In Search of Practical Esterification

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Esterification is one of the most important reactions in organic synthesis.[1] It has a long history in both laboratory work and industrial processes on account of its versatility. The simple condensation between a carboxylic acid and an alcohol is the most straightforward way to this end. Thus, numerous methods have been reported, yet they are not necessarily satisfactory from a practical point of view. The difficulty stems primarily from the equilibration of the condensation reaction. The commonest approach to bias the equilibrium in favor of the product side is either by the use of one reactant in excess over the other or the continuous removal of the water formed. The former treatment is not desirable in terms of "atom economy"[2] since the excess reactant remains to be separated from the product mixture. On the other hand, the complete removal of water is not easy, but a variety of dehydration methods have been put forth. Azeotropy is most frequently invoked, while the addition of dehydrating agents is an alternative choice, although 100% conversion and, hence, 100% yield are, in general, not easy to achieve. Another problem emerges from the base or acid catalysts which are inevitably employed in this reaction. Under such conditions, the tolerance of a wide spectrum of functional groups that is often required in modern synthetic chemistry is not achievable.

It follows from these circumstances that the ultimate goal of esterification should meet the following requirements: 1) the relative amounts of reactant carboxylic acid and alcohol are regulated to the precise 1:1 ratio, 2) the catalyst is neutral, 3) no dehydration technology is necessary, and 4) both conversion and yield are 100%. The esterification by the simplest combination of carboxylic acid, alcohol, and catalyst alone met with success on some occasions, yet the employment of one of the reactants in excess was necessary to attain the satisfactory conversion.[3] Therefore, a catalytic version that allows a 1:1 reactant stoichiometry has long been desired. Recently, two Japanese groups have come up with new protocols to overcome such difficulties (Table 1).

Table 1. Esterification by use of equimolar amounts of carboxylic acid and alcohol.

$$\underset{\text{1 equiv}}{\mathrm{RCOOH}} + \underset{\text{1 equiv}}{\mathrm{R'OH}} \xrightarrow{\text{cat.}} \mathrm{RCOOR'}$$

Author	Conditions
Yamamoto	$HfCl_4 \cdot 2THF$ (0.2 mol%); Soxhlet extraction with 4-Å molecular sieves; toluene, *o*-xylene, mesitylene
Tanabe	$Ph_2NH_2^+OTf^-$ (1–10 mol%); toluene, 80°C

Yamamoto and co-workers disclosed, after the screening of various Lewis acids, that commercially available $HfCl_4 \cdot 2THF$ was the most effective for the condensation between an equimolar mixture of carboxylic acid and alcohol.[4] The reaction was run in refluxing toluene, *o*-xylene, or 1,3,5-mesitylene and furnished nearly quantitative yields of esters (91 to >99%). The catalyst activity is so high that only a 0.2 mol% loading is necessary to achieve high conversions. Sterically hindered secondary alcohols as well as primary alcohols were used, although the reaction with tertiary alcohols did not proceed. Even the condensation between benzoic acid and phenol, which usually proceeds sluggishly, was feasible by increasing the catalyst concentration to 1 mol%. This result is indicative of the broad applicability of the present protocol. The application was further extended to polyester formation by polycondensing ω-hydroxycarboxylic acids or equimolar amounts of aliphatic dicarboxylic acids and aliphatic diols. Despite these advantages, the present protocol seems to suffer from some inconvenience. Although no mention was made on the compatibility of the functional groups, acid-sensitive groups are probably not tolerated as a result of the acidic nature of the catalyst. Moreover, the reaction system is sensitive to water and thus the rigorous dehydration by Soxhlet extraction with 4-Å molecular sieves is indispensable.

Tanabe and co-workers reported another approach which demands no dehydration reagents or equipment.[5] Diphenylammonium triflate, which is obtainable from diphenylamine and triflic acid, catalyzed the condensation of equimolar amounts of carboxylic acid and alcohol (Table 1). The reaction proceeded by heating the reactants in toluene at 80°C without recourse to any dehydration technique. The products were isolated by column chromatography in substantially, but not perfectly, high yields (89–96%, except for one case (78%)). Primary and secondary alcohols were used and some functionalities such as ketone and cyclopropane were tolerated.

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In the above protocols the reaction mixture was contaminated by small amounts of starting materials, but the high yields enabled facile isolation of the pure product esters by column chromatography.[6] There is no problem so long as the isolation of the esters is solely targeted. However, this is not the case in practical processes wherein the remaining reactants need to be recovered. The 1:1 stoichiometry is truly effective only if the 100% conversion is reached because otherwise the two components (recovered carboxylic acid and alcohol) should be separated from the product mixture, which is a less favorable situation than the reaction employing one of the reactants in excess. In this case, the recovery of only one reactant is necessitated on account of the more facile feasibility of the 100% conversion. As such, the 100% yield with equimolar amounts of the reactants which demands no purification step still remains a challenge. The levels of conversion and yield attained in the above studies are not satisfactory in such a strict sense. Nevertheless, these protocols have no doubt made a big step forward along this line and, accordingly, these achievements are expected to pave the way to the ultimate goal.

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Recent Advances in High-Resolution Solid-State NMR Spectroscopy**

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It has long been known that NMR spectroscopy can yield precise information about the structure and dynamics of large biological molecules. The vast majority of NMR studies have been carried out on liquid solution samples owing to the good resolution, namely narrower peaks, as compared to solid samples. Even so, it is often necessary to study the solid state for insoluble biopolymers, such as aggregates or amyloids. There are also significant classes of materials whose properties lie between the solid and liquid states: Membranes and membrane-bound proteins are not strictly solid and may be more accurately described as liquid crystals, since they have a high degree of molecular alignment. Other examples would be extremely viscous liquids or gels, where the molecular mobility is slow or limited. For all of these systems, solid-state NMR investigations can be particularly useful. The question then is not whether to study the liquid or solid form, but how one can get the best information from solid-state NMR methods.

The difficulties of solid-state NMR are due to large anisotropic interactions, namely the through-space dipole–dipole coupling, more often called the dipolar coupling, and the orientational dependence of the chemical shift, called the chemical shift anisotropy (CSA). (Some nuclei possess an electric quadrupole moment, which creates yet another anisotropic interaction, but that will not be discussed further in this article.) Rapid molecular motion in the liquid state removes anisotropic interactions, except for their effects on relaxation. However, in solids these interactions are present at their full strength and they must be dealt with appropriately. There are different experimental approaches in solid-state NMR spectroscopy, depicted in Figure 1, which either circumvent or utilize these anisotropic interactions in order to investigate structures of biological systems.

MAS Solid-State NMR

One approach is to use magic-angle spinning (MAS) in combination with high-power radio-frequency decoupling to remove the chemical shift anisotropy and the dipolar couplings (Figure 1 a). MAS spectra of solids often exhibit sharp resonances at frequencies determined solely by the isotropic chemical shift. In this respect, they resemble NMR spectra of liquids, and the information content is at least qualitatively similar. For example, in multidimensional MAS spectra, chemical-shift correlations are measured, and these yield information about connectivity and proximity, just as in multidimensional NMR of solutions. In the past, MAS solid-

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