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SELECTIVE AND DIRECT ACTIVATION OF *O*-ESTERS. CONVERSION OF PHENYL AND 2,2,2-TRIFLUOROETHYL ESTERS INTO ACYL IMIDAZOLIDES

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The protection and activation of carboxylic acids are important chemical operations. In particular, syntheses of naturally occurring macrolides very often require i) differentiation between two (or more) carboxylic acids of a synthetic intermediate by means of appropriate protection and further ii) selective activation of only one group under mild, neutral or nearly neutral conditions. Utilization of *S-tert*-butyl thiol esters in the synthesis of methymycin[1] illustrates the case. In further pursuing the project concerning macrolide syntheses, we felt that there was still a need to devise another such technique whereby only one of two *O*-esters (but not *O*- and *S*- mixed esters) of a compound could be transformed selectively and directly into a reactive functional group useful for further operations. A difficulty which commonly arises in the attempted direct activation of an ester is that the desired reaction is usually slow

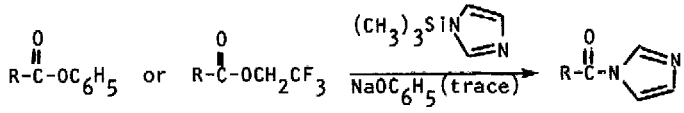
$$RCOOR' + Y^- \rightleftharpoons RCOY + OR'^- \qquad 1)$$

$$OR'^- + MY \longrightarrow MOR' + Y^- \qquad 2)$$

and/or proceeds more slowly than its reverse reaction (equation 1).[2] However, the reverse reaction can be suppressed by removing OR'^- from the above reaction system by selecting a proper reagent (MY in equation 2) which consists of a relatively hard acid (M^+) having a strong affinity for oxygen and a rather soft, compared with OR^-, base (Y^-). Obvious candidates for M^+ are, for example, R''_3Si^+, R''_2Al^+, and R''_2B^+. With this simple premise in mind, we have examined several combinations of R' and MY and have found a solution for the problem. Both phenyl and 2,2,2-trifluoroethyl (R') esters possess an acceptable degree of stability required for a protective group, yet they are readily converted into the corresponding acyl imidazolides upon treatment with *N*-

trimethylsilylimidazole (MY) at room temperature. A trace amount of sodium phenoxide is needed to produce Y^- and thus initiate the above cycle. The reaction mode and reactivity of an acyl imidazolide (I) in a sense resemble those of an acyl chloride and I can thus undergo many versatile transformations. In addition to reactions which are already well-documented for this reactive species,[3] several new reactions have been found to proceed satisfactorily. Given below is a summary of the present method for the preparation of I and its applications.

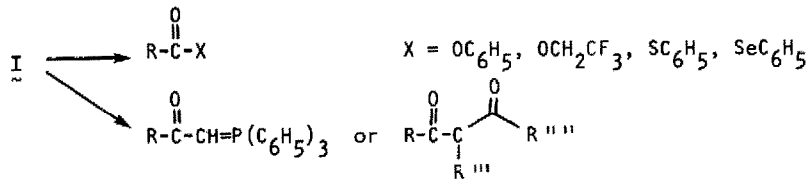
One equiv. of phenyl cyclohexanecarboxylate[4] (0.1 *M*) in tetrahydrofuran was treated with 1.1 equiv. of *N*-trimethylsilylimidazole in the presence of 0.01 equiv. of sodium phenoxide at room temperature for 15 min. Removal of the solvent and side products under reduced pressure and precipitation of the catalyst by dissolving the residue in cyclohexane provided a quantitative yield of the imidazolide of cyclohexanecarboxylic acid (isolated yield >95%). This conversion proceeded equally well with the phenyl esters of aromatic, primary, and secondary carboxylic acids (in all cases the isolated yields were more than 95%). The 2,2,2-trifluoroethyl ester of these carboxylic acids, prepared in the manner described below, also provided the corresponding acyl



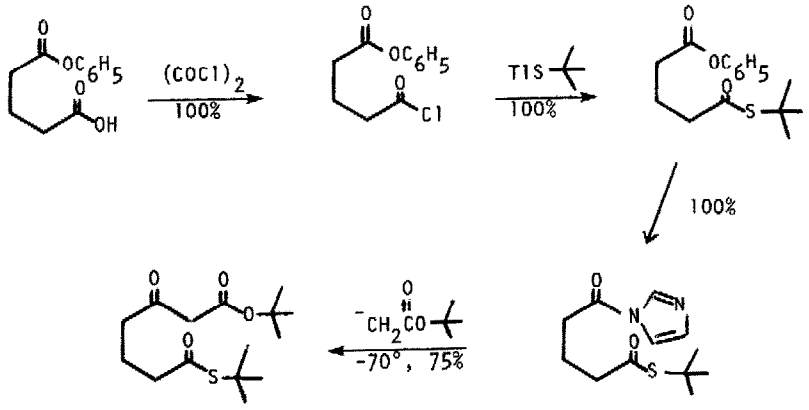
R = *c*-C_6H_{11}, $CH_3(CH_2)_4$-, $CH_3(CH_2)_3CHC_2H_5$, C_6H_5

imidazolides quantitatively under the same conditions. However, *S-tert*-butyl thiol and alkyl esters did not react, and even benzenethiol esters survived virtually untouched. The above method thereby provides a means to distinguish these esters from phenyl and 2,2,2-trifluoroethyl esters. Obviously R'OH (in equation 1) must have a certain degree of acidity for the reaction to proceed.

As mentioned above, acyl imidazolides resemble the corresponding acid chlorides. Thus, treatment of 1 equiv. of the imidazolide of cyclohexanecarboxylic acid (0.1 *M*) in cyclohexane with 1.2 equiv. of benzenethiol and 0.02 equiv. of sodium phenoxide provides the benzenethiol ester quantitatively in 15 min. at room temperature. Preparation of the benzeneselenol ester also proceeds satisfactorily, although excess benzeneselenol is required because of the facile formation of diphenyldiselenide apparently caused by technical problems. Conversion of the acyl imidazolide into the 2,2,2-trifluoroethyl and phenyl esters presents no difficulty (again 100%,



15 min.). Preparations of a triphenylacylmethylenephosphorane[1b] and a ketoester[5] utilizing an acyl imidazolide have already been examplified, and a reaction sequence which has been used as a model for the construction of a fragment of a macrolide is shown below.[6,7]



It should be pointed out that the activation of the esters by the present method does not require hydrolysis to the carboxylic acid, a process that very often induces undesired side reactions (such as reverse aldol condensation or dehydration, with for example β-hydroxy acids) in the reaction of complex molecules. Moreover, even in such molecules as γ- or δ-hydroxy esters where the free acid may be safely obtained by hydrolysis, the spontaneous formation of a γ- or δ-lactone makes the direct activation of the ester essential for further synthetic operations.

References

1. (a) S. Masamune, C.U. Kim, K.E. Wilson, G.O. Spessard, P.E. Georghiou, and G.S. Bates, *J. Amer. Chem. Soc.*, 97, 3512 (1975); (b) S. Masamune, H. Yamamoto, S. Kamata, and A. Fukuzawa, *ibid*, 97, 3513 (1975); (c) S. Masamune, S. Kamata, and W. Schilling, *ibid*, 97, 3515 (1975).
2. This is the case for example when one tries to prepare a carboxylic acid chloride from the corresponding methyl ester.
3. H.A. Staab, *Angew. Chem. Intern. Edit.*, 1, 351 (1962).
4. The esters of 2-methylphenol and 4-methoxyphenol are converted to the acyl imidazolides as rapidly as the phenol ester. However, the 2,6-dimethylphenol ester fails to react even in refluxing tetrahydrofuran, presumably because of the steric demands of the reaction.
5. Unpublished results obtained in this laboratory. See also S.L. Hartzell and M.W. Rathke, *Tet. Lett.*, 2757 (1976).
6. For the use of thallium (I) thiolates for the formation of thiol esters see: S. Masamune, S. Kamata, Y. Sugihara, J. Diakur, and G.S. Bates, *Can. J. Chem.*, 53, 3693 (1975).
7. A phenyl ester is a relatively reactive species but its reactivity is much less than an acyl imidazolide. In fact, the last step of this sequence did not proceed satisfactorily with the phenyl ester.