



The effect of solvent polarity on the rate of the Mitsunobu esterification reaction



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ARTICLE INFO

Article history:

Received 16 January 2015

Received in revised form 19 March 2015

Accepted 13 April 2015

Available online 18 April 2015

Keywords:

Mitsunobu

Rate

Ion-pair

Solvent-polarity

Mechanism

ABSTRACT

The rate of the Mitsunobu esterification reaction of ethanol or isopropanol with benzoic acid was found to be much faster in non-polar solvents. The logarithm of the rate constant was inversely proportional to the solvent polarity, as defined by E_T values. Typically, the rate constant for ethyl benzoate formation in THF was 100 times greater than that in MeCN. The presence of either sodium benzoate or excess benzoic acid resulted in a decrease in rate. Each of the main species involved in the Mitsunobu esterification reaction, the alcohol starting material, dialkoxyphosphorane, alkoxyphosphonium salt and ester product, was detected by proton NMR analysis. The possible role of ion pair aggregates or clusters, prior to rate-determining S_N2 attack of carboxylate on the alkoxyphosphonium ion, is discussed. An explanation is provided as to why the yield in the Mitsunobu reaction is often higher in non-polar solvents.

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1. Introduction

The Mitsunobu reaction was discovered 47 years ago^{1,2} and remains one of the most useful reactions in organic synthesis, particularly for the esterification of alcohols where inversion of configuration of the hydroxyl group is required. A number of reviews are available.^{3–12} A SciFinder search of ‘Mitsunobu Reaction’ gave more than 2600 hits, with over half of these in the last 10 years. Although the mechanism of the Mitsunobu reaction (Scheme 1) has been the subject of a large number of investigations^{13–47} including DFT,⁴⁶ as far as we are aware there have been no specific studies of the effect of solvent polarity on the rate of the Mitsunobu esterification reaction. Yet, the solvent can sometimes have a dramatic effect on the outcome of the Mitsunobu reaction. For example, Dodge et al.⁴⁸ have shown that the Mitsunobu inversion of menthol with 4-nitrobenzoic acid in THF gives an 83% yield, but when the reaction is carried out in CH_2Cl_2 the yield is only 3%. Similarly, Loibner and Zbiral⁴⁹ obtained a 73% yield of an inverted steroid benzoate when the reaction was carried out in benzene, but no product was observed in THF. Hughes et al.²² have studied the rate of the Mitsunobu esterification reaction as a function of acid pKa, but in only one solvent (CH_2Cl_2). In a later study,

Hughes and Reamer³³ reported that the betaine **1**, reacts with carboxylic acids to form acylhydrazines, and that this reaction was faster in more polar solvents.

In this paper, we report a study of the relative rate of the Mitsunobu esterification reaction as a function of solvent polarity. The choice of solvent and its effect upon the rate of a homogeneous chemical reaction can often provide an insight into the mechanistic pathway of the reaction.

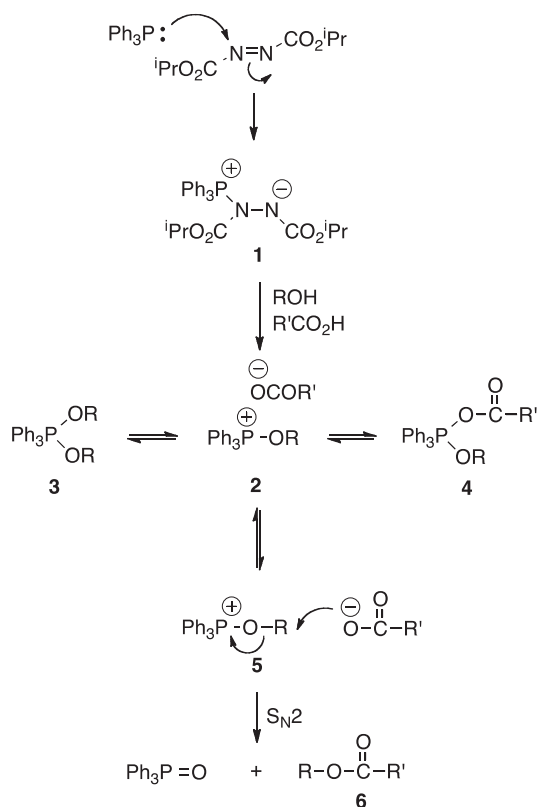
2. Results and discussion

A simple system was chosen for this study, the esterification of ethanol (or isopropanol) by benzoic acid with triphenylphosphine/diisopropyl azodicarboxylate (TPP/DIAD). It should be noted that the acids of choice for the stereochemical inversion/esterification of hindered secondary alcohols are 4-nitrobenzoic acid^{27,36} and chloroacetic acid.^{27,50} We chose benzoic acid for this study to ensure that the rate-determining step was the final S_N2 displacement (Scheme 1). With stronger acids, especially when excess acid is used, the alcohol activation step (**1** → **2**, Scheme 1) can become rate-determining.²²

The procedure initially followed (Protocol A) involved the dropwise addition of DIAD (0.5 mmol) to a pre-mixed solution of TPP (0.5 mmol), benzoic acid (0.34 mmol), benzophenone (0.08 mmol as internal standard) and alcohol (0.34 mmol) in dry solvent (5 mL) at 0 °C under a nitrogen atmosphere. At recorded time intervals, small aliquots were removed from the reaction mixture and added to a known volume of an acetonitrile/water

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solution to quench the reaction prior to analysis by HPLC. A standard curve was created using mixtures of benzophenone and ethyl (or isopropyl) benzoate at known concentrations. From this calibration plot, a linear relationship was calculated between the integral ratio and the molar ratio of the product versus internal standard, thus providing an indication of the experimental yield at a given reaction time. Half-lives were estimated by plotting the experimental yield against reaction time (for very fast reactions) or from the apparent first-order rate constants when these could be determined.

A total of eight different solvents were studied (Table 1).

The dielectric constant (ϵ_R) provides a rough measure of a solvent's polarity and ability to dissolve ionic salts, but is generally not as useful for organic reactions as the more comprehensive E_T solvent polarity scale determined by Dimroth and co-workers.⁵² The E_T scale is an empirical scale of solvent polarity derived from the change of color of a solvatochromic dye in response to solvent polarity. This empirical scale and others such as Kosower's Z -values,⁵³ generally provide a more useful scale of solvent polarity than any one physical characteristic, such as the dielectric constant. Note that the order of E_T values correlates well with other empirical

Table 1
Some parameters of solvent polarity^a (25 °C)

Solvent	E_T (kcal.mol ⁻¹)	Z (kcal.mol ⁻¹)	ϵ_R
THF	37.4	58.8	7.58
CHCl ₃	39.1	63.2	4.81
HMPA	40.9	62.8	29.60
DMF	43.8	68.4	36.71
DMSO	45.1	71.1	46.45
MeCN	45.6	71.3	35.94
<i>i</i> -PrOH	48.4	76.3	19.92
EtOH	51.9	79.6	24.55

^a Data obtained from Ref. 51.

scales such as Z -values⁵³ but that there is no correlation whatsoever between these two empirical parameters and the dielectric constant.

Table 2 presents the half-lives for alkyl benzoate synthesis and demonstrates the influence of temperature and solvent. The entries are arranged in order of increasing solvent polarity (as listed in Table 1) and the results indicate that ester formation is very fast regardless of reaction medium. Due to the speed and complexity of the reaction, a detailed investigation of the reaction kinetics and the determination of absolute rate constants was not attempted. However, a comparison of the half-lives clearly shows that an increase in solvent polarity results in a significant reduction in the rate of esterification. In chloroform at 0 °C, for example, the synthesis of ethyl benzoate was essentially complete within 1 min of DIAD being added. Use of acetonitrile, on the other hand, resulted in a decrease in reaction rate to give a half-life of several minutes. At 0 °C, ethyl benzoate synthesis in acetonitrile is thus ≥ 15 times slower than in chloroform.

Replacement of ethanol as substrate by a secondary alcohol resulted in a significant rate decrease as expected. Hence, the reaction half-lives at 0 °C in both chloroform and acetonitrile were increased by a factor of >20 when isopropanol was used. This observation is consistent with reports in the literature^{25,26,54–58} that regioselective esterification is generally obtained with polyhydroxylic compounds. For example, the primary position of 1,3-diols is the least hindered and therefore, the favored reaction site.⁵⁹

The data for the esterification of the more sterically hindered isopropanol followed the same trend observed for ethanol (i.e., a decrease in esterification rate with increasing solvent polarity, as indicated by E_T values, was evident). The major difference noted was when each alcohol was also used as the solvent. With ethanol as solvent/reactant, esterification was very much slower than when isopropanol was the solvent/reactant. We attribute this to a combination of a higher solvent polarity (E_T 51.9 vs 48.4) and lower pKa (15.85 vs 16.48)⁶⁰ for ethanol compared with isopropanol. Both factors would reduce the rate of the reaction. Hughes et al.²² have shown how sensitive the reaction is to the pKa of the acid component and the amount of acid present. In the more acidic ethanol, the nucleophilicity of the benzoate ion would be reduced, thereby slowing down the S_N2 step of the reaction (5 \rightarrow 6, Scheme 1).

Table 2
Influence of temperature and solvent on ester synthesis^{a,b}

Solvent	$t_{1/2}$ (min) ^c Ethyl benzoate 0 °C	$t_{1/2}$ (min) ^c Ethyl benzoate 20 °C	$t_{1/2}$ (min) ^c Isopropyl benzoate 0 °C	$t_{1/2}$ (min) ^c Isopropyl benzoate 20 °C
THF	<0.1			0.3
CHCl ₃	<0.1		2.2 ^a	1.0
CHCl ₃ (25 mL)	0.22			
HMPA	~0.2			
DMF	~0.3 ^a			1.5 ^a
DMF (2 equiv NaOCOPh)	1.0			
DMSO		1.5 ^a		3.4
MeCN	1.5 ^a		51 ^a	9.5 ^a
MeCN (10 mL)	2.2			
MeCN (2 equiv acid)	3.5 ^a			
MeCN (2 equiv NaOCOPh)	2.2			
<i>i</i> -PrOH			52	11.2
EtOH	315			

^a Standard reaction conditions: alcohol (0.34 mmol), benzoic acid (0.34 mmol), TPP (0.50 mmol) and benzophenone (0.08 mmol) pre-mixed in solvent (5 mL) before final addition of DIAD (0.50 mmol) at 0 °C.

^b * indicates the result of at least two separate determinations.

^c Error in half-life determination is approximately $\pm 20\%$.

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