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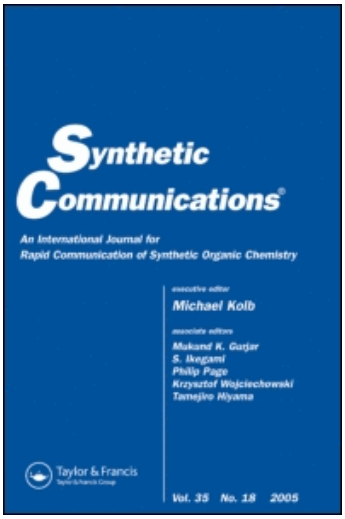

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The Economic Synthesis of Pyridinium Fluorochromate(VI), $C_5H_5NH[CrO_3F]$ (PFC), and Solvent-Free Oxidation of Organic Substrates with PFC

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The Economic Synthesis of Pyridinium Fluorochromate(VI), $C_5H_5NH[CrO_3F]$ (PFC), and Solvent-Free Oxidation of Organic Substrates with PFC

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ABSTRACT

A 1 : 1 : 1 stoichiometric reaction among CrO_3, aqueous HF and pyridine affords orange crystalline pyridinium fluorochromate(VI), C_5H_5NH-$[CrO_3F]$ (**PFC**), in 99.2% isolated yield. The reagent under solvent-free conditions readily converts benzylic, secondary, and allylic alcohols to the corresponding carbonyls and selectively oxidizes secondary alcohols in the presence of primary alcohols, polycyclic hydrocarbons to cyclic ketones, benzoin to benzil, PPh_3 to $O{=}PPh_3$, methylphenyl sulfide to sulfoxide, cyclohexanone oxime to cyclohexanone, an allylic Δ^5-steroid

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to the corresponding α,β-unsaturated ketone and deprotects dioxolanes and dithiolanes to aldehydes; the economic synthesis of **PFC**, its ease of reaction without solvent, versatility, and high isolated yields of the products are the significant features of the protocol.

Key Words: Pyridinium fluorochromate; Oxidations; Solvent-free; Δ^5-steroid; Deprotection.

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INTRODUCTION

Partial oxidations play an important role in organic synthesis and chemical technology. The oxidized products of alcohols and hydrocarbons, for instance, are valuable as precursors for fine and specialty chemicals, pharmaceuticals, and agrochemicals. It is because of this that a number of oxidants have been introduced.[1] However, the reagents based on chromium(VI) have been very popular, useful, and successful. They are easy to handle, cost-effective, and readily available. This caused Cr(VI)-reagents to metamorphose over the decades from Collins' reagent,[2] CrO_3-3,5-dimethyl pyrazole complex,[3] pyridinium chlorochromate(VI) **PCC**,[4] pyridinium dichromate (**PDC**),[5] 2,2′-bipyridinium chlorochromate (**BiPCC**),[6] through pyridinium fluorochromate(VI) (**PFC**),[7] quinolinium fluorochromate(VI) (**QFC**),[8] and 3,5-dimethyl pyrazolium fluorochromate(VI) (**DmpzHFC**),[9] to overcome the typical problems encountered in the oxidations and improve the selectivity. Among these, **PCC** and **PFC** stand out to be highly potential with **PFC** having additional advantages in terms of stability, versatility, controlled acidity, selectivity, operational simplicity, and capability of functioning well under mild conditions, thereby assuming significant importance over the years. To date, there have been a large number of reports on the use of **PFC** in the studies of oxidative transformations. Thus, it very efficiently oxidizes primary, secondary, and allylic alcohols, fused ring hydrocarbons, benzylic systems, toluenes, sulfides, benzyl ethers, phosphorus compounds, arylalkanes, hydroxy acids, thio acids, benzaldehydes, and aromatic anils, for instance.[10–14] **PFC**, owing to its controlled acidity (pk_a, 2.7),[7,9] was successful in oxidizing acid sensitive substrates such as 5-andostene-3β,17$\tilde{\beta}$-diol to the corresponding 17-keto-steroid,[10] and was used in the synthesis of biochemically important S-(+)-4-formyl-4-butanolide, chiral synthon (R)-1-benzoyloxy-3-buten-2-ol, derivatives of dimethyl penam and dimethyl penam-S,S-dioxide[14] and 3β-acetoxy-lanost-8-en-24-one (24-ketolanosteryl acetate).[14] It also permits oxidative deprotection of oximes and desilylative oxidations of alkyl trimethyl silyl ethers.[15] This reagent has been used extensively in the studies of reaction dynamics of a variety of substrates. All these

investigations were conducted in solutions. Having been intrigued by the outstanding performance of **PFC**, it was considered worthwhile to try out its economic synthesis to enable waste minimization and then ascertain its efficacy in solvent-free oxidative transformations including selective oxidations, Δ^5-steroidal oxidations, deoximations, and deprotections. The reactions under solvent-free conditions have been gaining importance[16,17] because they may offer several advantages including improved yield, selectivity, and procedural simplicity. Reported herein are the results of our investigations as addressed to in the title.

RESULTS AND DISCUSSION

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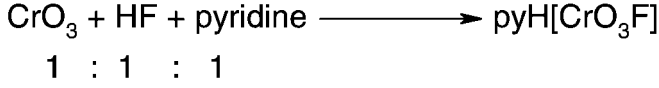
Thus, in a typical economic synthesis (Scheme 1), to a solution of 15.0 g (150 mmol) of CrO_3 in 6.25 mL (150 mmol) of 48% HF and 9.0 mL of water made in a polyethylene beaker was added under stirring 12.1 mL (150 mmol) of pyridine leading to an exothermic reaction to afford 29.63 g (99.2%) of orange-colored crystalline pyridinium fluorochromate, $C_5H_5NH[CrO_3F]$ (**PFC**).

PFC melts at 106–108°C and the results of analysis and characterization data compare very well with those reported earlier.[7] No recrystallization is required. The reaction can be scaled up to 500 g, if desired.

The oxidant worked very well under solvent-free conditions, and the reactions proceeded with alacrity. The reactions were carried out by grinding the mixture of stoichiometric amounts of the substrate and the reagent in an agate mortar or in a silica boat with an agate pestle, either at ambient temperature or at temperatures between 50 and 70°C in a hot air oven for the time period as shown against the entries in Table 1. The solid substrates and the reagent were powdered separately before mixing together. The progress was monitored with TLC and GC. The product was extracted with diethylether (ca. 50 mL/mmol of substrate) followed by filtration through a short silica gel column. The solvent was removed in a rotary evaporator to get the product. This procedure was adopted for **1–5**, **8–10**, and **12–15**. However, for **6**, **7**, and **11**, the product was purified by column chromatography over a short pad of silica gel using ethylacetate-hexane (1 : 9) as eluent. Isolation of anthracene-9, 10-dione (**6a**) was possible also by sublimation from a



Scheme 1.

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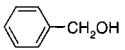
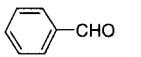
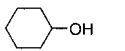
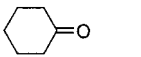
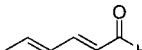
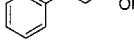
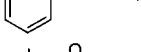
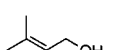
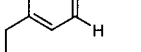
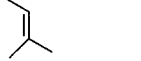
Table 1. Solvent-free oxidative transformations of some organic substrates using PFC.

Substrate	Sub./PFC molar ratio	Temp. (°C)	Time	Product	Yield[a]
 (1)	1 : 1	rt	10 min	 (1a)	93
 (2)	1 : 1	rt	15 min	 (2a)	86
(3)	1 : 1	rt	10 min	 (3a)	85
 (4)	1 : 1	rt	10 min	 (4a)	82
 (5)	1 : 1	rt	7 min	 (5a)	87
 (6)	1 : 2.2	50	2 hr	 (6a)	75

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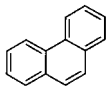
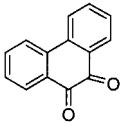
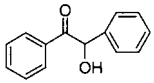
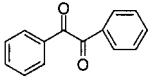
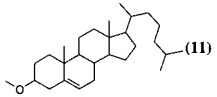
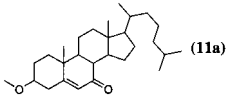
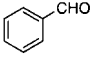
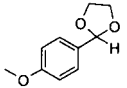
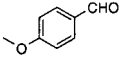
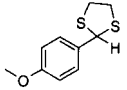
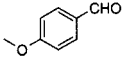
	(7)	1 : 2.2	70	2 hr		(7a)	79
	(8)	1 : 1	55	30 min		(8a)	85
PPh_3	(9)	1 : 1	55	5 min	$O{=}PPh_3$	(9a)	95
	(10)	1 : 1	rt	5 min		(10a)	65
	(11)	1 : 4	65	2 hr		(11a)	64
	(12)	1 : 2	60	30 min		(12a)	85
	(13)	1 : 2	60	25 min		(13a)	82
	(14)	1 : 2	60	20 min		(14a)	86
	(15)	1 : 6	70	2 hr		(15a)	83

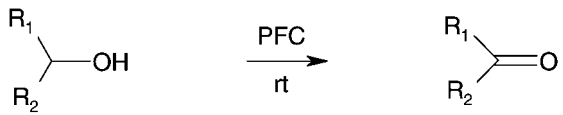
[a]Isolated yields are reported.

mixture after conducting a separate reaction. This represents a case of all-solid-phase reaction and may serve as a paradigm for similar or related transformations. In all cases, the transformations were selective, and the conversions (GC) were quantitative except for **6**, **7**, and **11**. Isolated yields are reported in Table 1. As evident, the reagent worked very well to convert benzylic (**1**), allylic (**3, 4**) and secondary (**2, 5**, and **8**) alcohols to the corresponding carbonyls (Scheme 2).

It is important that the acid-sensitive transformation like geraniol (**4**) to geranial (**4a**) occurred smoothly. Such reactions in solution often require buffer. Notably important are also the selective oxidation of a secondary alcohol in the presence of a primary alcohol (**5** to **5a**). Oxidation of poylcyclic hydrocarbons generally requires stringent conditions. Under the present experimental conditions, both anthracene **(6)** and phenanthene **(7)** were readily oxidized to anthracene-9, 10-dione (**6a)** and phenanthene-9, 10-dione (**7a**), respectively. The very facile oxidation of PPh_3 **(9)** to $O{=}PPh_3$ **(9a)** provides a good example to show that an oxo-transfer reaction can be carried out easily in a solid-phase reaction. Also important is the oxidation of organic sulfide to the corresponding sulfoxide (**10** to **10a**) without over oxidation. Incidentally, selective oxidation of sulfides to sulfoxides is an important synthetic problem for which not many suitable reagents and protocols are available in literature.[18]

An important concern of the present investigation was the oxidation of Δ^5-steroids to the corresponding α,β-unsaturated ketone owing to their intrinsic importance.[19] This was because the literature methods have one or more of the following limitations (i.e., requirement of a large excess of the oxidants, use of very expensive reagents, stringent reaction conditions, and very sluggish reactions with poor yields of the products in many instances). It was significant that under the solvent-free conditions 3-acetoxy cholesterol (**11**) was typically oxidized by **PFC** to 3-acetoxy-7-ketocholesterol (**11a**) in 64% isolated yield in about 2 hr at 65°C. Incidentally, although oxidation of Δ^5-steroids in refluxing benzene with **PFC** was quite effective,[20] a similar oxidation in CH_2Cl_2 or CH_3CN under prolonged reflux did not afford any promising results.[9]

The efficacy of the protocol is demonstrated also by the alacrity with which the deoximation of **12** to the corresponding ketone (**12a**) occurred. Deoximations are important as alternative pathways to the synthesis of



Scheme 2.

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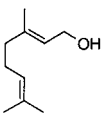
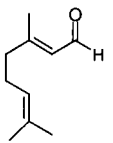
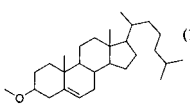
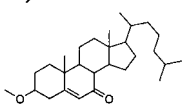
Table 2. Comparison of in-solvent vs. solvent-free oxidations by **PFC**.

Substrate	PFC-CH_2Cl_2 or CH_3CN/Time	Yield (%)	PFC, Solvent-free/ Time	Yield (%)	Product
 **(2)**	3.5 hr[7]	89	15 min	86	 **(2a)**
 **(4)**	2 hr[10]	80	10 min	82	 **(4a)**
 **(11)**	10–12 hr	Very poor[9]	2 hr	64	 **(11a)**

aldehydes and ketones from noncarbonyl substrates. It is pertinent that conventional oxidations do not seem to work satisfactorily especially because of long reaction times and low yields. To generalize the superiority, similar solvent-free transformations with other oxidants such as **QFC**, **DmpzHFC** are now underway. The results obtained so far are in the affirmative.

To extend the scope of the protocol, the deprotection of dioxolanes and a dithiolane were investigated. This attracted our attention especially because selective protection and deprotection of carbonyl groups constitute key steps in many synthetic reactions.[21] Moreover, the deprotection of thioacetals, which are important as acyl carbanion equivalent in organic synthesis, is rather challenging because of their stability toward normal acidic and basic conditions. The deprotection of dioxolanes (**13** and **14**) and a dithiolane (**15**) went off very readily to afford the corresponding aldehydes (**13a**, **14a**, and **15a**, respectively) in high isolated yields.

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A comparison of the results of **PFC** oxidations in solvents with those of the solvent-free conditions shows that the reactions work much faster without solvent (present results). Three selected examples are cited in Table 2 for comparison. Notable is that the yields of the products are either similar (**2, 4**) or remarkably higher (**11**) for solvent-free reactions. Rapidity of the solid-phase reactions is believed to be facilitated by the intervention of a liquid phase, which is formed at a stage of initiation of the reaction from the interaction of a very small amount of the product and the reagent. This is important particularly when both the substrate and the reagent are solid and happens possibly owing to the existence of a lower melting eutectic. Indeed, the appearance of a liquid or melt phase was observed in each reaction reported herein. This might have imbued the individual molecules with required mobility enabling productively important reactive collisions, thereby allowing for rapid reactions to take place between the two solid reactants.

Notable in conclusion is that **PFC** is capable of being synthesized in an economic way and very effectively used as an oxidant under solvent-free conditions. The new protocol is not only facile and selective but also more versatile in that it can readily oxidize certain substrates (c.f. Δ^5-steroidal systems), which were not possible in the corresponding solution phase reaction. Further studies are now in progress to show that solvent-free oxidations proceed with a much greater alacrity than their solution counterparts.

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