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3,5-Dimethylpyrazolium fluorochromate(VI), $C_5H_8N_2H[CrO_3F]$, (DmpzHFC): a convenient new reagent for oxidation of organic substrates

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Abstract—A new chromium(VI) reagent, 3,5-dimethylpyrazolium fluorochromate, $C_5H_8N_2H[CrO_3F]$ (DmpzHFC), has been developed by reacting dmpz with CrO_3 and aqueous HF for the selective oxidation of primary, secondary and allylic alcohols to the corresponding carbonyl compounds, polycyclic hydrocarbons to cyclic ketones and allylic Δ^5-steroids to the corresponding α,β-unsaturated ketones.

Over recent years, chromium(VI) based oxidising agents have been extensively worked on leading to the development of a good number of reagents, some of which have become quite popular and performing well as oxidising agents. Some of the important entries in the list of reagents are the Collins reagent,[1] chromium trioxide-3,5-dimethylpyrazole complex,[2] pyridinium chlorochromate (PCC),[3] pyridinium dichromate (PDC)[4] and 2,2′-bipyridinium chlorochromate (BiPCC).[5] Over several years our group has been involved in developing newer reagents and methodologies[6] allowing oxidations to be performed under mild conditions. The versatility of pyridinium fluorochromate (PFC)[6a,6b,6c,7] goes well to prove the point. However, the chromium based reagents that have been developed so far have some limitations that cannot be overlooked. These include the inherent problems of acidity of the reagents and their limited solubility in organic solvents. As a consequence of the aforementioned problems, these reagents have proved to be unsuitable for oxidations on several occasions. Consequently, the search for a pre-eminent new reagent persisted which has now led to the synthesis of 3,5-dimethylpyrazolium fluorochromate(VI), $C_5H_8N_2H[CrO_3F]$ (DmpzHFC).

The reagent 3,5-dimethylpyrazolium fluorochromate(VI), $C_5H_8N_2H[CrO_3F]$, (DmpzHFC), can be easily prepared in excellent yield from the reaction of CrO_3 with aqueous hydrofluoric acid and 3,5-dimethylpyrazole in the molar ratio of 1:2:1. The compound analysed very well. It is soluble in dichloromethane and highly soluble in acetonitrile, chloroform, ethanol, methanol and acetone. The solubility of DmpzHFC is comparatively higher than PFC, PCC and PDC. The reagent is diamagnetic, EPR silent and melts at 56°C. It is a 1:1 electrolyte (Λ_M= 107 Ω^{-1} cm^2 mol^{-1}, in CH_3CN), showing a pH value of 4.9 (0.01 M aqueous solution) and pK_a 7.8. The pH of 0.01 M solutions of PCC, PFC and quinolinium fluorochromate (QFC) were found to be 1.75, 2.45 and 3.35, respectively, with the corresponding pK_a values being 1.4, 2.7 and 4.7.[6d] A higher pH value of DmpzHFC compared to its companion reagents attests to its far less acidic character.

In order to ascertain the efficacy of the reagent as an oxidant, it has been tested on a wide array of substrates. DmpzHFC readily oxidises primary (entry 1–4, Table 1) and secondary alcohols (entry 5–9, Table 1) in dichloromethane (Scheme 1) to their corresponding aldehydes and ketones. Similar oxidations can be performed in acetonitrile without compromising the yield of the products.

Fused ring hydrocarbons such as anthracene (entry 10, Table 1) and phenanthrene (entry 12, Table 1) are oxidised to 9,10-anthraquinone and phenanthrene-9,10-quinone, respectively. These oxidations can be performed not only in dichloromethane but also in acetonitrile or acetic acid. Importantly, the reagent is found to be quite effective for the oxidation of Δ^5-steroid systems, (entry 13–15, Table 1) (Scheme 2) to the corresponding α,β-unsaturated ketones. In all these cases the products were obtained in moderate to

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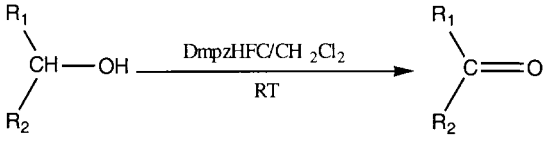
Table 1. Oxidation of organic substrates with DmpzHFC

Entry	Substrates	Solvent/time (h)	Substrate:oxidant	Product[a]		Yield (%)[b]
1.	1-Butanol	CH_2Cl_2/1.5	1:1.1	1-Butanal	**1a**	80
2.	Benzyl alcohol	CH_2Cl_2/0.5	1:1.25	Benzaldehyde	**2a**	78
3.	Citronellol	CH_2Cl_2/1	1:1.25	Citronellal	**3a**	70
4.	Geraniol	CH_2Cl_2/1.5	1:1.5	Geranial	**4a**	95
5.	Cyclohexanol	CH_2Cl_2/0.5	1:1.25	Cyclohexanone	**5a**	70
6.	2-Propen-1-ol	CH_2Cl_2/1.5	1:1.1	Acrolein	**6a**	95
7.	Menthol	CH_2Cl_2/2	1:2.5	Menthone	**7a**	65
8.	Glycerol	CH_2Cl_2/1	1:1	Glyceraldehyde	**8a**	35
9.	Benzoin	CH_2Cl_2/1.5	1:1.25	Benzil	**9a**	70
10.	Anthracene	CH_2Cl_2/3.5	1:2.5	9,10-Anthraquinone	**10a**	58
11.	Anthrone	CH_3CN/3	1:2	9,10-Anthraquinone	**11a**	90
12.	Phenanthrene	CH_2Cl_2/4	1:2.5	Phenanthrene-9,10-quinone	**12a**	70
13.	3-Acetoxy cholesterol	CH_3CN/10	1:6	3-Acetoxy-7-keto-cholesterol	**13a**	75
14.	3-Benzoyloxy cholesterol	CH_3CN/10	1:6	3-Benzoyloxy-7-keto-cholesterol	**14a**	70
15.	Pregnonalone acetate	CH_3CN/12	1:6	7-Keto-pregnonalone acetate	**15a**	60
16.	6-Methoxy tetralene	CH_3CN/10	1:6	6-Methoxy-1-tetralone	**16a**	60
17.	Triphenylphosphine	CH_2Cl_2/2 min	1:1.1	Triphenylphosphine oxide	**17a**	70

[a] Products were characterised by comparison with authentic samples (NMR, IR and mass spectra, TLC and mp/bp measurements).
[b] Isolated yields are reported.

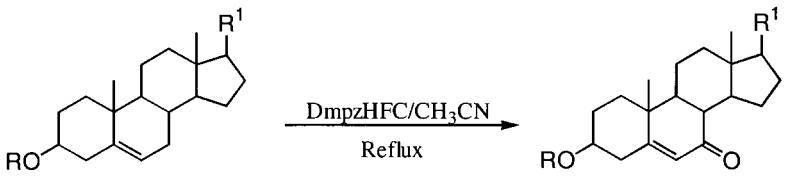
high yields (Table 1). Notably, Δ^5-steroids are more than mere probes for oxidation as Δ^5-steroids with a ketone function at C-7 (Δ^5-7-ketones) are found in animal tissues[8] and food stuffs[9] and are known to be inhibitors of mammalian sterol biosynthesis[10–12] and cell replication.[13,14] Though such oxidations are not unprecedented in the literature, the allylic oxidation of Δ^5-systems carried out with chromic acid reagents,[15] PCC,[16] PDC[17] and $RuCl_3$-TBHP[18] has only a limited success, has involved prohibit ably expensive reagent or has required a large excess of the reagent (1:25–120, substrate:oxidant), stringent reaction conditions and a longer reaction time. Thus, for instance, an amount of 25–30 molar equivalents of PCC in refluxing dichloromethane required 48 h to afford ca. 55% yield of the product.[16] Likewise, a reaction time of 24 h was reported to be needed for similar oxidations involving 25 molar equivalents of PCC or PDC in refluxing benzene or in dimethylsulfoxide or pyridine at 100°C.[17] In so far as $RuCl_3$-TBHP oxidations of Δ^5-steroids are concerned, it is not only that the reagent is expensive with the oxidation procedure being tedious but also that the reaction time is much longer (typically ca. 30 h) compared to the present protocol. It has been now demonstrated through entries 13–15 (Table 1) that a six molar equivalent of DmpzHFC in dry acetonitrile afforded the desired products in good yields in a comparatively much shorter time (10 h). Notably, Δ^5-steroidal oxidations involving one of our previously developed reagents, $C_5H_5NH[CrO_3]F$ (PFC), has not provided very promising results so far.



Scheme 1.

In yet another example, 6-methoxy tetralene (c.f. activated hydrocarbon; entry 16, Table 1) was oxidised to 6-methoxy-1-tetralone as a case of ketone formation at the C-1 position. Incidentally, this product appears to be the key building block for several life saving drugs and steroid molecules.[19] Here again, the reaction time in our case was relatively short (10 h) with the molar equivalent of the oxidant required being far less (6 equiv.) compared to literature procedures (13–48 h, 60–120 equiv.).[16,20] In addition, a very facile oxidation of triphenylphosphine to triphenylphosphine oxide (entry 17, Table 1) suggests that DmpzHFC is also capable of acting as an efficient oxo-transfer reagent.

A brown microcrystalline product isolated after the oxidation, as the reduced product, has been identified to be a chromium(IV) species, $C_5H_8N_2H[CrO_2F]$, as ascertained from the results of chemical analyses, chemical determination of oxidation level of the metal (3.9–4.1), magnetic



13, R = Ac, $R^1 = C_8H_{17}$
14, R = -CO_2Ph, $R^1 = C_8H_{17}$
15, R = Ac, R^1 = -$COCH_3$

13a, R = Ac, $R^1 = C_8H_{17}$
14a, R = -CO_2Ph, $R^1 = C_8H_{17}$
15a, R = Ac, R^1 = -$COCH_3$

Scheme 2.

susceptibility ($\mu_{eff} = 2.92$ BM at rt) and EPR (single line at $g = 1.935 \pm 0.005$) measurements in addition to IR spectroscopy. This suggests very clearly that DmpzHFC serves as a 2-electron-transfer reagent.

To sum up, the easily prepared new reagent (DmpzHFC) has a number of advantages over its companion reagents like PCC, PDC and PFC, or $RuCl_3$-TBHP as evident from the consideration of the amount of the reagent required for a large variety of oxidations, solubility in different solvents, controlled acidity, shorter reaction time and high to very high yields of products. The reduced chromium species can be trapped on a silica gel or a Celite® column for safe disposal. Based on all the results hitherto obtained it may be stated that DmpzHFC is an important addition to the realm of oxidising agents.

1. Experimental

1.1. General

IR spectra were recorded using a Perkin Elmer Model No 983 spectrophotometer. ^{1}H NMR spectra were recorded using 300 MHz Bruker AC-F instrument, GC mass spectra were recorded in Fission 8000 series using capillary column. Elemental analyses were performed using Perkin Elmer C, H, N analyser. ESR spectra were recorded at ambient temperature by a Varian E-109 ESR spectrometer (X-band) with 100 kHz field modulation. Magnetic susceptibility measurements were conducted by the Gouy method using $Hg[Co(NCS)_4]$ as calibrant.

1.1.1. Preparation of 3,5-dimethylpyrazolium fluorochromate, DmpzHFC, $C_5H_8N_2H[CrO_3F]$. To a solution of 5.6 g (56 mmol) CrO_3 in 2.5 mL water in a 100 mL polyethylene beaker, 5 mL (120 mmol) 48% HF was added with stirring. An orange red solution was obtained. The reaction mixture was then cooled in an ice-bath (temperature, 0–5°C) and 5.6 g (58.33 mmol) 3,5-dimethylpyrazole was added portion-wise, with stirring, when an orange crystalline compound separated out. This was filtered under vacuum, using a polyethylene funnel, washed with petroleum ether (3×10 mL), rapidly dried in a vacuum desiccator and finally stored in a sealed polyethylene bag in a freezer. The yield of $C_5H_8N_2H[CrO_3F]$ was found to be 11.6 g (92%). The melting point of the compound was found to be 56°C. Electrical conductance (in CH_3CN) was 107 Ω^{-1} cm^2 mol^{-1}, IR ν(KBr): 954(s, Cr–O), 921(s, Cr–O) and 633(m, Cr–F), 800–1600 cm^{-1} (originating due to the 3,5-dimethylpyrazolium cation). Electronic absorption at 27,701 cm^{-1}, corresponded to $^1A_1 \rightarrow {}^1E$ ($\epsilon =$ 1641 M^{-1} cm^{-1}); 36,765 cm^{-1} to $^1A_1 \rightarrow {}^1A_1$ ($\epsilon =$ 4101 M^{-1} cm^{-1}) and 46,296 cm^{-1} to $^1A_1 \rightarrow {}^1E$ ($\epsilon =$ 9706 M^{-1} cm^{-1}). Analysis: found Cr, 24.35%; F, 8.95%; C, 27.80%; N, 12.98%; H, 3.91%. $C_5H_8N_2H[CrO_3F]$ calculated: Cr, 24.06%; F, 8.80%; C, 27.78%; N, 12.96%; H, 4.21%.

1.2. General procedure for the oxidation of alcohols

1.2.1. Oxidation of geraniol. To a stirred solution of DmpzHFC (1.57 g, 7.26 mmol) in 10 mL of CH_2Cl_2 was added a solution of geraniol (1.02 g, 6.6 mmol) in 10 mL of CH_2Cl_2 in one portion. Stirring was continued for 30 min to give a yellow solution. The progress of the reaction was monitored by TLC. After completion of the reaction, 50 mL of dry diethyl ether was added to the reaction mixture and the whole mass was shaken well, the organic layer decanted and the residue washed with dry diethyl ether (3×20 mL). The combined organic layers were passed through a short pad of Celite®, to trap the reduced chromium, and washed thoroughly with diethyl ether. The combined filtrate was evaporated in a rotavapor under reduced pressure to give a crude, gummy material which was subjected to column chromatography over a short pad of silica gel using ethyl acetate–hexane (1:9) as an eluent to afford geranial (**4a**, Table 1) as a colourless liquid. Yield was 1 g (95%), bp 228°C (lit.[21a] bp 229°C).

1.2.2. Oxidation of glycerol. An amount of 1.08 g (5 mmol) DmpzHFC was dissolved in 10 mL of CH_2Cl_2. To it was added a solution of glycerol (0.36 mL, 5 mmol) in 10 mL of CH_2Cl_2, and the whole was stirred for 1 h. The progress of the reaction was monitored by GC. An amount of 50 mL of diethyl ether was added to the reaction mixture and the whole mass was shaken well, the organic layer decanted and the residue washed with diethyl ether ($3 \times$ 20 mL). The combined organic layer was concentrated in a rotavapor and then passed through a short pad of silica gel to trap the reduced product of the reagent, and washed repeatedly with diethyl ether. The filtrate was evaporated in a rotavapor to give a crude material which was subjected to column chromatography over a pad of silica gel using ethyl acetate–hexane (9:1) as eluent to afford glyceraldehyde as DL-mixture. Yield was 0.16 g (35%), mp 143°C (lit.[21b] mp 144–145°C).

1.2.3. Oxidation of anthracene. In a dry round-bottomed flask, 0.18 g (1 mmol) of anthracene was dissolved in 10 mL of CH_2Cl_2. To the solution, 0.54 g (2.5 mmol) of DmpzHFC was added and refluxed for 3.5 h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated using a rotavapor and then washed with 50 mL of diethyl ether. The combined organic layer was passed through a short pad of Celite® to trap the reduced product of the reagent and washed thoroughly with diethyl ether. The filtrate was evaporated in a rotavapor to give a crude product which was purified by column chromatography over a short pad of silica gel using ethylacetate–hexane (1:9) as eluent. 9,10-Anthraquinone was obtained as a yellow crystalline compound having mp 271°C (lit.[22] mp 273°C). Yield of the compound was 0.12 g (58%).

1.2.4. Oxidation of triphenylphosphine. The oxidation was conducted under nitrogen atmosphere. In a 100 mL round-bottomed flask was placed 1.81 g (8.39 mmol) of DmpzHFC and 4 mL of CH_2Cl_2. PPh_3 (2.4 g, 9.16 mmol) dissolved in 3 mL of CH_2Cl_2 was added in one portion maintaining the substrate: oxidant mol ratio of 1:1.1. An instantaneous exothermic reaction set in and the oxidation was complete in 2 min. The reaction solution was separated by centrifugation and then filtered through a short silica gel column. The column material was washed thoroughly with diethyl ether and filtered. The combined filtrate and washings were evaporated on a steam-bath and the white highly

crystalline product thus obtained was ascertained to be $OPPh_3$.[6b,6d] Yield of $OPPh_3$ was 1.78 g (70%).

The products were all characterised by NMR, IR and mass spectral measurements, mp/bp recording and by comparison with authentic samples.

1.2.5. Oxidation of Δ^5-steroids: a typical procedure. Cholesterol acetate (entry 13, Table 1) (0.43 g, 1 mmol) was dissolved in anhydrous CH_3CN (10 mL) containing molecular sieves (0.02 g, type 3 Å). DmpzHFC (1.3 g, 6 mmol) was added to the substrate and the mixture stirred under reflux for 10 h. The progress of the reaction was monitored by TLC. Diethyl ether (50 mL) was then added to the reaction mixture, the ether layer decanted and the residue further washed with ether (3×30 mL). The combined ether layers were passed through a short pad of Celite® to trap the reduced chromium. The ethereal solution was evaporated and the crude material subjected to column chromatography over silica gel using ethyl acetate–hexane (1:20) to afford **13a** (Table 1) in 0.3 g (75%) yield as a white crystalline compound having mp 155–156°C (lit.[23] mp 157–159°C). [Analysis: found C, 78.61%; H, 10.22%; O, 10.78%. $C_{29}H_{46}O_3$ calculated C, 78.68%; H, 10.49%; O, 10.84%]. IR, ν (KBr): 1741, 1671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) $\delta_H = 5.7$ (s, 1H, –CO–CH═); 4.68 (m, 1H, –CHOAc); 2.05 (s, 3H, $-OCOCH_3$); 1.2 (s, 3H, $-CH_3$); 0.95 (s, 3H, $-CH_3$); 0.9 (s, 3H, $-CH_3$); 0.88 (s, 3H, $-CH_3$); 0.78 ppm (s, 3H, $-CH_3$).

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