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Molecular oxygen induced free radical oxythiocyanation of styrenes leading to α-oxothiocyanates

Kui Liu[a], Da-Peng Li[a], Shao-Fang Zhou[a], Xiang-Qiang Pan[a,*], Adedamola Shoberu[a], Jian-Ping Zou[a,b,*]

[a] Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering, Soochow University, 199 Renai Street, Suzhou, Jiangsu 215123, China
[b] Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

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ABSTRACT

A facile and efficient protocol of oxythiocyanation of styrenes with ammonium thiocyanate has been developed. The reaction proceeded at room temperature using oxygen as sole oxidant to afford the α-oxothiocyanates via radical pathway in moderate to good yields. This method is straightforward, green and cost-effective, requires no catalyst and additives.

1. Introduction

Difunctionalization of alkenes has become a powerful tool in modern synthetic chemistry.[1] The radical difunctionalization reaction has attracted more attention in recent years because of its mild conditions, high selectivity and convenient work-up.[2] α-Oxothiocyanates find wide application as intermediates in pharmaceuticals, chemicals, and material sciences.[3] One of the most useful method for synthesis of α-oxothiocyanates is the thiocyanation of ketones promoted or catalyzed by I_2, $FeCl_3$, NBS, heteropolyacid and Cu (I,II).[4] Thiocyanation of α-haloketones is an alternative way to α-oxothiocyanates.[5] Nair and Badri groups both reported the synthesis of phenacylthiocyanates via the thiocyanation of styrenes promoted by excess of cerium(IV) ammonium nitrate (CAN) and *cis*-1,4-bis(triphenylphosphonium)-2-buteneperoxodisulfate (BTPBPD) at 0 °C, respectively.[6] In our previous paper, we reported a $Mn(OAc)_3$-mediated difunctionalization reaction involving the acetoxyphosphorylation of styrenes.[7] This encouraged us to further search for more novel difunctionalization reactions. Herein, we report a free radical oxidative oxythiocyanation of styrenes in the presence of molecular oxygen leading to α-oxothiocyanates.

2. Results and discussion

At the initial stage, the reaction of styrene (**1a**, 1 equiv) with ammonium thiocyanate (**2**, 2 equiv) in the presence of air and $Mn(OAc)_3$ was conducted. The result showed that a mixture of oxythiocyanation (**3a**) and dithiocyanation products (**4a**) were obtained even when the amount of $Mn(OAc)_3$ was varied (Table 1, entries 1–4), although the yield of **4a** decreased with decrease in $Mn(OAc)_3$ loading. Thus we concluded that the presence of $Mn(OAc)_3$ favors the formation of **4a**, so the same reaction was performed in the absence of $Mn(OAc)_3$. This time, the yield of **3a** increased to 50%, but **4a** was also isolated in 23% yield (Table 1, entry 5). In order to improve the selectivity of the reaction, the ratio of reactants and the reaction environment were screened. To our delight, as the ratio of styrene/ammonium thiocyanate was changed from 1:2 to 2:1 and the reaction being carried out in an oxygen atmosphere, the ratio of products **3a**/**4a** changed from 50:23 to 79:0 (Table 1, entries 5–8). After screening the solvents, temperature, time and reaction environment (Table 1, entries 9–19), the optimal reaction conditions were determined to be: styrene (**1a**, 2.0 equiv), ammonium thiocyanate (**2**, 1 equiv) in acetic

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* Corresponding authors. Tel.: +86 512 65880336; fax: +86 512 65880335; e-mail address: jpzou@suda.edu.cn (J.-P. Zou).

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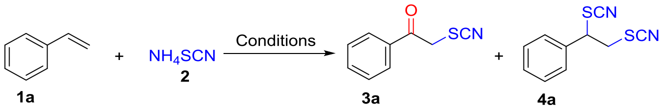
0040-4020/

Table 1
Optimization of the reaction conditions[a]



Entry	Oxidant	Solvent	Temp (°C)	Time (h)	Yield %[b]	
					3a	**4a**
1[c]	$Mn(OAc)_3$ (2 equiv)/air	HOAc	25	8	6	83
2[c]	$Mn(OAc)_3$ (1 equiv)/air	HOAc	25	8	13	78
3[c]	$Mn(OAc)_3$ (0.5 equiv)/air	HOAc	25	8	35	40
4[c]	$Mn(OAc)_3$ (0.1 equiv)/air	HOAc	25	8	47	33
5[c]	Air	HOAc	25	8	50	23
6[d]	Air	HOAc	25	8	63	13
7	Air	HOAc	25	8	73	5
8	O_2	HOAc	25	8	79	0
9	O_2	DMSO	25	8	27	0
10	O_2	CH_3CN	25	8	33	0
11	O_2	THF	25	8	17	0
12	O_2	1,4-Dioxane	25	8	13	0
13	O_2	Toluene	25	8	0	0
14	O_2	CH_2Cl_2	25	8	0	0
15	O_2	HOAc	0	8	15	0
16	O_2	HOAc	50	8	30	0
17	O_2	HOAc	25	4	35	0
18	O_2	HOAc	0	12	60	0
19[e]	No	HOAc	0	12	0	0

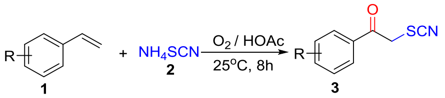
[a] Styrene (2 mmol) and NH_4SCN (1 mmol).
[b] Isolated yield.
[c] Styrene (1 mmol) and NH_4SCN (2 mmol).
[d] Styrene (1 mmol) and NH_4SCN (1 mmol).
[e] The reaction was carried out in argon atmosphere.

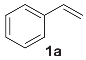
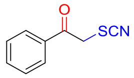
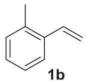
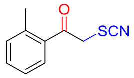
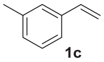
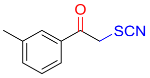
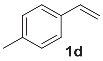
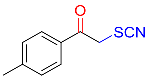
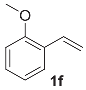
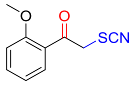
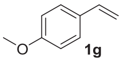
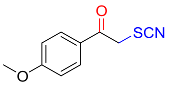
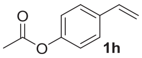
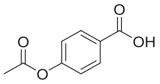
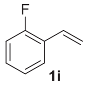
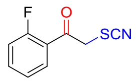
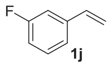
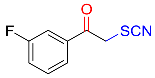
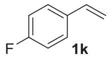
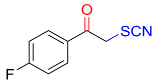
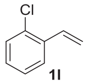
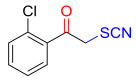
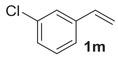
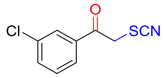
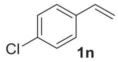
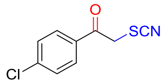
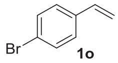
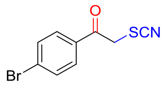
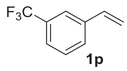
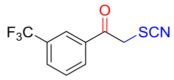
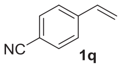
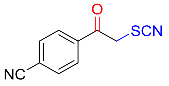
acid at 25 °C in oxygen atmosphere for 8 h to afford the selective oxythiocyanation product (**3a**) in 79% yield (Table 1, entry 8).

Subsequently, the above optimal reaction conditions were applied to different styrene derivatives. We found that styrenes bearing electron-donating groups such as methyl on the phenyl ring gave the expected oxythiocyanation product **3** in good yields (Table 2, entries 2–4). However, methoxy substituted styrenes (**1f** and **1g**) did not react with ammonium thiocyanate while 4-acetoxystyrene (**1h**) was oxidized to 4-acetoxybenzoic acid (**3h**), the reason for these results remains unknown (Table 2, entries 5–7). On the other hand, the reaction of *para*-halogenated (F, Cl and Br) styrenes gave the products in slightly lower yields (57–66%, Table 2, entries 10, 13 and 14), while the *ortho* and *meta*-fluorinated styrenes afforded the products in even much lower yields (28–30%, Table 2, entries 8 and 9). It is noteworthy that styrenes bearing electron-withdrawing groups such as CF_3 gave the oxythiocyanation product **3p** in 16% yield (Table 2, entry15), while CN and NO_2 derivatives did not react at all (Table 2, entries 16–17). These results showed that the electron-withdrawing groups on the phenyl ring suppressed the reaction.

To determine the effect of α- or β-substituents of styrene on the reaction, CH_3 and Br substituted styrenes were employed (Scheme 1). No reactions were observed with α- and β-methylstyrenes (**1s**, **1t**) and β-bromostyrene (**1v**), although α-bromostyrene (**1u**) gave the oxythiocyanation product **3a**. **1t** or **1v** bearing β-CH_3 or β-Br group, which impeding the thiocyano radical attack make the reaction not to go. While **1u** bearing α-Br group leading to form **3a** can be rationalized on the premise that the Br• radical left during the course of the reaction, however, **1s** with α-CH_3 group is unable to CH_3• radical left, thus leading to no reaction. Finally, non-conjugated terminal alkenes (**1w**–**1x**) were investigated but no reactions were observed. This might arise from both the low electron density of the unconjugated C=C double bond and the formed intermediate carbon radical instable. This revealed that conjugated

Table 2
Reactions of styrenes (**1**) with ammonium thiocyanate (**2**)[a]



Entry	Styrene	Product	Yield(%)[b]
1	 1a		**3a** (79)
2	 1b		**3b** (78)
3	 1c		**3c** (75)
4	 1d		**3d** (80)
5	 1f		**3f** N.D.[c]
6	 1g		**3g** N.D.[c]
7	 1h		**3h** (30)
8[d]	 1i		**3i** (28)
9[d]	 1j		**3j** (30)
10[d]	 1k		**3k** (57)
11[d]	 1l		**3l** (68)
12[d]	 1m		**3m** (42)
13[d]	 1n		**3n** (66)
14[d]	 1o		**3o** (58)
15[e]	 1p		**3p** (16)
16[e]	 1q		**3q** N.D[c]