Note

A Mild Method for the Protection of Aldehydes as Dithioacetals and Dithiolanes Catalyzed by I_2 Generated *in situ* Using $Fe(NO_3)_3.9H_2O/NaI$ Under Heterogeneous Conditions

Amin Rostami,[a] Heidar Ali Alavi Nik,[b] Zahra Toodeh Roosta[b] and Ardeshir Khazaei[b,*]
[a]*Department of Chemistry, Faculty of Science, University of Kurdistan, Sanandaj, 66135, Iran*
[b]*Faculty of Chemistry, Bu-Ali Sina University, Hamedan 6517838683, Iran*

Structurally diverse aromatic aldehydes were thioacetalated in a clean and efficient reaction with ethane-1,2-dithiol and thiophenol based on the use of I_2 generated *in situ* from $Fe(NO_3)_3.9H_2O/NaI$. The reaction occurs in good to high yield in dichloromethane at room temperature and the use of toxic and corrosive molecular iodine is avoided.

Keywords: Aldehydes; Ethane-1,2-dithiol; Thiophenol; $Fe(NO_3)_3.9H_2O/NaI$; *in situ* I_2; Thioacetalization; Dithiolanation.

INTRODUCTION

The protection of the carbonyl functionality as a dithioacetal is a common practice in multistep synthesis of natural[1] and non-natural[2] products due to the group's inherent stability under both acidic and basic conditions. In addition, thioacetals are also utilized as masked acyl anions or masked methylene functions in carbon-carbon bond forming reactions.[3] In the literature there are numerous methods reported for the preparation of thioacetals from carbonyl compounds.[4-10] All of these methods have some drawbacks such as difficulties in work-up, the requirement for an inert atmosphere, and the use of relatively expensive reagents.[4-10] Therefore, there is still a need to develop a simple and efficient method for thioacetalization of aldehydes.

Although molecular iodine is a versatile reagent in organic synthesis,[11] it is highly corrosive and toxic, making its use somewhat unattractive; in order to overcome these disadvantages with molecular iodine, Bailey et al. reported a convenient method for *in situ* generation of I_2 using $CuSO_4/NaI$.[12]

RESULTS AND DISCUSSION

In our ongoing research program to develop new synthetic methodologies for protection and deprotection of organic functional groups,[13] we have developed a simple method for dithioacetalization of various aromatic aldehydes in the presence of I_2 generated *in situ* from $Fe(NO_3)_3.9H_2O/KI$ under mild and heterogeneous conditions (Scheme I).

It should be mentioned that molecular iodine was generated *in situ* by oxidation of NaI using $Fe(NO_3)_3.9H_2O$. We measured the amount of I_2 generated *in situ* in CH_2Cl_2 by the UV-Visible spectrophotometer method (NaI is the limiting reagent). It was found that 0.142 mmol of I_2 is produced for every mmol of NaI.

In the beginning, the thioacetalization of *p*-methylbenzaldehyde with ethane-1,2-dithiol in the presence of various salts and NaI in diethyl ether at room temperature was studied; the results have been summarized in Table 1.

Scheme I

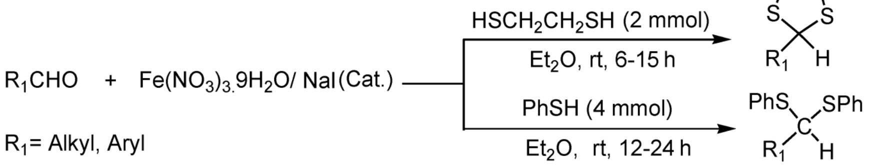


Table 1. The thioacetalization of *p*-methyl benzaldehyde (1 mmol) with ethane-1,2-dithiol (2 mmol) in the presence of various salts (0.1 mmol) and NaI (0.2 mmol) in dichloromethane at room temperature

Entry	Mineral salts	Time (h)	Yield (Conversion)%
1	$Fe(NO_3)_3.9H_2O$	3	80
2	$Fe_2(SO_4)_3.5H_2O$	3	15
3	$FeCl_3.6H_2O$	3	50
4	$ZnNO_3.6H_2O$	3	-
5	$CrCl_3.6H_2O$	3	40
6	$CuCO_3.Cu(OH)_2$	3	
7	$Cu(NO_3)_2.3H_2O$	3	25
8	$CuCl_2.2H_2O$	3	10
9	$CuSO_4.5H_2O$	3	35
10	$Cu(CH_3CO_3)_2.H_2O$	3	-

Table 2. The thioacetalization of *p*-methyl benzaldehyde (1 mmol) with ethane-1,2-dithiol (2 mmol) in the presence of $Fe(NO_3)_3.9H_2O$ (0.1 mmol) and various halide salts (0.2 mmol) in dichloromethane at room temperature

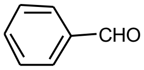
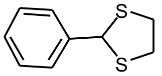
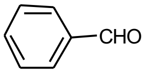
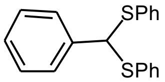
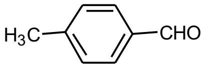
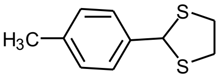
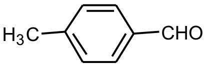
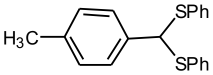
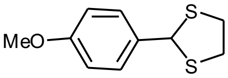
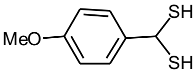
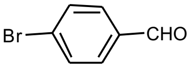
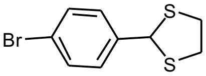
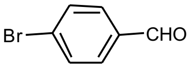
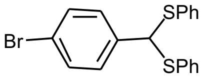
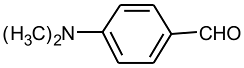
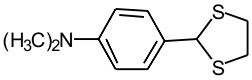
Entry	Halide salts	Time (h)	Yield (Conversion)%
1	KI	2	30
2	NaI	2	70
3	KCl	2	-
4	NaCl	2	10
5	KBr	2	15
6	NaBr	2	50

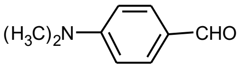
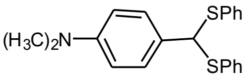
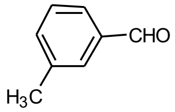
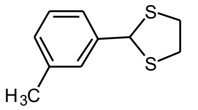
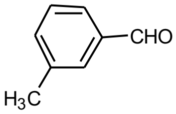
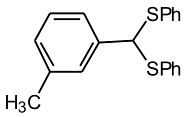
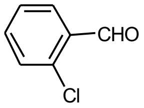
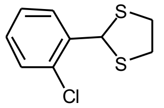
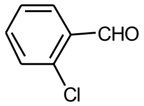
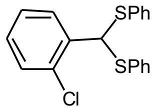
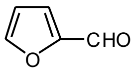
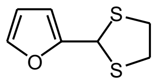
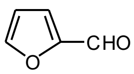
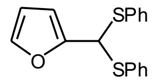
Among the presented salts, $Fe(NO_3)_3.9H_2O$ is the best one (Table 1, Entry 1).

Therefore, we chose it for accomplishing the desired thioacetalization of carbonyl compounds. Then the thioacetalization of *p*-methylbenzaldehyde with ethane-1,2-dithiol in the $Fe(NO_3)_3.9H_2O$ in the presence of various halides in diethyl ether at room temperature was investigated; the results have been summarized in Table 2. The result in Table 2 shows that the system of $Fe(NO_3)_3.9H_2O$/NaI gave the best result for the thioacetalization of *p*-methyl benzaldehyde with ethane-1,2-dithiol.

As shown in Table 3, the protection of various aromatic aldehydes occurred as the corresponding dithioacet-

Table 3. Protection of various aldehydes as the corresponding dithioacetals catalyzed with I_2 generated *in situ* from $Fe(NO_3)_3.9H_2O$/NaI in CH_2Cl_2 at room temperature

Entry	Substrate	Thiol used (mmol)	Time (h)	Product[a]	Yield (%)
1		$HSCH_2CH_2SH$ (2 mmol)	5		80
2		PhSH (4 mmol)	17		95
3		$HSCH_2CH_2SH$ (2 mmol)	7		85
4		PhSH (4 mmol)	16		80
5		$HSCH_2CH_2SH$ (2 mmol)	2.5		90
6		PhSH (4 mmol)	12		82
7		$HSCH_2CH_2SH$ (2 mmol)	8.5		87
8		PhSH (4 mmol)	5		60
9		$HSCH_2CH_2SH$ (2 mmol)	19		80

10		PhSH (4 mmol)	22		86
11		$HSCH_2CH_2SH$ (2 mmol)	8		75
12		PhSH (4 mmol)	12		90
13		$HSCH_2CH_2SH$ (2 mmol)	16		100
14		PhSH (4 mmol)	11		50
15		$HSCH_2CH_2SH$ (2 mmol)	2.5		94
16		PhSH (4 mmol)	11		90

[a] All products were characterized by comparison of their spectral data (^{1}H-NMR; IR) with those of authentic samples

als catalyzed with I_2 generated *in situ* from $Fe(NO_3)_3.9H_2O$/NaI in good yields.

In summary, a mild method for the *in situ* generation of I_2 from inexpensive starting materials, $Fe(NO_3)_3.9H_2O$/NaI, has been developed. The I_2 generated *in situ* has been shown to be an effective promoter for thioacetalization and dithiolanations of aldehydes using ethane-1,2-dithiol and thiophenol under mild, heterogeneous and neutral conditions.

EXPERIMENTAL SECTION

General procedure for thioacetalization and dithiolanation of aldehydes using ethane-1,2-dithiol and thiophenol catalyzed with I_2 generated *in situ* from $Fe(NO_3)_3.9H_2O$/NaI in CH_2Cl_2

The aldehyde (1 mmol) and ethane-1,2-dithiol (2 mmol) or thiophenol (4 mmol) were added to a mixture of $Fe(NO_3)_3.9H_2O$ (0.1 mmol) and NaI (0.2 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for the specified time (Table 3). After completion of the reaction (TLC), the mixture was filtered and the solids were washed with CH_2Cl_2 (5 mL). Powdered $Na_2S_2O_3$ (≈2 g. portionwise) was added, the mixture was stirred for an additional 5 min, and the resultant mixture was filtered. The organic layer was washed with water (25 mL), brine (25 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the reaction mixture was passed through a short column of silica gel using n-hexane as an eluent. Then n-hexane was evaporated to dryness to afford the pure product.

ACKNOWLEDGEMENT

The authors acknowledge to Bu-Ali Sina University Research Councils, University of Kurdistan Research Councils, the Center of Excellence in Development of Chemistry Methods (CEBCM) and National Foundation of Elites (NFE) for support of this work.

Received August 18, 2008.

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