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3-Carboxypyridinium trichloroacetatochromate (CPTCAC): as a mild and effective new reagent for the thiols to disulfides

Fatma Aydin[a]* and Recep Ozen[b]

[a]Department of Chemistry, Faculty of Science, Canakkale Onsekiz Mart University, 17020,Canakkale, Turkey

[b]Department of Chemistry, Faculty of Science, Mersin University, 33342, Mersin, Turkey

A new chromium(VI) reagent, 3-carboxypyridinium trichloroacetatochromate (CPTCAC) was prepared by reacting 3-carboxypyridine (nicotinic acid) and trichloroacetic acid with CrO_3 in water. This oxidising agent oxidised the thiols to disulfides selectivily and in very high yields.

Keywords: 3-carboxypyridine, trichloroacetic acid, CrO_3, oxidation, S–S coupling.

Oxidation of organic compounds under nonaqueous and aprotic conditions is an important reaction in synthetic organic chemistry. For this purpose, different Cr (VI) based oxidants are reported in the literature.[1-6] However, some of the reported reagents suffer from disadvantages such as low selectivity, instability, hygroscopicity, long reaction time, difficulty of preparation and need for a large excess of the reagent and work-up. Thus, a mild, a more selective and inexpensive reagent is still in demand.

We now report the oxidising property of a new mild oxidising agent, 3-carboxypyridinium trichloroacetatochromate (CPTCAC). This reagent was prepared by the addition of 3-carboxypyridine to a solution of an equimolar amount of CrO_3 and trichloroacetic acid at 0 °C and obtained in 86 % yield as an orange solid. CPTCAC was stable when kept at room temperature for a long period of time. This oxidising agent is soluble in polar solvent such as water, dimethylformamide, dimethylsulfoxide, acetone, ethylacetate, acetonitrile, but insoluble in dichloromethane, benzene, carbon tetrachloride and ether.

The molar conductance of CPTCAC in water at 25 °C is 143 Ω^{-1} cm^2 mol^{-1}. The acidity of CPTCAC (pH of a 0.01 M solution 1.91) is less than that of PCC, (pH of a 0.01 M solution 1.75)[4] and is approximatly the same acidity as CPCC (pH of 0.01 M solution 2.02).[7]

This reagent can be stored as a solid for long periods without decomposition in dry medium. The structure of CPTCAC was determined by IR spectra and elemental analysis. The amount of chromium (IV) was determined by colorimetric methods using diphenylcarbazide solution.[8] Anal. cal. for $C_8H_6Cl_3CrNO_7$: Cr: 13.45; Calc. 13.41.

Disulfides are useful reagents in organic synthesis. The transformation of thiols to disulfides is important, synthetically as well as biologically.[9] Various reagents for oxidative coupling of thiols to disulfides are described, *e.g.* nitric acid/methylene chloride,[10] 2,6-dicarboxypyridinium-chlorochromate,[11] quinolinium fluorochromate on silica gel,[12] molecular bromine on hydrated silica gel,[13] pyridinium chlorochromate,[14] cobalt(II) and manganese(II) salts of 4-aminobenzoic acid supported on silica gel,[15] ammonium persulfate,[16] trichloronitromethane/NaOEt,[17] bismuth(III) nitrate pentahydrate,[18] CsF-celite,[19] Magtrieve™.[20] However, some of these methods have disadvantages such as requiring strong oxidising agents, strongly acidic or basic media, over-oxidation, use of expensive reagents, long reaction time, low yields of products and acidic work-up. Therefore the introduction of a clean, mild, and efficient method to synthesise aliphatic, aromatic, and heteroaromatic disulfides is still needed.

$$2RSH \xrightarrow[CH_2Cl_2 \quad r.t]{CPTCAC} RSSR$$

Scheme 1

In this paper, we have now used a new reagent CPTCAC utility for the oxidation of thiols to disulfides, under mild reaction conditions (Scheme 1).

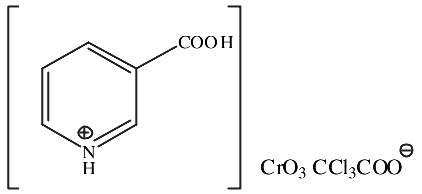
As shown in Table 1, all of thiols reacted efficiently and the corresponding disulfides were isolated in excellent yield.

To sum up, easily prepared new reagent 3-carboxypyridinium trichloroacetatochromate (CPTCAC) is very similar to its companion reagents such as PCC, CPCC in terms of oxidising properties, solubility in different solvents, being and an oxidant which is chrom (VI) based. In addition, like its companion reagents, it is non-hygroscopic and shelf stable. However, the present investigation revealed that CPTCAC has a number of advantages over its companion reagents. First of all, it has lower acidity than the PCC. Furthermore, trichloroacetic acide used for the synthesis of CPTCAC is non-corrosive in comparison to vapour of concentrated hydrochloric acide solutions. In conclusion, the easy work-up, anhydrous reaction condition, the chemoselectivity, the commericial availability and high yields of the new reagent (CPTCAC) makes it attractive for the labscale oxidation the thiols to disulfides.

Experimental

M.p.s were determined on Electrothermal 9100® apparatus. IR spectra were recorded on a Win First Satellite® model spectrophotometer. ^{1}H-NMR spectra were obtained using a 400 MHz Bruker DPX® instrument. Chromium analyses were performed using UV-1601 Shimadzu®.

Preparation of 3-Carboxypyridinium trichloroacetatochromate: A solution of chromium trioxide (10 g, 0.10 mol) in water (10 ml) cooled to 0 °C was added trichloroacetic acid (16.3 g, 10 mol) in a 50 ml glass beaker. The mixture was stirred to give an red-orange solution for 2–3 min. The solution was then cooled in an ice bath (0–5°C) for 5 min and 3-carboxypyridine (12.3 g, 10 mmol) was added portionwise and the mixture was stirred at 0 °C for 1 h. The cold mixture was filtered on a sintered glass funnel and the orange solids were collected. The product was dried *in vacuo* desicator over P_2O_5 to give CPTCAC in 87% yield, m.p. 208–210 °C (dec). IR (KBr pellet) 3145, 1657, 1342, 952, 903, 740, 700 cm^{-1}. Anal. cal. for $C_8H_6Cl_3CrNO_7$: C, 24.86; H, 1.56; Cl, 27.52; N, 3.62. Found: C, 24.82; H, 1.54; Cl, 27.54; N, 3.66.



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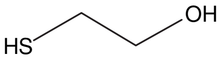
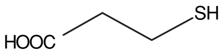
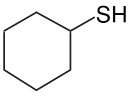
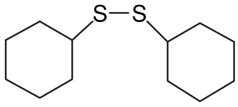
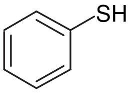
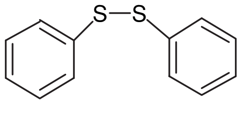
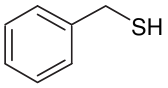
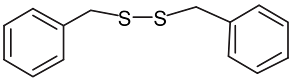
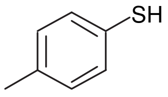
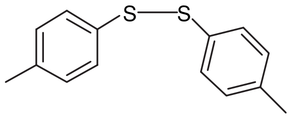
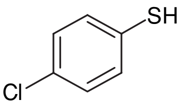
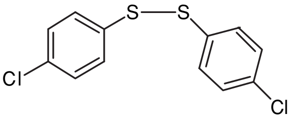
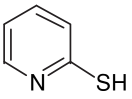
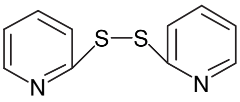
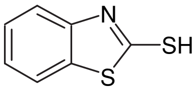
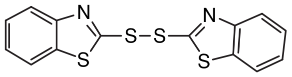
* Correspondent. E-mail: faydin@comu.edu.tr

Table 1 Oxidation of thiols to disulfides with CPTCAC

No	Substrate[a]	Product[b]	Time/min Yield/%	M.p. /°C (Lit)
1	C_4H_9S	$C_4H_9SSC_4H_9$	40/90	Oil[21]
2	$C_8H_{17}SH$	$C_8H_{17}SSC_8H_{17}$	60/87	Oil[22]
3			25/92	Oil[23]
4			20/90	Oil[14]
5			40/88	Oil[24]
6			30/90	59–61 (61)[23]
7			35/87	72–73 (71–72)[20]
8			90/86	43–45 (45–46)[26]
9			10/92	70–72 (72–74)[26]
10			45/90	56–57 (57)[23]
11			60/89	183–185 (183–184)[25]

[a]All the reactions were carried out with equimolar of CPTCAC at room temp. in DCM.

[b]The products were characterised by comparision with authentic samples ^1H NMR, FT-IR and m.p. measurements (except for oil compounds).

General procedure for the conversion of thiols to disulfides by 3-carboxypyridinium trichloroacetatochromate in dichloromethane: A solution of the thiols compounds (Table 1, 10 mmol) in 10 ml of dichloromethane was added to CPTCAC (3.86 g, 10 mmol). The mixture was stirred magnetically at 0 °C temperature until the complete consumption of the substrate. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, 50 ml of water was added to the reaction mixture and extracted with ether (3 × 20 ml). The combined organic layer was dried over $MgSO_4$ and evaporated on a rotary evaporator under reduced pressure. Then the product was chromatographed over silica gel using ethyl acetate–hexane (1:4) as the eluent to separate the product. Evaporation of the solvent gave fairly pure solids which were crystallised; the melting point of solid compounds was checked, the solid and oil compounds were identified by spectral data like IR and ^1H NMR.

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