Organic Process Research & Development **1997**, *1*, 264–267

Industrially Viable Alternative to the Friedel–Crafts Acylation Reaction: Tamoxifen Case Study

Timothy P. Smyth* and Brian W. Corby

Department of Chemical and Environmental Sciences, University of Limerick, National Technological Park, County Limerick, Ireland

Abstract:

A mixed anhydride, formed in situ by reaction of trifluoroacetic anhydride and an alkanoic acid, has been successfully used as an acylating agent in an industrially based synthesis of Tamoxifen. This acylation process has a number of advantages over the classic Friedel–Crafts route. Thus the use of thionyl chloride, aluminium trichloride, and a chlorinated hydrocarbon solvent are all eliminated. The trifluoroacetic anhydride is recovered from the reaction system as trifluoroacetic acid, which can be efficiently converted back to the anhydride using phosphorus pentoxide. The general applicability of this acylation process is discussed.

Introduction

Increasingly tighter restrictions on the use of chlorinated compounds in industrial synthesis have driven a fresh look at some old reactions. One such case is Friedel–Crafts acylation. There are a number of features of this reaction which detract considerably from its viability in modern large-scale synthesis. Firstly, a carboxylic acid is converted into an acid chloride using thionyl chloride; this latter is not a particularly desirable compound to work with on large scale. Secondly, chloride is lost as HCl in the acylation step itself and ultimately is lost as waste which must be treated. Thirdly, aluminium trichloride is not a true catalyst in that frequently more than 1 equiv is needed and, more significantly, this material is also lost as waste to be treated. Finally the solvent of choice for the acylation process is a chlorinated hydrocarbon. There is no clear-cut choice of a chlorine-free alternative solvent.[1] Friedel–Crafts reactions work well in nitromethane, but there exist too many reactivity hazards[2] with nitromethane for this to be used widely as a replacement solvent. Clearly the place of the classical Friedel–Crafts acylation reaction in modern large-scale synthesis is limited.

Modified Friedel–Crafts catalysts have been developed. Montmorillonite clays, modified to support zinc, nickel, or iron chlorides or by ion exchange to incorporate various inorganic cations, have been extensively studied as Friedel–Crafts alkylation and acylation catalysts.[3] In general, acid chlorides have been used for acylations although some success with the use of alkanoic acids[4] and anhydrides[3c,3e,5] has been reported. A solid supported form of $AlCl_3$ has also been prepared and found to be a useful alkylating agent.[6] Solid superacids such as Nafion-H, a perfluorinated sulfonic acid resin, has also been found to be an effective catalyst for Friedel–Crafts acylations starting from acid anhydrides or acid chlorides[7a] and was also successfully used starting with carboxylic acids.[7b] Lanthanide and scandium trifluoromethanesulfonates have been reported as reusable Friedel–Crafts catalysts for acylations using acid chlorides or the corresponding anhydrides.[8]

The use of acyl trifluoroacetates as general acylating agents is well documented in the older literature.[9] Their in situ preparation for aromatic acylation has been reported on more recently, and the requirement for acid catalysis when dealing with electron-deficient aromatic substrates was noted.[10] This method has some features which make it attractive as a potential alternative, suitable for large-scale use, to the classic Friedel–Crafts acylation process. Thus the use of thionyl chloride, aluminium trichloride, and chlorinated hydrocarbon solvents can all be dispensed with, and furthermore, the trifluoroacetic anhydride (TFAA) should be recoverable as trifluoroacetic acid (TFA), which can be converted back to the anhydride.[11]

We have examined the applicability of this process in a current industrial synthesis of tamoxifen and report here on our findings. A key step in the present synthesis is the acylation of *N*,*N*-dimethyl-2-phenoxyethylamine (**1**) with 2-phenylbutanoic acid chloride (**2**) to produce the intermediate 1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenyl-1-butanone (**4**) (Scheme 1). We have examined the use of 2-phenylbutanoic acid (**3**) to directly acylate **1** in a single-step reaction involving the in situ formation of the trifluoroacetyl mixed anhydride **5** with a view to transfer of this process to production-level scale-up. The viability of this

(1) (Trifluoromethyl)benzene (benzotrifluoride) has recently been reported as an alternative solvent to dichloromethane but was found not to be suitable for use with $AlCl_3$: Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450.

(2) Sax, N. I. *Dangerous Properties of Industrial Materials*, 6th ed.; Van Nostrand Reinhold Co.: New York, 1984.

(3) (a) Laszlo, P. *Acc. Chem. Res.* **1986**, *19*, 121. (b) Clark, J. H.; Kybett, A. P.; Macquarrie, D. J.; Barlow, S. J.; Landon, P. *J. Chem. Soc., Chem. Commun.* **1989**, 1353. (c) Cornelis, A.; Gerstmans, A.; Laszlo, P.; Mathy, A.; Zieba, I. *Catal. Lett.* **1990**, *6*, 103. (d) Barlow, S. J.; Clark, J. H.; Darby, M. R.; Kybett, A. P.; Landon, P.; Martin, K. *J. Chem. Res. Synop.* **1991**, 74. (e) Bastock, T. W.; Clark, J. H.; Landon, P.; Martin, K. *J. Chem. Res., Synop.* **1994**, 104. (f) Clark, J. H.; Cullen, S. R.; Barlow, S. J.; Bastock, T. W. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1117.

(4) Chiche, B.; Finiels, A.; Gauthier, C.; Geneste, P.; Graille, J.; Pioch, D. *J. Mol. Catal.* **1987**, *42*, 229.

(5) Cornelis, A.; Laszlo, P.; Wang, S.-F. *Catal. Lett.* **1993**, *17*, 63.

(6) Clark, J. H.; Martin, K.; Teasdale, A. J.; Barlow, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, 2037.

(7) (a) Olah, G. A.; Malhotra, R.; Narang, S. C.; Olah, J. A. *Synthesis* **1978**, 672. (b) Yamato, T.; Hideshima, C.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1991**, *56*, 3955.

(8) (a) Kawada, A.; Mitamura, S.; Kobayashi, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1157. (b) Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett* **1994**, 545.

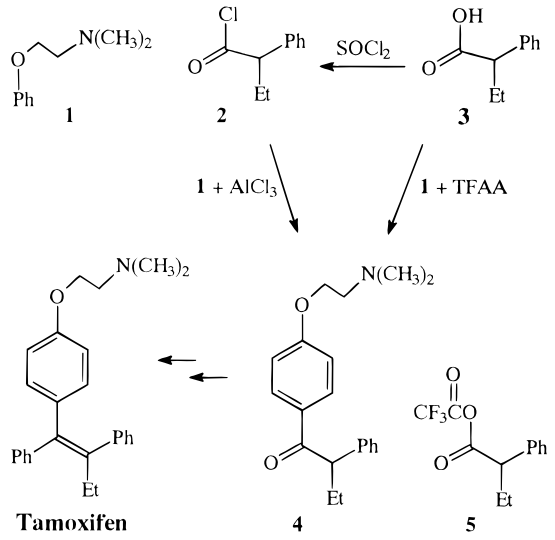
(9) (a) Tedder, J. M. *Chem. Rev.* **1955**, 787. (b) Bourne, E. J.; Stacey, M.; Tatlow, J. C.; Worrall, R. *J. Chem. Soc.* **1954**, 2006 and references therein.

(10) Galli, C. *Synthesis* **1979**, 303.

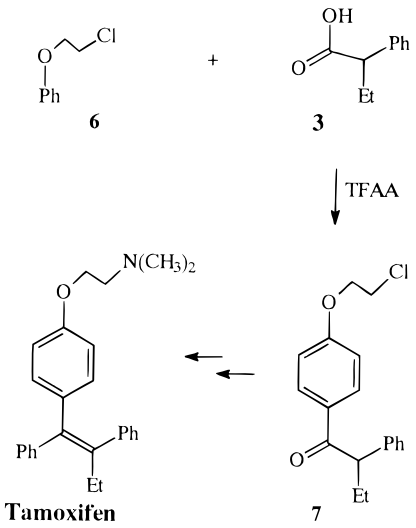
(11) Swarts, F. *Bull. Cl. Sci., Acad. R. Belg.* **1922**, *8*, 343.

 S1083-6160(97)00013-3 CCC: $14.00

Scheme 1



Scheme 2



process as an alternative to the standard Friedel−Crafts process is dependent on a number of key factors: (a) high yield, (b) high throughput per batch, (c) effective recycling of the trifluoroacetic anhydride, and (d) a well-behaved reaction calorimetry pattern.

McCague[12] has previously shown that the TFAA-mediated acylation worked well, on a laboratory scale, in a related synthesis of tamoxifen (Scheme 2). An attractive feature of this synthesis is the use of a relatively activated aromatic substrate, phenoxyethyl chloride (**6**); the acylation process gave a high yield of **7** after reaction at room temperature for 72 h. A second feature, less attractive for large-scale work, is the requirement for a large excess of ethanolic dimethylamine and a long reaction time (68 h) for the subsequent displacement of chloride. (The use of 1,2-dichloroethane in the synthesis of **6** is also unattractive for scale-up.) The ease with which the acylation occurred in this system was grounds for optimism in applying the TFAA-mediated reaction to the acylation of **1**. Clearly the *N*,*N*-dimethylamino group brings a different component into play, and it was anticipated that this might influence the ease of the acylation step. One finding already documented in the literature on the TFAA-mediated acylation reaction is the successful use of phosphoric acid as a catalyst with less activated aromatic substrates.[10]

Results and Discussion

The initial evaluation of the mixed-anhydride method clearly indicated that acid catalysis was an essential requirement with **1** as the substrate to be acylated. TFA was not adequate as a catalyst, but phosphoric acid proved quite successful. This finding had a direct bearing on the number of equivalents of TFAA required. Anhydrous phosphoric acid (orthophosphoric acid) did not work well due to its lack of solubility in TFAA. Phosphoric acid (85%) added to an appropriate excess of trifluoroacetic anhydride (4 equiv/equiv of **3**) resulted in a solvent mix of TFA and TFAA in which the phosphoric acid was quite soluble. This reaction system, heated to reflux for 2 h, proved to be highly successful for the direct acylation of **1** by 2-phenylbutanoic acid, giving **4** in excess of 96% yield (isolated crude product). One recrystallisation yielded 85% of isolated analytically pure product (HPLC); this is a higher yield than that achieved in the Friedel−Crafts acylation process. The throughput per batch on a 5 L reactor scale was in excess of 1.3 kg.

The isolation procedure was initiated by simple distillation of excess TFAA and TFA (other aspects of the product recovery are detailed in the Experimental Section). The total volume recovered was 90% of the starting volume of TFAA. This solvent mixture of TFAA/TFA was found to contain 0.80 mol fraction of TFA by ^{19}F NMR analysis. Treatment of this with phosphorus pentoxide (4.2 equiv/equiv of TFA)[11] at room temperature for 1 h followed by simple distillation yielded a solvent mixture with 0.90 mol fraction of TFAA. The quantity of TFAA recovered in this way corresponded to 75.6% of the quantity of TFAA used at the start of the acylation reaction. This recovered solvent system was reusable directly in another cycle of the acylation process. The yield and purity of the product were unaffected while the throughput was marginally lower as a slightly larger volume of TFAA/TFA (0.90 mol fraction of TFAA) is required to deliver the original starting quantity of TFAA. The phosphoric acid residue from the above process was neutralised with calcium hydroxide, and the precipitated hydroxyapatite[13] was filtered off prior to discharge of this stream for waste treatment.

Calorimetric measurements were carried out on the distinct stages in the acylation process. This involved determination of the rate of heat flow and the total heat liberated. The first exotherm monitored was that due to the addition of **1** to a solution of **3** in TFAA. A second exotherm (the larger of the two) was observed on the addition of phosphoric acid to this solution and is largely due to reaction of the water content of the 85% phosphoric acid with TFAA. A final exotherm was observed on raising the temperature of the reaction mixture to 60 °C: this exotherm was small and corresponded to about 20% of the total heat liberated. The measured heat flow varied from 100 W/L at the start of the phosphoric acid addition to 65 W/L towards the end. As both the first and second exotherms were characteristic of

(12) McCague, R. *J. Chem. Res., Miniprint* **1986**, 0771.

(13) Eilbeck, W. J., Matlock, G., Eds. *Chemical Processes in Waste Water Treatment*; Ellis Horwood: Chichester, 1987; Chapter 6.

dose−rate-controlled processes, the above heat flow rates can be readily attenuated and safely carried out on scale-up. The temperature in the reaction vessel for the calorimetric measurements was maintained at 10 °C during the two addition steps. This is not a critical parameter, however, as both the purity and yield of the final product was not affected in reactions where the temperature during the addition stages was allowed to reach 30 °C. This is obviously advantageous for scale-up in that the cooling capacity requirements are not so high. The calorimetry also indicated that, in the event of uncontrolled addition of phosphoric acid, a temperature of 99 °C would be reached; as the boiling point of the reaction mixture is around 60 °C this exothermic heat would be consumed as heat of vaporisation while at reflux and should not lead to a runaway reaction.

The relevance of a chemical process for large-scale synthesis depends critically on the economics of that process and also on its general applicability. Comparison of the cost of a process and a proposed alternative involves more than just a comparison of the costs of the raw materials. Product throughput per batch and improved yield must also be taken into account: these factors will be highly dependent on the value of an intermediate within company costings. TFAA is not an inexpensive material even when bought in bulk and is considerably more expensive than aluminium trichloride. On the positive side, however, two wasteful reaction steps are eliminated involving the use of thionyl chloride, aluminium trichloride, and a chlorinated hydrocarbon solvent. Furthermore, 75.6% of the TFAA can be recycled. The scope and limitations of this process as an economically viable alternative for the Friedel−Crafts acylation in large-scale synthesis are further discussed below.

The reactivity of the aromatic substrate is known to play a major role in the anhydride method of acylation. As pointed out earlier, McCague found that **3** and **6**, when reacted with 1 equiv of TFAA in the absence of phosphoric acid, gave a 94% yield of **7** after 72 h at room temperature. For this reaction we found that use of 85% phosphoric acid (0.5 equiv) with 2 equiv of TFAA gave a similar yield after 3 h at room temperature. The greater number of equivalents of TFAA required in the acylation of **1** must be due to the presence of the *N*,*N*-dimethylamino group. The reaction of this group directly with the anhydride would lead to a (trifluoroacetyl)ammonium trifluoroacetate salt. Also the substituent effect of such an ammonium group would be to deactivate **1** toward acylation via electrophilic aromatic substitution. The requirement for phosphoric acid as a catalyst would indicate that **1** in the reaction system is deactivated. We speculate that the role of the phosphoric acid is to generate some of the protonated form of the mixed anhydride **5** thereby increasing its electrophilic character and so facilitating its reaction with deactivated substrates. One result which appears to be clear-cut from this and other work[10] is that acylation by an acyl trifluoroacetate works quite well for aromatic hydrocarbons; no trifluoroacylated material is detected. Aromatic heterocycles such as furan and thiophene give good yields of acylated products also, whereas pyrrole and 2-methylpyrrole gave largely trifluoroacylated products.[14] A failure with the TFAA-mediated process that we have identified is that benzoylation with a benzoyl trifluoroacetate did not work even with activated substrates such as anisole. Benzoylation of aromatic hydrocarbons is known to occur using the mixed anhydride of benzoic acid and trifluoromethansulfonic acid.[15] This mixed anhydride contains a particularly good leaving group and for this reason works well in the acylation process. A drawback with this process as reported is that preparation of the trifluoromethanesulfonic mixed anhydrides required the use of acid chlorides. Benzoylation of activated aromatic hydrocarbons such as anisole has been reported using (benzoyloxy)pyridine in trifluoroacetic acid.[16] Continuing work on probing the mechanism of the acylation using TFAA and the role of phosphoric acid in this process may indicate ways of surmounting the problems associated with benzoylation, but at present this remains a definite limitation.

Experimental Section

^{1}H and ^{19}F NMR spectra were recorded on a Jeol FX90Q instrument. Reaction calorimetry was carried out by Dr. David am Ende, Pfizer Inc., Groton, NY.

Preparation of 1-[4-[2-(Dimethylamino)ethoxy]phenyl]-2-phenyl-1-butanone (4) via the Trifluoroacetic Anhydride Route. TFAA (2.5 L, 17.7 mol) was added directly to 2-phenylbutanoic acid (**3**) (726 g, 4.42 mol) to generate the mixed anhydride **5**. Phenoxy amine **1** (730 g, 4.42 mol) was added at such a rate that the temperature of the reaction mixture did not exceed 30 °C. Then 85% phosphoric acid (510 g, 4.42 mol) was added at such a rate that the reaction temperature did not exceed 30 °C. The mixture was heated to reflux for 2 h. Distillation yielded a solvent mixture of TFAA/TFA (2.25 L) which contained 0.80 mol fraction of TFA as assayed by ^{19}F NMR (TFAA δ −76.33; TFA δ −77.0 with respect to $CFCl_3$).[17] Toluene (2 L) was added to the residue, and this solution was added to distilled water (1.5 L) containing ice (1 kg). The pH was adjusted to approximately 12.5 by addition of 30% NaOH (2.6 L), and the two layers were separated. The aqueous layer was extracted with toluene (1 L). The combined toluene layers were dried and concentrated under reduced pressure to yield crude **4** as an oil which solidified on standing (1326 g, 96.5%). HPLC analysis indicated an assay of 92% purity. Recrystallisation from light petroleum (bp 40−60 °C) yielded material which gave an assay of 99.8%: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7 Hz, 3H), 1.60−2.40 (m, 2H), 2.30 (s, 6H), 2.70 (t, J = 6 Hz, 2H), 4.09 (t, J = 6 Hz, 2H), 4.40 (t, J = 7 Hz, 1H), 6.89 (d, J = 9 Hz), 7.26 (br s, 5H), 7.95 (d, J = 9 Hz, 2 H).

Conversion of Trifluoracetic Acid to Trifluoroacetic Anhydride. Phosphorus pentoxide (103 g, 0.725 mol) was added with cooling to TFAA/TFA (100 mL, 0.80 mol fraction of TFA), which had been recovered above, and the mixture stirred at room temperature for 1 h. Distillation yielded a mixture of TFAA/TFA (90 mL, 0.90 mol fraction

(14) Marino, G. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1971; Vol. 13, p 235.
(15) Effenberger, F.; Epple, G. *Angew. Chem., Ed. Engl.* **1972**, *11*, 299.
(16) Keumi, T.; Taniguchi, R.; Kitajima, H. *Synthesis* **1980**, 139.
(17) Kemp, W., Ed. *NMR in Chemistry*; The Macmillan Press: London, 1986; Chapter 9.

of TFAA). Water (30 mL) was added with cooling to the phosphoric acid residue. The pH was adjusted to 11 by the slow addition of calcium hydroxide (178.5 g, 2.41 mol), and the precipitated hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, 240 g, 0.24 mol, 99%) was filtered off.

Acknowledgment

B.W.C. would like to acknowledge Klinge Pharma, Killorglin, County Kerry, and the Irish American Partnership for financial support. We are also grateful to Mr. Max Stern and, in particular, Dr. Bob Khan of Klinge Pharma for their invaluable support and advice throughout this work. We also acknowledge Dr. David am Ende of Pfizer Inc., Groton, NY, for helpful advice on the reaction calorimetry results.

Received for review March 14, 1997.[⊗]

OP9700136

[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1997.