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A rapid microwave-assisted esterification utilizing the Mukaiyama supported reagent

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Abstract—Microwave heating was applied to a modified Mukaiyama reagent supported on a PS-DVB resin to develop a rapid and efficient protocol for the solution-phase synthesis of esters and lactones starting from alcohol and carboxylic acids. The products were obtained in high purity (NMR analysis) after a simple resin filtration.

Recently, polymer-supported reagents have received considerable interest with the growth of high throughput solution-phase synthesis.[1] This approach allows the preparation of arrays of compounds using reactions that are often clean, that can be monitored using standard analytical techniques and that give the products with work-up involving simple filtration and evaporation of the solvents. In addition, several polymer supported reagents for synthesis and purification have become available from commercial suppliers.

Although polymer-supported reagents have been described for many synthetic processes,[2] there are some basic transformations for which few polymer-supported reagents are available. For example, the direct alkylation of carboxylic acids with alcohols to make esters has been described for the first time very recently using methods that often require anchoring the acids or alcohols on the resin followed by removal from the solid support.[3]

Microwave-assisted chemistry is also emerging as a powerful tool in combinatorial chemistry and drug discovery because reactions are speeded up and there is less formation of by products than with conventional heating.[4] Very recently, several authors described examples of microwave-assisted syntheses utilizing supported reagents where the combination of the convenience of supported reagents with the speed of microwaves gave excellent results in the preparation of arrays of compounds.[5]

2-Chloro-1-methylpyridinium iodide (the Mukaiyama reagent) is one of the most efficient reagents for the activation of carboxylic acids and the one-pot preparation of esters.[6] Recently, we described the preparation of a supported version of a 2-iodo-1-methylpyridinium salt on a microporous PS-DVB resin and its use in the parallel synthesis of β-lactams in solution.[7] At the same time, Swinnen and co-workers reported the use of a different Mukaiyama coupling agent for the synthesis of esters and amides.[8] Stimulated by this letter, we now report an example of microwave-assisted synthesis of esters in solution promoted by a polymer-supported Mukaiyama-type reagent.

For the microwave-assisted esterification, we employed resin **1** prepared as previously described.[7] In order to find the best reaction conditions, we tried the reaction between phenoxyacetic acid **2** and benzyl alcohol **8** in the presence of our supported reagent **1** (Scheme 1). Using dichloromethane as solvent,[9] we found that mixing together different amounts of the reagents in the presence of 2 equiv of **1** and 5 equiv of triethylamine in a sealed vial and irradiating for 6 min inside the cavity of a monomode Microwave reactor for organic synthesis,[10] provided the expected ester in very good yields.

These reaction conditions were extended to other acids and in many cases we obtained good results in terms of yields and purity (see Table 1). When the reagents

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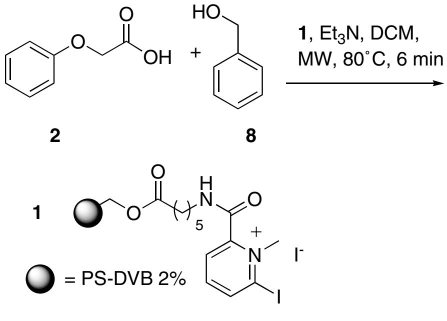
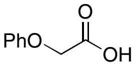
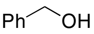
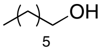
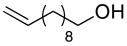
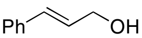
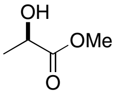
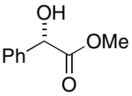
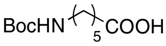
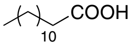
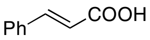
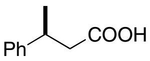


Scheme 1.

were still present after three cycles of irradiation, further addition of the resin **1** and triethylamine allowed a complete conversion. Hindered alcohols (**10**, **13** and **14** in Table 1) reacted with good to acceptable yields. Long chain acids (**3** and **4**) and alcohols (**9**, **11**) also reacted successfully. Finally, the reaction between (*S*)-2-phenylbutanoic acid **7** and (*R*)-methyl lactate **13** gave ester **34** as a single diastereoisomer (NMR analysis). At the end of the reaction, the salts of triethylammonium and the resin were separated via a rapid passage through a short column filled with a porous material as Celite or silica gel. Parallel evaporation of the solvent allowed isolation of esters as single compounds. In the case of esters (**28**–**32**), an additional step of scavenging is necessary to remove various amounts of the alcohols still present after filtration.

In conclusion, we have described a new microwave-assisted protocol for a rapid preparation of esters using a supported version of the Mukaiyama reagent. The products could be obtained in good yields and purity and the overall protocol could be easily automated.

Table 1. Esters prepared

Acid	Alcohol	Time (min), Temp.[a] (°C)	Ester, yield[b] (%)	Purity[c] (%)
 **2**	 **8**	6, 80	**15**, 96	95
2	 **9**	6, 80	**16**, 94	$\geqslant$90
2	 **10**	10, 80	**17**, 90	$\geqslant$90
2	 **11**	10, 80	**18**, 86	95
2	 **12**	6, 80	**19**, 87	$\geqslant$90
2	 **13**	10, 80	**20**, 96	$\geqslant$90
2	 **14**	10, 80	**21**, 76	$\geqslant$90
 **3**	**8**	8, 80	**22**, 66	95
3	**10**	12, 80	**23**, 72	95
3	**12**	6, 80	**24**, 70	$\geqslant$90
 **4**	**8**	14, 80	**25**, 91	$\geqslant$90
4	**10**	14, 80	**26**, 90	$\geqslant$90
4	**13**	18, 80	**27**, 78	90
Ph–COOH **5**	**10**	18, 80	**28**, 76	64
5	**12**	18, 80	**29**, 64	56
 **6**	**9**	18, 80	**30**, 80	55
6	**10**	18, 80	**31**, 71	65
6	**13**	18, 80	**32**, 70	60
 **7**	**10**	4, 80	**33**, 84	92
7	**13**	8, 80	**34**, 66	90

[a] Overall time obtained with cycles of 2 min of irradiation followed by 1 min of hold.

[b] Isolated yields.

[c] Determined by NMR analysis of the crude product.

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9. Although dichloromethane is considered an unsuitable solvent for microwaves, we obtained a reproducible temperature of 80 °C in the reactor that allowed a rapid formation of the ester.
10. *Phenoxyacetic acid benzyl ester*. General procedure: the resin **1** (loading 1.0 mmol/g, 0.2 mmol) and phenoxyacetic acid **2** (18 mg, 0.12 mmol) are placed in a sealed vial for microwave-assisted reactions. Dry DCM (1 mL) is added under nitrogen followed by benzyl alcohol (0.010 mL, 0.1 mmol) and TEA (70 μL, 0.5 mmol). The vial is heated in microwave cavity (CEM Discover apparatus) at 80 °C for 2 min (internal pressure 150 psi). The mixture is filtered through a short pad of dry silica gel that is washed with Et$_2$O. The solvents are evaporated and the product (23 mg) characterized by NMR and ES-MS analysis or comparison with an authentic sample.