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A solvent-free synthesis of (thio)ester derivatives using FeCl_3 as a heterogeneous catalyst

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ABSTRACT

A simple, solvent-free method for the synthesis of (thio)esters from simple acid chlorides at room temperature is reported. Simple FeCl_3 (5 mol%) enables facile, near complete conversion of equimolar starting materials in high selectivity. Recycling of the catalyst has been demonstrated.

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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 CeliteTM [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).

All of the earth abundant metal salts evaluated significantly accelerated the thioester formation but $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ clearly stood out in terms of conversion. We, therefore, continued our investigations with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$.

Interestingly, even though $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ is commonly used as a catalyst for example for the hydroarylation of styrenes [14], synthesis of *cis*-oxazolines [15], or the hydroalkoxylation of alkenes [16,17], to the best of our knowledge, it has so far not been considered as catalyst for (thio)ester synthesis.

In the preliminary screening, a comparably high catalyst loading of 20 mol% was used. With $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, 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).

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Table 1
Evaluation of different salts as catalysts for the formation of ethyl thiobenzoate.

Entry	Catalyst	(mol%)	Isolated yield (%) ^a
1	None	–	0
2	CaO	20	30
3	CaCl ₂	20	30
4	FeCl₃	20	100
5	Al ₂ O ₃	20	40
6	MgSO ₄	20	50
7	AlCl ₃	20	60

General reaction conditions. Benzoyl chloride (1 mmol), ethanethiol (1 mmol), catalyst 20 mol%, rt, t = 24 h. (a) based on ¹H NMR analysis.

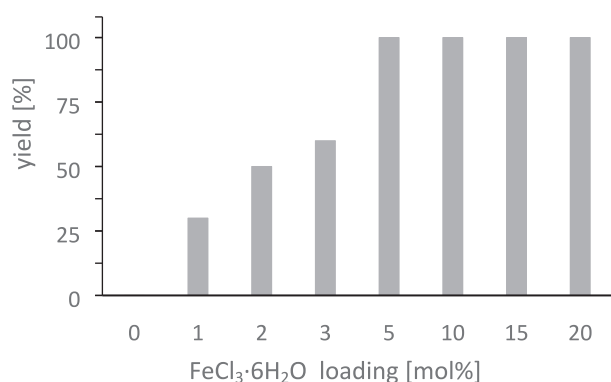


Fig. 1. Influence of the FeCl₃·6H₂O loading on the yield of ethyl thiobenzoate. General conditions. benzoyl chloride (1 mmol), ethanethiol (1 mmol), rt, t = 24 h.

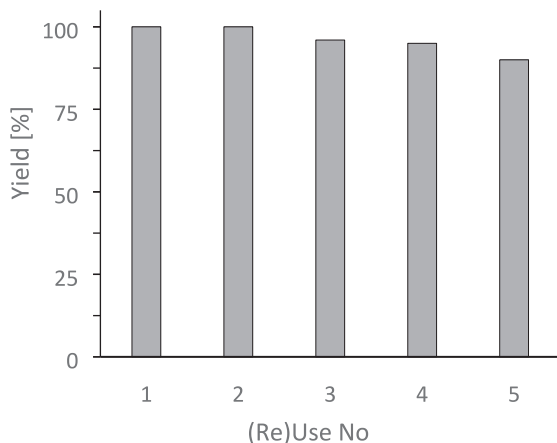


Fig. 2. Recycling trials for the FeCl₃·6H₂O catalyst. General conditions: benzoyl chloride (1 mmol), ethanethiol (1 mmol), FeCl₃·6H₂O (5 mol%) rt, t = 24 h. After the completion of the reaction, the mixture was diluted with ethyl acetate and filtrated. The isolated catalyst was washed with ethyl acetate, air-dried and used for the next cycle.

Also the recyclability of the FeCl₃·6H₂O 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 FeCl₃·6H₂O-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.

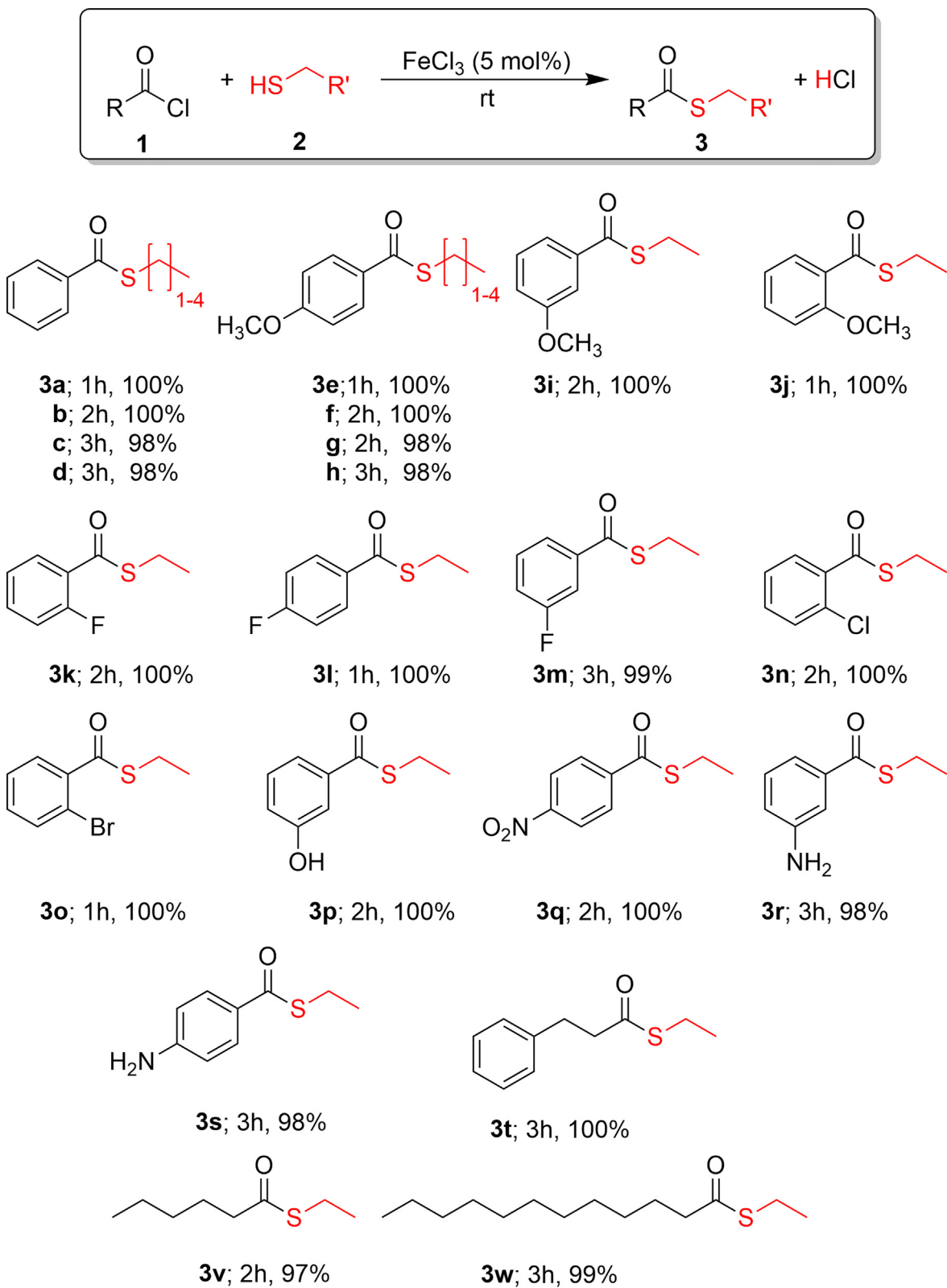


Fig. 3. Scope and generality in the synthesis of thioesters using acid chloride derivatives and thiols. General conditions. Acid chloride derivatives (1 mmol), alkanethiol (1 mmol), $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (5 mol%), rt. The reaction progress was monitored by TLC, times indicated correspond to the reaction time after which no starting materials were observable.

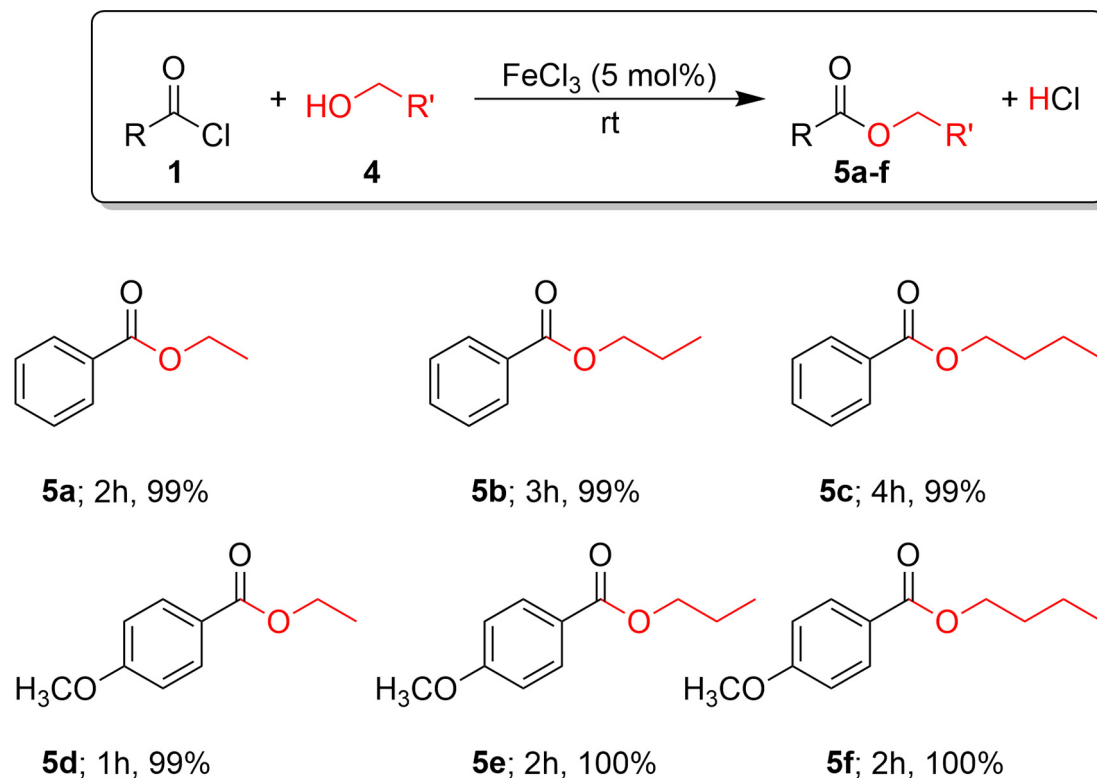


Fig. 4. Synthesis of esters using acid chlorides and ethanol derivatives. General conditions. Acid chloride derivatives (1 mmol), alcohol (1 mmol), $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (5 mol%), rt. The reaction progress was monitored by TLC, times indicated correspond to the reaction time after 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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