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An Efficient Preparation of β-Aryl-β-ketophosphonates by the TFAA/H_3PO_4-Mediated Acylation of Arenes with Phosphonoacetic Acids

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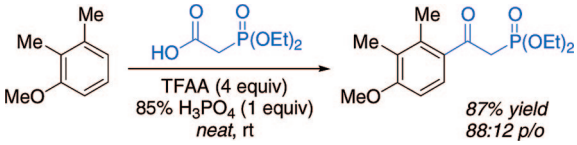
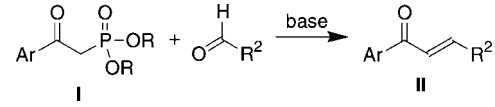


β-Aryl-β-ketophosphonates can be efficiently prepared in good yield by using a TFAA/85% H_3PO_4-mediated acylation of electron-rich arenes with phosphonoacetic acids. The conditions offer advantages over existing methods of preparing these useful compounds by not requiring the use of strong base, cryogenics, or an anhydrous and inert atmosphere. Furthermore, some functional groups not tolerated with the reaction conditions used in existing methods are compatible with the herein described conditions.

β-Aryl-β-ketophosphonates (**I**) are frequently used reagents in Horner−Wadsworth−Emmons (HWE) olefination reactions with aldehydes or ketones to produce acrylophenones (**II**, eq 1).[1] Furthermore, β-aryl-β-ketophosphonates can serve as precursors in the preparation of γ-aryl-γ-ketophosphonates,[2a] certain β-phosphonic acid α-amino acid derivatives,[2b] as well as aryl-substituted 3-furylphosphonates.[2c] In addition to their synthetic utility, β-aryl-β-ketophosphonates are known to possess a range of biological activity.[3] Some β-aryl-β-ketophosphonates inhibit the proliferation of tumor cells,[3a] some possess bone anabolic activity,[3b] and others have been identified as thyroid receptor ligands.[3c]

Several methods of preparing β-aryl-β-ketophosphonates have been described in the literature.[4] All of the literature methods



(1)

generally utilize the same basic strategy of elaborating a benzoyl derivative to the targeted ketophosphonate (Scheme 1). Additionally, many of the literature methods require the use of strong base and cryogenics, which can limit their utility in certain instances.

As part of a recent development project, we required supplies of several novel β-aryl-β-ketophosphonates (**1**, Scheme 2), which were to be used in subsequent HWE reactions in the preparation of key acrylophenone intermediates. These closely related 2,3-dimethylphenol derivatives differ primarily in the length of the hydroxyalkyl chain appended to the phenol oxygen. In considering a strategy for the preparation of **1**, we recognized that the only commercially available derivative of 2,3-dimethylphenol that appeared to be a suitable substrate for the existing methods of preparing β-aryl-β-ketophosphonates was 2,3-dimethylanisaldehyde, which was rather expensive. Preparing related benzoyl derivatives to serve as suitable substrates for existing methods would only add steps to our process. Furthermore, the reaction conditions used in some of the existing methods were not compatible with some of the functionality in our system and/or were not attractive from a process chemistry standpoint. We therefore began to consider alternative methods of preparing β-aryl-β-ketophosphonates. The goal was to identify an efficient process that utilizes relatively mild reaction conditions. We knew that the Friedel−Crafts acylation of 2,3-dimethylanisole (**2a**) with simple acid chlorides was a regioselective, high-yielding reaction,[5] so we considered an approach whereby we would use a phosphonoacetic acid to acylate an appropriate 2,3-dimethylphenol derivative (**2**, Scheme 2), directly affording a β-aryl-β-ketophosphonate. This successful strategy is the subject of this paper.

At the outset, we considered using the known diethylphosphonoacetyl chloride,[6] prepared from commercially available diethylphosphonoacetic acid (**3a**), in the Friedel−Crafts acylation; however, we experienced some difficulties in isolating the acid chloride. We therefore quickly turned our attention to the more direct approach of using diethylphosphonoacetic acid (**3a**) itself in the acylation. 2,3-Dimethylanisole (**2a**) was chosen as the model substrate for surveying various reaction conditions. We had little success using some of the more common promoters of Friedel−Crafts acylations with carboxylic acids, such as $MeSO_3H$, H_2SO_4, trifluoroacetic anhydride (TFAA), or $POCl_3$.

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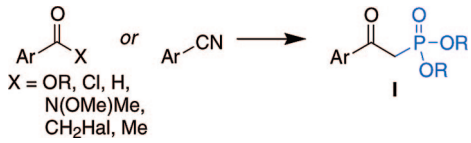
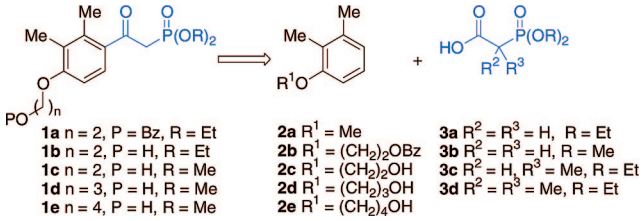
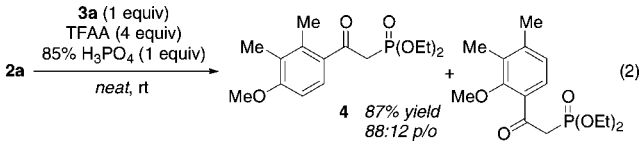
SCHEME 1. General Approach of Existing Methods to Prepare β-Aryl-β-ketophosphonates



SCHEME 2. Proposed Strategy for the Preparation of β-Aryl-β-ketophosphonates



However, employing the rarely used combination of TFAA and 85% phosphoric acid—conditions originally described by Galli[7] and later studied in greater detail by Smyth[8]—we were pleased to find the desired reaction had occurred, and the corresponding β-aryl-β-ketophosphonate **4** was isolated in very good yield (87%), albeit as an 88:12 mixture of the desired para isomer and the undesired ortho isomer (eq 2). While we were certainly pleased with this initial result, we were somewhat disappointed the reaction was not as regioselective as the Friedel–Crafts acylation of **2a** with simple acid chlorides.

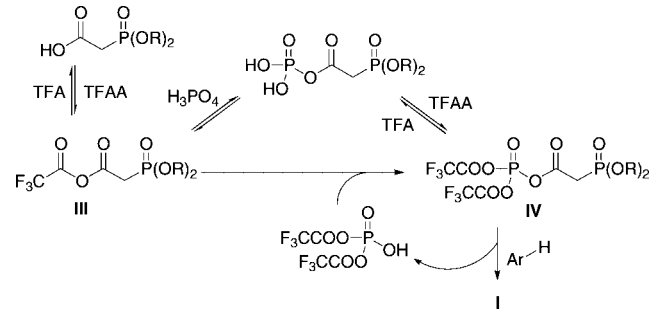


(2)

We next looked at the acylation of **2b**, which incorporates a hydroxyethyl chain protected as a benzoate ester, with **3a** using the TFAA/H_3PO_4 conditions. Once again, we were pleased to find the desired reaction had taken place to deliver **1a** in very good yield; however, no improvement in the regioselectivity of the reaction was observed. Furthermore, since **1a** is a syrup, it could not be purified by crystallization, which would be the most preferred method of purification on scale.

Our inability to easily separate the two regioisomers was not our only concern at this point. Our plan for the HWE reaction in our system was to use a slight excess of **1** to ensure complete consumption of our aldehyde, and then simply wash out unconsumed **1** with an alkaline aqueous extraction during the workup. Unfortunately **1a** was too lipophilic to be easily washed out in an alkaline aqueous extraction. However, saponification of **1a** with LiOH yielded **1b**, which possesses the desired solubility in aqueous base. This observation prompted us to consider preparing **1b** directly by using **2c**, which has no protecting group, in the acylation reaction. We did not need the protecting group for any of the planned downstream chemistry, including the HWE reaction and, prior to identifying conditions for preparing **1**, had simply assumed a protecting group was needed for the acylation step. Proceeding without a protecting group would further streamline our process by eliminating protection–deprotection steps. Gratifyingly, we were indeed able to acylate **2c** with **3a** using TFAA and 85% phosphoric acid to afford **1b** in comparable yield and selectivity. Unfortunately, however, this material is also a syrup and therefore could not be purified by crystallization.

SCHEME 3. Smyth's Proposed Acylation Mechanism Applied to Phosphonoacetic Acids



In an effort to identify a solid product, we prepared the dimethyl ketophosphonate **1c**. Thus, TFAA/H_3PO_4-mediated acylation of **2c** with dimethylphosphonoacetic acid (**3b**) produced **1c** with comparable efficiency and selectivity as previously observed (~85% yield, 88:12 para/ortho). We were pleased to find that in this instance the product turned out to be a solid as hoped. Simple crystallization of the crude product from *n*-BuOAc afforded **1c** in 66% isolated yield and >98% purity with <1% of the undesired ortho isomer.

By analogy to Smyth's proposed acylation mechanism,[8b] the phosphoric acid presumably serves to convert an initially formed acyl trifluoroacetate (**III**) to the much more reactive acyl bis(trifluoroacetyl)phosphate (**IV**, Scheme 3). The amount of TFAA required is determined by the amount of phosphonoacetic acid and phosphoric acid used in the reaction. For every equivalent of phosphonoacetic acid, 1 equiv of TFAA is consumed in forming **III**. For every equivalent of 85% phosphoric acid used, an additional 3 equiv of TFAA are required—one is hydrolyzed by the ca. 1 molar equiv of water, and two are consumed in the formation of **IV**. The carboxylic acids surveyed by Galli and Smyth were simple, unfunctionalized carboxylic acids, and no phosphonoacetic acids were used.[9]

In the TFAA/H_3PO_4-mediated acylations of **2a** and **2b** with **3a**, we used 4 equiv of TFAA and 1 equiv of 85% H_3PO_4. When **2c** was used as the substrate, an additional equivalent of TFAA, which effectively served to protect the alcohol as a TFA ester in situ, was required. The TFA ester readily hydrolyzed during the workup. We were concerned with the expense associated with using 5 equiv of TFAA on scale, so we explored reducing the stoichiometry of the phosphoric acid and TFAA. Smyth had demonstrated that substoichiometric amounts of phosphoric acid are sufficient with some of the more reactive arenes, as his proposed mechanism would suggest.[10] Indeed we were able to reduce the amounts of H_3PO_4 and TFAA required to 0.2 and 3.0 equiv, respectively (in theory, only 2.6 equiv of TFAA is required with 0.2 equiv of 85% H_3PO_4; we used 3.0 equiv out of convenience). We found that with the reduced quantities of

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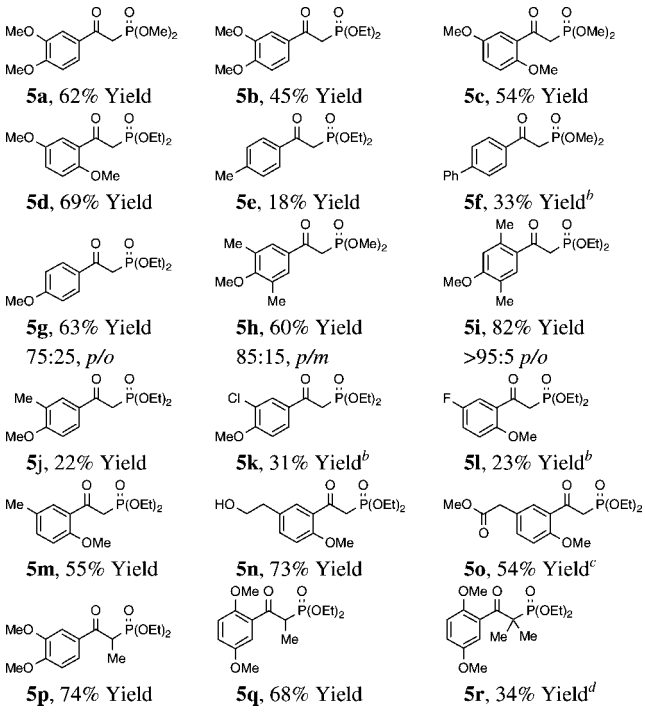
(8) (a) Smyth, T. P.; Corby, B. W. *Org. Process Res. Dev.* **1997**, *1*, 264. (b) Smyth, T. P.; Corby, B. W. *J. Org. Chem.* **1998**, *63*, 8946.
(9) The acylation of indole and 2-methylindole with diethylphosphonoacetic acid (**3a**) activated by acetic anhydride has previously been described: Slätt, J.; Janosik, T.; Wahlström, N.; Bergman, J. *J. Heterocycl. Chem.* **2005**, *42*, 141. When we attempted to prepare **4** from **2a** using these same conditions, we saw no reaction. Upon addition of 85% H_3PO_4 to the reaction mixture, **2a** was converted to 2,3-dimethyl-4-methoxyacetophenone nearly quantitatively.
(10) Smyth also demonstrated that the TFA generated in the reaction can be recovered and converted back to TFAA. See ref 8a.

TABLE 1. β-Aryl-β-ketophosphonates (5) Prepared by the TFAA/H_3PO_4-Mediated Acylation of Arenes with Phosphonoacetic Acids (3)[a]

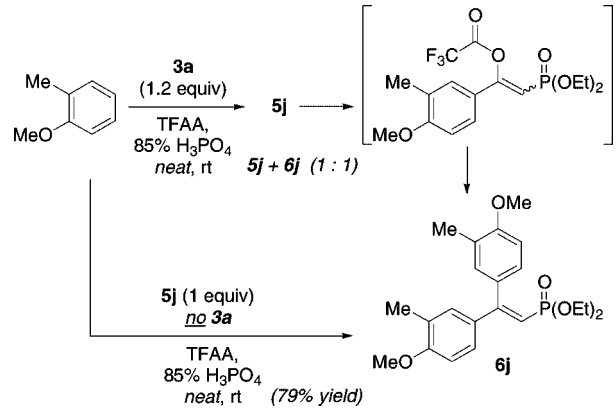


[a] All reactions were run neat with 1.0 equiv of arene, 4.0−4.8 equiv of TFAA, 1.0−1.2 equiv of phosphonoacetic acid, and 1.0−1.2 equiv of 85% H_3PO_4. All reactants were combined at 0 °C, and the reaction mixture then warmed to rt (except where noted) for a period of 2−24 h. Products were isolated by using the extractive procedure described in the text, except where noted. In cases where regioisomeric mixtures were produced, the ratio is noted below the yield. [b] Run at 50 °C. [c] Product extracted at pH 8−9, then purified by column chromatography. [d] Product only extracted at pH 8−9

these reagents, heating to 50 °C was necessary to achieve the desired conversion in a reasonable period of time. With these modified conditions, **2c** was acylated with **3b** to provide **1c** in comparable yield and selectivity as in the stoichiometric case. In similar fashion, **2d** and **2e** were converted to ketophosphonates **1d** and **1e**, respectively. In all cases, simple crystallization delivered the desired para isomer in very pure form.

We have explored the generality of the TFAA/H_3PO_4-mediated acylations of electron-rich arenes with phosphonoacetic acids as a means of preparing β-aryl-β-ketophosphonates. Table 1 lists several of the β-aryl-β-ketophosphonates we prepared. In this survey, we used one standard set of conditions that may not be optimal for all substrates. Briefly, the reactions were run by combining 1.0 equiv of the arene, 4.0−4.8 equiv of TFAA, and 1.0−1.2 equiv of the phosphonoacetic acid, followed by adding 1.0−1.2 equiv of 85% H_3PO_4 at 0 °C. The reaction mixtures were then stirred at rt or, in some cases, 50 °C for a period of 2−24 h. Better yields were typically obtained with the more reactive substrates. With less reactive substrates such as toluene, biphenyl, 2-chloroanisole, and 4-fluoroanisole lower yields were observed, primarily due to lower conversion (**5e**, **5f**, **5k**, and **5l**). With the less reactive substrates, heating to 50 °C was beneficial. Most reactions were simply run by using commercially available diethylphosphonoacetic acid (**3a**). However, other phosphonoacetic acids can be used. Dimethylphosphonoacetic acid (**3b**) worked just as well (**5a** and **5c** vs **5b** and **5d**). In certain instances, the dimethylphosphonate products may be preferred over the diethylphosphonate products for potentially different physical properties (crystallinity, aqueous solubility, etc.). Phosphonoacetic acids bearing α-substituents can also be used in the reaction (**5p**−**r**). As already demonstrated in the case of **2**, some functional groups, such as alcohols and esters (**5n** and **5o**), which may not be compatible with literature methods of preparing β-aryl-β-ketophosphonates, are tolerated by using the TFAA/H_3PO_4 conditions.

SCHEME 4. Formation of a β,β-Diarylvinylphosphonate



The workup was designed to minimize or eliminate subsequent purification procedures. For most substrates the following workup was used. Once the reaction was deemed complete (either because of complete consumption of starting arene or no further conversion), the reaction mixture was cooled to 0 °C and diluted with water. The pH of the mixture was then adjusted to 8−9 by the addition of aqueous NaOH. After warming to rt, the mixture was then extracted with an organic solvent (typically CH_2Cl_2, toluene, or MTBE). The phosphate and TFA salts, as well as any unconsumed phosphonoacetic acid, remain in the aqueous layer, which is discarded. The product-containing organic extract is then extracted with 1 N aq NaOH. The acidic β-aryl-β-ketophosphonate partitions into the aq NaOH layer, while the uncharged components, including any remaining starting arene and diarylvinylphosphonate (vide infra), remain in the organic layer.[11] The product-containing aqueous layer is then acidified with concentrated HCl and extracted with fresh organic solvent (typically CH_2Cl_2, toluene, or MTBE). This extract is then concentrated to yield pure product, which can be used in subsequent chemical transformations without further purification. This generalized workup procedure was not optimized for every example, and differences were noted in the relative solubilities of the various β-aryl-β-ketophosphonates. Therefore some of the yields in Table 1 may be improved with further optimization in the workup.

In general, the acylations are reasonably clean reactions. Modest to low yields can generally be attributed to incomplete conversion or low recovery in the extractive workup due to solubility issues. The only byproduct of note is a β,β-diarylvinylphosphonate (**6**) resulting from incorporation of a second equivalent of the starting arene into the product. In many cases, diarylvinylphosphonate formation was minimal. One notable exception was the acylation of 2-methylanisole, where diarylvinylphosphonate formation was rather significant (1:1 mixture of **5j/6j**, Scheme 4). Fortunately, the diarylvinylphos-

(11) A similar purification procedure has previously been described. See ref 4e.

phonate can be separated from the desired β-aryl-β-ketophosphonate in the extractive workup. At this point it is not completely clear how the diarylphosphonate is formed nor why it is more favorable in certain cases versus others. However, we believe its formation may involve an intermediate vinyl trifluoroacetate. In some instances we have seen mass spectral evidence (from LCMS analysis of the reaction mixture prior to workup) for the presence of low levels of this intermediate.[12] The vinyl trifluoroacetate is simply hydrolyzed during the workup and not detected in the crude product or the neutral extracts. Separately, we have found that isolated **5j** can be subsequently treated with 2-methylanisole in the presence of TFAA and 85% H_3PO_4 to form **6j** in 79% isolated yield.[13]

We have attempted to expand the scope of the TFAA/H_3PO_4-mediated acylations with phosphonoacetic acids to other electron-rich systems such as furan, 2-methylthiophene, and ferrocene. However the reaction mixtures in these cases have been much more complex, with only low yields of the desired ketophosphonates being produced. We have also just begun to extend the utility of the TFAA/H_3PO_4 acylation conditions to the preparation of β-aryl-β-ketoesters with malonic acid monoesters; those results will be reported in due course.

In summary, we have described a simple and efficient method of preparing β-aryl-β-ketophosphonates using the TFAA/H_3PO_4-mediated acylation of arenes with phosphonoacetic acids. The conditions offer advantages over existing methods in that they do not require the use of strong base, cryogenics, or an anhydrous and inert atmosphere. Furthermore, some functional groups not tolerated with the reaction conditions used in existing methods are compatible with the herein described conditions. This methodolgy was used successfully in the efficient preparation of over 80 kg of a key β-aryl-β-ketophosphonate intermediate for a development program at Neurogen.

Experimental Section

Representative Acylation Procedure: Preparation of Dimethyl [2-(2,5-Dimethoxyphenyl)-2-oxoethyl]phosphonate (5c). A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with 1,4-dimethoxybenzene (1.38 g, 10 mmol) and TFAA (6.7 mL, 48 mmol). The mixture was cooled to 0 °C with stirring and treated with dimethylphosphonoacetic acid (**3b**) (2.02 g, 12.0 mmol) followed by 85% H_3PO_4 (1.38 g, 12.0 mmol). After 5 min, the ice bath was removed, and the orange reaction mixture was stirred at rt. After 24 h, the reaction mixture was cooled to 0 °C and diluted with water (30 mL). Next, the pH was adjusted to ~9 by the careful addition of 10 N aq NaOH (~12 mL). The ice bath was removed, and the mixture was stirred for 10−15 min before it was extracted with toluene (2 × 30 mL). The combined toluene extracts were then extracted with 1 N aq NaOH (1 × 40 mL, then 1 × 20 mL). The combined NaOH extracts were acidified to pH <2 by the addition of concd HCl (~5 mL). This acidified aqueous layer was then extracted with dichloromethane (1 × 50 mL, then 1 × 25 mL). The combined dichloromethane extracts were then concentrated in vacuo to afford **5c** (1.57 g, 54%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 3.0 Hz, 1H), 7.07 (dd, J = 9.1, 3.3 Hz, 1H), 6.03 (d, J = 8.8 Hz, 1H), 3.90 (s, 3H), 3.86 (d, $^2J_{HP}$ = 21.4 Hz, 2H), 3.79 (s, 3H), 3.76 (d, $^3J_{HP}$ = 11.0 Hz, 6H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 25.34; ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4 (d, $^2J_{CP}$ = 7.8 Hz), 153.3, 153.2, 127.1, 121.3, 113.9, 113.1, 56.0, 55.6, 52.7 (d, $^2J_{CP}$ = 5.9 Hz), 41.4 (d, $^1J_{CP}$ = 133 Hz). Exact mass ($C_{12}H_{17}O_6P$ + H) calculated 289.0841, measured 289.0845.

The toluene extract was separately concentrated to yield 749 mg of a ~7:1 mixture of dimethyl [2,2-bis(2,5-dimethoxyphenyl)vinyl]phosphonate (**6c**) and 1,4-dimethoxybenzene as a yellow syrup. Characterization of **6c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, J = 2.8 Hz, 1H), 6.86−6.76 (m, 4H), 6.67 (d, J = 3.0 Hz, 1H), 6.37 (d, $^2J_{HP}$ = 18.1 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 3.60 (s, 3H), 3.52 (d, J = 11.3 Hz, 6H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 20.40; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6 (d, $^2J_{CP}$ = 5.9 Hz), 153.1, 152.9, 151.4, 150.7, 131.2 (d, $^3J_{CP}$ = 23.4 Hz), 129.6 (d, $^3J_{CP}$ = 7.8 Hz), 119.8, 117.3, 116.6, 116.4, 114.7, 114.5, 114.1, 113.2, 112.1, 56.5, 56.2, 55.7, 55.6, 51.9 (d, $^2J_{CP}$ = 5.9 Hz) ($^1J_{CP}$ not determined due to complexity of the spectrum at >100 ppm). Exact mass ($C_{20}H_{25}O_7P$ + H) calculated 409.1416, measured 409.1394.

Acknowledgement. We gratefully acknowledge the contributions of Mark T. Kershaw, Neurogen Corporation, who performed the HRMS analyses. We also thank Dr. Andrew Staab, Neurogen Corporation, for helpful discussions.

Supporting Information Available: Experimental procedures for the preparation of compounds **3b**, **3c**, **5j**, and **6j**, characterization data for compounds **1c**−**e**, and copies of ^{1}H, ^{31}P, and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A vinyl trifluoroacetate product has previously been observed when arylacetic acids were used in TFAA/H_3PO_4-mediated acylations of arenes: Veeramaneni, V. R.; Pal, M.; Yeleswarapu, K. R. *Tetrahedron* **2003**, *59*, 3283.

(13) It has been reported that ferrocene will react with diethyl (2-oxo-2-phenylethyl)phosphonate and diethyl (2-oxopropyl)phosphonate in the presence of triflic or methanesulfonic acid to form the corresponding β-ferrocenylvinylphosphonates: Plaøuk, D.; Rybarczyk-Pirek, A.; Zakrzewski, J. *J. Organomet. Chem.* **2004**, *689*, 1165.