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Younes, Sabry H.H.; Hollmann, F.

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A solvent-free synthesis of (thio)ester derivatives using FeCl₃ as a heterogeneous catalyst

Sabry H.H. Younes a,b,* F. Hollmann a,*

a Department of Biotechnology, Delft University of Technology, 2629 HZ Delft, the Netherlands
b Department of Chemistry, Faculty of Sciences, Sohag University, Sohag 82524, Egypt

ABSTRACT

A simple, solvent-free method for the synthesis of (thio)esters from simple acid chlorides at room temperature is reported. Simple FeCl₃ (5 mol%) enables facile, near complete conversion of equimolar starting materials in high selectivity. Recycling of the catalyst has been demonstrated.

Introduction

Thioesters are biologically and synthetically important compounds [1,2] used in a broad range of transformations including acyl transfer [3], peptide coupling [4,5] and thiol protection group [6,7].

Traditionally, thioesters are synthesised from carboxylic acids. The poorly reactive carboxyl group, however, needs activation prior the thioester formation [8–11] thereby adding complexity to the synthesis. Often extensive downstream processing and product purification are necessary.

Therefore, starting from commercially available, already activated carboxyl halides appears an interesting alternative. Interestingly enough, the direct reaction between acid chlorides and thiols is rather slow necessitating catalysis to become preparatively interesting. For example elementary zinc [12] or CsF on Celite® [13] have been reported. As both catalytic systems are challenged by the high catalyst loading (around 1 eq of ‘Catalyst’) as well as by safety and environmental issues, we asked ourselves if somewhat less problematic and readily available metal salts may also catalyse the desired acylation of thiols.

Results and discussion

A preliminary test incubating benzoyl chloride with ethanethiol (1 eq. each) at room temperature was unsuccessful and the starting materials were fully recovered after 24 h. We therefore tested a range of Lewis acids to facilitate the nucleophilic attack of the thiol to the carbonyl group (Table 1).

In the preliminary screening, a comparably high catalyst loading of 20 mol% was used. With FeCl₃, this catalyst loading, however, can be reduced significantly and already at 5 mol% full conversion was attained after 24 h incubation at room temperature (Fig. 1).
Also the recyclability of the FeCl₃/C₆H₂O catalyst was satisfactory as after 5 consecutive re-uses still 90% of conversion could be attained (Fig. 2).

Next, we evaluated the product scope of the proposed FeCl₃/C₆H₂O-catalysed thioester formation (Fig. 3). A range of aromatic and aliphatic acid chlorides as well several thiols were evaluated. It is worth noting that all reactions performed resulted in full conversion of the starting materials and that only the desired products were observed (i.e. close to 100% conversion and yield).

Encouraged by these excellent results, we also tried our catalytic system for the esterification of acid chlorides with alcohols (Fig. 4). Again, all target products were obtained in quantitative yields.

### Conclusion

In conclusion, with this contribution we demonstrate that (thio)esterification reactions of simple acid chlorides with a broad range of thiols and alcohols can easily be accelerated by simple FeCl₃. Especially the high yield and superb purity of the desired products using equimolar amounts of starting materials makes this approach attractive for the synthesis of (thio)esters. It is worth noting that in these experiments no additional solvent was used and that the reactions have been performed at room temperature. Hence, neither energy-intensive reaction conditions nor extensive DSP apply. Together with the full conversion and exclusive selectivity of the reactions, we believe that this methodology represents an example of Green Chemistry wherein the environmental impact of the (thio)ester formation is minimised. Admittedly, the stoichiometric by-product (HCl) is a strong, corrosive acid; but it can be recovered at larger scale and be used as industrial reagent itself.
Fig. 3. Scope and generality in the synthesis of thioesters using acid chloride derivatives and thiols. General conditions. Acid chloride derivatives (1 mmol), alkanethiol (1 mmol), FeCl₃·H₂O (5 mol%), rt. The reaction progress was monitored by TLC, times indicated correspond to the reaction time after which no starting materials were observable.
Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References


Fig. 4. Synthesis of esters using acid chlorides and ethanol derivatives. General conditions. Acid chloride derivatives (1 mmol), alcohol (1 mmol), FeCl₃ / C₆H₂O (5 mol%), rt. The reaction progress was monitored by TLC, times indicated correspond to the reaction time after which no starting materials were observable.