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Investigation of the Yamaguchi Esterification Mechanism. Synthesis of a Lux-S Enzyme Inhibitor Using an Improved Esterification Method

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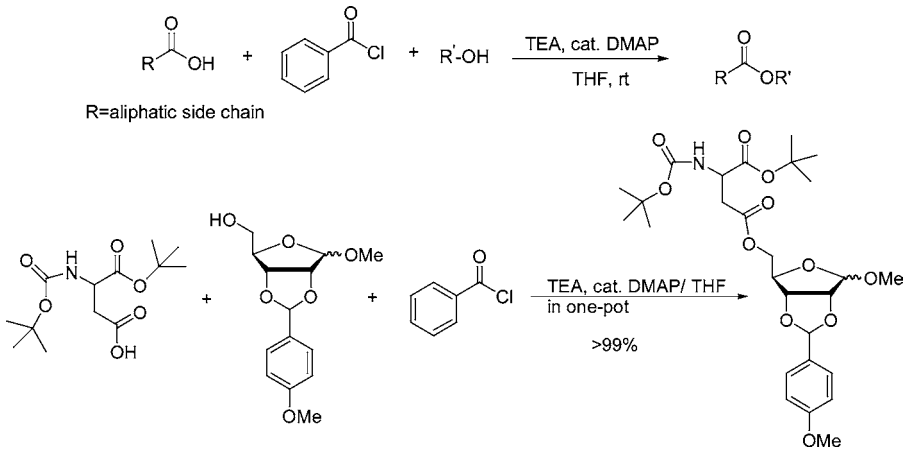
ABSTRACT



A one-pot procedure for the regioselective synthesis of aliphatic esters is described. This was a result of a study on mixed aliphatic–aromatic anhydrides. The data suggest that during the Yamaguchi esterification reaction, a symmetric aliphatic anhydride is produced in situ, which upon reaction with an alcohol yields the ester. We confirmed that benzoyl chloride could be used instead of the sterically hindered Yamaguchi acid chloride. This method was successfully applied in the synthesis of Lux-S aspartic acid inhibitor.

The coupling of carboxylic acids with alcohols to produce esters is a fundamental synthetic process. A variety of conditions have been developed to accommodate different synthetic scenarios.[1−3] The ongoing theme in these new procedures is the use of equimolar amounts of carboxylic acid and alcohol, mild conditions, and the elimination of toxic byproducts. Most notably Yamamoto and co-workers reported the effective synthesis of esters using equimolar amounts of acids and alcohols mediated only by hafnium(IV) salts.[4] Yamaguchi esterification, commonly used in the synthesis of macrolactones, has found great use in regioselective synthesis of highly functionalized esters.[5,6] Using the

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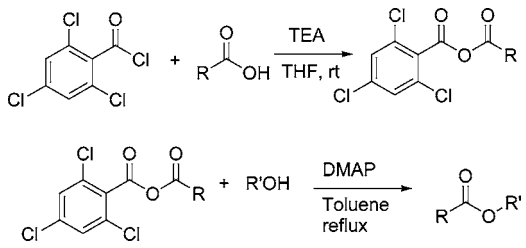
Yamaguchi esterification conditions as a template, new procedures making use of aromatic anhydrides instead of the acid chlorides in the presence of Lewis acids have been reported.[7−11] An adapted protocol making use of aromatic anhydrides and DMAP as coupling agents was also reported.[12] In all of these cases, the in situ synthesis of a mixed aliphatic−aromatic anhydride was assumed.[7−12] The Yamaguchi esterification involves the reaction of an aliphatic acid with 2,4,6-trichlorobenzoyl chloride to form the mixed aliphatic-2,4,6-trichlorobenzoyl anhydride.[13] The isolated mixed anhydride, upon reaction with an alcohol, in the presence of DMAP, produces the aliphatic ester regioselectively. The mixed anhydrides with sterically hindered aromatic counterparts were thought to ensure the regioselective synthesis of the corresponding ester. This line of logic initially was advanced by Yamaguchi and co-workers in their original publication.[13] However, during the selection of the appropriate acid chloride, Yamaguchi and co-workers assumed that upon the reaction of a carboxylic aliphatic acid with an aromatic acid chloride the mixed anhydride would be formed exclusively (Scheme 1). Investigation of the mixed

Scheme 1. Yamaguchi Esterification

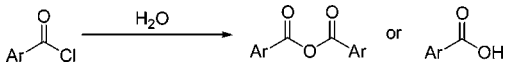


anhydride formation led us to postulate a different mechanism.

While optimizing the synthesis of several aromatic anhydrides, we observed that acyl-pyridinium or triethylammonium salts of 2,6-substituted benzoyl chlorides react differently compared to unhindered ones.[14] The acid chlorides were chosen from literature examples to compare the advantage of using equivalent amounts of substrates in acetone. In the case of unhindered acid chlorides, the data indicate that even for reactive anhydrides our procedure works well, without need for extensive purification (Table 1).

To our surprise, upon quenching with excess water, the unhindered aromatic acid chlorides afforded the corresponding anhydrides instead of the acids (Table 1, entries 1−5). The 2,6-disubstituted benzoyl chlorides afforded exclusively

Table 1. Reaction of Aromatic Acid Chlorides with Water in the Presence of Triethylamine or Pyridine

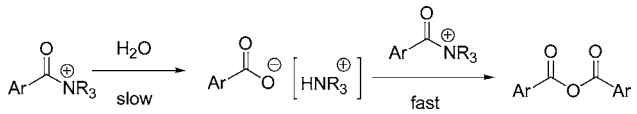


entry	acid chloride	product	min (a/b)	% (a/b)
1	benzoyl	anhydride	20/60	85/97
2	*p*-toluoyl	anhydride	15/60	83/96
3	*p*-nitrobenzoyl	anhydride	10/60	78/98
4	*p*-methoxybenzoyl	anhydride	120[b]	99
5	2-furoyl	anhydride	5/30	78/99
6	2,6-dichlorobenzoyl[c]	acid	18 h	99
7	2,4,6-trichlorobenzoyl[c]	acid	18 h	99

[a] The acid chloride was dissolved in pyridine at room temperature, stirred to allow the formation of the pyridinium complex, and quenched with excess water. The precipitate was filtered to afford the pure solid product. [b] Acid chloride, TEA, and 0.5 equiv of water were dissolved in acetone. When the reaction was completed, triethylammonium chloride was filtered, and washed with acetone. Acetone was evaporated to afford the pure product. [c] The reaction was performed as described in (b). The residue was partitioned between water and ethyl acetate. The organic phase was dried and evaporated to afford the product.

the corresponding carboxylic acids (Table 1, entries 6 and 7). Intially, the acylammonium complex reacts with water to form the aromatic carboxylate. The unhindered carboxylate formed in situ must react faster with the acylammonium complex than water, thus leading to the formation of the anhydrides. However, in the case of hindered acylammonium complexes, the hindered acid salt formed in situ does not react with the remaining acylammonium complex, most probably due to steric hindrance (Scheme 2).

Scheme 2. Reaction of Unhindered Acylammonium Complexes with Water



These findings prompted us to investigate the reaction of propionic acid with various aromatic acid chlorides. The acid chlorides were reacted with 1 equiv of propionic acid in the presence of triethylamine (Table 2). In the case of the Yamaguchi acid chloride, the reaction, according to chromatographic analysis, proceeded very slowly at room temperature without reaching completion. After 16 h, propionic anhydride, propionic acid, and 2,4,6-trichlorobenzoic acid were isolated. There was very little (less than 1%) mixed anhydride detectable by NMR in the reaction mixture. However, benzoyl chloride and *p*-toluoyl chloride gave a mixture of symmetric aromatic, symmetric aliphatic, and mixed anhydride in quantitative overall yield (Table 2).

The following reaction pathway was postulated on the basis of the fact that aliphatic carboxylates are more reactive than aromatic ones (Scheme 3).

Propionic carboxylate should be more reactive toward the aliphatic moiety of the mixed anhydride formed by 2,4,6-

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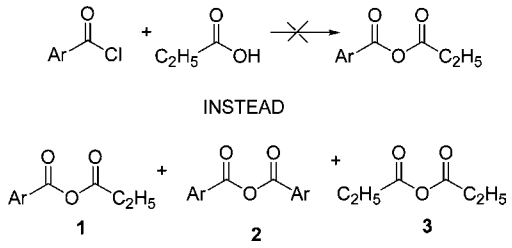
Table 2. Reaction of Acyl Chlorides with Propionic Acid[a]

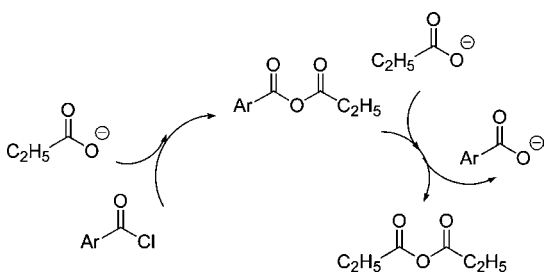


entry	acid chloride	h	ratio 1:2:3
1	benzoyl chloride	2	3:1:1
2	*p*-toluoyl chloride	2	4:1:1
3	2,4,6-trichlorobenzoyl chloride[d]	16	only 3

[a] Acyl chloride, propionic acid, and TEA dissolved in THF were used in equimolar amounts. One equivalent of triethylamine was added all at once. The reactions were monitored by TLC. Quenching with water and extraction with ethyl acetate afforded the products.

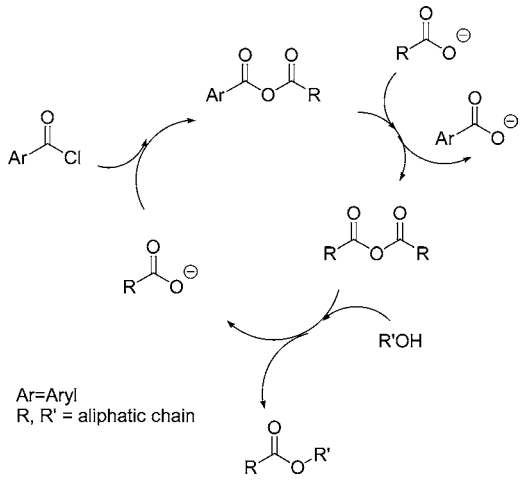
trichlorobenzoyl chloride (Scheme 3). Although acid chlorides are known to be more electrophilic than anhydrides, the steric environment makes the Yamaguchi acid chloride less reactive compared to the mixed anhydride. Thus, once the mixed anhydride is formed, it reacts to form propionic anhydride. The byproduct, 2,4,6-trichlorobenzoic acid salt, did not react with 2,4,6-trichlorobenzoyl chloride to form the anhydride, as demonstrated previously (Table 1, entry 7). The same process happens with benzoyl or *p*-toluoyl chloride, resulting in the formation of propionic anhydride, in this case due to the propionic carboxylate reacting at the most electrophilic carbonyl of the mixed anhydride. However, once all propionic acid is consumed, the remaining aromatic carboxylate reacts with the remaining aromatic acid chloride to form the observed aromatic anhydride (Table 1, entries 1 and 2). The formation of a symmetric aliphatic anhydride in situ explains the regioselectivity observed during the Yamaguchi esterification. Using 2,4,6-trichlorobenzoyl chloride ensures that the aromatic domain of the mixed anhydride, if present in the reaction mixture, is inaccessible to any nucleophile regardless of the nucleophile's steric environment. However, the data so far indicate that the symmetric anhydride might be the reactive species that ensures the desired outcome of the Yamaguchi reaction. We

Scheme 3. Cascade of Reactions Leading to the Symmetric Anhydride; Byproduct of this Process Is the Aromatic Acid



postulate that the Yamaguchi esterification proceeds according to the mechanism in Scheme 4.

Scheme 4. Postulated Mechanism of the Yamaguchi Esterification



The key element of this process is the in situ synthesis of the symmetric aliphatic anhydride. Note that all reactions involved are reversible, except for the last ester formation step. The byproduct of this step is the aliphatic carboxylate, which reenters the cycle. Thus, until the regioselective completion of the reaction, there is always aliphatic carboxylate remaining, competing with the aromatic carboxylate, and the alcohol. The mechanism is based on the assumption that aliphatic carboxylates are better nucleophiles than aromatic carboxylates and alcohols. This proposed mechanism suggests that any aromatic acid chloride capable of producing preferentially and in situ the symmetric aliphatic anhydrides could be used in the regioselective synthesis of aliphatic esters. It is important to consider the relationship between steric effects, electronic effects, and reactivity. The aliphatic anhydride produced in situ must be more electrophilic toward the alcohol than the aromatic carbonyl of the mixed aliphatic−aromatic anhydride for this procedure to succeed. Therefore, whether one chooses to use an unhindered acid chloride such as the inexpensive benzoyl chloride would depend on the esterification substrates being used. There is literature precedent to support our proposed mechanism. Yonemitsu and co-workers reported an improved one-pot Yamaguchi procedure.[15] The use of benzoic anhydride instead of the Yamaguchi acid chloride was reported as well.[16] Since the mechanism we propose is based on competing reactivities, there is no need for a two-step procedure or excess DMAP.

A model study supported our postulated mechanism. Toluoyl chloride proved to be ideal when dealing with primary acids in combination with primary and secondary

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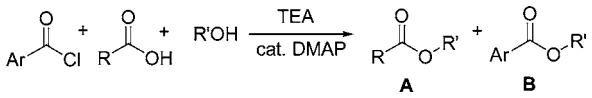
Table 3. One-Step Esterification Procedure[a]



entry	acid chloride	R′/R	h	% (A/B)
1	*p*-toluoyl	Bn/Et	1	98 (>200:1)
2	*p*-toluoyl	cyclohexyl/Et	1	97 (>200:1)
3	benzoyl	Bn/Et	1	98 (97.5:2.5)
4	benzoyl	cyclohexyl/Et	1	92 (97:3)
5	*p*-toluoyl	Bn/^{i}Pr	1.5	98 (96:4)
6	*p*-toluoyl	Bn/^{t}Bu	6	98 (68:32)
7	*p*-nitrobenzoyl	Bn/^{t}Bu	1.5	99 (45:55)
8	*p*-anisoyl	Bn/^{t}Bu	6	96 (60:40)

[a] One equivalent of each reactant was dissolved in dry THF at room temperature. Subsequently 2 equiv of TEA followed by 25% cat. DMAP were added.

alcohols (Table 1, entries 1−4). When 2-methyl propionic acid was used, the desired ester was produced in 96% yield with only a very small amount of the aromatic ester produced (0.5%) (Table 1, entry 5). However, when 2,2-dimethylpropionic acid was tested, a mixture of aromatic and aliphatic esters was obtained, regardless of the acid chloride (Table 1, entries 6−8). Benzoyl chloride perfomed similarly to *p*-toluoyl chloride.

We applied our esterification methodology to the synthesis of Lux-S aspartic acid enzyme inhibitor (Scheme 5). The family of Lux-S enzymes is responsible for cell communication and signaling.[18,19] Inhibitors of such an enzyme could provide potential new antibiotics. GC−MS analysis revealed no undesired product. In this instance benzoyl chloride performed better than in the model study. This provides further evidence for our initial assumption that the outcome of the reaction is system-dependent.

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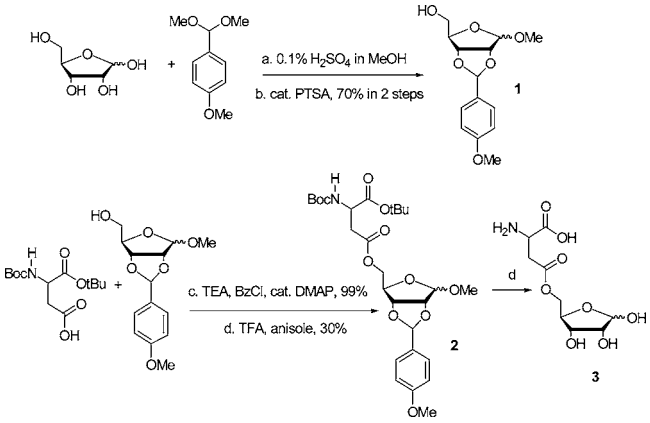
Scheme 5. Synthesis of Lux-S Aspartic Acid Inhibitor



We have demonstrated that other inexpensive acid chloride options are available as reagents in the regioselective esterification process. This reaction provides the chemist with a convenient one-pot procedure using mild conditions and only catalytic amounts of DMAP and generating nontoxic byproducts. Benzoyl chloride, which gives benzoate ion byproduct, can be used in many real scenarios, thus making this reaction ideal for scale-up. The Yamaguchi acid chloride encompasses the whole spectrum of possible systems. However, as demonstrated, it is not always necessary.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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