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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3553–3557

A convenient procedure for the esterification of benzoic acids with phenols: a new application for the Mitsunobu reaction

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Received 1 February 2007; revised 6 March 2007; accepted 17 March 2007
Available online 9 April 2007

Abstract—The Mitsunobu reaction was found to be a convenient and effective method for the esterification of various benzoic acids with differentially functionalized phenols producing the corresponding phenyl esters in good to excellent yields.

The esterification of carboxylic acids has been the subject of numerous accounts throughout the years owing to the fundamental importance of this synthetic transformation. Early methods called for heating the carboxylic acid in an alcoholic solvent under acid catalysis. Other procedures involve conversion of the carboxylic acid to its corresponding acid chloride or mixed anhydride, followed by the addition of an alcohol nucleophile. Other coupling reagents have been utilized extensively for the synthesis of ester functional groups from their corresponding carboxylic acids in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP). Examples include 1,3-dicyclohexylcarbodiimide (DCC),[1,2] di-(2-pyridyl)carbonate,[3] *O*,*O*′-di-(2-pyridyl)thiocarbonate,[4] 2-CH_3-6-NO_2-benzoic anhydride,[5,6] and di-2-thienylcarbonate (2-DTC).[7]

During the course of a natural product synthesis, we required the conversion of benzoic acid **1** to phenyl ester **2** as depicted in Figure 1. We initially envisioned a carbodiimide-mediated coupling using DCC in combination with a catalytic amount of DMAP. Surprisingly, the reaction proved to be problematic, providing the desired ester **2** in only 44% yield after a prolonged reaction time (48 h) and use of a large excess (5 equiv) of DCC. Unfortunately, our attempts to optimize the conditions did not result in a significant enhancement of the reaction rate or yield.

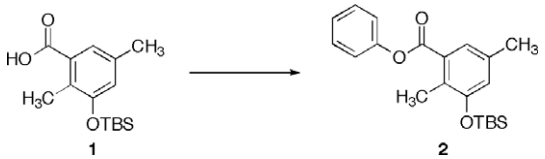

Figure 1.

While we briefly investigated employing traditional addition–elimination chemistry involving acid chlorides or mixed anhydrides derived from **1**, we were intrigued by the possible application of the Mitsunobu reaction to construct our desired C–O bond and furnish phenyl ester **2**. The Mitsunobu reaction, discovered in 1967,[8–10] is a robust and invaluable synthetic transformation that allows for the stereoselective incorporation of azides,[11,12] esters,[9,13] nitriles,[14] phthalimides,[15] and sulfonamides[16,17] with inversion of configuration. Moreover, various protocols based on the Mitsunobu reaction have been developed for the coupling of alkyl alcohols with phenols or carboxylic acids as substrates. Many of these procedures have been modified for use on solid-phase supports.[18–22] As such, we envisioned the Mitsunobu reaction as an attractive route to pursue for the synthesis of phenyl ester **2**.

To our surprise, after an extensive survey of the literature, we were unable to retrieve any examples detailing the use of the Mitsunobu reaction within the context of coupling benzoic acids with phenolic nucleophiles. While phenols have been previously employed in cou-

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0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.03.095

pling reactions with other functional groups, there were no accounts of the reactivity or overall effectiveness of this process utilizing benzoic acids as starting materials. To our knowledge, this methodology has not been explored and we now wish to report our findings regarding this new application for the Mitsunobu reaction.

Our initial efforts in the development of this methodology began with screening various reaction solvents as well as investigating the effects of temperature as noted in Table 1. For the coupling of *o*-toluic acid (**3**) with *p*-cresol (**4**), taken as our standard reaction, we found that most of the commonly utilized solvents for the Mitsunobu reaction fared poorly in terms of reaction yields. For example, use of methylene chloride (CH_2Cl_2, entry 1) or benzene (Ph–H, entry 2) resulted in very low conversions to the desired coupled product. Furthermore, use of *N*,*N*-dimethylformamide (DMF, entry 3) gave only a 29% yield of ester **5**. However, upon employing tetrahydrofuran (THF, entry 4) as the reaction solvent, the desired phenyl ester **5** was produced in a synthetically viable 60% yield. Moreover, we were extremely pleased to find that further investigations involving refluxing THF (entry 5) resulted in a dramatically increased yield, 99%, of **5**.[23]

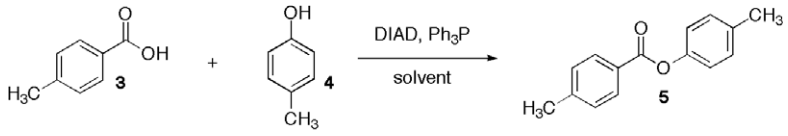
After securing the optimal reaction conditions, we turned our attention to a thorough exploration of the substrate scope. As outlined in Table 2, we sought to determine the effects of incorporating various functional groups as well as differing substitution patterns on the phenol component. As expected, the reaction works best with unhindered phenolic nucleophiles (entries 1–3 and 7–9) which generally provided yields in excess of 70%. As the steric hindrance surrounding the reacting nucleophilic oxygen atom on the phenol increases, we observed a decrease in the overall efficiency of the process with *ortho*-substituted phenols (entries 4–6 and 10) resulting in lower yields than the corresponding *meta*-substituted phenols (entries 3 and 8). It is worth noting that the sterically encumbered 2,6-dimethyl phenol (**9**) provided the coupled product in a synthetically useful 50% yield, a demonstration of the overall robustness of this process. Furthermore, the reaction is tolerant of both strong electron-donating (entries 7 and 8) as well as electron-withdrawing (entries 9 and 10) groups.

Next, we examined the effects of differentially-substituted benzoic acids as outlined in Table 3. Yields were generally good overall with *ortho*- (entry 1) and *meta*- (entry 2) substituted benzoic acids working well within the context of the coupling reaction. Additionally, the use of electron-rich benzoic acids such as 4-ethoxybenzoic acid (**26**, entry 3) did not hinder the C–O bond forming event leading to phenyl ester product **29** in excellent yield. A noteworthy aspect of this reaction is that *ortho*-substituted benzoic acids (entry 1) demonstrated a negligible effect on the efficiency of the coupling process contrary to that observed when *ortho*-substituted phenols were employed (Table 2, entries 4–6 and 10).

The Mitsunobu reaction is widely accepted to involve a triphenylphosphine–azodicarboxylate adduct such as **30** illustrated in Figure 2a. Following nucleophilic addition of alcohol **31** to produce phosphonium ion **32** and hydrazine byproduct **33**, an S_N2 reaction occurs involving carboxylate anion **34** resulting in inversion of configuration for the isolated ester product **35**. In terms of the reaction reported in this Letter, this pathway would require a S_N2 displacement occurring at a sp^2-center. We believe this to be an unfavorable and therefore unlikely process. As such, we believe that the formation of phenyl esters from benzoic acids and phenols under Mitsunobu conditions proceeds via a non-classical mechanism.

With this in mind, we invoke the existence of an acyloxyphosphonium ion such as **37** (Fig. 2b) which originates from adduct **30** by displacement with carboxylate anion **34**. Next, reaction with phenoxide anion **38** via an addition–elimination manifold produces the corresponding phenyl ester **39**. The intermediacy of acyloxyphosphonium ions was previously postulated by Hughes et al.[24,25] in his studies on delineating the mechanism of the Mitsunobu reaction. Later, DeShong and co-workers[26,27] also suggested the existence of an acyloxyphosphonium ion when he observed that lactonization of bicyclic lactones under Mitsunobu conditions resulted in either inversion or retention of configuration depending upon the steric environment surrounding the nucleophilic alcohol functional group. DeShong and co-workers went on to demonstrate that treatment of

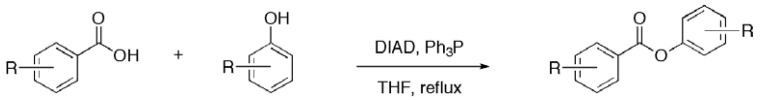
Table 1. Solvent and temperature effects on the coupling of benzoic acids with phenols via the Mitsunobu reaction

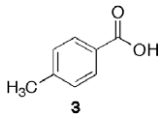
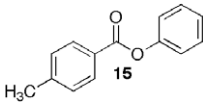
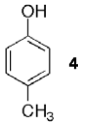
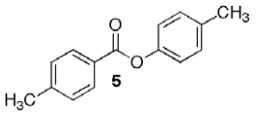
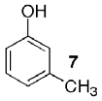
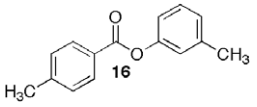
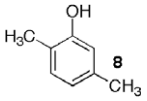
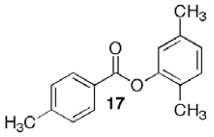
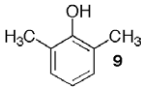
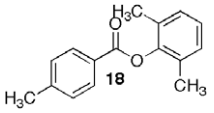
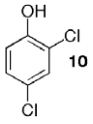
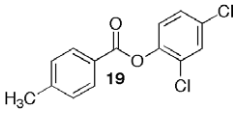
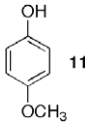
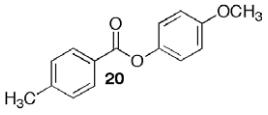
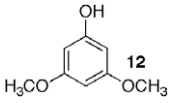
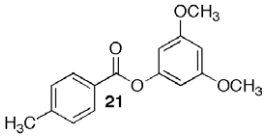
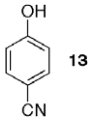
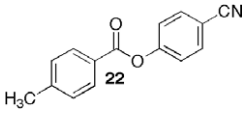
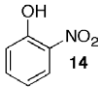
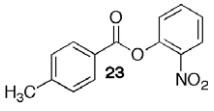


Entry	Solvent	Temperature (°C)	Yield[a,b] (%)
1	CH_2Cl_2	25	20
2	Ph–H	25	17
3	DMF	25	29
4	THF	25	60
5	THF	65	99

[a] Products obtained were >95% pure by ^1H and ^{13}C NMR.
[b] Reported yield for 3.6 mmol scale reaction.

Table 2. Preparation of phenyl esters via the Mitsunobu reaction



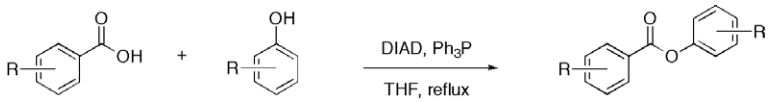
Entry	Benzoic acid	Phenol	Product[a]	Yield[b] (%)
1				89
2				99
3				74
4				67
5				50
6				45
7				79
8				81
9				69
10				42

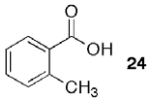
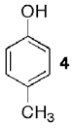
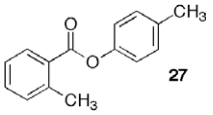
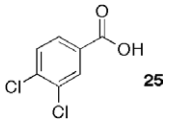
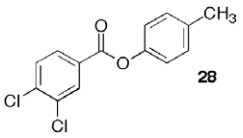
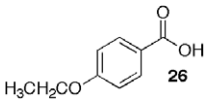
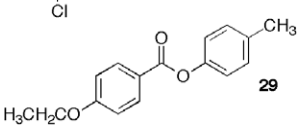
[a] Products obtained were >95% pure by ^{1}H and ^{13}C NMR.
[b] Reported yield for 3.6 mmol scale reaction.

benzoic acid with Ph_3P/DEAD in the absence of an alcohol produced benzoic anhydride which is consistent with the involvement of an acyloxyphosphonium ion.[26] We believe that the pathway outlined in Figure 2b is in accord with our own mechanistic hypothesis for the coupling of benzoic acids with phenols under Mitsunobu conditions.

In summary, we have developed a new method for the esterification of benzoic acids by phenolic nucleophiles employing Mitsunobu conditions. The reaction is tolerant of varying substitution patterns on both the benzoic acid and phenol components. Moreover, the reaction progresses well with either electron-donating or electron-withdrawing functional groups. We believe this methodology will find wide use within the realm of natural products synthesis and our own applications in this context will be presented in due course.

Table 3. Evaluation of structurally different benzoic acids in the Mitsunobu coupling with phenols



Entry	Benzoic acid	Phenol	Product[a]	Yield[b] (%)
1				92
2				71
3				82

[a] Products obtained were >95% pure by ^{1}H and ^{13}C NMR.
[b] Reported yield for 3.6 mmol scale reaction.

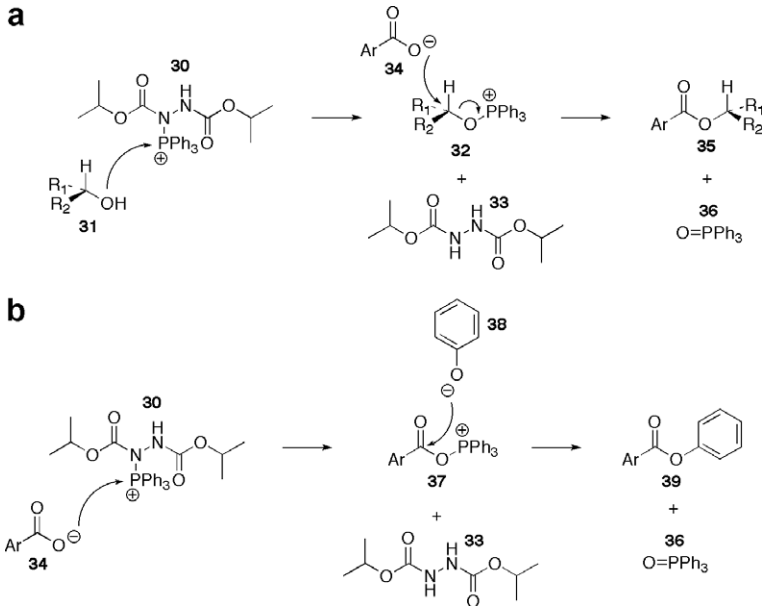


Figure 2.

Acknowledgements

This Letter is dedicated to Professor Gary A. Sulikowski for his significant contributions to the education of R.P. Generous financial support from The Colorado College is gratefully acknowledged. High resolution mass spectrometry analyses were performed by Dr. Shane E. Tichy of the Laboratory for Biological Mass Spectrometry at Texas A&M University.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.095.

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22. Lepore, S. D.; He, Y. *J. Org. Chem.* **2003**, *68*, 8261–8263.
23. *General procedure for the formation of phenyl esters from benzoic acids and phenols via the Mitsunobu reaction:* Triphenylphosphine (1.05 equiv), the phenol (1.05 equiv), and the benzoic acid (1.00 equiv) were dissolved in THF (0.2 M solution) at room temperature and allowed to stir for 10 min. Diisopropylazodicarboxylate (1.05 equiv) was then added dropwise and the reaction was heated to reflux overnight (16 h) at which time the solvent was removed in vacuo and the resulting residue purified by flash column chromatography (50:1 hexanes/EtOAc) to afford the desired phenyl ester.
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