Toward a Clean Alternative to Friedel−Crafts Acylation: In Situ Formation, Observation, and Reaction of an Acyl Bis(trifluoroacetyl)phosphate and Related Structures

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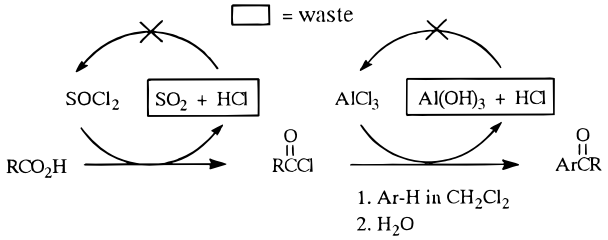
Reaction of acyl trifluoroacetates with phosphoric acid in the presence of trifluoroacetic anhydride (TFAA) leads to the ready formation of acyl bis(trifluoroacetyl)phosphates, which are powerful acylating agents. Formation of these species and the subsequent acylation reaction are carried out, without added solvent, in a single in situ reaction process. In this reaction system, anisole is rapidly acylated at ambient temperature using a variety of carboxylic acids giving the para isomer exclusively. TFAA acts as an activating agent and can be recovered from the reaction system as trifluoroacetic acid (TFA) and converted back to TFAA using a dehydrating agent, while phosphoric acid behaves as a covalent catalyst in the process. This reaction system has many features which are required elements of a clean alternative to the Friedel−Crafts process.

Introduction

Friedel−Crafts (FC) acylation has found widespread and successful application in industry for over a century.[1] In the current drive toward less wasteful and more environmentally friendly processes, where the emphasis is on atom efficiency and recyclability, it has many shortcomings. It is instructive to examine briefly the various stages of this reaction (Scheme 1) in order to identify the origin of these disadvantages and to attempt to make a rational approach to the development of a viable, more benign alternative. Activation of a carboxylic acid is achieved in two distinct stages in FC acylation. Conversion of the carboxylic acid to an acid chloride provides partial activation through covalent bond formation. Complexation of this with a strong Lewis acid provides further essential activation. For reasons of solubility, this last step is most efficiently carried out in dichloromethane. Strong Lewis acids, such as $AlCl_3$, also complex, however, to a very significant extent with the carbonyl group of the product.[2] Because of this, more than a stoichiometric amount of Lewis acid is frequently used and hydrolysis of the $AlCl_3$ is required to liberate the product. The atom inefficient and hence wasteful aspect of FC acylation is due to the loss of both the "catalyst" ($AlCl_3$) and the activating agent ($SOCl_2$); both chlorine atoms of this latter are ultimately lost as HCl. The requirement of using a strong Lewis acid, in more than stoichiometric amount, in dichloromethane, is due in essence to the low degree of activation attained in the covalent bond formation step. This imposes the need for significant additional activation, which necessitates use of a strong Lewis acid.

One approach to a potential alternative process would be to achieve a much greater degree of activation at the covalent bond formation stage. Further activation through complex formation, if required, should then be achievable with a mild Lewis acid, and as such, this should not complex significantly with the product and so its action should be catalytic in nature. Ideally, the formation of the activated covalent complex should occur in situ in a facile reaction starting from a carboxylic acid. Furthermore, there should be no specific solvent requirements; the spent activating agent should be fully recoverable and recylable in high yield, while the acylation reaction itself should occur at moderate temperatures in high yield and with high selectivity. The challenge is to achieve this using reagents/catalysts that are not unduly hazardous and are readily recyclable.

Scheme 1



Acyl trifluoromethanesulfonates (acyl triflates) go some way to meeting these requirements. As the conjugate base of a superacid,[3] the triflate moiety provides significant activation of the acyl carbonyl group, and acyl triflates have been found to effect acylation of benzene (90%, 5 h) and of chlorobenzene (67%, 5 h), when used in stoichiometric amounts at moderate temperatures (60 °C) without any added Lewis acids.[4] Their preparation, as reported to date, however, started with acid chlorides and required the use of triflic acid, a hazardous material and one not easily recoverable (bp 162 °C). Nafion-H

(1) Olah, G. A. *Friedel−Crafts Chemistry*; John Wiley & Sons: New York, 1973.

(2) Ashfort, R.; Desmurs, J.-R. In *The Roots of Organic Development*; Desmurs, J.-R., Ratton, S., Eds.; Elsevier: Amsterdam, 1996; p 3 and references therein.

(3) (a) A value of −14 has been determined for H_o (in essence an apparent pK_a) of triflic acid. See: Farcasiu, D.; Miller, G. *J. Phys. Org. Chem.* **1989**, *2*, 425. (b) See also: Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; Wiley-Interscience: New York, 1985.

(4) (a) Effenberger, F.; Epple, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 299. (b) Effenberger, F.; Eberhard, J. K.; Maier, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 12572.

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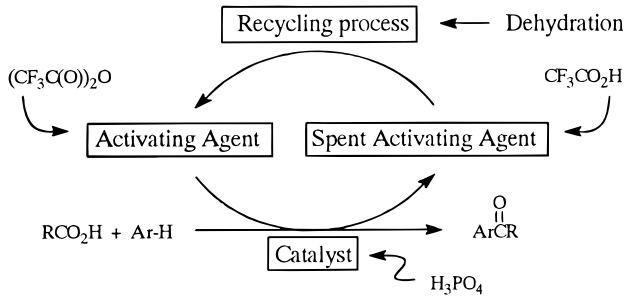
Scheme 2



provides triflic acid in an immobilized form[5] and, as such, furnishes a potential solution both to the hazardous nature of triflic acid and to its recovery and reuse. So far, the use of Nafion-H has met with limited success in aromatic acylation reactions; the heterogeneity of the reaction system may be a restricting factor. Olah and co-workers[6] found that it worked well (85−96% of acylated product) only when a reactive acid chloride (*p*-nitrobenzoyl chloride) was heated to reflux (usually >100 °C) in an excess of various aromatic hydrocarbons; a drawback was the occurrence of a distribution of isomers (*o*, 16−22%; *m*, 1−3.5%; *p*, 68−74%) the formation of which may have been due to the high temperatures used. More recently, Yamato and co-workers[7] found that a limited number of intramolecular acylations worked well (>90%, 0.5 h, 80 °C) with Nafion-H and acid chlorides; use of the corresponding carboxylic acids was considerably less efficient.

We recently reported on the successful use of an acyl trifluoroacetate, formed in situ from a carboxylic acid and trifluoroacetic anhydride (TFAA), as an acylating agent in an industrially based synthesis of a key tamoxifen intermediate.[8] It was noted that the in situ reaction of phosphoric acid with the acyl trifluoroacetate resulted in an entity with enhanced acylation potential and that acylation occurred exclusively in the para position at a reaction temperature of approximately 60 °C. In addition, we demonstrated that the spent TFAA could be recovered as trifluoroacetic acid (TFA) and readily converted back to TFAA using a dehydrating agent.[9] Product throughput per batch was very high, and furthermore, reaction calorimetry indicated that the process was suitable for scale-up. On the basis of these findings and observations, we felt that TFAA/H_3PO_4-mediated acylation warranted detailed evaluation as a viable, clean alternative to FC acylation (Scheme 2). We have carried out a mechanistic study that has provided an incisive picture on the unique role of H_3PO_4 as a covalent catalyst in this reaction. We report here on the mechanistic work and on the scope of this acylation process.

Results and Discussion

In our preliminary mechanistic work, we used anisole as the aromatic substrate, as it underwent TFAA/H_3PO_4-mediated acylation with carboxylic acids at reaction rates that were convenient to monitor using NMR spectroscopy. Reaction progress was monitored by adding 1 drop of the (neat) reaction mixture into $CDCl_3$ (0.5 mL) and recording the ^1H NMR spectrum; the dilution process was found to quench the reaction very effectively. The initial results provided an exemplary illustration of the value of this acylation process and unambiguous proof of the strong catalytic effect of phosphoric acid. Some of these results are presented here and are discussed in terms of the reactions outlined in Scheme 3, which shows the various acylated phosphoric acid structures that can occur on reaction of acid anhydrides with H_3PO_4. The chemical shift of H-α (i.e., α to the acyl carbonyl group) in the various structures is quoted below as a key identifier of reaction progress.

Reaction of TFAA (2 equiv) with 2-phenylbutanoic acid (**1a**) (1 equiv) (H-α, 3.45 ppm) led to the rapid formation of the trifluoroacetate **2a** (H-α, 3.66 ppm). Addition of anisole (1 equiv) resulted in the quantitative formation of the acylated product **3a** (H-α, 4.48 ppm), with a reaction half-life at 10 °C of approximately 2 h (Figure 1c). The splitting pattern of the aromatic hydrogens of the anisole moiety of **3a** (Figure 1d) indicated a para-substituted structure exclusively, and the presence of a clean singlet for the methoxy group was further proof for the formation of a single isomeric product.[11] In a repetition of this reaction, 85% phosphoric acid (0.1 equiv) was added after the formation of **2a**. Addition of anisole (1 equiv) again led to the quantitative formation of the same acylated product **3a**, but, significantly, the half-life at 10 °C was now less than 3 min. When 0.01 equiv of H_3PO_4 was used, the half-life at 10 °C was 30 min, clearly indicating that the concentration of the active acylating agent was dependent on the concentration of H_3PO_4.[12]

By carrying out the acetylation of anisole using acetic acid with H_3PO_4 (0.1 equiv) and with either TFAA or Ac_2O as the added anhydride (2 equiv in each case), we were able to confirm the key role of TFAA in forming the active acylating agent. Using TFAA, the yield of acetylated product **3b** was 68% after 1 h at 10 °C, while the yield was less than 25% after 24 h at 25 °C using Ac_2O. These observations provided an unequivocal illustration of the key role of both H_3PO_4 and TFAA in this acylation process. Questions were still unanswered, however, as to the precise identity of the active acylating agent. Chemical logic would dictate that acyl bis(trifluoroacetyl)-phosphate (**6**) should have the most polarized acyl carbonyl group of the phosphate structures shown in Scheme 3 and hence should be the most active acylating agent. It is relevant to note that acyl dichlorophosphoric acids, $RC(O)OP(O)Cl_2$, are known to be reactive acylating agents,[13] and, given that the inductive effect of $OC(O)-CF_3$ (σ_m, 0.56) is larger than that of Cl (σ_m, 0.37),[14] it is logical that acyl bis(trifluoroacetyl)phosphates should

(5) Nafion is the trade name of Du Pont for perfluorinated sulfonic acid polymer, which is available in a variety of physical forms. See: *Aldrichimica Acta* **1986**, *19* (3), 76.

(6) Olah, G. A.; Malhortra, R.; Narang. S. C.; Olah, J. A. *Synthesis* **1978**, 672.

(7) Yamato, T.; Hideshima, C.; Prakesh, G. K. S.; Olah, G. A. *J. Org. Chem.* **1991**, *56*, 3955.

(8) Smyth, T. P.; Corby, B. W. *Org. Process Res. Dev.* **1997**, *1*, 264.

(9) TFAA is produced commercially by dehydration of TFA. Some processes use SO_3 as the dehydrating agent giving H_2SO_4 as a coproduct. On a laboratory scale, P_2O_5 was more convenient to use.

(10) The unusual chemical shift for this peak is due to frequency folding as a result of the narrow (1000 Hz) sweep width used. See: Günther, H. *NMR Spectroscopy*, 2nd ed.; John Wiley & Sons: Chichester, 1995; pp 255−256.

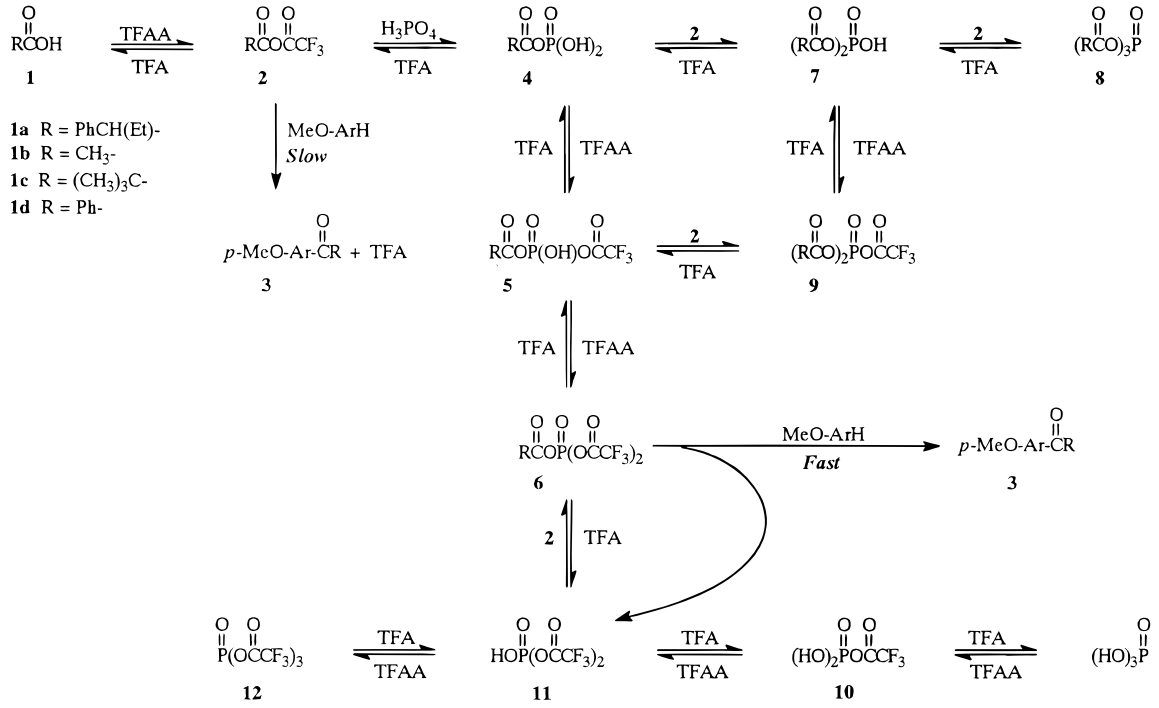
(11) This regiospecificity has also been reported by others. See: Ranu, C.; Ghosh, K.; Jana, U. *J. Org. Chem.* **1996**, *61*, 9546.

(12) The second equivalent of TFAA served to react with the water content of the H_3PO_4 when this was present and maintained essentially constant the volume of the reaction mixture between these runs and that carried out without H_3PO_4.

(13) Effenberger, F.; Konig, G.; Klenk, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 695.

(14) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 185.

Scheme 3



have superior acylation potential. A σ_m value of 1.00 was evaluated for $P(O)(OC(O)CF_3)_2$ from the correlation shown in Figure 2 ($R^2 = 0.84$; data in Table 1), and from this, a value of 0.71 was estimated for $OP(O)(OC(O)CF_3)_2$ by subtracting 0.29, which is the difference in the experimentally determined σ_m values of $P(O)(C_3F_7)_2$ and $OP(O)(C_3F_7)_2$.[14,15]

In an effort to directly observe and characterize the active acylating agent in this reaction system, we used ^{19}F and ^{31}P NMR to study the reaction patterns shown in Scheme 3; key characterization data are given in Table 2. Species **10**−**12** were formed by reacting TFAA with 85% phosphoric acid. The ^{31}P NMR spectrum obtained shortly after mixing these materials in a ratio of 3:1 is shown in Figure 3a. The spectrum changed with time, and the formation of a precipitate occurred after 10−20 min;[18] the spectrum of the resulting supernatant is shown in Figure 3b. The assignment of the chemical shifts to the mono-, bis-, and tris(trifluoracetyl)phosphates **10**, **11**, and **12**, respectively, was supported by observing the disappearance of the peak assigned to **10** and an increase in those assigned to **11** and **12** on addition of a further equivalent of TFAA, whereas addition of D_2O resulted in the rapid disappearance of all these peaks and the formation of phosphoric acid. In our previous work on the acylation of *N*,*N*-dimethyl-2-phenoxyethylamine (PA), the formation of a precipitate did not occur at any stage during the reaction.[8] We found that addition of PA to the reaction solutions used here similarly prevented precipitate formation, and this stratagem facilitated spectroscopic study of the species occurring in these reaction systems (the acylation of PA itself did not interfere as at room temperature this process was quite slow).[8] The spectrum resulting from the reaction of TFAA and 85% H_3PO_4 (4:1 equiv) followed by the addition of PA (1 equiv) is shown in Figure 3c; the presence of tris(trifluoroacetyl)phosphate (**12**) was clear, while the presence of the other large peak was interpreted as corresponding to ion pairs of PA with phosphoric acid species. Formation of tight ion pairs of such acids with PA was viewed as being at least partly responsible for the lack of formation of a precipitate. The ^{19}F chemical shift values of **10**−**12** were also recorded (Table 2).[19] The mono-, bis-, and trisacetyl phosphates **4b**, **7b**, and **8b**, respectively were formed by reacting phosphoric acid and acetic anhydride (a precipitate was not observed in this instance, a finding which was consistent with the considerably poorer leaving group ability of acetate compared to trifluoroacetate).

Having thus established a set of reference ^{31}P and ^{19}F NMR chemical shift data, we proceeded to study solutions in which the formation of the acyl bis(trifluoroacetyl)-phosphate **6a** could occur. The ^{31}P NMR spectrum of the solution obtained from the reaction of **1a**, TFAA, 85% H_3PO_4, and PA (1:4:1:1 equiv) is shown in Figure 4a. The appearance of the peak at −18.70 ppm was significant as this was not observed in the reaction mixture of the above components when **1a** was omitted (Figure 3c). Addition of anisole (1 equiv) resulted in rapid decrease in this peak (Figure 4, a → b → c). This observation was paralleled in the ^{19}F spectrum of the same solution by the decrease in the peak at −76.79 ppm (Figure 4, a′ → b′); the concomitant acylation of anisole was confirmed

(15) Yagupol'skii, L. M.; Pavlenko, N. V.; Ignat'ev, N. V.; Matyushecheva, G. I.; Sementii, V. Ya. *Zh. Obsh. Khim.* **1984**, *54*, 297EE.

(16) Günther, H. *NMR Spectroscopy—An Introduction*; John Wiley & Sons: Chichester, 1980; Chapter 10.

(17) Tebby, J. C., Ed. *CRC Handbook of Phosphorous-31 Nuclear Magnetic Resonance Data*; CRC Press: Boca Raton, 1991; Chapter 1.

(18) The peaks assigned to **11** and **12** increased in intensity, while the broad peaks became broader at the onset of precipitate formation. The precipitate was considered to arise from pyro- and polyphosphate-type materials. Displacement of trifluoroacetate from **10**−**12** by the hydroxy group of some other phosphoric acid structure can lead to pyrophosphate formation. This type of reaction has been used to form specific pyrophosphates. See: Corby, N. S.; Kenner, G. W.; Todd, A. R. *J. Chem. Soc.* **1952**, 1234.

(19) The spectra are included in Supporting Information. The ion pair TFA^- PA^+ was observed in these solutions; assignment of this peak was confirmed by reaction of PA with TFA separately.

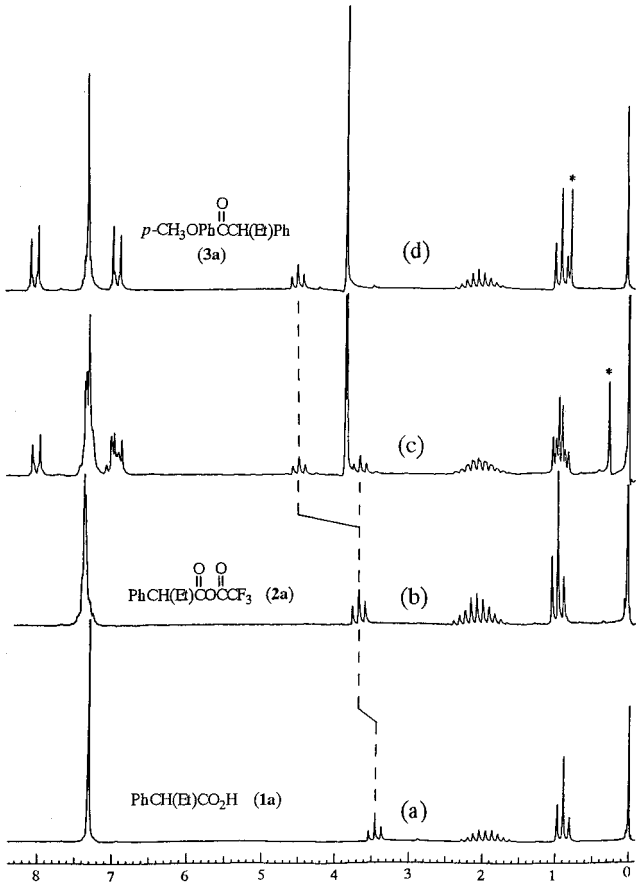


Figure 1. ^{1}H NMR spectra of (a) 2-phenylbutanoic acid (**1a**), (b) reaction sample 15 min after addition of TFAA (2 equiv) to **1a**, (c) this reaction sample 2 h after addition of ansiole (1 equiv), and (d) reaction sample 15 h after addition of ansiole. The reaction mixture was maintained at 10 °C, and in each case, a sample (1 drop) of the neat reaction mixture was added directly to $CDCl_3$ (0.5 mL). The labeled peak (*) was exchangeable on addition of D_2O and was attributed to the acidic hydrogen of TFA.[10]

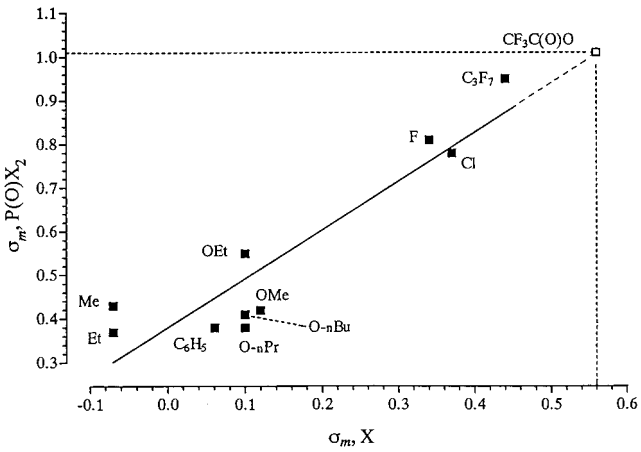


Figure 2. Correlation of the Hammet σ_m values of selected groups X and the corresponding groups $P(O)X_2$.

by ^{1}H NMR.[20] Further addition of **2a** to the reaction solution at this point led to the reappearance of the aforementioned ^{19}F and ^{31}P peaks, which once more readily disappeared on addition of another equivalent of anisole.[21] Attributing the ^{31}P chemical shift at −18.70 ppm to a species such as **6a** was reasonable, as this value was bracketed by those of tris(trifluoroacetyl)phosphate (**12**) (−24.8) and trisacetyl phosphate (**8b**) (−17.7) and was similar to that observed for bis(trifluoroacetyl)-phosphoric acid (**11**) (−18.57 ppm) (Table 2). On the basis of the chemical shift value alone, we could not distinguish between **6a** and **9a** as the observed species; however, the former ought to be the more predominant species present given that the mixed anhydride **2a** and TFAA were in a ratio of 1:3 at the outset (although 4 equiv of TFAA were added at the outset 1 equiv was consumed by the water content of 85% H_3PO_4). The ^{19}F peak at −76.79 ppm must also be assigned to the active acylating species, putatively **6a**, and this assignment was consistent with the general pattern of chemical shifts observed for species such as **11** and **12**, although the small span of the ^{19}F NMR chemical shifts observed for these structures made absolute assignment difficult. Overall, the foregoing ^{31}P and ^{19}F peaks (Figure 4, spectra a and a′) were attributed to the active acylating agent in the system and they unambiguously showed that this species contained a trifluoroacetyl moiety and a phosphoric acid moiety (and ipso facto an acyl entity), which concurred with our earlier observations on the key role of TFAA and of H_3PO_4.

We then focused on determining the range of aromatic structures that could be readily acylated in this reaction system (without PA) with a variety of carboxylic acids including benzoic acid.[22] The nature of both the aromatic substrate and the carboxylic acid played a major role in the acylation reaction (Table 3). Anisole was very readily acylated by a variety of carboxylic acids giving a quantitative yield of the para isomer, while 2-phenylbutanoic acid was the best carboxylic acid in terms of acylating a wide range of aromatic structures. One parameter that was varied was the number of equivalents of TFAA and H_3PO_4 used per equivalent of RCO_2H. A reaction system that could form only a low concentration of **6**, i.e., with H_3PO_4 (0.1 equiv), was adequate for rapid acylation of an activated substrate such as anisole with most carboxylic acids. To acylate a less activated substrate such as toluene at a reasonable rate, a higher concentration of **6** was necessary. This was acheived by the use of TFAA/H_3PO_4 (4:1 equiv). Under these conditions, a precipitate formed in every case, indicating that **6** could not have been present at its maximum stoichiometric concentration with respect to the concentration of H_3PO_4 added at the outset. Formation of the precipitate was viewed as a key factor in defining the present limitations with nonactivated aromatic substrates such as benzene; addition of triethylamine to prevent formation of the precipitate, in lieu of PA (which was acylated at a comparable rate to toluene), did not provide a solution.

The exclusive formation of the para isomer of the product **3** is not likely to have resulted from product stability as, even with quite a bulky group such as 2-phenylbutanoyl, the carbonyl group positions the bulky moiety some distance out from the substituents on the aromatic ring. The fact that the reactions were under kinetic control was substantiated by the results obtained

(20) The acylation of anisole was slower in the presence of PA than in the absence of PA.

(21) The full sequence of ^{31}P and ^{19}F NMR spectra showing this double acylation cycle is included in Supporting Information.

(22) In our previous work (ref 8) we indicated that benzoylation did not work. We wish to clarify here that benzoylation of anisole does occur, albeit somewhat slowly, with benzoyl trifluoroacetate.

Table 1. Hammett σ_m Values[a] for Groups Shown in Figure 2

X	C_3F_7	Cl	F	OMe	OEt	O^{n}Bu	O^{n}Pr	C_6H_5	Me	Et
σ_m of X	0.44	0.37	0.34	0.12	0.10	0.10	0.10	0.06	−0.07	−0.07
σ_m of P(O)X_2	0.95	0.78	0.81	0.42	0.55	0.41	0.38	0.38	0.43	0.37

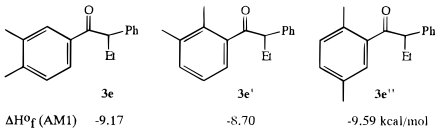
[a] Data from ref 14.

Table 2. Chemical Shifts (ppm) of Key Structures

	^{1}H (H-α)	^{19}F[a]	^{31}P[b]
1a; **2a**; **3a**; **4a**	3.45; 3.66; 4.48; 3.55	*f*; −77.10; *f*; *f*	
1b; **2b**; **3b**	2.10; 2.40; 2.55	*f*; −77.10; *f*	
4b; **7b**; **8b**	2.20; *c*; *c*		+1.28; −7.67; −17.70
TFA; TFAA; TFA$^-$PA$^+$		−77.00; −76.05;[d] −76.57	
10; **11**; **12**		−76.88;[e] −76.86;[e] −76.60	−6.13; −18.57; −24.8
6a	*c*	−76.79	−18.70

[a] TFA was used as the internal reference ($\delta = -77.00$ with respect to $CFCl_3$).[16] [b] Phosphoric acid was used as the reference, and peaks upfield of this are reported as negative values.[17] [c] Not readily discernible. [d] The chemical shift of TFAA was observed to vary slightly with respect to TFA depending on the composition of the reaction mixture; addition of extra TFAA made assignment unambiguous. [e] These may correspond to the ion pairs of **10** and **11** with PA, respectively. [f] No ^{19}F resonance present for these structures.

with *o*- and *p*-xylene. The half-life for acylation of *o*-xylene with 2-phenylbutanoic acid was 20 min at 25 °C, giving the para-acylated product **3e**, while that for



p-xylene was 120 min at 25 °C, giving an ortho-acylated product **3e″**; the latter was estimated[23] to be the more stable product on the basis of ΔH^o_f. It is probable that the regiospecificity was determined by the differing stability of the ortho and para addition intermediates or transition states leading to these, as here the intact acylating agent must interact with the aromatic substrate. This would also imply that free acylium ions were not involved, as then the difference in stability of the ortho and para intermediates, or transition states leading to these, should mirror the pattern of product stability shown above.

We examined the effect of BF_3 etherate as a homogeneous catalyst in the reaction system; it did not, however, have any beneficial effect with activated or with the nonactivated aromatic substrates. Use of $AlCl_3$, $BiCl_3$, or Bi_2O_3[24] as a heterogeneous catalyst was similarly without useful effect. A good deal of the corresponding acid chloride resulted from treatment of **2a** with $AlCl_3$; a similar result was observed in the reaction system involving **6a**.

Conclusions

The TFAA/H_3PO_4-mediated acylation system is clearly a practical, atom efficient alternative to FC acylation suitable for the production of a variety of fine chemical intermediates[8] and also for the bulk production of some simple acylated aromatics. The process allows for the in situ assembly and reaction of a highly active acylating species, an acyl bis(trifluoroacetyl)phosphate, starting from a carboxylic acid. There are limitations with nonactivated substrates, but there is scope for further development.

Experimental Section

General Acylation Procedure. TFAA (5.20 mL, 36.7 mmol) was added directly to the appropriate carboxylic acid (9.2 mmol). The solution was cooled to below 10 °C and 85% phosphoric acid (1.06 g, 9.2 mmol) was added with stirring.

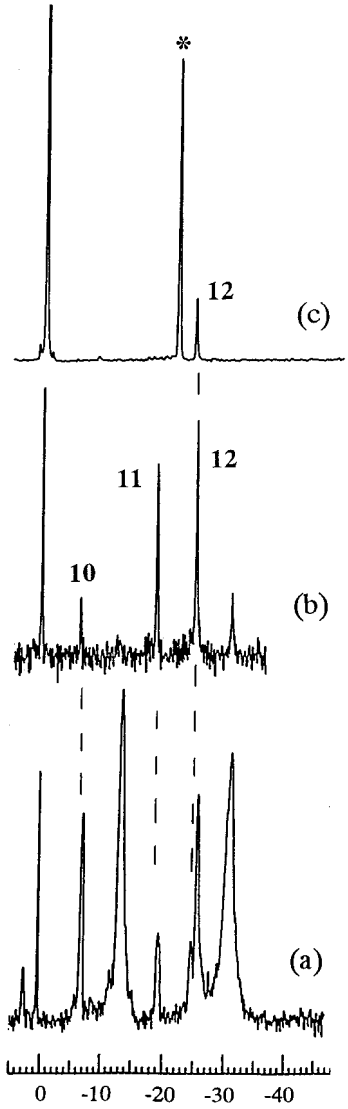


Figure 3. The ^{31}P NMR spectrum of (a) the neat solution obtained 5 min after addition of TFAA to 85% H_3PO_4 (3:1 equiv), (b) the supernatant obtained from this solution after 15 min, and (c) the neat solution obtained after addition of PA to a mixture of TFAA and 85% H_3PO_4 (4:1 equiv) (no precipitate formed here). The labeled (*) peak was attributed to ion pair(s) of PA with phosphoric acid based species.

(23) *Ampac 5.0*; Semichem: Shawnee, KS, 1994.

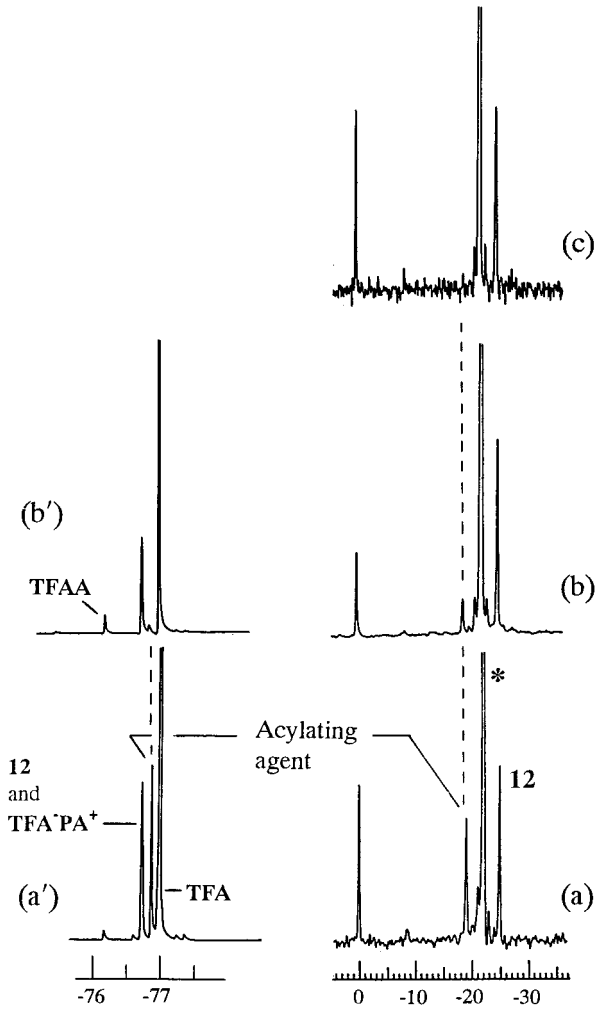
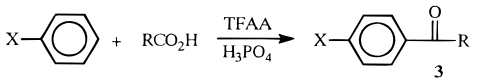


Figure 4. The ^{31}P NMR spectrum of (a) the neat solution obtained from the combination of **1a**, TFAA, 85% H_3PO_4, and PA (1:4:1:1 equiv) (see Figure 3 for assignment of the labeled (*) peak). Anisole (1 equiv) was then added. Spectrum b is that obtained over a full 10 min accumulation time, and (c) is that obtained after a further 5 min. The ^{19}F NMR spectra of (a′) the initial solution above and (b′) the same solution 10 min after addition of anisole are also shown; these latter spectra were taken of reaction samples added to $CDCl_3$, and the acquisition time was quite short.

After complete dissolution of the phosphoric acid, the aromatic substrate (9.2 mmol) was added and the reaction mixture was stirred at the required temperature; where TFAA (4 equiv) was used, heating to reflux maintained a solution temperature of approx 60 °C. Reaction progress was monitored by adding a small aliquot (1 drop) of the neat reaction mixture, taken at various time intervals, directly to $CDCl_3$ (0.5 mL) and recording the ^{1}H NMR spectrum (data below). The ratio of TFAA and H_3PO_4 was varied as indicated in the text and in Table 3; the time required for complete dissolution of small quantities (0.1 equiv) of 85% H_3PO_4 in TFAA (on the scale detailed above) was approximately 20 min. The isolation procedure involving the recovery of TFA has previously been described.[8] For small-scale work, product isolation is best achieved by quenching the reaction mixture in aqueous base and extracting with an organic solvent.

Preparation of Samples for Spectroscopic Examination. Reaction mixtures were prepared as above using TFAA/H_3PO_4 in a ratio of 3:1 (equiv). The ^{31}P (36.23 MHz) NMR spectra of the neat solution was recorded using a 10 mm tube with an insert that contained 85% H_3PO_4 in D_2O to provide a reference and lock signal. To a freshly made solution, *N*,*N*-dimethyl-2-phenoxyethylamine (PA) (1.52 g, 9.2 mmol) was added once dissolution of the 85% H_3PO_4 was complete. The ^{31}P NMR spectra of the neat solution was recorded as indicated above, while the ^{19}F (84.25 MHz) NMR spectrum was recorded in a 5 mm tube of solutions made by adding one drop of the reaction mixture to $CDCl_3$ (0.5 mL).

Table 3. General Results for TFAA/H_3PO_4-Mediated Acylation of X−Ar−H (1 equiv/equiv of RCO_2H)



	R				
X	Ph(Et)CH	Me	$(Me)_3C$	Ph	labels
MeO	2/0.1	4/1	2/0.1	2/0.1	*n*/*m*[a]
	10, 20 m	10, 5 m	10, 4 h	60, 4 h	*T*,[b] *t*[c]
	100	100	100	100	*Y*[d]
	3a	**3b**	**3c**	**3d**	L[e]
1,2-diMe	4/1	4/1	4/1	4/1	*n*/*m*[a]
	25, 3 h	25, 24 h	60, 24 h	60, 24 h	*T*,[b] *t*[c]
	100	70	0	100	*Y*[d]
	3e	**3f**	**3 g**	**3h**	L[e]
Me	4/1	4/1	4/1	4/1	*n*/*m*[a]
	60, 2.5 h	60, 24 h	60, 24 h	60, 96 h	*T*,[b] *t*[c]
	100	∼5	0	60	*Y*[d]
	3i	**3j**	**3k**	**3l**	*L*[e]

[a] *n*/*m* = equiv of TFAA/H_3PO_4. [b] Temperature (°C). [c] Reaction time. [d] Yield (%) from ^{1}H NMR data. [e] Product label.

Product Characterization Data. ^{1}H NMR ($CDCl_3$, 90 MHz). 1-[4-[methoxy]phenyl]-2-phenyl-1-butanone (**3a**): δ 0.90 (t, J = 7.5 Hz, 3H), 1.70−2.30 (m, 2H), 3.85 (s, 1H), 4.48 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 10.5 Hz, 2H), 7.29 (br s, 5H), 8.0 (d, J = 10.5 Hz, 2H) (see Figure 1d). 4-Methoxy acetophenone (**3b**): δ 2.68 (s, 3H), 3.84 (s, 3H), 7.00 (d, J = 10.5 Hz, 2H), 8.10 (d, J = 10.5 Hz, 2H).[25] 1-[4-[Methoxy]phenyl]-2,2-dimethyl-1-propanone (**3c**): δ 1.45 (s, 9H), 3.90 (s, 3H), 6.95 (d, J = 10.5 Hz, 2H), 7.87 (d, J = 10.5 Hz, 2H). 4-Methoxy benzophenone (**3d**): δ 3.95 (s, 3H), 7.00 (d, J = 10.5 Hz, 2H), 7.50−7.91(m, 7H).[25] 1-[3,4-[Dimethyl]phenyl]-2-phenyl-1-butanone (**3e**): δ 0.90 (t, J = 7.5 Hz, 3H), 1.7−2.3 (m, 2H), 2.3 (s, 6H), 4.52 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 10.5 Hz, 1H), 7.30 (s, 5H), 7.72 (d, J = 10.5 Hz, 1H), 7.77 (s, 1H). 1-[2,5-[Dimethyl]phenyl]-2-phenyl-1-butanone (**3e′′**): δ 0.95 (t, J = 7.5 Hz, 3H), 1.70−2.30 (m, 2H), 2.3 (s, 6H), 4.35 (t, J = 7.5 Hz, 1H), 7.00−7.50 (m, 8H). 3,4-Dimethylacetophenone (**3f**): δ 2.37 (d, 6H), 2.70 (s, 3H), 7.26 (d, J = 10.5 Hz, 1H), 7.75 (d, J = 10.5 Hz, 1H), 7.80 (s, 1H).[25] 3,4-Dimethylbenzophenone (**3h**): δ 2.36 (s, 3H), 2.40 (s, 3H), 7.25−7.85 (m, 8H).[25] 1-[4-[Methyl]phenyl]-2-phenyl-1-butanone (**3i**): δ 0.90 (t, J = 7.5 Hz, 3H), 1.70−2.30 (m, 2H), 2.35 (s, 3H), 4.51 (t, J = 7.5 Hz, 1H), 7.10−7.50 (m, 7H), 7.89 (d, J = 10.5 Hz, 2H). 4-Methyl benzophenone (**3l**): δ 2.46 (s, 3H), 7.20−7.90 (m, 9H).[25]

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Supporting Information Available: The following spectra are available: ^{19}F NMR of solutions containing **10**−**12**; ^{31}P and ^{19}F NMR showing the formation and disappearance of **6a** in a double cycle of acylation of anisole (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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