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THE SELECTIVE SOLID-PHASE OXIDATION OF ALCOHOLS AND OTHER ORGANIC SUBSTRATES BY 3,5-DIMETHYLPYRAZOLIUM FLUOROCHROMATE

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(11/07/06)

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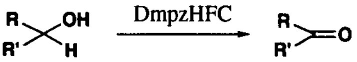
Selective oxidation has been a fundamental procedure in organic chemistry and finds application not only in basic research and in the pharmaceutical industries but is also regarded as a core technology for the conversion of petroleum based materials or bio-mass based feed stocks to useful chemicals.[1] Although a wide variety of oxidants, catalysts and reaction systems have been developed for the purpose, Cr(VI)-based oxidants are extensively used owing to their excellent performance under mild conditions with high efficiency and operational simplicity. Endeavors have been made to overcome the problems of over-oxidation and diminished selectivity. This has led to the development of a number of oxidants such as Collins reagent,[2] CrO_3-3,5-dimethylpyrazole complex,[3] pyridinium chlorochromate(VI) (**PCC**),[4] pyridinium dichromate (**PDC**),[5] 2,2'-bipyridinium chlorochromate (**BiPCC**),[6] pyridinium fluorochromate(VI) (**PFC**),[7] quinolinium fluorochromate(VI) (**QFC**),[8,9] imidazolium fluorochromate(VI) (**IFC**),[10] 3,5-dimethylpyrazolium fluorochromate(VI) (**DmpzHFC**),[11] tetramethylammonium fluorochromate(VI) (**TMAFC**)[12] and benzimidazolium fluorochromate(VI) (**BIFC**).[13] However, some of the distinctive features of **DmpzHFC** compared to its companion reagents are quite evident from its higher solubility in organic solvents, efficiency to perform under mild conditions, controlled acidity, shorter reaction time and high yields of products.



As a prerequisite to alcohols oxidation, the reactions are better performed in anhydrous conditions to avoid over-oxidation. Accordingly, one could carry out oxidations in the absence of solvent.[14,15] Apart from this, if oxidations are carried out in an acidic environment, formation of hemiacetals from reaction of oxidized product and the unreacted alcohol can cause problems. In order to circumvent many of these problems, it was thought worthwhile to conduct the reactions under solvent-free conditions with a reagent having inherently controlled acidity. In fact, the far less acidic character of DmpzHFC (pk_a, 7.8)[11] compared to some of comparable reagents such as PCC (pk_a, 1.4), PFC (pk_a, 2.7) and QFC (pk_a, 4.7) and its efficacy encouraged us to study its solid-phase oxidation chemistry. Herein, we report the results of solid-phase oxidation of a variety of organic substrates using **DmpzHFC**.

In the solid-phase reactions, **DmpzHFC** readily oxidized primary, secondary alcohols and cholesterol to the corresponding carbonyl compounds (Table, runs 1-3 and 16). A secondary alcohol is chemoselectively oxidized to ketone in the presence of primary hydroxy group (run 4). The products are isolated in high yields. Benzyl alcohols (runs 5-11) underwent oxidation selectively to the corresponding benzaldehydes without over-oxidation. The reactions proceeded rapidly providing products in high yields. Experiments carried out with benzyl alcohols having both electron-donating and electron-withdrawing groups showed that the oxidation of substrates having electron-donating groups *e. g.*, $-CH_3$ and $-OCH_3$, proceeded more rapidly compared to those having electron-withdrawing groups *e. g.* $-NO_2$; 2-nitrobenzyl alcohol (run 9) was oxidized at a comparatively faster rate than 4-nitrobenzyl alcohol (run 10). Allylic alcohols, *e. g.* cinnamyl alcohol and geraniol (runs 12 and 13) were very easily and stereoselectively oxidized to the corresponding aldehydes. No stereochemical change was observed in the oxidized product of (*E*)-cinnamyl alcohol and (*E*)-geraniol. It is significant to note that alcohols having acid-sensitive protecting groups such as tetrahydropyranyl (THP) and *t*-butyldimethylsilyl (TBS) ethers (runs 14 and 15) were oxidized efficiently without cleavage of these groups. Notably the oxidation of alcohols by the present protocol is far more facile than with **PCC**,[14a] **PFC**,[7e] **CrO_3**[14b] or **BIFC**[13] under solvent-free conditions, thus indicating a definite advantage of the present reagent. The reagent also oxidized polycyclic aromatic hydrocarbons such as anthracene and phenanthrene to the corresponding quinones (runs 17 and 18). As representative examples of oxo-transfer reaction, **DmpzHFC** oxidized methyl phenyl sulfide and triphenylphosphine to methyl phenyl sulfoxide and triphenylphosphine oxide, respectively, in the solid-phase (runs 19 and 20) very readily. Notable is that in the sulfide oxidation, a reagent stoichiometry of 0.66 mole equivalent to that of the substrate was sufficient for complete conversion to the corresponding sulfoxide.

Significantly, **DmpzHFC** oxidized cyclohexanone oxime (run 21) to cyclohexanone demonstrating the oxidation of an oxime to a carbonyl compound in the solid-phase.[14a] Such reaction is important as it provides an alternative pathway to the regeneration of carbonyl compounds from a non-carbonyl substrate. The selective protection and deprotection of carbonyl groups frequently represent a key step in synthetic organic chemistry and many reagents have been introduced over the years[16] for the purpose.

Table. Solvent-free Oxidation using DmpzHFC

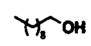
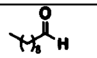
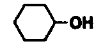
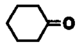
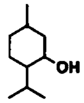
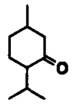
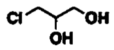
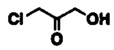
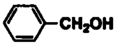
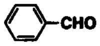
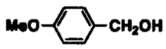
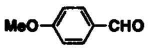
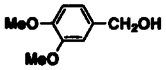
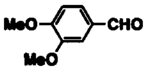
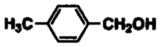
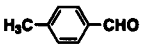
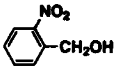
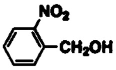
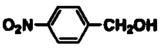
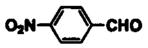
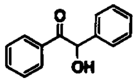
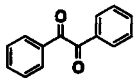
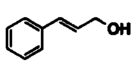
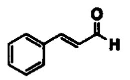
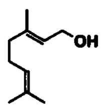
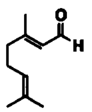
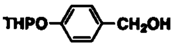
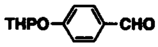
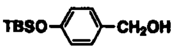
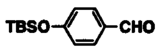
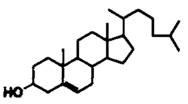
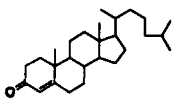
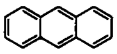
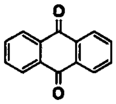
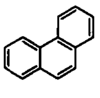
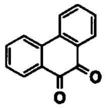
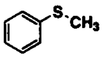
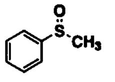
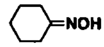
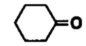
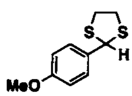
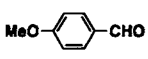
Run	Substrate	Product	Yield (%)	mp(bp)[a]	Yield(%) (time, min)			
		DmpzHFC	(Time, min)	(°C)	PCC[14a]	PFC[7c]	CrO_3[14b]	BIFC[12]
1			91(2)	(207-209)	----	----	----	80 (300)
2			93(2)	(155-156)	----	86 (15)	----	----
3			95(2)	(207-210)	----	----	----	70 (480)
4			86(2)	(187-189)	----	87 (7)	----	----
5			85(1)	(178-179)	96 (15)	93 (10)	90 (180)	83 (180)
6			92(2)	(248)	94 (5)	----	83 (240)	85 (210)
7			95(2)	58	----	----	----	----
8			88(2)	(204)	96 (10)	----	----	87 (150)
9			98(45)	44	94 (20)	----	----	----
10			93(60)	106	----	----	----	75 (480)
11			95(10)	95	----	85 (30)	----	----
12			89(2)	(252)	95 (15)	85 (10)	87 (240)	92 (60)
13			93(2)	(229)	----	82 (10)	----	85 (320)
14			82(4)	dec. (>250)	----	----	----	----
15			85(3)	(185-187)/ 1 mm	----	----	----	----
16			78(10)	79-82	----	----	----	----

Table. Continued...

Run	Substrate	Product DmpzHFC	Yield (%) (Time, min)	mp(bp)[a] (°C)	Yield(%) (time, min)			
					PCC[14a]	PFC[7e]	CrO_3[14b]	BIFC[12]
17[b]			84(20)	284-286	----	75 (120)	----	----
18[b]			78(20)	209-212	----	79 (120)	----	----
19[c]			96(2)	26-29	----	65 (5)	----	----
20	Ph_3P	Ph_3PO	96(2)	156-157	----	95 (5)	----	----
21			97(2)	(155-156)	----	95 (30)	----	----
22[d]			85(5)	(248)	----	83 (120)	----	----

a) All mps and bps are within 2° of the values reported in reference 17. b) Ratio of substrate to DmpzHFC is 1: 2 .1. c) 1: 0.66. d) 1:6

However, a very facile deprotection of dithiolanes with Cr(VI)-reagents under solvent-free conditions is not commonly encountered. In order to demonstrate efficacy of the present protocol, the deprotection of a dithiolane was conducted with **DmpzHFC** in the solid phase (run 22). The reaction was complete in 5 min. In order to extend the scope further, an experiment on a larger scale (50 mmol of run 1) was performed. The reaction proceeded as rapidly giving a 92% yield, showing the potential for large scale reactions.

In conclusion, 3,5-dimethylpyrazolium fluorochromate(VI) appears to be a reagent of high selectivity for a variety of oxidations under different reaction conditions (solution and solid-phase) and reacts more efficiently than comparable reagents **PCC**,[14a] **PFC**,[7e] **CrO_3**[14b] and **BIFC**.[13] Its diminished acidity is an important advantage for oxidations of acid-sensitive substrates.

EXPERIMENTAL SECTION

All procedures were carried out on the bench top. Reagent-grade chemicals were used without further purification. The substrates and solvents were used as received. The products were characterized by comparison of their spectral data recorded on Nicolet Impact–410 Fourier Transform Infra Red Spectrophotometer and Varian-400 MHz NMR. Elemental analyses were performed on Perkin Elmer CHNS analyzer. 3,5-Dimethylpyrazolium fluorochromate(VI), $C_5H_8N_2H[CrO_3F]$ (**DmpzHFC**),[11] was prepared by the addition of 48% HF (60 mmol) to a solution of CrO_3 (28 mmol) in 1.3 mL water in a 50 mL polythene beaker, cooling the reaction mixture at ice-bath for *ca.* 10 min, followed by the addition of 29.2 mmol of 3,5-dimethylpyrazole portionwise with stirring. The compound was obtained as orange crystals (5.8 g, 92%).

General Procedure.- DmpzHFC (1.08 g, 5 mmol) was added to the substrate (5 mmol) in a mortar. The whole was mixed thoroughly and left standing at room temperature with occasional agitation or soft grinding for the period of time shown in the Table. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was extracted with ethyl acetate (3 x 15 mL). Evaporation of the organic solvent and purification of product by column chromatography (hexane-ethyl acetate, 95/5, v/v) afforded the product (*Table*). The reduced chromium obtained after extraction of the oxidized product, was dissolved in dilute H_2SO_4 (6M) and oxidized by boiling with potassium persulfate (7.5 mL of 20% solution) in presence of a catalytic amount (0.1 mL of 0.1M solution) of Ag^+. The potassium dichromate thus obtained may be recycled, thus minimizing the chance of the metal into the environment.

All spectral data have been reported in literature and Sigma-Aldrich spectral library.[17,18] The spectral data of new compounds are given below:

1-Chloro-3-hydroxyacetone, colorless liquid, bp 185-187°C, IR: 3402, 2931, 2877, 1713, 1375, 1107, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.16 (bs, 1H), 4.64 (s, 2H), 4.81 (d, 2H, J = 4.1Hz)

Anal. Calcd for $C_3H_5O_2Cl$: C, 32.20, H, 4.64. Found C, 31.94, H, 4.73.

4-(Tetrahydropyran-2-yloxy)benzaldehyde, purified by column chromatography (neutral alumina, hexane-ethyl acetate, 95:5), colorless liquid, decomposes >250°C, IR: 2945, 2858, 1696, 1609, 1511, 1358, 1306, 1250, 1209, 1163, 1112, 1040 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ 1.49-1.78 (m, 4H), 1.81-1.99 (m, 2H), 3.57-3.62 (m, 1H), 3.80-3.86 (m, 1H), 5.47-5.51 (m, 1H), 7.12 (d, J = 8.8Hz, 2H), 7.79 (d, J = 8.8Hz, 2H), 9.84 (s, 1H); ^{13}C NMR(100 MHz, $CDCl_3$): δ 18.4, 24.9, 30.6, 62.0, 96.0, 116.4 (2C), 131.8 (2C), 132.3, 162.1, 191.1.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89, H, 6.84. Found, C, 69.81, H, 6.89.

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