Monatshefte für Chemie 138, 871–873 (2007)
DOI 10.1007/s00706-007-0685-3
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Ethylenebis(*N*-methylimidazolium) Chlorochromate (*EBMICC*): An Efficient and Selective Reagent for the Oxidation of Thiols to Disulfides

Rahman Hosseinzadeh*, **Mahmood Tajbakhsh, Hamid Khaledi,** and **Keivan Ghodrati**

Department of Chemistry, Mazandaran University, Babolsar, Iran

Received March 19, 2007; accepted (revised) March 30, 2007; published online June 22, 2007

Summary. Ethylenebis(*N*-methylimidazolium) chlorochromate was prepared by addition of *N*-methylimidazole to 1,2-dibromoethane to form the corresponding dibromide salt and subsequent treatment of this salt with CrO_3 in 6 *N* HCl solution. It is a stable yellow-orange solid, which oxidized thiols to the corresponding disulfides at room temperature. Selective oxidation of thiols in the presence of sulfides and hydroxyl groups was also achieved with this reagent.

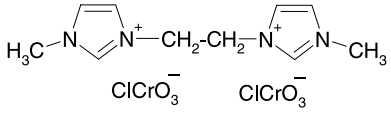
Keywords. Ethylenebis(*N*-methylimidazolium)chlorochromate; Oxidation; Thiols; Sulfides.

Introduction

Most methods to prepare disulfides involve oxidation of thiols. Oxidation of thiols to disulfides without over-oxidation is an important process in organic chemistry and biochemistry, which has been extensively investigated over the years. Disulfide bond formation is important in peptides [1] and bioactive molecules [2]. This conversion has been accomplished using reagents, such as molecular oxygen [3a], metal ions [3b], $Bu_3SnOMe/FeCl_3$ [3c], nitric oxide [3d], halogens [3e–h], sodium perborate [3i], the borohydride exchange resin (BER)-transition metal salt system [3j], a morpholine iodine complex [3k], *PCC* [3l], 2,6-dicarboxylic pyridinium chlorochromate [3m], ammonium persulfate [3n], $KMnO_4/CuSO_4$ [3o], H_2O_2 [3p], solvent free permanganate [3q], *PVP*-N_2O_4 [3r], and the cesium fluoride – Celite – O_2 system [3s]. However, while all these methods can generate the desired products efficiently, many of them have certain limitations, such as instability, the need of an excess amount of the reagent, and poor selectivity to substrate. Therefore the introduction of a clean, mild, and efficient method to synthesize disulfides is still needed.

Results and Discussion

As part of our continuous effort to develop new efficient oxidizing agents [4], we synthesized ethylenebis(*N*-methylimidazolium) chlorochromate (*EBMICC*) and studied its oxidizing properties for thiols.



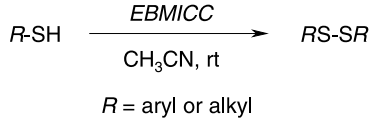
EBMICC

EBMICC is easily and cheaply prepared from *N*-methylimidazole and 1,2-dibromoethane followed by treatment with CrO_3 in the presence of HCl in high yield. It is soluble in *DMF*, acetone, and acetonitrile, and insoluble in methylenechloride, *n*-hexane, and diethyl ether. It shows a *pH* value of 2.6 (0.01 *N* aqueous solution) that attest to its less acidic character

* Corresponding author. E-mail: r.hosseinzadeh@umz.ac.ir

in comparison to *PCC* and *N*-methylpiperidinium chlorochromate (the *pH* of 0.01 *N* solutions of *PCC* and *N*-methylpiperidinium chlorochromate were found to be 1.75 and 1.85 [5]). One more advantage of *EBMICC* is that it is much less hygroscopic and can be used after one year of its preparation without any decomposition, which is not the case with *PCC* and similar Cr(VI) reagents. Thiols can be oxidized to the corresponding disulfides with *EBMICC* in acetonitrile at room temperature (Scheme 1).

The results presented in the Table 1 indicate that aromatic and aliphatic thiols were oxidatively coupled very fast in excellent yields. Heteroaromatic thiols, such as 2-mercaptobenzothiazole and 2-mercaptobenzimidazole were converted to the corresponding disulfide partially (Table 1, entries 13 and 14), and after longer reaction time with a higher molar ratio of reagent no more coupling was observed. Interestingly, 2-hydroxyethylthiol gave only bis(2-hydroxyethyl) disulfide (Table 1, entry 12). This shows that the reagent selectively oxidizes the mercapto group in the presence of a hydroxyl group under the present reaction conditions. Moreover, as shown in Table 1, although *EBMICC* oxidizes thiols very fast it is inert toward sulfides even in refluxing acetonitrile (Table 1, entries 15–18). These results attest to the very high selectivity of this reagent in the oxidation of thiols in the presence of sulfides.



Scheme 1

In order to show the advantages and drawbacks of this reagent over some other oxidants we have compared some of our results with those reported in literature in Table 2. Thus *EBMICC* oxidizes thiophenol very fast at room temperature in excellent yield while other similar reagents take rather long reaction times to dimerize thiophenol.

In conclusion, we showed that *EBMICC* is an efficient, rapid, mild, and inexpensive reagent for the oxidation of thiols to the corresponding disulfides. This reagent oxidizes thiols quntitatively in the presence of sulfides or hydroxyl groups. We consider that our procedure represents a useful addition to the array of procedures for the oxidation of thiols.

Table 1. Coupling of thiols using *EBMICC* in CH_3CN

Entry	Substrate	Product	Yield/%[a,b]	Ref.[c]
1	*Ph*-SH	(*Ph*-S-)$_2$	94	[6a]
2	4-*Me*-*Ph*-SH	(4-*Me*-*Ph*-S-)$_2$	95	[6b]
3	4-Cl-*Ph*-SH	(4-Cl-*Ph*-S-)$_2$	92	[6c]
4	4-Br-*Ph*-SH	(4-Br-*Ph*-S-)$_2$	92	[6d]
5	2-Naphthyl-SH	(2-Naphtyl-S-)$_2$	91	[6d]
6	2-HOOC-Ph-SH	(2-HOOC-Ph-S-)$_2$	91	[6e]
7	*Ph*CH_2-SH	(*Ph*CH_2-S-)$_2$	92	[6d]
8	HOOCCH_2-SH	(HOOCCH_2-S-)$_2$	93	[6f]
9	1-Pentyl-SH	(1-Pentyl-S-)$_2$	90	[3o]
10	1-Octyl-SH	(1-Octyl-S-)$_2$	90	[6g]
11	Cyclohexyl-SH	(Cyclohexyl-S-)$_2$	92	[6d]
12	HOCH_2CH_2-SH	(HOCH_2CH_2-S-)$_2$	91	[6h]
13	2-1,3-Benzodiazole-SH	(2-1,3-Benzodiazole-S-)$_2$	27	[6i]
14	2-1,3-Benzothiazole-SH	(2-1,3-Benzothiazole-S-)$_2$	30	[6j]
15	*Ph*-S-*Me*	–	N.R.[d]	–
16	^{n}*Bu*-S-^{n}*Bu*	–	N.R.[d]	–
17	*Ph*CH_2-S-CH_2*Ph*	–	N.R.[d]	–
18	CH_2CHCH_2-S-CH_2CHCH_2	–	N.R.[d]	–

[a] All the reactions for thiols were completed in less than 5 min
[b] Yields refer to isolated products
[c] All products were identified by comparing melting point, IR, and NMR with those of authentic samples reported in literature
[d] Reactions are carried out in refluxing acetonitrile for 2 h

Table 2. Comparison of *EBMICC* with some of the other reagents for the oxidation of thiophenol

Reagent	Conditions	Time/min (Yield/%)	Ref.
EBMICC	CH_3CN/rt	5 (94)	–
$Bu_3SnOMe/FeCl_3$	CH_3CN/rt	120 (99)	[3c]
PCC	CH_2Cl_2/rt	114 (97)	[3l]
$(NH_4)_2S_2O_8$	Solid state	10 (79)	[3n]
Caro's acid/SiO_2	CH_3CN/20°C	270 (93)	[7]
Piperazinium dichromate	$CHCl_3$/rt	210 (92)	[8]

Experimental

Preparation of Ethylenebis(N-methylimidazolium) Chlorochromate (EBMICC)

A mixture of 4.0 g *N*-methylimidazole (48.7 mmol) and 1.9 cm^3 1,2-dibromoethane (22 mmol) was stirred in 40 cm^3 *DMF* at 120°C for 2 h. After cooling the mixture the white solid formed was filtered off, washed with diethyl ether, and dried under vacuum. Then it was dissolved in 40 cm^3 6 *N* HCl and was slowly added to a stirred solution of 4.4 g CrO_3 (44 mmol) in 40 cm^3 6 *N* HCl. The reaction mixture was cooled to 0°C and the yellow-orange solid formed was collected by filtration, washed with cold H_2O, and dried under vacuum to give 7 g *EBMICC* (69%). Mp: 99–101°C; ^{1}H NMR (300.13 MHz, *DMSO*-d_6): $\delta = 3.75$ (s, 2CH_3), 4.60 (s, 2CH_2), 7.43 (s, 2H-imi), 7.49 (s, 2H-imi), 8.78 (s, 2H, NC*H*N) ppm; ^{13}C NMR (75.48 MHz, *DMSO*-d_6): $\delta = 36.4$ (*C*H_3), 48.9 (*C*H_2), 122.8 (imi-*C*), 124.4 (imi-*C*), 137.6 (N*C*HN) ppm; IR (KBr): 945, 897, 740 cm^{-1}; Anal. calcd for $C_{10}H_{16}Cl_2Cr_2N_4O_6$: C 25.93, H 3.48, Cr 22.45, found: C 25.97, H 3.54, Cr 22.12.

General Procedure for the Oxidation of Thiols with EBMICC

In a round-bottomed flask a solution of 5 mmol thiol in 50 cm^3 MeCN was treated with 5 mmol *EBMICC* and the mixture stirred at room temperature. The progress of the reaction was monitored by GC or TLC. The solvent was evaporated in vacuum and 100 cm^3 diethyl ether were added to the residue. The supernatant was decanted and the insoluble residue was washed with diethyl ether (3×25 cm^3). The ether extracts were concentrated under reduced pressure and the crude product was purified by distillation or by passing through a short column of silica gel.

Acknowledgements

We are thankful to the Mazandaran University Research Council for the partial support of this work.

References

[1] Bodanszky M (1984) Principles of Peptide Synthesis. Springer, Berlin, Chapter 4

[2] Johnson JR, Bruce WF, Dutcher JD (1943) J Am Chem Soc **65**: 2005

[3] a) Liu KT, Tong YC (1978) Synthesis 669; b) Wallace TJ (1996) J Org Chem **31**: 3071; c) Sato T, Otera J, Nozaki H (1990) Tetrahederon Lett **31**: 3591; d) Pryor WA, Church DF, Govindan CK, Crank G (1982) J Org Chem **47**: 156; e) Schaeffer JR, Goodhue CD, Risle HA, Stevens RE (1967) J Org Chem **32**: 392; f) Drabowicz J, Mikolajczyk M (1980) Synthesis 32; g) Ali MH, McDermott M (2002) Tetrahedron Lett **43**: 6271; h) Aida T, Akasaka T, Furukawa N, Oae S (1976) Bull Chem Soc Jpn **49**: 1441; i) McKillop A, Koyuncu D (1990) Tetrahedron Lett **31**: 5007; j) Choi J, Yoon NM (1995) J Org Chem **60**: 3266; k) Ramadas K, Srinivasan N (1996) Synth Commun **26**: 4179; l) Salehi P, Farrokhi A, Gholizadeh M (2001) Synth Commun **31**: 2777; m) Tajbakhsh M, Hosseinzadeh R, Shakoori A (2004) Tetrahedron Lett **45**: 1889; n) Varma RS, Meshram HM, Dahiya R (2000) Synth Commun **30**: 1249; o) Noureldin NA, Caldwell M, Hendry J, Lee DG (1998) Synthesis 1587; p) Evans BJ, Doi JT, Musker WK (1990) J Org Chem **55**: 2337; q) Shaabani A, Lee DG (2001) Tetrahedron Lett **42**: 5833; r) Iranpoor N, Firouzabadi H, Paurali AR (2002) Tetrahedron **58**: 5179; s) Shah AST, Khan MK, Fecker M, Volter W (2003) Tetrahedron Lett **44**: 6789

[4] a) Hosseinzadeh R, Tajbakhsh M, Niaki MY (2002) Tetrahedron Lett **43**: 9413; b) Tajbakhsh M, Hosseinzadeh R, Sadatshahabi M (2005) Synth Commun **35**: 1547; c) Hosseinzadeh R, Tajbakhsh M, Vahedi H (2005) Synlett 2769

[5] Tajbakhsh M, Ghaemi M, Sarabi S, Ghasemzadeh M, Heravi MM (2000) Monatsh Chem **131**: 1213

[6] a) Field L, Lawson JE (1958) J Am Chem Soc **80**: 838; b) Wallace TJ (1964) J Am Chem Soc **86**: 2018; c) Yiannios CN, Karabinos JV (1963) J Org Chem **28**: 3246; d) Raghavan S, Rajender A, Joseph SC, Rasheed MA (2001) Synth Commun **31**: 1477; e) Champman H (1982) Dictionary of Organic Compounds, 5th edn, Vol. II. New York, p 2376; f) Harrison, DC (1927) Biochem J **21**: 1404; g) Sanz R, Aguado R, Pedrosa MR, Arnaiz FJ (2002) Synthesis 856; h) Meshram HM, Bandyopdhyay A, Reddy GS, Yadav JS (2000) Synth Commun **30**: 701; i) Khazaei A, Zolfigol MA, Rostami A (2004) Synthesis 2959; j) Firouzabadi H, Mohadjer D, Entezari-Moghadam M (1988) Bull Chem Soc Jpn **31**: 1217

[7] Movassagh B, Lakouraj MM, Ghodrati K (1999) Synth Commun **29**: 3597

[8] Movassagh B, Lakouraj MM, Ghodrati K (2002) Indian J Chem **41B**: 1293