

N-Ethylbenzylammonium Fluorochromate (VI) Adsorbed on Silica Gel, a Mild and Selective Heterogeneous Reagent

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Abstract. A mild and selective method for the oxidation of primary and secondary alcohols to their corresponding aldehydes and ketones with *N*-ethylbenzylammonium fluorochromate (VI), EBAFC, is reported. Stability, reaction rate, ease of work-up and efficiency of the EBAFC are considerably increased upon its adsorption on silica gel. The *N*-ethylbenzylammonium fluorochromate (VI) adsorbed on silica gel is inert to aldehydes, ketones, oximes, thiols, sulfides, phenols, pyrans, trimethylsilanes, malonates and thioacetamides.

Keywords: *N*-ethylbenzylammonium Fluorochromate (VI), Heterogeneous Oxidant, Alcohols, Aldehyde, Ketone.

Resumen. Se describe un método suave y selectivo para la oxidación de alcoholes primarios y secundarios a sus aldehídos y cetonas correspondientes, con el fluorocromato de *N*-etil bencil amonio (FCEBA). La estabilidad, la velocidad de la reacción, la facilidad en el trabajo de la reacción y la eficiencia del FCEBA se incrementan considerablemente cuando este reactivo se adsorbe sobre gel de sílice. El fluorocromato de *N*-etil bencil amonio (VI) adsorbido sobre gel de sílice es inerte con aldehídos, cetonas, oximas, tioles, sulfuros, fenoles, piranos, trimetilsilanos, malonatos y tioacetamidas.

Palabras clave: Fluorocromato de *N*-etil bencil amonio (VI), Oxidantes heterogéneos, Alcoholes, Aldehídos, Cetonas.

Introduction

In modern organic synthesis the oxidation of an organic substrate in anhydrous and aprotic solvent, under mild and neutral conditions is important [1]. Therefore, synthetic organic chemists pay attention to search for new oxidizing reagents. In recent years, investigators have been looking for the preparation of oxidants with a number of characteristics including lower cost, higher yields, better selectivity, performing in mild and neutral conditions, easy preparation, low toxicity and short reaction times. Extensive works have led to the development of a good number of chromium (VI) oxidizing agents such as pyridinium fluorochromate (PFC) [2, 3], pyridinium chlorochromate (PCC) [4], pyridinium dichromate (PDC) [5], 2,2'-quinolinium fluorochromate (QFC) [6], poly [vinyl (pyridinium fluorochromate)] [7], isoquinolinium fluorochromate (IQFC) [8], 3,5-dimethylpyrazolium fluorochromate (DmpzHFC) [9], 2,6-dicarboxypyridinium chlorochromate [10, 11], tetramethylammonium fluorochromate (TMAFC) [12], tetrabutylammonium fluorochromate (TBAFC) [13], morpholinium chlorochromate (MCC) [14], trialkylammonium fluorochromate [1], benzyltrimethylammonium fluorochromate [15], tripropylammonium fluorochromate [16], benzimidazolium fluorochromate [17], and benzyltriethylammonium chlorochromate [18], etc. Moreover, we have recently reported two new reagents as *N*-methylbenzylammonium fluorochromate (MBAFC) [19] and morpholinium fluorochromate [20] for the oxidation of alcohols. All these reagents are mostly used for the oxidation of alcohols to the corresponding aldehydes and ketones.

On the other hand, medicinal chemists in the pharmaceutical industry routinely make use of solid-phase organic synthesis (SPOS) to prepare libraries of small organic molecules for screening [21]. These techniques can be attractive and suitable

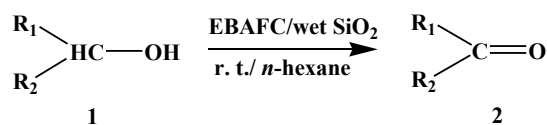
for oxidations of organic substrates. With this method, the oxidations often occur with high yields and the work-up involves simple filtration and evaporation of the solvent. For example, yields have been increased for the oxidation of alcohols by using PCC on alumina [22] instead of only PCC. In this case, Alumina is used as a solid-phase.

This work reports the *N*-ethylbenzylammonium fluorochromate (EBAFC) adsorbed on silica gel as a new promising reagent, which improves efficiency, selectivity, reaction rate, and stability, for the oxidation of alcohols to their corresponding aldehydes and ketones under mild and neutral conditions.

Results and Discussion

We are reporting the synthesis of *N*-ethylbenzylammonium fluorochromate EBAFC, adsorbed on wet SiO₂ (50% w/w) and the reaction with primary and secondary alcohols (**1**) in hexane to their corresponding aldehydes and ketones (**2**), (Scheme 1). These oxidations take place under mild and completely heterogeneous conditions giving good yields, (Table 1). Moreover, this oxidant is inert to aldehydes, ketones, oximes, thiols, sulfides, phenols, pyrans, trimethylsilanes, malonates and thioacetamides.

The EBAFC is easily synthesized in a relatively good yield, (78%). The synthesis is carried out from the reaction of CrO₃ with aqueous HF and *N*-ethylbenzylamine, in the molar ratio of 1:1.5:1. The reagent is obtained as an orange solid and elemental analyses, IR and NMR spectroscopy recognize its structure. In the IR spectrum, two absorptions at 905 and 940 cm⁻¹ appear due to Cr-O bond, together with a Cr-F band at 640 cm⁻¹. The NMR data are in agreement with the EBAFC structure. Moreover, the ¹⁹F NMR of this reagent shows a typical absorption at -132.09 ppm. The EBAFC is soluble in



Scheme 1.

solvents such as acetonitrile, DMF, acetone and chloroform, is less soluble in dichloromethane, dioxane and THF and not soluble in *n*-hexane.

The heterogeneous reaction mixtures are thoroughly stirred, for 22-59 min, at room temperature. During the reaction, the color of reagent changes from orange to brown, providing visual evidence for ascertaining the progress of the oxidation. The corresponding products, aldehyde or ketone (**2**) can be easily isolated by a simple filtration and evaporation of the solvent. In comparison to reported oxidants, the EBAFC adsorbed on wet SiO₂ (50% w/w) makes available relatively

higher yields of products, in lower molar ratio and shorter reaction times (Table 1).

Oxidations may occur using only EBAFC, in the absence of wet SiO₂, but considerable improvement of both yields and reaction times are obtained in the presence of this adsorbent. The wet SiO₂ (solid-phase) may act as a reaction medium, providing an effective heterogeneous surface for the oxidation and at the same time making an easy work-up.

Relatively higher conversions of primary and secondary alcohols (**1**) to their corresponding aldehydes and ketones (**2**) are obtained *via* EBAFC adsorbed on wet SiO₂, (Table 1). For example, yields obtained from the oxidation of 4-chlorobenzyl alcohol 95 %, benzyl alcohol 92% (reported 90%) [2, 3], and cyclohexanol 91% (reported 89%) [2, 3] are obtained. Neither carboxylic acids nor other by-products are formed upon oxidation of alcohols using this reagent. Moreover, this reagent does not oxidize a large variety of other substrates, including benzylaldehyde, acetophenone, diphenyl sulfide, thiophenol,

Table 1. Oxidations *via* EBAFC/silica gel, EBAFC, PFC^a and IQFC^b.

Alcohol	Product ^c	Molar Ratio (ROH/Ox)	EBAFC/silica gel		EBAFC		PFC		IQFC	
			Time (min)	Yield ^d (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1a , Benzyl Alcohol,	2a , Benzaldehyde	1:1.25	25	92	50	75	45	90	60	91
1b , <i>p</i> -Chlorobenzyl alcohol	2b , <i>p</i> -Chlorobenzaldehyde	1:1.25	44	95	75	73	-	-	-	NR
1c , <i>p</i> -Methoxybenzyl alcohol	2c , <i>p</i> -Methoxybenzaldehyde	1:1.25	32	90	45	62	50	90	-	NR
1d , <i>p</i> -Methylbenzyl alcohol	2d , <i>p</i> -Methylbenzaldehyde	1:1.25	22	93	80	75	-	-	-	NR
1e , <i>p</i> -Nitrobenzyl alcohol	2e , <i>p</i> -Nitrobenzaldehyde	1:1.25	43	85	70	45	-	-	-	NR
1f , <i>p</i> -Bromobenzyl alcohol	2f , <i>p</i> -Bromobenzaldehyde	1:1.25	35	87	60	70	-	-	-	NR
1g , Cyclohexanol	2g , Cyclohexanone	1:1.25 (1:1.5) ^a	40	91	80	65	210	89	240	90
1h , Cyclopentanol	2h , Cyclopentanone	1:1.25	33	89	85	67	-	-	-	NR
1i , 1-Phenyl ethanol	2i , Acetophenone	1:1.25	50	89	150	79	-	-	-	NR
1j , 3-Phenyl-2-propen-1-ol	2j , 3-Phenyl-2-propenal	1:1.25 (1:1.5) ^a	55	91	115	85	-	-	300	70
1k , Benzoin	2k , Benzyl	1:1.25	42	86	100	65	150	98	180	98
1m , 1-Heptanol	2m , Heptanal	1:1.25	59	88	300	50	60	84	-	-

^a Pyridinium fluorochromate used as the oxidant [2, 3].

^b Isoquinolinium fluorochromate used as the oxidant [8].

^c Products were characterized by comparison with authentic samples (NMR, IR, TLC and mp/bp measurement).

3,5-dimethoxyphenol, 2-benzyl-3,4-dihydro-2H-pyran, benzyloxytrimethylsilane, N-methyl-2-phenylthioacetamide, 1-phenyl-ethanone oxime and sodium 2-hydroxyimino-malonate. Groups such as methoxy and methyl attached on the phenyl ring are inert to this oxidant. Thus, this oxidant can be used for the synthesis of highly functionalized molecules.

It has been found that this reagent has many advantages in comparison to similar oxidizing reagents, such as easier preparations, application to pH sensitive molecules, good selectivity in the reaction, high yields, short reaction times, lower oxidant/substrate ratio, lower solvent requirement, and simple work-up.

Conclusion

A new reagent, N-ethylbenzylammonium fluorochromate (VI) adsorbed on silica gel, EBAFC/wet SiO₂, selectively oxidizes primary and secondary alcohols to the corresponding aldehydes and ketones. Many functional groups are inert towards this reagent, including aldehydes, ketones, oximes, thiols, sulfides, phenols, pyrans, trimethylsilanes, malonates, and thioacetamides. It proves to be of low cost, readily available, easy synthesis and simple work-up. Its advantages include higher yields, shorter reaction times, better selectivity, application to pH sensitive molecules, performing in a lower oxidant/substrate ratio, and with lower solvent requirement.

Experimental Materials and Methods

N-ethylbenzylamine and chromium trioxide (CrO₃) were obtained from Fluka (Buchs, Switzerland). Melting points were measured on an Electro thermal 9100 apparatus. Elemental analyses were performed for C, H, and N using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Bomen FT-IR-MB100 Spectrometer. ¹H NMR spectrum was recorded using 90 MHz JEOL JNM-EX90A instrument. ¹³C and ¹⁹F NMR spectra were determined on a BRUKER-DRX500 AVANCE instrument.

Synthesis of N-ethylbenzylammonium fluorochromate (VI)

Chromium (VI) oxide (CrO₃; 2g, 0.02 mol) was dissolved in water (5 mL) in a polyethylene beaker and 40% hydrofluoric acid (1.50 mL, 0.03 mol) was added with stirring. After 5 min, the homogenous solution was cooled to 0 °C. N-ethylbenzylamine (3 ml, 0.02 mol) was carefully added over 10 min. The resulting solution was stirred at 0 °C for 30 min. An orange solid was obtained. The crystals were collected on a sintered glass funnel and dried in vacuum (Yield: 4.00 g, 78%; mp 41-42 °C). IR ν_{\max} (KBr) 905, 940, 641 cm⁻¹; ¹H NMR (CDCl₃, 90 MHz) δ 1.34 (3H, t, CH₃), 3.18 (2H, q, CH₂), 4.20 (2H, s, CH₂), 4.99 (2H, s, NH₂), 7.5 (5H, s, -Ph). ¹³C NMR (CDCl₃,

125 MHz) δ 10 (-CH₃), 42 (-CH₂-N), 50 (=C-*CH₂-N-), 128-130 (-Ph). ¹⁹F NMR (CDCl₃, 470 MHz) δ -132.09. Anal. C 42.35%, H 5.49%, N 5.49%, Calcd for C₉H₁₄NCrO₃F, C 42.12%, H 5.35%, N 5.26%.

General procedure for oxidation of alcohols with EBAFC/wet SiO₂

To a stirred suspension of EBAFC/wet SiO₂ (0.5g EBAFC: 0.5g silica gel/4 drops H₂O) in n-hexane (5 mL), a solution of the alcohol in the minimum amount of n-hexane was added drop wise at room temperature, the molar ratio of alcohol to the oxidant being 1:1.25 (Table 1). The progress of the reaction was monitored by TLC (solvent, 5:1, n-hexane/ethyl acetate, v/v). The mixture was diluted with ether (1:1 vol/vol) and was filtered through a short column of silica gel to give a clear solution. The solvent was evaporated and the products were purified by distillation, crystallization and/or column chromatography. Products were characterized by comparison with authentic samples (NMR, IR, TLC and mp/bp measurement). Yields (%) were obtained as isolated product and/or determined *via* NMR analyses (Table 1).

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