A flexible Pinner preparation of orthoesters: the model case of trimethylorthobenzoate†

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In the absence of additional solvents, a novel procedure was implemented for the synthesis of trimethyl-orthoesters through the Pinner reaction. At 5 °C, the reaction of both aliphatic and aromatic nitriles (RCN; R = Et, Bu, Ph) with a moderate excess of MeOH and gaseous HCl gave the corresponding imidate hydrochlorides [RC(=NH)OR·HCl] in excellent yields (>90%). At 25–65 °C, the methanolysis of alkyl imidate salts provided trimethylortho-propionate and valerate, while only traces of trimethylorthobenzoate (TMOB) were observed. However, the aromatic hydrochloride could be readily converted into the hydrogenphosphate salt [PhC(=NH)OR·H₃PO₄] which, in turn, underwent a selective (>80%) reaction with MeOH to produce TMOB in a 62% isolated yield. This allowed for an unprecedented Pinner-type synthesis of TMOB starting from benzonitrile, rather than from the highly toxic trichloromethylbenzene. Overall, remarkable improvements in safety and process intensification were achieved.

Introduction

Orthoesters are important in carboxylic acid protective group chemistry. In particular, because they are among the few compounds that exhibit good stability toward strong nucleophiles and bases.

Beyond their protective group chemistry, a pharmaceutically relevant application of orthoesters is in the functionalization of steroidal derivatives. Orthoesters are applied for example to the selective esterification of the hydroxyl group of the 17 position of betamethasone (I), a potent topical glucocorticoid steroid with anti-inflammatory and immunosuppressive properties. This modification minimizes absorption of the molecule through the skin, increasing topical potency and decreasing systemic side effects. The selective esterification of (I) is possible because trimethyl orthoesters form the cyclic intermediate (II), which yields (III) by hydrolysis (Scheme 1).

The processes for the preparation of orthoesters can be grouped into five different types (Scheme 2): (a) the reaction of trihalogenated derivatives with alkoxides; (b) the addition of alcohols to ketene acetals; (c) the electrochemical oxidation of aldehyde acetals or toluene derivatives; (d) the reaction of Grignard reactants with orthocarbonates or trialkoxyacetonitriles; and (e) the reaction of nitriles with alcohols under acidic conditions followed by alcoholysis of the resulting imido ester. The latter (e) is best known as the Pinner synthesis, and it is perhaps the most popular method for the preparation of orthoesters.

The Pinner synthesis, improved by Hill and Rabinovitz and by Sah, offers two main advantages: (i) it uses rather safe starting materials (nitriles and alcohols are classified at most as irritant non-toxic compounds); (ii) it is relatively straightforward and readily applicable because operating conditions are mild and the overall transformation can be easily scaled up. These reasons account for the extensive application of the Pinner synthesis in the chemical industry. However, an analysis of the method shows aspects which pose concerns from both a synthetic and an environmental standpoint. The first issue relates to the first step of eqn (e) in Scheme 2, which yields the imidate hydrochloride salts. The major drawbacks are in the use of hazardous and/or volatile solvents including dichloromethane, chloroform, nitrobenzene, dioxane, benzene,
or ether, and the relatively low stability of the imidate hydrochloride intermediates. These compounds rapidly decompose, on heating, into the corresponding amides and alkyl halides (Scheme 3, top), and are sensitive to water that causes hydrolysis to the corresponding esters (Scheme 3, bottom). Light aliphatic imidate salts, in particular, are quite hygroscopic and hydrolysis is fast and complete.9

The imidate free bases \([RC(=NH)OR'\cdot HCl]\) can be easily obtained from the corresponding hydrohalide salts by treatment with aqueous base. However, while aliphatic imidate bases are stable liquids, the aromatic analogues revert to the parent nitriles upon heating.7

A second concern relates to the stability of the orthoester products [the second step, eqn (e), Scheme 2]. Orthoesters are very stable in the presence of bases, to the point that they can be safely handled with alkaline aqueous solutions. However, under acidic conditions that may occur during the work up of the Pinner synthesis, orthoesters hydrolyse to the corresponding esters and alcohols.8

A third, more general, issue concerns the starting materials. The Pinner synthesis is successful for aliphatic nitriles (Scheme 2, e), but not for aromatic ones. For example, aromatic trimethylorthobenzoate, required for preparing the topical corticosteroid anti-inflammatory betamethasone benzoate, is still made from toxic trichloromethylbenzene (Scheme 2, eqn (a)), and cannot be synthesized from the less harmful benzonitrile.10 Table 1 compares hazard-phrases for the two starting materials.

The concerns outlined above prompted us to revisit the Pinner procedure by focusing on three objectives: (i) the use of solventless conditions to improve the preparation and stability of the imidate hydrochlorides \([RC(=NH)OR'\cdot HCl]\); (ii) the synthesis of different imidate salts \([RC(=NH)OR'\cdot HX; X = H_2PO_4, HSO_4, HOTs]\) able to undergo selective alcoholysis reactions; and (iii) the use of safer reagents such as benzonitrile to devise a new procedure for the preparation of trimethylorthobenzoate (TMOB) as a model for aromatic orthoesters.

Here we demonstrate that the Pinner synthesis may be improved through an integrated procedure. Model aliphatic and aromatic orthoesters (trimethylorthopropionate, trimethylorthovalerate, and trimethylorthobenzoate, respectively) were prepared from the corresponding nitriles in the presence of MeOH both as a reagent and as a solvent. For the more challenging aromatic product, an original sequence was devised based on the use of a hydrogenphosphate imidate salt \([PhC(=NH)OMe\cdot H_3PO_4]\). This compound reacted with methanol to yield trimethylorthobenzoate (TMOB) with a good selectivity (80%). Such a reaction was a new route for the preparation of TMOB starting from benzonitrile.

Overall, this study is an example of the process intensification of the conventional Pinner synthesis, with further benefits due to the elimination of volatile and dangerous solvents, to the use of greener reagents, and to improved yields and selectivity.

### Results and discussion

#### Preparation of imidate intermediates

**Aliphatic nitriles.** The first step of the Pinner synthesis, i.e. the formation of imidate salts, was initially investigated. Two aliphatic nitriles (propionitrile and valeronitrile, 1a and 1b, respectively) and methanol were chosen as model reagents. The twofold aim of this screening was to eliminate the use of solvents11 other than methanol and to replace gaseous HCl with the more acceptable sulfuric and phosphoric acids. Gaseous HCl, in fact, poses corrosion issues especially for large scale preparations.

A number of experiments were carried out using different amounts of MeOH and the selected acid. MeOH served as both the reagent and the solvent. With respect to the nitrile,
the molar excesses of MeOH and the acid were varied in the range of 3–10 and 1–3, respectively.

Results partially met our goal: while we were successful in using only MeOH without added solvents, unfortunately all attempts to substitute HCl with H₂SO₄ or H₃PO₄ failed. Methanol in a moderate excess with respect to the nitrile formed a homogeneous solution throughout the reaction, but the key factor was to maintain the HCl:MeOH molar ratio greater than 1. The best conditions were obtained with a molar ratio of nitrile:MeOH:HCl of 1:3:3, at 5 °C for 24 hours (Scheme 4).

The gaseous acid was slowly bubbled in the reaction mixture (over 4 hours) in order to keep the temperature below 5 °C. The resulting mixture was allowed to react for 20 h. Then, volatiles (methanol and HCl) were removed under vacuum at 10 °C, and the imidate hydrochlorides 2a·b·HCl were recovered as white solids. These products were obtained in high yields (>90%) and purity (>95%, GC) without further purification. The results are reported in Table 2.

To explain that only HCl was able to activate the reactant nitriles, but not the other acids, we referred to the literature data that describe the formation of nitrile adducts (I in Scheme 5) with hydrochloric acid at low temperatures.1,2

Once the adduct I was formed, the chloride anion was sufficiently nucleophilic to produce an imido chloride intermediate (II in Scheme 5), which was activated towards methanolation to yield the imidate hydrochloride 2. An analogous reaction could not occur with non-nucleophilic HSO₄⁻ or H₂PO₄⁻ species.

Table 2 Isolated yields of imidate hydrochloride salts 2a·b·HCl obtained under solventless conditions*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrile</th>
<th>Product</th>
<th>Isolated yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂(CH₂)₃CN 1a</td>
<td>2a·HCl</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CH₂CN 1b</td>
<td>2b·HCl</td>
<td>92</td>
</tr>
</tbody>
</table>

* Reaction conditions: a 3:1 MeOH:nitrile molar ratio, a 1:1 HCl:MeOH molar ratio, 24 hours at 5 °C.

Although an excess of HCl was required, a major advantage of our procedure was the process intensification: the absence of additional solvents allowed the use of small batch reactors with a remarkable improvement of the reaction productivity.

**Benzonitrile.** Based on the encouraging results of Table 2, the investigation was continued using benzonitrile 1c to prepare the corresponding imidate salt (2c·HCl; Scheme 6).

Benzonitrile was expected to be less reactive than aliphatic analogues. The reaction was therefore examined through inspection of several aspects, including: (i) the HCl concentration; (ii) the MeOH:nitrile molar ratio; (iii) the HCl:nitrile molar ratio and (iv) the HCl:MeOH molar ratio. Moreover, the total volume of the reaction mixture was always kept constant (50 mL) by the addition of toluene as a co-solvent. Results are summarised in Table 3. The formation of the imidate 2c·HCl was not affected by the presence of toluene (entries 1 and 3). The same held true for MeOH if both the HCl:nitrile and the HCl:mechanol molar ratios were kept constant; any increase of the MeOH amount had no appreciable effects on the yield of 2c·HCl (56, 55, and 49% in entries 1, 3 and 5, respectively). Similarly, no direct relationship was manifest between the concentration of HCl (6th column) and the yield of 2c·HCl.

By contrast, the reaction outcome was deeply affected by increasing the HCl:MeOH molar ratio (4th column), whereby an almost linear increase on the yield of the product from 38 to 92% (entries 3–6 of Table 2, and Fig. 1) was observed. This happened irrespective of the presence of toluene (compare entries 1–2 and 5 and 7 of Table 2).

This optimization study not only proved that solventless conditions could be advantageous for aromatic nitriles, but also indicated that the reaction succeeded when MeOH and HCl were both in the same molar excess (≥3) with respect to the nitrile, regardless of the excess of each single reagent. A preparative experiment starting from 20 g of benzonitrile (conditions: 5 °C, 24 h, benzonitrile:MeOH:HCl molar ratio = 1:3:3) yielded 2c·HCl in a 98% isolated yield and thus confirmed the result. Although no clear reasons accounted for this behaviour, one hypothesis was that the two consecutive steps of Scheme 5 (activation of the nitrile and methanolysis of the chloride intermediate II) were mutually favoured and balanced if equimolar quantities of MeOH and HCl were used.

**Methanolation of the imidate salts**

**Imidate hydrochlorides.** As was done for their synthesis, also the alcoholysis of the imidate salts 2·HCl was investigated without additional solvents. Initially, the most convenient approach appeared to be the in situ methanolation of the above imidates (Schemes 4 and 6) – without isolation – to the
The reaction of the salts 2-HCl was therefore studied as a separate step. The reaction was initially carried out at 25 °C by simply adding an excess of methanol (5 molar equiv.) to the pure solid imidates 2-HCl. Three main differences were manifest between the behaviour of the aliphatic compounds (2a and 2b-HCl) and that of the benzonitrile-derived imidate 2c-HCl. (i) At t = 0 (the beginning of the reaction), the aliphatic salts gave clear solutions, while 2c-HCl was poorly soluble and a suspension was obtained. (ii) After 48 hours, a white precipitate (ammonium chloride) separated from the mixtures of 2a-HCl and 2b-HCl, while no changes were visible for 2c-HCl. (iii) GC/MS analyses showed not only that the reaction was slower for 2c-HCl than for 2a and 2b-HCl, but also that different product distributions were achieved. The expected orthoesters 3 were observed in all cases, along with different amounts of the methyl esters 4 and of the corresponding amides 5 as side products (Scheme 7). The results are reported in Table 4.

The reaction of the aliphatic salts 2a-HCl and 2b-HCl was complete once all the NH4Cl precipitated (48 h). The desired corresponding orthoesters. Our objective was to use the residual MeOH of the first step, as a reagent for the second step as well. However, attempts to integrate the synthesis of imidate hydrochlorides and their subsequent methanolysis proved unsuccessful. The two reactions required different temperatures (0–5 °C and ≥25 °C, respectively), and if a residual acidity (HCl) was present in methanol solutions of 2-HCl, then the salts readily reverted to parent nitriles on heating.

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Overall, the initial screening of the methanolyis of imidate hydrochloride salts 2\textbf{-HCl} showed that although the reaction was possible using MeOH as a reagent/solvent, both the selectivity and the separation of the desired orthoesters had to be improved in order to be synthetically appealing. This was especially true for the benzonitrile derived compound 2\textbf{-HCl}. Therefore we focused our efforts on the solventless synthesis of trimethylorthobenzoate (TMOB) from 2\textbf{-HCl}.

Trimethylorthobenzoate (TMOB). The first goal was to eliminate the formation of benzamide as a side product of the methanolysis of 2\textbf{-HCl}. As discussed in the Introduction, the conversion of imidate hydrochlorides to the corresponding amides occurs by an internal nucleophilic attack of the chloride ion (Scheme 3, top). We therefore envisaged that this reaction could be prevented by the presence of a less nucleophilic counteranion of the imidate salt. The phosphate ion was chosen as a model since the low volatility and the relatively low corrosivity of phosphoric acid made it an easy-to-use acid. However, we had already observed that the direct synthesis of imidate phosphate salts (2\textbf{-H3PO4}) was not feasible (Scheme 5). A two-step strategy was applied: (i) first, the benzoimidomethylester hydrochloride 2\textbf{-HCl} was obtained by the reaction of benzonitrile, MeOH and HCl (Scheme 6); (ii) then, 2\textbf{-HCl} was ion-exchanged with H3PO4 to produce the imidate dihydrogenphosphate salt 2\textbf{-H2SO4}. The procedure for the anion metathesis (ion exchange reaction) is presented in Scheme 8.

Treatment of the imidate hydrochloride (8.36 mmol) with aqueous potassium carbonate yielded benzoimidomethylester 2c in the neutral form (free base, eqn (a)). Compound 2c was then recovered by extraction with an eco-friendly solvent such as ethyl acetate or dimethylcarbonate. To the clear solution of 2c, anhydrous H3PO4 (pK\textsubscript{a} = 2.12\textsuperscript{14}) diluted in the minimum amount of methanol (1 mL g\textsuperscript{-1} acid; 2c: acid molar ratio = 1:1) was added. The desired imidate dihydrogenphosphate 2\textbf{-H2PO4} precipitated as a white microcrystalline solid (eqn (b)) in almost quantitative yield (98%). Both reactions (a) and (b) were carried out at 0–5 °C. Only the first dissociation of phosphoric acid took place: the titration of a solution of neutral imidate 2c by H3PO4 proved that a single mole of acid was consumed.

The anion metathesis procedure was then extended to different acids: CH\textsubscript{3}COOH, H2SO4, HOTs. Acetic acid (pK\textsubscript{a} = 4.76\textsuperscript{15}) proved too weak to protonate the imidate, while the stronger sulphuric and p-toluenesulfonic acids (pK\textsubscript{a} = −3.0\textsuperscript{14} and −2.8,\textsuperscript{15} respectively) yielded the corresponding salts. Sulphate 2\textbf{-H2SO4} separated from the organic solution as a liquid. The solvent was decanted and the oily product was used thereafter without any further purification. The p-toluene-sulfonate salt 2\textbf{-HOTS} precipitated as a white solid (93%) and was isolated by filtration.

The three available imidate salts (2\textbf{-H3PO4}, 2\textbf{-H2SO4}, and 2\textbf{-HOTS}) were investigated for the synthesis of TMOB.

The reaction of 2\textbf{-H3PO4} (7.90 mmol) was initially explored at 25 °C in the presence of an excess of MeOH (20 molar equiv.). The methanolysis was even slower than that observed using 2\textbf{-HCl}: after 24 hours, the conversion was only 20%. However, the selectivity was greatly improved. Major products were the desired orthoester 3c and methyl benzoate 4c (13% and 7%, respectively), while benzamide 5c was detected in a remarkably low amount (1%). This seemed to confirm our assumption that the poorly nucleophile dihydrogenphosphate anion inhibited the side-formation of benzamide. Encouraged by this result, we continued the study at a higher temperature. The reaction of each imidate salt (2\textbf{-H3PO4}, 2\textbf{-H2SO4} and 2\textbf{-HOTS}) with excess methanol (20 molar equiv.) was carried out at the reflux temperature (65 °C). After 4 hours, the reaction mixtures were analysed by GC/MS. The results are presented in Table 5.

The higher temperature (65 °C) prompted substantially quantitative conversions (85–90%) in all cases. Remarkably, the alcoholysis of 2\textbf{-H3PO4} corroborated the product distribution observed at 25 °C: the reaction gave mainly the desired orthoester (3c: 64%) along with methyl benzoate (4c: 16%) and negligible amounts of benzamide 5c (2%) (entry 1). This result was, by far, superior to that achieved with 2\textbf{-HCl} at both 25 and 50 °C (Table 4 and below).

The reaction of the hydrogensulphate imidate 2\textbf{-H2SO4} with methanol yielded mainly the methyl ester 4c (entry 2: 88%), along with some unrecognised side products. Not even traces of either 3c or 5c were detected. Plausibly, also the hydrogensulphate anion was not sufficiently nucleophilic to promote the formation of benzamide; nevertheless, its strongly acidic nature and the problematic isolation of 2\textbf{-H2SO4} made the preparation of 3c not viable.

### Table 5 Methanolation of imidate salts 2c\textbf{-H3PO4}, 2c\textbf{-H2SO4} and 2c\textbf{-HOTS} at 65 °C\textsuperscript{a}

<table>
<thead>
<tr>
<th>#</th>
<th>Anion</th>
<th>Conversion % by GC/MS\textsuperscript{b}</th>
<th>Orthoester 3c</th>
<th>Ester 4c</th>
<th>Amide 5c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[H3PO4]\textsuperscript{−}</td>
<td>82</td>
<td>64</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>[HSO4]\textsuperscript{−}</td>
<td>100\textsuperscript{c}</td>
<td>—</td>
<td>88</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>[p-CH3C6H4SO3]\textsuperscript{−}</td>
<td>90</td>
<td>—</td>
<td>49</td>
<td>41</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Methanol : substrate molar ratio = 20 : 1. \textsuperscript{b} The mixture composition after 4 hours. \textsuperscript{c} Unrecognised compounds were observed (12%).
Finally, methanolysis of the tosylate salt 2c·HOTs provided almost equal amounts of methyl benzoate and benzamide (entry 3: 49 and 41%, respectively). In this case, methyl p-toluene-sulfonate (p-CH₃C₆H₄SO₃CH₃) was also detected (by GC/MS) as a side-product in an amount comparable to that of the amide 5c. The presence of methyl tosylate substantiated the mechanism of Scheme 5 for the formation of benzamide.

Among the tested imidates, only 2c·H₃PO₄ was able to undergo a selective methanolysis to TMOB (3c) at 65 °C. Under such conditions, a detailed investigation of the reaction was carried out over a period of 8 hours. Samples of the reaction mixture were withdrawn at selected time intervals and analysed by GC/MS to obtain a reaction profile. The results are reported in Fig. 2.

The optimal reaction time was 6 hours when the conversion was quantitative and the selectivity towards the desired orthoester was 82%. The formation of the major by-product, methyl benzoate, could be further reduced to 15% by operating under strictly anhydrous conditions. The amount of benzamide was ≤3%.

These observations allowed us to set up a process for the preparation of TMOB using benzonitrile as the starting material. Starting from 20 g of benzonitrile (194 mmol) and applying the optimal ratio of 1c : MeOH : HCl equal to 1 : 3 : 3, the nitrile was converted into the imidate hydrochloride 2c·HCl. The latter was then anion exchanged to the corresponding imidate dihydrogenphosphate (2c·H₃PO₄). Yields of the two salts were 98 and 97%, respectively. In the second step, at 65 °C, 2c·H₃PO₄ was treated with methanol to yield trimethylorthobenzoate. The product was then distilled under vacuum and isolated in 65% yield (98% purity GC). The overall yield of TMOB was 62%.

A scale up of the overall procedure was also performed. The test was conducted starting from 120 g of benzonitrile (1.17 mol). In this case, yields of the two salts 2c·HCl and 2c·H₃PO₄ were 97 and 98%, respectively. After the alcoholysis step of 2c·H₃PO₄, TMOB was isolated by distillation in an overall yield of 56% (118 g).

To the best of our knowledge, this was the first ever accomplished high-yielding synthesis of TMOB via the Pinner reaction from benzonitrile. The imidate formation and alcoholysis steps were both carried out without added solvents except MeOH which also acted as a reagent. Gaseous HCl and anhydrous H₃PO₄ were used in 3 : 1 and 1 : 1 molar ratios over benzonitrile and 2c·HCl, respectively.

**Conclusions**

A greener Pinner synthesis of trimethylorthoesters RC(OCH₃)₃ (R = Et, Bu, Ph; 3a, b, and c, respectively) was developed through a two-step sequence carried out in the absence of solvents, using MeOH that also acted as a reagent.

In the first step, nitriles R-CN (1a–c) were converted into the corresponding imidate hydrochlorides 2a–c·HCl which were isolated with excellent yields (>90%). Although it was not possible to replace gaseous HCl with more manageable common acids such as sulphuric, phosphoric or supported sulfonic acids, we were able to set up conditions whereby only a moderate excess of methanol (3 molar equiv. with respect to the nitrile) was used. The elimination of additional hazardous solvents improved the safety and allowed a remarkable process intensification.

In the second step, the methanolysis of imidate salts was performed successfully on alkyl derivatives 2a–b·HCl, achieving the corresponding trimethylorthoesters 3a–b. On the other hand, by using the same strategy, the aromatic analogue trimethylorthobenzoate (TMOB) 3c could not be obtained due to the major formation of benzamide as a side-product. As predicted from the available literature data, this compound (amide) was formed by the presence of the chloride counterion in the reacting salt 2c·HCl. To overcome this bottleneck, we implemented an original sequence whereby the hydrochloride salt was ion-exchanged with phosphate to yield 2c·H₃PO₄. This in turn reacted selectively (>80%) with methanol to afford the desired pure product 3c in up to 62% isolated yield.

In conclusion, our new procedure not only eliminated the use of noxious chlorinated solvents for the preparation of trimethylorthoformates 3a–c, but also, for the case of 3c, it allowed the unprecedented Pinner-type synthesis starting from benzonitrile. This circumvented the need to prepare TMOB by the traditional method using the very toxic and suspected carcinogenic trichloromethylbenzene as a reagent. In our view, although an additional step (the anion metathesis to produce 2c·H₃PO₄) was required, the gain in “greenness” due to the use of a non-toxic starting material largely offset the increased mass flow.

**Experimental section**

**General**

The chemicals used were of reagent grade and used as received. Trimethylorthopionate, trimethylorthovalerate, trimethylorthobenzoate, propionitrile, valeronitrile, benzonitrile, phosphoric acid, acetic acid, trifluoroacetic acid,
**p-toluenesulfonic acid, and sulphuric acid were from Aldrich. Gaseous hydrogen chloride was from SIAD (Italy).

GC/MS (EI, 70 eV) analyses were performed with an HP5890 gas chromatograph equipped with an HP5 MS capillary column (30 m × 0.25 mm; coating thickness 0.25 μm) and an HP-5970 quadrupole mass detector (EI, 70 eV).

NMR spectra were recorded using a Varian Unity 400 MHz spectrometer. Chemical shifts were reported in δ values downfield from TMS; CDCl₃ was used as a solvent.

The structures of orthoesters and by-products were assigned by both comparison to authentic samples and GC/MS and ¹H NMR analyses.

**The Pinner synthesis with no added solvents. A typical procedure**

The preparation of imidate hydrochlorides 2-HCl. A mixture of the chosen nitrile (140 mmol, 1a: 7.71 g, 1b: 11.64 g, 1c: 14.44 g) and methanol (13.4 g, 420 mmol) was charged in a 50 mL flask, and cooled to 5 °C in an ice bath. Gaseous HCl was slowly bubbled into the methanolic solution of the nitrile until the required amount was reached (HCl: 15.30 g, 420 mmol). The quantity of HCl was determined by weighing the reaction vessel at time intervals (3 min). The resulting mixture was kept at 5 °C for 24 hours. Then, the excess of methanol and HCl was removed by rotary evaporation under vacuum. A white solid of highly pure (>98%) imidate hydrochloride separated (2a-HCl: 15.75 g, 91%; 2b-HCl: 19.50 g, 92%; 2c-HCl: 22.6 g, 94%). The product was dried under vacuum at rt, and used as such for the subsequent methanolysis step.

The alcoholsysis of imidate hydrochlorides 2-HCl. At rt, a mixture of methanol (19.8 g, 620 mmol) and the solid imidate hydrochloride 2-HCl (125 mmol; a: 15.45 g; b: 18.95 g; c: 21.45 g) was set to react under stirring for 48 hours. A clear solution was obtained with 2a- and 2b-HCl, while for 2c-HCl a white suspension was observed. A white solid (ammonium chloride) formed during the reaction. Ethyl acetate (50 mL) was then added with vigorous stirring. Solid NH₄Cl was allowed to settle and the supernatant clear solution was transferred, by means of a needle, to a 500 mL flask containing a 0.5 M aqueous solution of Na₂CO₃ (200 mL). The aqueous phase was then discharged and extracted with 2 × 20 mL of ethyl acetate. The extracts were collected and dried on Na₂SO₄ and the solvent was removed by rotary evaporation. The pale yellow liquid thus obtained was purified by distillation, yielding trimethylorthopropionate (3a, 9.89 g, 59%) or trimethylorthovalerate (3b, 11.76 g, 58%). Trimethylorthobenzoate 3c was not obtained using this procedure.

The synthesis of trimethylorthobenzoate (TMOB)

**Study of the synthesis of benzoimide 2c-HCl using toluene as the co-solvent.** Benzonitrile 1c (20 g, 194 mmol) and the required amount of methanol (6.88, 13.76, 23.76 g; 215, 429, 742 mmol, see Table 3) were introduced into a 100 mL flask. Toluene was added to reach a total volume equal to 50 mL and the resulting mixture was cooled to 5 °C by means of an ice bath. Gaseous hydrogen chloride was bubbled into the cooled mixture. After the required amount of HCl was added (8.19–25.25 g, see Table 3) the reaction mixture was kept at 5 °C for 24 hours. The formed methylbenzoimidate hydrochloride 2c-HCl was filtered and washed with 2 × 10 mL diethyl ether.

Anion metathesis of benzoimide hydrochloride salt. A mixture of benzoimidate hydrochloride [2e-HCl: PhC(=NH)-OCH₃·HCl; 1.60 g, 8.36 mmol] and ethyl acetate (15 mL) was charged to a 50 mL flask. The resulting suspension was cooled to 5 °C. To this, a 1.8 M aqueous solution of K₂CO₃ (15 mL) was added with vigorous stirring until complete dissolution of the starting salt 2c-HCl was obtained. Then, the organic phase was separated, while the aqueous phase was extracted with ethyl acetate (2 × 2 mL). The combined organic extracts were dried over Na₂SO₄, filtered, introduced in a 50 mL flask, and cooled to 5 °C. To this solution, a selected Brønsted acid HX (phosphoric acid: 8.36 mmol, 819 mg; sulfuric acid: 820 mg, p-toluenesulfonic acid: 1.44 g) dissolved in the minimum volume of methanol (2 mL) was added. The molar ratio 2e : HX was 1. Both the hydrogenphosphate and the p-toluenesulfonate salts precipitated as white solids and were filtered (2e-H₃PO₄: 1.84 g, 7.89 mmol, 94%; and 2e-HOTs: 2.28 g, 7.42 mmol, 89%). The hydrogensulfate salt 2e-H₂SO₄ separated as an oil from which ethyl acetate and methanol were removed at reduced pressure.

The three anion exchanged salts were then used as such, without any further purification.

**Alcoholysis of 2c-HX.** The reaction was carried out as follows: a mixture of the selected benzoimide 2c-HX (see above) and methanol (4.98 g, 155 mmol) was heated to reflux temperature for 4 to 6 hours (see Table 5 and Fig. 2). Mixtures were sample and analysed by GC/MS. At this stage, products were not isolated.

**Preparation of trimethylorthobenzoate.** The above described procedures for the synthesis of imidate salts, the anion exchange, and the alcoholysis reaction were used for the preparation and isolation of TMBO. Benzoimidate hydrochloride 2c-HCl was obtained starting from 194 mmol of benzonitrile (20 g) and methanol (25 mL, 617 mmol). The mixture was placed in a 250 mL flask, cooled to 5 °C, and set to react with gaseous HCl (22.5 g, 617 mmol) from a commercial cylinder. The whole addition of the gas took 4 hours, and the reaction was allowed to proceed for an additional 20 hours keeping the temperature below 10 °C by means of an ice bath. 2c-HCl was obtained as a white solid in a 98.5% yield (32.8 g, 191 mmol).

The salt was suspended in ethyl acetate (200 mL) and neutralized with a 1.8 M aqueous solution of Na₂CO₃ (200 mL). The resulting methyl benzoimide 2c dissolved in ethyl acetate was treated with anhydrous H₃PO₄ (16.4 g, 167.2 mmol) dissolved in MeOH (20 mL) at 5 °C, for 30 minutes. A white, microcrystalline solid of O-methyl benzoimide dihydrogenphosphate [2e-H₃PO₄: 43.4 g, 186 mmol; 97.5%] was isolated. This compound was set to react with MeOH (150 mL, 3.66 mol) at the reflux temperature (65 °C) with stirring, for 6 hours. The mixture was then allowed to cool to room temperature and the excess methanol was removed under vacuum. Ethyl acetate (50 mL) was then added with vigorous stirring.
Solid [NH₄][H₂PO₄] was allowed to settle and the supernatant clear solution was transferred, by means of a needle, to a 500 mL flask containing a 0.5 M aqueous solution of Na₂CO₃ (200 mL). The white solid NH₄Cl was extracted with an additional 2 × 10 mL of ethyl acetate. The aqueous phase was then discharged and extracted with 2 × 10 mL of ethyl acetate. The extracts were collected, dried on Na₂SO₄ and the solvent was removed by rotary evaporation. The pale yellow liquid thus obtained was purified by distillation at reduced pressure (80 °C at 5 torr), yielding trimethylorthobenzoate in 65.0% yield (22.0 g, 121 mmol).

**Scale up of the synthesis of trimethylorthobenzoate.** TMOB was also prepared on a larger (6 times higher) scale. Benzo-imidate hydrochloride 2c·HCl was obtained starting from 1.17 mol of benzonitrile (120 g) and methanol (150 mL, 3.70 mol). The mixture was placed in a 250 mL flask and cooled to 5 °C. Once the temperature was stable, gaseous HCl (127.0 g, 3.50 mmol) was slowly added keeping the temperature below 10 °C. After 20 hours at 5 °C, 2c·HCl was obtained as a white solid in a 92.1% yield (184 g, 1.07 mol).

The salt was slowly added over a mixture of ethyl acetate with anhydrous H₃PO₄ (109 g, 1.11 mol) dissolved in MeOH (50 mL) at 5 °C, for 60 minutes. A white, microcrystalline solid of O-methyl benzoimidate dihydrogenophosphate [2c·H₂PO₄; 240 g; 1.03 mol; 96.3%] was isolated. This compound was set to react with MeOH (900 mL, 22.2 mol) at the reflux temperature (65 °C) with stirring, for 8 hours. The mixture was then treated as in the previous preparation, increasing all the quantities by a factor equal to 6, yielding trimethylorthobenzoate in 62.9% yield (118 g, 648 mmol).

**Characterisation data**

All the compounds were characterised by GC/MS and ¹H NMR. Spectroscopic properties were in agreement with those reported in the literature.

**Methylpropioimidate 2a.**

<table>
<thead>
<tr>
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<tbody>
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<td>GC/MS (relative intensity, 70 eV)</td>
<td>123 (101 [%M+], 100), 122 (100), 77 (100), 55 (100); ¹H NMR (CDCl₃) δ 7.67 (1H, 7.6 Hz, 1H), 7.52 (1H, 7.6 Hz, 2H), 6.95 (1H, 7.6 Hz, 1H), 1.11 (t, J = 7.6 Hz, 3H).</td>
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**Methyvalerate 4b.**

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**Trimethylorthobenzoate 3c.**

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**Notes and references**


13 Toluene was chosen given its inertness in the reaction environment.


