Tetrahedron xxx (2015) 1–7

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

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

David Camp, Peta J. Harvey [†], Ian D. Jenkins [*]

Eskitis Institute, Griffith University, Brisbane, QLD, 4111, Australia

ARTICLE INFO

Article history:
Received 16 January 2015
Received in revised form 19 March 2015
Accepted 13 April 2015
Available online xxx

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.

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 Zbiral[49] 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 Reamer[33] 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.

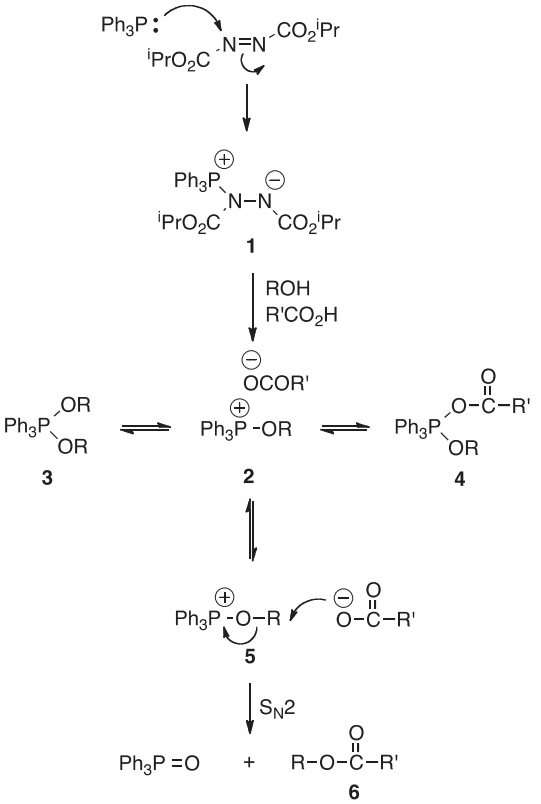
2. Results and discussion

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

* Corresponding author. Tel.: +61 (07) 3735 6025; fax: +61 (07) 3735 6001; e-mail address: i.jenkins@griffith.edu.au (I.D. Jenkins).
† Present address: Institute of Molecular Bioscience, University of Queensland, Australia.

http://dx.doi.org/10.1016/j.tet.2015.04.035
0040-4020/



Scheme 1. Mechanism of the Mitsunobu reaction.

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 scales such as *Z*-values[53] 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**→**6**, Scheme 1).

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*PrOH	48.4	76.3	19.92
EtOH	51.9	79.6	24.55

[a] Data obtained from Ref. 51.

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*	1.0
$CHCl_3$(25 mL)	0.22			
HMPA	~0.2			
DMF	~0.3*			1.5*
DMF (2 equiv NaOCOPh)	1.0			
DMSO		1.5*		3.4
MeCN	1.5*		51*	9.5*
MeCN (10 mL)	2.2			
MeCN (2 equiv acid)	3.5*			
MeCN (2 equiv NaOCOPh)	2.2			
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 ± 20%.

Please cite this article in press as: Camp, D.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.04.035

The definitive mechanistic work of Hughes and co-workers[22] established that the rate of esterification is reduced in the presence of an excess of carboxylic acid. This effect was confirmed in the esterification of benzoic acid with ethanol. Thus, in acetonitrile at 0 °C, the half-life for formation of ethyl benzoate increased from 1.5 min to 3.5 min with the use of two equivalents of acid. As suggested by Hughes and co-workers,[22] increasing the amount of benzoic acid results in a decrease in the kinetic reactivity of the benzoate anion thereby reducing the rate of the final S_N2 displacement reaction.

We also investigated the effect of added sodium benzoate on the rate of esterification. The addition of sodium benzoate has previously been found by Walker et al.[20] to dramatically accelerate the synthesis of trifluoroacetate esters via the Mitsunobu reaction. Under the present experimental conditions in DMF and acetonitrile, the addition of 2 M equivalents of sodium benzoate resulted in a significant decrease in the rate of ethyl benzoate formation. This apparently anomalous result is readily explained as Walker and co-workers[20] employed a much stronger acid (trifluoroacetic acid) in their Mitsunobu reaction. Benzoate, being a much stronger base than trifluoroacetate, results in acceleration of the alcohol activation step (**1**→**2**, Scheme 1) rather than the S_N2 step as discussed by Hughes et al.[22] The reduction in rate observed in the present study is consistent with a kinetic salt effect where the addition of an external salt affects the rate of the reaction in the same way as an increase in the solvent polarity.[51,61]

It is clear from Table 1 that increasing the solvent polarity results in a significant reduction in the rate of Mitsunobu esterification with an approximately linear relationship between the logarithm of the reaction half-life and the solvent polarity (Fig. 1). This decrease in rate with increasing polarity is readily explained by the Hughes-Ingold rules[62–64] if we assume that the rate-determining step is the final S_N2 reaction (**5**→**6**, Scheme 1). As summarized by Reichardt,[51] an increase in solvent polarity leads to a rate decrease for those reactions in which the activated complex has a lower charge density than the reactant molecules. In the present case, the charge in the transition state relative to the reactants (the alkoxyphosphonium cation and benzoate anion) will be decreased. For example, if the transition state resembles the products, by the Hammond postulate[65] the charge would be close to zero as the ester and triphenylphosphine oxide are both neutral. If, on the other hand, the transition state is early as suggested by the kinetic results of Hughes et al.,[22] and recent theoretical calculations,[46] then there will still be a reduction in charge in the transition state, but it will be a more modest reduction. The decrease in rate of the Mitsunobu reaction with increasing polarity of the solvent contrasts with analogous nucleophilic substitution reactions where the leaving group is halide, mesylate or triflate for example. In these latter reactions, the S_N2 reaction rate *increases* with increasing polarity of the solvent.[51]

There is evidence that the mechanism of the Mitsunobu esterification reaction may involve the formation of ion pair aggregates,[20,25,66–70] wherein a positive phosphorus ion in one ion pair is in part electrically neutralized by the negative carboxylate moiety of another ion pair (Fig. 2, shown as a linear array for illustrative purposes). A duplex mechanism involving a 12-membered ring (Fig. 3) is also possible.[25] Polar solvents and salts could easily interfere with the formation of such ion pair aggregates (or break the chain depicted in Fig. 2), thereby inhibiting the S_N2 process.

2.1. Apparent first-order kinetics

In an attempt to slow the reaction (being too fast to measure accurately in non-polar solvents), an excess of benzoic acid was employed (Protocol B). DIAD (0.66 mmol) was added dropwise to a stirred solution of TPP (0.66 mmol), ethanol (0.34 mmol) and benzophenone (0.05 mmol) in solvent (4 mL) under a nitrogen atmosphere at −15 °C. An excess of benzoic acid (1.31 mmol, four-fold relative to alcohol; two-fold relative to betaine) in solvent (1 mL) was then added and the solution maintained at 0 °C. Under these conditions, all of the alcohol was consumed to form dialkoxytriphenylphosphorane (**3**, R=Et). Addition of benzoic acid led to rapid formation of the corresponding alkoxyphosphonium benzoate (**2**, R=Et, R′=Ph). Both of these steps were confirmed by proton NMR experiments (described later). The excess acid solvates the benzoate nucleophile slowing the reaction as described by Hughes.[22] The kinetics were roughly first-order (i.e., first-order in alkoxyphosphonium carboxylate), consistent with the results obtained by Hughes et al.[22] for the esterification of a secondary alcohol with formic acid. It should be noted, however that although the rate of formation of ester appeared to follow first-order kinetics, at least in the early stages of the reaction, the half-life was not independent of the concentration of alkoxyphosphonium salt. For example, in MeCN using protocol A, halving the concentration of ethoxyphosphonium benzoate resulted in an increase in the half-life from 1.5 min to 2.2 min (Table 1). Similarly, in DMF using protocol B, halving the concentration of ethoxyphosphonium benzoate resulted in an increase in the half-life from 6.6 min to 14 min. As the half-life of a first-order reaction is *independent* of the initial concentration, then the reaction cannot be a true first-order reaction. The data is more consistent with a second-order reaction (as expected for an S_N2 process), where the half-life is inversely proportional to the initial concentration.

Hughes and co-workers attributed this unusual rate dependency (S_N1 kinetics, first-order in alkoxyphosphonium ion, zero-order in carboxylate) to salt effects. However, apparent first-order kinetics could also be a result of ion pair clustering. Thus, if the alkoxyphosphonium carboxylate were to form ion pair aggregates prior to (rate-determining) S_N2 displacement as in Fig. 2 or Fig. 3, each benzoate ion is associated with *one* alkoxyphosphonium ion. External benzoate ion would have no effect on the concentration of benzoate within the ion pair aggregates. The rate of ester formation would be dependent on the concentration of ion pair aggregates that, in turn, would depend on the concentration of alkoxyphosphonium benzoate. Conversely, in the presence of a swamping electrolyte (n-Bu_4NBF_4 was used by Hughes et al.[22]),

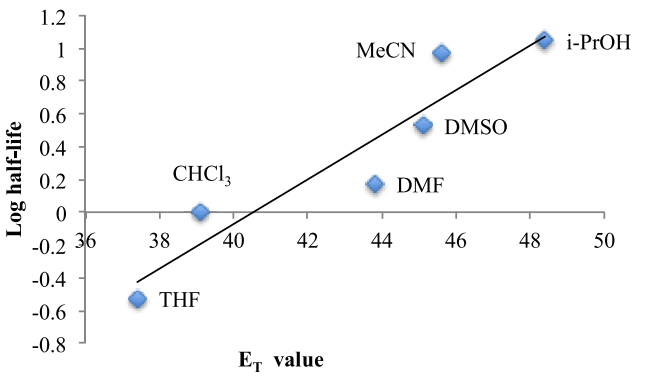


Fig. 1. Correlation between E_T values and log half-lives for the Mitsunobu esterification of benzoic acid with isopropanol at 20 °C.

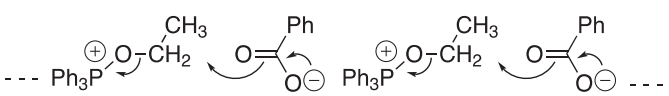


Fig. 2. Possible mechanism of S_N2 step via an ion-pair aggregate.

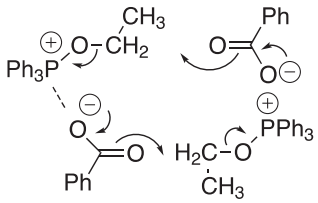


Fig. 3. Alternative mechanism of S_N2 step via an ion-pair duplex.

the ion pair aggregates would be broken down and the rate of ester formation would revert to a normal second-order reaction (first-order in alkoxyphosphonium ion, first-order in carboxylate as observed by Hughes et al.[22]). We believe that the ion pair clustering concept provides a more mechanistically satisfying explanation for the unusual rate dependency than attributing it to 'salt effects'. It is also interesting to note that the formation of ion pair aggregates would be enhanced in non-polar solvents.[71] Very polar or protic solvents on the other hand would favour the formation of solvent-separated ion pairs. Whether ion pair aggregate formation might under some circumstances (high polarity solvent, low concentrations) become rate-limiting is not clear.

The influence on the Mitsunobu esterification by four different solvents using Protocol B (2 equiv of benzoic acid relative to betaine **1**) can be seen in Table 3.

Using Protocol B (slower reaction), it was possible to obtain initial first-order reaction rate constants in each of the four solvents. It is again evident from the data that the rate of reaction is inversely proportional to the polarity of the solvent. Fig. 4 illustrates the linear relationship between the logarithm of the rate constant and the solvent polarity, as defined by E_T values.

The effect of using an excess of carboxylic acid was also studied with Protocol B. Table 4 presents the results with four, six, and ten equivalents of benzoic acid (relative to ethanol) in chloroform.

It is clear that the rate of esterification drops significantly as the concentration of benzoic acid increases, consistent with the results of Hughes et al.[22]

2.2. Ester formation by ^{1}H NMR

We also examined the use of ^{1}H NMR to study the rate of ester formation. Initially, DIAD (two equivalents) was added to a $CDCl_3$ solution of TPP (two equivalents), ethanol and benzoic acid at 0 °C. Immediate formation of ester (i.e., within 40 s) was evidenced by the loss of ethanol resonances and the appearance of a quartet at δ 4.35 ppm and a triplet at δ1.36 ppm. These shifts were confirmed by comparison with an authentic sample of ethyl benzoate in $CDCl_3$. In order to slow the rate of the esterification, an excess of benzoic acid was used. Four equivalents of acid again gave immediate ester formation, but when six equivalents of acid were used, a new quintet at δ 4.25 ppm (J=7 Hz) was observed. This quintet rapidly

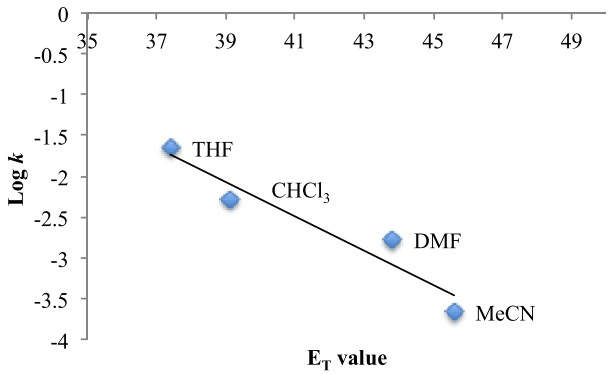


Fig. 4. Correlation between E_T values and log rate constants for the Mitsunobu esterification of benzoic acid with ethanol at 0 °C. (Protocol B).

decreased in intensity with time as the ester methylene resonance at δ 4.35 ppm grew. This quintet has been assigned to the methylene protons of the ethoxytriphenylphosphonium salt intermediate (**2**, R=Et, R′=Ph) by comparison with literature values (Ph_3POEt^+ ClO_4^-, δ 4.41, quintet, J=7 Hz;[72] Ph_3POEt^+ BF_4^- δ 4.44, quintet, J=7Hz[73]—the benzoate salt would be expected to be slightly upfield of these salts due to equilibrium with the alkoxyacyloxyphosphorane **4**). The use of ten equivalents of acid slowed the reaction rate further and proton spectra for this reaction are shown in Fig. 5.

Unfortunately, no accurate integrations of the ester and salt methylene resonances could be obtained since they were almost coincident. Deuterated benzene was briefly examined as a solvent but did not provide any more resolution of the two peaks.

In order to provide further evidence that the quintet close to the ester methylene resonance was due to the ethoxyphosphonium carboxylate species, ethanol was replaced by neopentyl alcohol. DIAD was added to an equimolar mixture of TPP and neopentyl alcohol in $CDCl_3$ at 0 °C. The methylene resonance of the alcohol at δ 3.20 ppm was replaced by a doublet at δ 2.10 ppm, J_{POCH}=4.0 Hz, indicative of the dialkoxyphosphorane (**3**, R=neopentyl, lit.[18] δ 2.30 ppm, J_{POCH}=4.3 Hz). Complete reaction required several hours, as shown in Fig. 6.

Upon addition of benzoic acid, the dialkoxyphosphorane was observed to decompose immediately to form the alkoxyphosphonium benzoate salt (**2**, R=neopentyl, R′=Ph) and one equivalent of alcohol. The methylene resonance of the salt was visible as a doublet at δ 3.80 ppm, J_{POCH}=4.2 Hz (lit.[25,26] δ 4.30 ppm, J_{POCH}=4.2 Hz; lit.[67] for triflate salt at δ 3.95 ppm, J_{POCH}=4.0 Hz; lit.[69] for chloride salt at δ 4.17 ppm, J_{POCH}=4.3 Hz) Fig. 7.

At room temperature, this salt resonance was slowly replaced by that of neopentyl benzoate at δ 3.94 ppm. Ester formation at 0 °C was significantly slower, with a reaction time of over 4 h necessary before any ester was observed.

The mechanism of esterification using the sterically hindered neopentyl alcohol is probably via slow S_N2 decomposition of the

Table 3
Influence of solvent on ester synthesis by protocol B[a,b]

Solvent	$t_{1/2}$ (min)[c]	10^3 k (s^{-1})
THF	0.5*	22.5±5
$CHCl_3$	2.2*	5.2±1.4
DMF	6.6*	1.7±0.1
MeCN	52.9*	0.22±0.01

[a] Standard reaction conditions: addition of DIAD (0.66 mmol) to ethanol (0.34 mmol), TPP (0.66 mmol) and benzophenone (0.05 mmol) pre-mixed in solvent (4 mL) at −15 °C, followed by final addition of benzoic acid (1.32 mmol) in solvent (1 mL). Reaction mixture then maintained at 0 °C.
[b] * indicates the result of at least two separate determinations.
[c] Error in half-life determination is approximately ± 20%.

Table 4
Influence of excess acid on the rate of ester synthesis in $CHCl_3$ by protocol B[a]

Acid equivalents	$T_{1/2}$ (min)[b]	10^3 k (s^{-1})
4.0	2.2	5.2
6.0	5.1	2.3
10.0	11.1	1.0

[a] Standard reaction conditions: addition of DIAD (0.66 mmol) to ethanol (0.34 mmol), TPP (0.66 mmol) and benzophenone (0.05 mmol) pre-mixed in solvent (4 mL) at −15 °C, followed by final addition of benzoic acid (as shown) in solvent (1 mL). Reaction mixture then maintained at 0 °C.
[b] Error in half-life determination is approximately ± 20%.

Please cite this article in press as: Camp, D.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.04.035

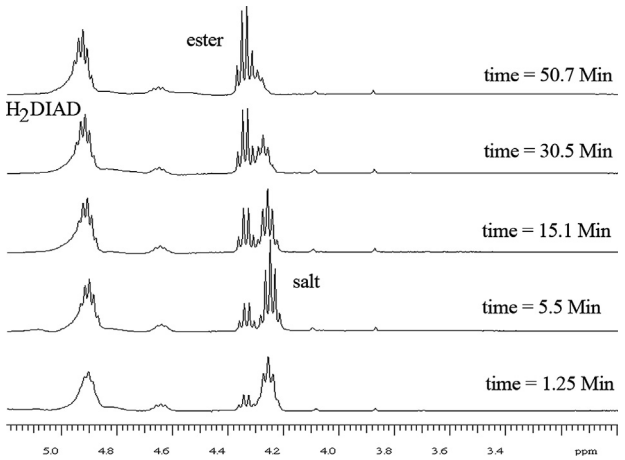


Fig. 5. ^{1}H NMR spectra for the reaction of TPP (two equivalents), ethanol (one equivalent) and benzoic acid (ten equivalents) with DIAD (two equivalents) in $CDCl_3$ at 0 °C.

alkoxyphosphonium salt (**2**, R=neopentyl, R′=Ph) although, acylation could also occur via the small equilibrium concentration of alkoxyacyloxyphosphorane species **4**. By adopting a conformation with an equatorial neopentyloxy group and an apical benzoate group, the oxygen of the neopentyloxy group is in close proximity to the acyloxy carbonyl carbon (Fig. 8), thus providing a pathway to esterification with retention of configuration of the alcohol, as described by Enders et al.[46]

The ^{1}H NMR results obtained for neopentyl benzoate formation parallel those obtained for ethyl benzoate formation. The methylene signal of ethyl benzoate (δ 4.35 ppm) is approximately 0.1 ppm downfield of the methylene signal of the ethoxyphosphonium salt (δ 4.25 ppm); similarly, the methylene signal of neopentyl benzoate (δ3.94 ppm) is also approximately 0.1 ppm downfield of the methylene signal of the neopentyloxyphosphonium salt (δ 3.80 ppm). The relatively rapid build-up of the alkoxyphosphonium salt signal, followed by its slow decline with concomitant increase of ester signal, is consistent with rate-determining S_N2 attack of benzoate on the alkoxyphosphonium ion, even in the presence of excess benzoic acid.

These results confirm that the alkoxyphosphonium benzoate is an intermediate in ethyl benzoate formation and that it is possible for this salt to be identified by proton NMR. In fact, each of the main species involved in alkyl benzoate synthesis via the Mitsunobu reaction can be detected by proton NMR analysis. These include the alcohol starting material, dialkoxyphosphorane, alkoxyphosphonium salt and ester product. However, ethyl benzoate

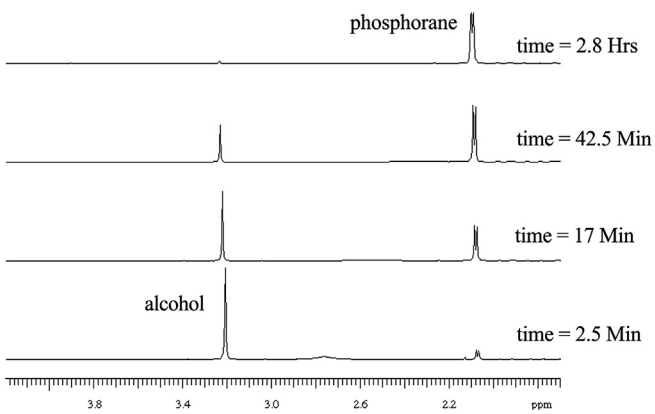


Fig. 6. ^{1}H NMR spectra for the reaction of TPP/DIAD with neopentyl alcohol in $CDCl_3$ at 0 °C.

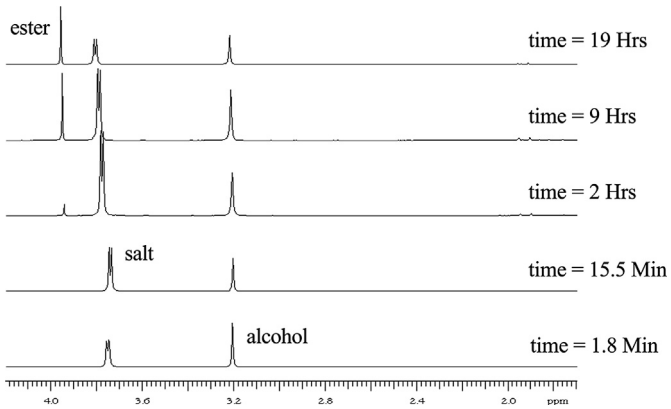


Fig. 7. ^{1}H NMR spectra for the reaction of dineopentyloxytriphenylphosphorane with benzoic acid in $CDCl_3$ at 24 °C.

formation was found to be too rapid and the intermediates insufficiently resolved for accurate kinetic data for the esterification reaction to be obtained by ^{1}H NMR.

3. Conclusions

The rate of the Mitsunobu esterification reaction was found to be much faster in non-polar solvents. This provides an explanation as to why the yield in the Mitsunobu reaction, particularly with sterically hindered alcohols, is often higher in non-polar solvents: side reactions, such as acylation of the hydrazine, are much faster in polar solvents,[33] and therefore slower and less likely to be competitive in non-polar solvents.

The logarithm of the rate constant was inversely proportional to the solvent polarity, as defined by E_T values. The presence of excess benzoic acid resulted in a rate decrease, as did the presence of sodium benzoate.

Each of the main species involved in the Mitsunobu esterification reaction, including the alcohol starting material, dialkoxyphosphorane, alkoxyphosphonium salt and ester product, was detected by proton NMR analysis. The NMR data support rapid formation of the alkoxyphosphonium salt intermediate with simple alcohols such as ethanol, followed by rate-determining S_N2 attack of benzoate on the alkoxyphosphonium ion even in the presence of a large excess of benzoic acid. The unusual kinetic data (S_N2 reaction but apparent first-order kinetics) can be explained by the formation of ion pair aggregates or clusters, prior to rate-determining S_N2 attack of benzoate on the alkoxyphosphonium ion.

4. Experimental section

4.1. General

Analytical grade THF was refluxed over sodium–potassium alloy under nitrogen, fractionally distilled and stored over 4 Å molecular sieves and sodium wire. Chloroform was pre-dried over calcium

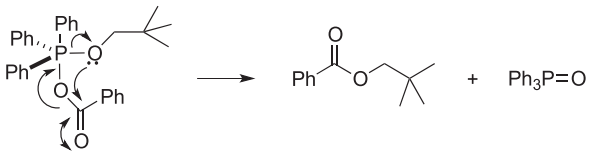


Fig. 8. Esterification with retention of configuration via an alkoxyacyloxyphosphorane species.

Please cite this article in press as: Camp, D.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.04.035

chloride, refluxed over P_2O_5, distilled, and stored over 4 Å molecular sieves. DMF was pre-dried over barium oxide for twelve hours, distilled at reduced pressure and stored over 4 Å molecular sieves. DMSO was refluxed over calcium oxide for several hours, distilled at reduced pressure and stored over 4 Å molecular sieves. Acetonitrile was refluxed over calcium hydride, distilled and stored over 4 Å molecular sieves. Analytical grade isopropanol was pre-dried over calcium oxide and stored over 4 Å molecular sieves. Dry ethanol was prepared by distillation from magnesium ethoxide and stored over 4 Å molecular sieves. Deuterated chloroform was stored over 4 Å sieves. HPLC grade acetonitrile and distilled water were filtered through 0.22 μm Millipore filter paper. Molecular sieves were activated in a furnace at approximately 300 °C for 12 h.

Triphenylphosphine, DIAD, benzoic acid and sodium benzoate were commercially available and were not further purified. Authentic samples of ethyl benzoate and isopropyl benzoate were prepared by the method of Vogel.[74]

Analytical HPLC was performed using a Dynamax-60A 8 μm 4.6 mm ID X 200 mm reverse phase C18 analytical column fitted with a Whatman C18 reverse phase guard column. An ETPKortec K35M HPLC Pump provided a flow of 0.7 mL/min of the eluent (60% acetonitrile, 40% water) and an ETPKortec K95 Variable Wavelength HPLC UV Detector was set to a wavelength of 230 nm for detection. Data was recorded with a Shimadzu C-R6A Chromatopac. A calibration curve was constructed from mixtures of internal standard and authentic product samples in known concentrations.

All NMR spectra were acquired at Griffith University Magnetic Resonance Facility, on a Varian Unity-400 spectrometer at 400.016 MHz using a 45° pulse width and 1.66 s acquisition time. 4 to 64 scans were acquired. ^{1}H chemical shifts are reported in δ (parts per million) relative to internal TMS.

4.2. Rate experiments

4.2.1. Protocol A: standard reaction conditions. Triphenylphosphine (132.0 mg, 0.50 mmol), benzoic acid (40.5 mg, 0.34 mmol), ethanol (20 μL, 0.34 mmol), or isopropanol (26 μL, 0.34 mmol), and benzophenone (15.0 mg, 0.08 mmol) were stirred in solvent (5 mL) at 0 °C under a nitrogen atmosphere. DIAD (98 μL, 0.50 mmol) was then added dropwise. At recorded time intervals, 20 μL aliquots were removed from the reaction mixture and added to an acetonitrile/water solution (1.0 mL, 60:40). This also served to quench the reaction. A minimum of two 5 μL injections were performed for each of these 1 mL volumes. The integral ratio of the ethyl benzoate peak (retention time: 13.0 min) versus the benzophenone peak (retention time: 15.4 min) was compared to a calibration curve to determine the percentage yield of product as a function of time. Integral ratios and calculated yields of ester for each reaction are tabulated in the Supplementary Data.

4.2.2. Protocol A: reaction performed at 20 °C. Reagents (as described above) were stirred in solvent (5 mL) at 12 °C under a nitrogen atmosphere. DIAD (98 μL, 0.50 mmol) was added dropwise and the reaction mixture warmed to 20 °C. Aliquots were removed as described above.

4.2.3. Protocol A: addition of sodium benzoate. Reagents (as described above) and sodium benzoate (95.0 mg, 0.66 mmol) were stirred in solvent (5 mL) at 0 °C under a nitrogen atmosphere. DIAD (98 μL, 0.50 mmol) was added dropwise and aliquots were removed as described as above.

4.2.4. Protocol B: standard reaction conditions. Triphenylphosphine (174.0 mg, 0.66 mmol), ethanol (20 μL, 0.34 mmol) and benzophenone (10.0 mg, 0.05 mmol) were stirred in solvent (4 mL) under a nitrogen atmosphere at −15 °C in an ice-salt bath. DIAD (130 μL, 0.66 mmol) was then added dropwise. The mixture was maintained at −15 °C until the yellow color characteristic of DIAD had dissipated (approximately 1 min) after, which time benzoic acid (160.0 mg, 1.31 mmol) in solvent (1 mL) was added. The reaction flask was transferred to an ice bath and maintained at 0 °C. Aliquots were removed as described above. Integral ratios and calculated yields of ester for each reaction are tabulated in the Supplementary Data.

4.3. NMR experiments

4.3.1. NMR protocol A: standard reaction conditions. To a 5 mm NMR tube was added triphenylphosphine (43.2 mg, 0.16 mmol), ethanol (5 μL, 0.08 mmol), benzoic acid (10.0 mg, 0.08 mmol) and chloroform-*d* (1.25 mL) under a nitrogen atmosphere. The sample was cooled to 0 °C and DIAD (32 μL, 0.16 mmol) then added. Proton NMR spectra were acquired as described above.

4.3.2. NMR protocol B: standard reaction conditions. To a 5 mm NMR tube was added triphenylphosphine (43.2 mg, 0.16 mmol), ethanol (5 μL, 0.08 mmol) and chloroform-*d* (1.25 mL) under a nitrogen atmosphere. The sample was cooled to 0 °C and DIAD (32 μL, 0.16 mmol) then added. The mixture was shaken briefly and benzoic acid (40.0 mg, 0.33 mmol) was added. Proton NMR spectra were acquired as described above.

4.3.3. Use of neopentyl alcohol. To a 5 mm NMR tube was added triphenylphosphine (43.2 mg, 0.16 mmol), neopentyl alcohol (15 mg, 0.17 mmol) and chloroform-*d* (1.25 mL) under a nitrogen atmosphere. The sample was cooled to 0 °C and DIAD (32 μL, 0.16 mmol) then added. Proton NMR spectra were acquired as described above. After several hours, benzoic acid (21.0 mg, 0.17 mmol) was added and proton NMR spectra were acquired as described above at 24 °C.

Acknowledgements

We thank Griffith University for financial support.

Supplementary data

Supplementary data (Integral ratios and calculated yields of ester as a function of time. Sample calculation of first-order rate constant and half-life.) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.04.035.

References and notes

1. Mitsunobu, O.; Yamada, M. .; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935–939.
2. Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2383.
3. Mitsunobu, O. *Synthesis* **1981**, 1–28.
4. Castro, B. R. *Org. React.* **1983**, *29*, 1–162.
5. Hughes, D. L. *Org. React.* **1992**, *42*, 335–656.
6. Jenkins, I. D.; Mitsunobu, O. In *Encyclopaedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, NY, 1995; Vol. 8, pp 5379–5390.
7. Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164.
8. Dandapani, S.; Curran, D. P. *Chem.—Eur. J.* **2004**, *10*, 3130–3138.
9. Dembrinski, R. *Eur. J. Org. Chem.* **2004**, *69*, 2763–2772.
10. But, T. Y. S.; Toy, P. H. *Chem.—Asian J.* **2007**, *2*, 1340–1355.
11. Reynolds, A. J.; Kassiou, M. *Curr. Org. Chem.* **2009**, *13*, 1610–1632.
12. Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. *Chem. Rev.* **2009**, *109*, 2551–2651.
13. Brunn, E.; Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 513–515.
14. Guthrie, R. D. G.; Jenkins, I. D. *Aust. J. Chem.* **1982**, *35*, 767–774.
15. Heesing, A.; Steinkamp, H. *Chem. Ber.* **1982**, *115*, 2854–2864.
16. Grochowski, E.; Hilton, B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876–6877.
17. Von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1983**, *36*, 557–563.
18. Adam, W.; Narita, N.; Nishizawa, Y. *J. Am. Chem. Soc.* **1984**, *106*, 1843–1845.
19. Von Itzstein, M.; Jenkins, I. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 437–445.

20. Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235–4238.
21. Von Itzstein, M.; Jenkins, I. D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2057–2060.
22. Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487–6491.
23. Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257–259.
24. Pautard-Cooper, A.; Evans, S. A., Jr. *J. Org. Chem.* **1989**, *54*, 2485–2488.
25. Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045–3049.
26. Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3049–3054.
27. Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017–3020.
28. Camp, D.; Jenkins, I. D. *Aust. J. Chem.* **1992**, *45*, 47–55.
29. Wilson, S. R.; Perez, J.; Pasternak, A. *J. Am. Chem. Soc.* **1993**, *115*, 1994–1997.
30. Macor, J. E.; Wehner, J. M. *Heterocycles* **1993**, *35*, 349–365.
31. Kodaka, M.; Tomohiro, T.; Okuno, H. *J. Chem. Soc., Chem. Commun.* **1993**, 81–82.
32. Camp, D.; Hanson, G. R.; Jenkins, I. D. *J. Org. Chem.* **1995**, *60*, 2977–2980.
33. Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967–2971.
34. Moravcova, J.; Rollin, P.; Lorin, C.; Gardon, V.; Capkova, J.; Mazac, J. *J. Carbohydr. Chem.* **1997**, *16*, 113–127.
35. Harvey, P. J.; von Itzstein, M.; Jenkins, I. D. *Tetrahedron* **1997**, *53*, 3933–3942.
36. Dodge, J. A.; Jones, S. A. *Recent Dev. Org. Chem.* **1997**, *1*, 273–283.
37. Eberson, L.; Persson, O.; Svensson, J. O. *Acta Chem. Scand.* **1998**, *52*, 1293–1300.
38. Watanabe, T.; Gridnev, I. D.; Imamoto, T. *Chirality* **2000**, *12*, 346–351.
39. Kumar, N. S.; Kommana, P.; Vittal, J. J.; Swamy, K. C. K. *J. Org. Chem.* **2002**, *67*, 6653–6658.
40. Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751–1753 (addendum). Ahn, C.; Correia, R.; DeShong, P. J. Org. Chem. 2003, 68, 1176.
41. Elson, K. E.; Jenkins, I. D.; Loughlin, W. A. *Org. Biomol. Chem.* **2003**, *1*, 2958–2965.
42. McNulty, J.; Capretta, A.; Laritchev, V.; Dyck, J.; Robertson, A. J. *J. Org. Chem.* **2003**, *68*, 1597–1600.
43. McNulty, J.; Capretta, A.; Laritchev, V.; Dyck, J.; Robertson, A. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4051–4054.
44. Shi, J. Y.; Hughes, D. L.; McNamara, J. M. *Tetrahedron Lett.* **2003**, *44*, 3609–3611.
45. Kumar, N. S.; Kumar, K. P.; Kumar, K. V. P.; Kommana, P.; Vittal, J. J.; Swamy, K. C. K. *J. Org. Chem.* **2004**, *69*, 1880–1889.
46. Schenk, S.; Weston, J.; Anders, E. *J. Am. Chem. Soc.* **2005**, *127*, 12566–12576.
47. Swamy, K. C. K.; Kumar, K. P.; Kumar, N. N. B. *J. Org. Chem.* **2006**, *71*, 1002–1008.
48. Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234–236.
49. Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1977**, *60*, 417–425.
50. Saiah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317–4320.
51. Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VSH: Weinheim, Germany, 1988; chapter 2 and chapter 7.
52. Dimroth, K.; Reichardt, C.; Siepmann, T.; Bohlmann, F. *Liebigs Ann. Chem.* **1963**, *661*, 1–37.
53. Kosower, E. M. *J. Am. Chem. Soc.* **1958**, *80*, 3253–3260.
54. Mitsunobu, O.; Kimura, J.; Iiizumi, K.; Noboru, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 510–513.
55. Bottle, S.; Jenkins, I. D. *J. Chem. Soc., Chem. Commun.* **1984**, 385.
56. Jenkins, I. D.; Thang, S. *Aust. J. Chem.* **1984**, *37*, 2447–2451.
57. Guthrie, R. D.; Jenkins, I. D.; Thang, S.; Yamasaki, R. *Carbohydr. Res.* **1988**, *176*, 306–308.
58. Jenkins, I. D.; Goren, M. B. *Chem. Phys. Lipids* **1986**, *41*, 225–235.
59. Pautard, A. M.; Evans, S. A., Jr. *J. Org. Chem.* **1988**, *53*, 2300–2303.
60. Reeve, W.; Erikson, C. M.; Aluotto, P. F. *Can. J. Chem.* **1979**, *57*, 2747–2754.
61. Smith, B. M.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley: New York, NY, 2001; pp 450–454.
62. Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1935**, 244–255.
63. Cooper, K. A.; Dhar, M. L.; Hughes, E. D.; Ingold, C. K.; MacNulty, B. J.; Woolf, L. I. *J. Chem. Soc.* **1948**, 2043–2049.
64. Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell Univ.: Ithaca, 1969; pp 457–680.
65. Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.
66. Ramos, S.; Rosen, W. *Tetrahedron Lett.* **1981**, *22*, 35–38.
67. Ramos, S.; Rosen, W. *J. Org. Chem.* **1981**, *46*, 3530–3533.
68. Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1970**, *35*, 1627–1632.
69. Jones, L. A.; Sumner, C. E., Jr.; Franzus, B.; Huang, T.-S.; Snyder, E. I. *J. Org. Chem.* **1978**, *43*, 2821–2827.
70. Slagle, J. D.; Huang, T.-S.; Franzus, B. *J. Org. Chem.* **1981**, *46*, 3526–3530.
71. See for example: MacMillar, S.; Fang, Y.; Westaway, K. C.; Matsson, O.; Beronius, P. *J. Phys. Org. Chem.* **2008**, *21*, 237–241.
72. Maeda, H.; Koide, T.; Maki, T.; Ohmori, H. *Chem. Pharm. Bull.* **1995**, *43*, 1076–1080.
73. Crich, D.; Dyker, H. *Tetrahedron Lett.* **1989**, *30*, 475–476.
74. Vogel, A. I. *A Textbook of Practical Organic Chemistry*, 3rd ed.; Longman: London, UK, 1956; pp 780–790.

Please cite this article in press as: Camp, D.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.04.035