An E-factor minimized protocol for the preparation of methyl β-hydroxy esters†

Francesco Fringuelli, Daniela Lanari, Ferdinando Pizzo and Luigi Vaccaro*

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We report the optimization of the preparation of methyl β-hydroxy esters (**3a–l**) in 75–93% yield by a solvent-free aldol reaction of aldehydes (**1a–l**) with KSA (**2**) followed by a de-silylation step. Amberlite IRA900F and Dowex 50Wx8 H were found to be the most efficient solid catalysts for the aldol addition and de-silylation steps, respectively. In order to minimize the use of organic solvent and automate the recovery of the catalysts and reaction products, we have developed an automated cyclic continuous-flow reactor operating under solvent-free or highly concentrated conditions. This system, applied to the reactions of **1a–c** with **2**, avoids the mechanical degradation of the catalysts and allowed reduction of the E-factor of the process to a very low value that ranges from 1.41 to 2.09.

Introduction

Recently, development of polymer-supported materials as reagents or organocatalysts has greatly increased.[1] The reason for this tendency is due to promising results in terms of chemical efficiency and environmental sustainability.[2]

Lately, our attention has been captured by the tremendous development of continuous flow reactors, as such devices are innovative tools for various applications in organic chemistry and in the synthesis of compound libraries.[3]

Our research program is committed to the optimization of synthetic procedures by employing eco-friendly reaction protocols, including the use of water[4] and solvent-free conditions (SolFC).[5] We believe that the use of an unconventional reaction medium as a simple substitute for classic organic solvents does not make a process "greener". In fact, our goal is to investigate the influence of novel reaction media on the reactivity of organic molecules in order to increase both the chemical knowledge and the efficiency of a process.

In accordance with this, we have been trying to focus our work on those processes that can be realized only if water or SolFC are used in place of an organic solvent, i.e. processes that are not efficient or are sometimes impossible in the latter. [4,5a,g,6]

Recently, we have found that combining the use of polymer-supported organocatalysts and SolFC is an attractive approach to overcome the significant loss in terms of efficiency of a supported catalyst compared to that of its non-supported counterpart. Under SolFC, the close proximity of the reactants results in a higher reactivity and the choice of the solid polymer used as support may reduce the problems related to the swelling process.[5a,e–g]

In addition and based on our experience, when solid catalysts are used under SolFC, a crucial issue is the stirring of the reaction mixture, which causes crunching of the catalyst hampering its repeated recovery and reuse. Generally, an organic solvent is necessary to isolate the final products when they are solid compounds (work-up process).[5a,e–g,6]

To minimize these problems we have planned to realize a cyclic continuous-flow reactor able to improve SolFC reactions allowing a) the optimal intimacy between the reactants and the catalyst without mechanical stirring, and b) the recovery of the product with a negligible amount of organic solvent. As a first approach to this area we have reported the nucleophilic addition of nitroalkanes to α-β-unsaturated carbonyl compounds catalyzed by the strongly basic polystyryl-BEMP and performed on a solvent-free cyclic continuous-flow reactor.[6] The next step of our project is therefore to set-up a more sophisticated cyclic continuous-flow reactor that would allow the combination of several reaction steps to be realized in an innovative automated procedure.

In this paper, we report an efficient protocol for the preparation of methyl β-hydroxy esters **3a–l** consisting of the 1) Amberlite IRA900F[7]-catalyzed Mukaiyama aldol reaction under SolFC;[8] and 2) Dowex 50Wx8 H-catalyzed de-silylation process. In addition, we have realized a cyclic continuous-flow reactor to perform the automated preparation of β-hydroxy esters **3a–c** to further reduce the E-factor of this process.

Some efforts have been devoted to the development of environmentally-friendly Mukaiyama procedures by employing water or ionic liquids as reaction media or under SolFC.[9] On the other hand the use of polymer-supported catalysts to promote this reaction has been little exploited so far.[10] In addition, the use of fluoride salts to promote Mukaiyama aldol reaction in

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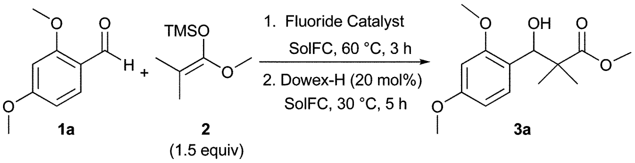
Laboratory of Green Synthetic Organic Chemistry, CEMIN - Dipartimento di Chimica, Università di Perugia, Via Elce di Sotto, 8, Perugia, Italy. E-mail: luigi@unipg.it; Fax: +39 075 5855560; Tel: +39 075 5855541

† Electronic supplementary information (ESI) available: Products **3b**,[16] **3g**,[10d] **3h**,[10d] **3i**,[16] **3k**,[10b] and **3l**[9a] are known compounds, products **3a**, **3c**, **3d**, **3e**, **3f**, **3g**, **3j** and **6h** are new compounds. Characterization data and copies of the ^{1}H and ^{13}C NMR spectra for all compounds **3a–l** and **6h**, and details for the calculation of E-factor. See DOI: 10.1039/c004461j

Table 1 Optimization of the Mukaiyama aldol reaction of **1a** with KSA **2**



Entry	Medium	Fluoride Catalyst (mol%)	Conversion (%)[a]
1	SolFC	F (5)[b]	68
2	SolFC	F (5)	97[c]
3	SolFC	F (2)	68
4	SolFC	Br (5)	—
5	THF	Amb-F (5)	63
6	$C_2H_4Cl_2$	Amb-F (5)	58
7	Et_2O	Amb-F (5)	34
8	SolFC	TBAF-SiO_2 (5)	89
9	SolFC	KF-Alumina (5)	30

[a] Conversion to **3a**, after the complete consumption of **2** and after hydrolysis by using 20 mol% of DOWEX 50Wx8 H wet, the remaining material was unreacted **1a**. [b] Not-dried Amb-F. [c] Pure product **3a** was isolated in 91% yield.

an organic reaction medium is known, but compared to the immense literature on this topic can be certainly considered rare,[11] and to our knowledge a solid fluoride source has never been used in this context.

The test case for our study was the preparation of methyl 3-(2′,4′-dimethoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (**3a**) from the reaction of 2,4-dimethoxy benzaldehyde (**1a**) with methyl trimethylsilyl dimethylketene acetal (KSA) (**2**).

Results and discussion

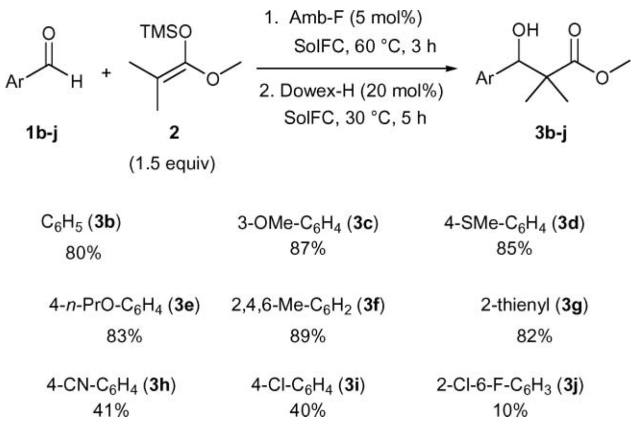
Various reaction media and solid fluoride sources were considered and the data obtained have been reported in Table 1. The most efficient result in the reaction between **1a** and **2** was accomplished under SolFC by using 5 mol% of dried Amb-F[7] and 1.5 equiv. of KSA **2**. The de-silylation reaction was optimized by using Dowex 50Wx8 H[12] allowing the desired product **3a** to be isolated as pure product in 91% yield (Table 1, entry 2).

5 mol% of dried Amb-F represents the amount of catalyst generally used in this type of process and it is a reasonable quantity with the intention of studying its recoverability and reusability in more cycles. In the de-silylation step, we have been pleased to find that this can be performed by using only 20 mol% of Dowex 50Wx8 H, instead of the over-stoichiometric amounts of aqueous HCl that are routinely employed.

No result was obtained when Amb-Br was employed (Table 1, entry 4). In addition, the use of other commercially available solid fluoride sources gave less efficient or discouraging results (Table 1, entries 8 and 9).

The choice of solvent-free conditions in this case is essential, because when an organic solvent (such as THF, $C_2H_4Cl_2$ or Et_2O) was used as medium the reaction did not proceed to completeness (Table 1, entries 5–7).

To verify the application range of the experimental conditions described, the protocol was extended to aldehydes **1b–j** (Scheme 1).



Scheme 1 Preparation of β-hydroxy esters **3b–j** by reaction of **1b–j** with KSA **2**.

At this stage, it should be noted that the optimized protocol using two recoverable and reusable solid catalysts is very efficient both from the chemical and environmental points of view. In fact, calculation of the E-factor[13] confirmed that the solvent-free approach is very efficient for the waste reduction. In our case E-factor ranges from *ca.* 20 to *ca.* 29, and it is significantly smaller than other protocols recently reported in the literature, where an average of *ca.* 127 has been obtained (see ESI†).[14]

With our protocol, yields were excellent for all the aldehydes tested except in the cases of electron-poor substrates 4-CN-benzaldehyde (**1h**), 4-Cl-benzaldehyde (**1i**), and 2-Cl-6-F-benzaldehyde (**1j**). Improvements were not obtained even with longer reaction time due to the concurrent hydrolysis of **2**. Such behaviour of electron-poor aldehydes is known and this synthetic problem is still unsolved.

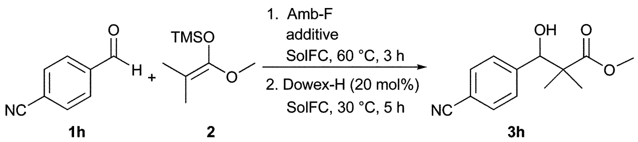
GC/EIMS and ^{1}H NMR analyses of the reaction mixture of **1** with **2**, revealed that together with the silylated product **5**, an acetal by-product **6** was also formed, which after hydrolysis again gave the product **3** and the starting aldehyde **1**, therefore lowering the yield of the β-hydroxy ester product **3** (Scheme 2).

Formation of **6** can be explained by considering that along with the fluoride-activated enolate a "naked" enolate, derived from the Si–O bond cleavage, was also formed. Such an intermediate can react with aldehyde **1** giving non-silylated product **4** which can lead to the formation of the undesired acetal compound **6**. This is in agreement with the results obtained in the base-catalyzed Mukaiyama reaction where fluoride was used as catalyst.[11,15]

In order to minimize the formation of the acetal by-product **6**, we selected aldehyde **1h** as a representative electron-poor substrate and tried several reaction conditions. The results are reported in Table 2. We have reduced the amount of Amb-F used (entry 1), increased that of KSA (**2**) (entry 2), added a silylating agent to convert **4** to **5** (entries 3 and 4),[8b] but in all the cases the results were unsatisfactory.

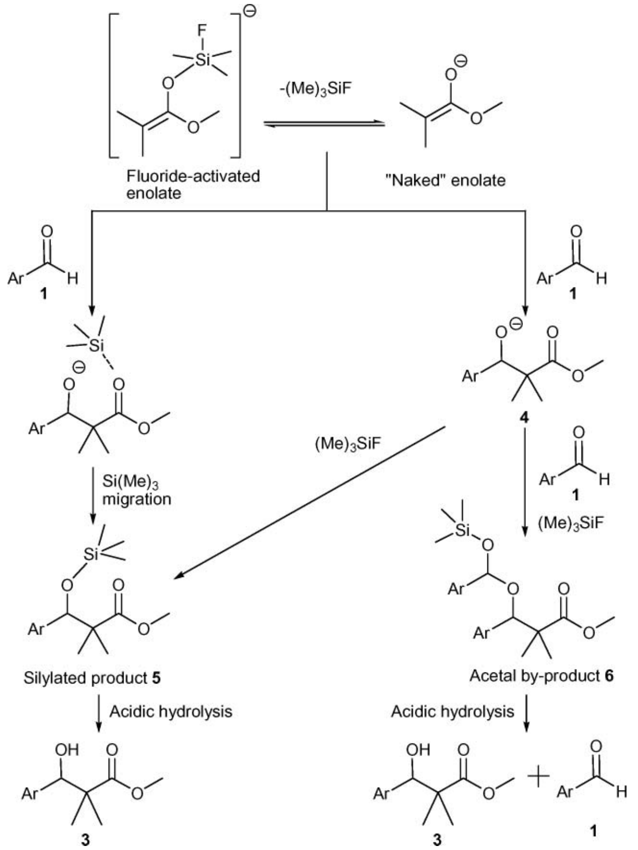
Successful results were finally obtained by adding water (50 mol% with respect to aldehyde **1h**) to the SolFC reaction mixture. In this case no presence of by-product **6** was observed. Water also caused the hydrolysis of **2**, therefore a higher amount of KSA (**2**) (3.0 equiv.) was necessary to reach an excellent yield (Table 2, entries 5 and 6).

Table 2 Optimization of Mukaiyama aldol reaction of aldehyde **1h** with KSA **2** catalyzed by Amb-F under SolFC



Entry	KSA (equiv.)	Amb-F (mol%)	Additive (equiv.)	Conversion (%)[a]
1	1.5	2	—	55[b]
2	3.0	5	—	64[c]
3	1.5	5	BSA [d](1.0)	50
4	1.5	5	TMS-PY [e](1.0)	77
5	1.5	5	H_2O (0.5)	64[f]
6	3.0	5	H_2O (0.5)	94

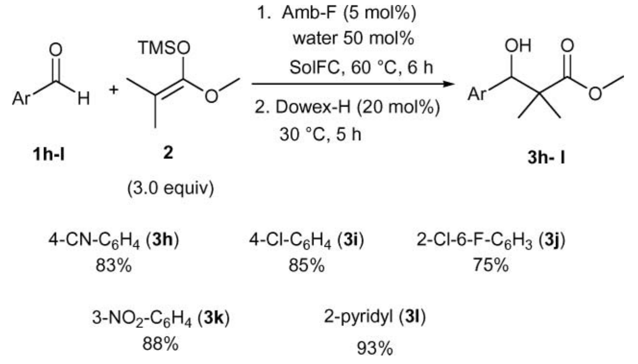
[a] After hydrolysis by using 20 mol% of DOWEX 50Wx8 H wet. [b] After 24 h a highest conversion of 68% was reached. [c] After 24 h a highest conversion of 83% was reached. [d] *N*,*O*-Bis(trimethylsilyl) acetamide. [e] 1-TMS-2-pirrolidinone. [f] After 6 h complete consumption of **2** was observed due to its hydrolysis.



Scheme 2 Plausible fluoride-catalyzed Mukaiyama reaction pathways.

This procedure was applied to aryl aldehydes bearing electron-withdrawing groups **1h–l** giving products **3h–l** in high yields (Scheme 3), GC and ^{1}H-NMR analyses revealed that the formation of the by-product **6** was largely avoided.

In summary, optimized chemical preparation of a variety of β-hydroxy esters has been realized by using two novel polystyrene-supported catalysts (Amb-F and Dowex 50Wx8 H).



Scheme 3 Reactions of aldehydes **1h–l** with KSA **2** catalyzed by Amb-F (5 mol%) in the presence of water (50 mol%) under SolFC.

SolFC is necessary for the reactivity of the aldol process. The use of an organic solvent resulted in uncompleted reactions and the necessity for higher amounts of nucleophile **2**.

However, although our batch protocol reduces significantly the amount of organic solvents and eliminates the need for aqueous HCl, in our conditions some organic solvent is intrinsically needed to recover Amb-F and transfer the Mukaiyama reaction mixture into the hydrolysis reactor containing Dowex 50Wx8 H and then to isolate the pure aldol product after drying over sodium sulfate (see Experimental procedure or ESI†).

According to our project, and starting from the optimized batch protocol we have investigated how to realize a cyclic continuous-flow reactor that would allow minimization of the E-factor by reducing the amount of organic solvent needed for the isolation of the pure β-hydroxy ester product **3** in high yield. The flow reactor should also allow preservation of the physical integrity of the solid catalysts making their recovery and reuse easier and more efficient.

We will describe here the cyclic continuous-flow reactor that we have built for reaching this goal (Fig. 1).

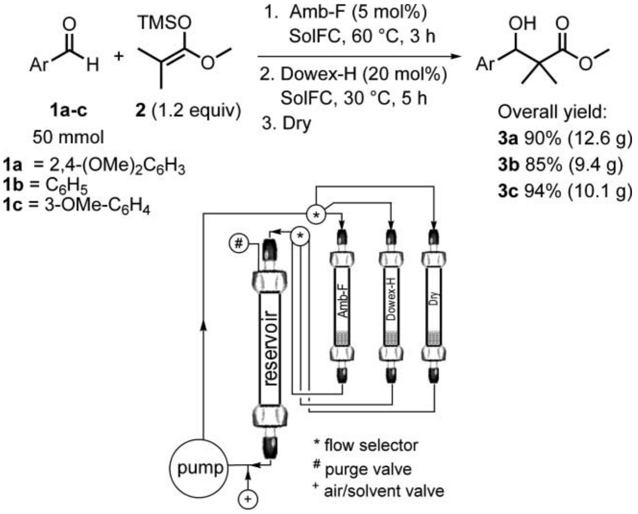


Fig. 1 Schematic cyclic continuous-flow reactor.

Automated cyclic continuous-flow reactor

We have set up three different low-pressure glass columns (10 mL volume each) labelled as Amb-F, Dowex-H, and Dry (drying/neutralizing solid containing a 2 : 1 mixture of dry Na_2SO_4/K_2CO_3) (Fig. 1). Reactants **1** and **2** were charged into a fourth column used as a reservoir (20 mL volume).

The equipment was connected, by using the appropriate valves, to a pump and installed into a thermostatted box (not shown in Fig. 1 for clarity).

Liquid aldehydes such as **1b** and **1c** formed a viscous mixture with **2**. After setting the temperature (60 °C) the reaction mixture previously charged into the reservoir was pumped continuously through the Amb-F catalyst at a 0.5 mL min^{-1} flow rate for 3 h. After this time, temperature was set to 30 °C, the air/solvent valve was opened and the pump was set to work at 5 mL min^{-1} in order to transfer the liquid into the reservoir and empty the Amb-F column. To completely wash the Amb-F column some THF (0.05 mL $mmol^{-1} \times 2$ at a 0.2 mL min^{-1}) was pumped from the air/solvent valve and collected in the reservoir as well.

Then, by appropriately selecting the valves, the liquid reaction mixture was continuously passed through Dowex 50Wx8 H column and after 5 h the reaction mixture was re-collected as before in the reservoir and THF (0.05 mL $mmol^{-1} \times 2$ at a 0.5 mL min^{-1}) was used to wash Dowex's column. Finally, the reaction mixture was passed through the third column (dry) for the final drying/neutralizing step to eliminate traces of residual acidity coming from the hydrolysis step (formation of trimethyl silicic acid).

At the end, the reservoir containing the product **3** and methyl 2-methylpropionate coming from the hydrolysis of the excess of **2** was warmed at 50 °C and high vacuum was applied to furnish pure product **3** (**3b**: 85%, **3c**: 94% yield).

For the correct functioning of the pump the reaction mixture must be liquid and macroscopically homogeneous. Although we were aware of the dramatic influence of a reaction medium on the reaction rate, we have also tested this reactor in the case of a solid aldehyde that under the reaction conditions form a partially heterogeneous mixture with **2**, such as **1a**. In this case, to form a homogeneous reaction mixture, 0.2 mL $mmol^{-1}$ of THF were used from the beginning to run the aldol reaction and not only in the product recovery stage. The combination of the use of the automated reactor with highly concentrated reaction conditions still ensured an excellent result for the preparation of **3a** in a very good yield of 90% and an E-factor of 2.09.

It is remarkable that by using this reactor compared to the batch process, the excess of **2** could be reduced to 1.2 equiv. In addition, the recovery issue has been eliminated since the catalysts are safely charged into the glass column and have been directly reused for consecutive runs showing identical results.

The reactions have been performed on 100 mmol scale and it is noteworthy that on this scale the automated reactor we have realized is even more efficient because the organic solvent needed for cleaning the reactors' system and recover the product may be proportionally reduced.

In the cyclic continuous-flow protocol, the E-factor is dramatically reduced from 29 (our batch conditions) to 1.70 in the case of benzaldehyde (**1b**) and is in the range of 1.41–2.09 for the three substrates **1a–1c** (see ESI†). Besides the significance of these calculations made at this level, this result is very important because it proves that our approach is very efficient both at very small and large scales.

Conclusions

In conclusion, we have reported that Amberlite IRA900F is an efficient and reusable solid source of fluoride able to effectively activate Si–O bonds under SolFC and catalyze the Mukaiyama aldol reaction of trimethylsilyl dimethylketene acetal (KSA) (**2**) with a variety of aldehydes (**1a–l**), and that Dowex 50Wx8 H was found to be the most appropriate solid catalyst for the de-silylation step, avoiding the use of an aqueous HCl/THF system. This approach led to a procedure with very good E-factor values for each substrate (20–29; see ESI†). The protocol is also applicable to electron-poor aldehydes.

We have reported for the first time a solvent-free multistep process performed by an automated cyclic continuous-flow reactor that allows β-hydroxy esters **3a–c** to be isolated in excellent yields. The significant optimization achieved by using the solvent-free reactor approach is shown by the very low E-factor, falling in the range 1.41–2.09. The combination of flow conditions, solvent-free conditions and recoverable solid catalysts, represents a very promising approach for minimizing the environmental cost of organic synthesis.

This technique opens the route to the realization of automated green reactors able to reduce both labour and environmental costs.

Experimental

All chemicals were purchased and used without any further purification. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100.6 MHz respectively, using a convenient deuterated solvent (reported in the characterization charts) and the residual peak as internal standard, or TMS in the case of $CDCl_3$. IR spectra were recorded with FT-IR instrument, using $CHCl_3$ as the solvent. Column chromatographies were performed by using silica gel 230–400 mesh and eluting as reported in the following characterization charts. Amberlite IRA900F (Amb-F) was purchased from Aldrich as "Fluoride on polymer support".

Products **3b**,[16] **3g**,[10d] **3h**,[10d] **3i**,[16] **3k**,[10b] and **3l**[9a] are known compounds, products **3a**, **3c**, **3d**, **3e**, **3f**, **3g**, **3j** and **6h** are new compounds.

Characterization data and copies of the ^1H and ^{13}C NMR spectra for all compounds **3a–l** and **6h**, and details for the calculation of E-factor are reported in the ESI.†

Representative batch experimental procedure

In a screw capped vial equipped with a magnetic stirrer, 2,4-dimethoxybenzaldehyde (**1a**) (0.166 g, 1.0 mmol), methyl trimethylsilyl dimethylketene acetal (**2**) (0.319 mL, 1.5 mmol) and Amb-F (0.020 g, 0.05 mmol, 2.5 mmol g^{-1}) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 3 h THF (2 mL) was added and the catalyst was filtered off. 20 mol% of DOWEX 50Wx8 H wet (25 mg) was added and the mixture was stirred at 30 °C for 5 h. Brine (1 mL) was then added, the solid catalyst filtered off and the organic phase was extracted with Et_2O. The organic layer was dried over sodium sulfate/potassium carbonate (2 : 1 mixture). Both methyl 2-methylpropionate, coming from the hydrolysis of the excess of **2**, and solvent were removed under high vacuum at 50 °C to give pure product methyl 3-(2′,4′-dimethoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (**3a**) as a colourless oil (91% yield, 0.244 g).

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7 Amberlite IRA900F is a trimethylammonium fluoride on macroreticular polystyrene resin which is commercially available from Aldrich as "Fluoride on polymer support" or as "Fluoride on Amberlyst A-26". Commercially available Amb-F is a hygroscopic solid which contains *ca.* 20 wt% of water. In general we have used water-free Amb-F which was obtained by drying the commercial product under vacuum.

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