	**4g**	15	75	>98
8[c]	**4h**	20	85	>98

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] 2.5 equiv of **2** were used.

The most important feature of this reagent is, however, the simplicity of the workup: simple filtration of the resin, followed by evaporation of the solvent afforded the desired products, in all cases with purities of at least 98% (determined by ^{1}H and ^{13}C NMR). No further purifications were performed on any of the products obtained.

The combination of microwave technology, which considerably cuts down reaction times, and polymer-supported reagents, which simplifies workup procedures, enables the synthetic chemist to obtain the pure methyl esters in less than an hour.

In conclusion, we have studied the effect of microwave irradiation on the reaction of carboxylic acids with three different *O*-alkylisoureas. All reactions are complete within 5 min for homogeneous reactions and within a maximum of 20 min when the solid-supported reagent was used. In all cases the chemoselectivity of the reaction is excellent. The use of a polymer-bound reagent enabled us to maximize the timesaving effect of microwave technology.

Acknowledgment. The authors thank Personal Chemistry for the donation of a Smith Synthesizer. 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, CN Biosciences, Inc., Organon, Pfizer, and Roche. The authors thank Joan Street and Neil Wells for assistance with NMR.

Supporting Information Available: Experimental procedures for microwave assisted esterifications with isoureas **1**−**3** and ^{1}H and ^{13}C NMR spectra of compounds **5** synthesized with isourea **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) A typical procedure is as follows: the carboxylic acid **4** (0.175 mmol) is dissolved in 2 mL of THF. The solution is added to resin **2** (200 mg, 0.35 mmol) in a microwave vial. The vial is heated at 120 °C for 15 min in a Smith Synthesizer, followed by filtration of the resin with subsequent resin wash (MeOH, 3 × 2 mL and DCM, 3 × 3 mL). The solvent is then evaporated under reduced pressure to give the desired product.