Simple and quick preparation of α-thiocyanate ketones in hydroalcoholic media. Access to 5-aryl-2-imino-1,3-oxathiolanes

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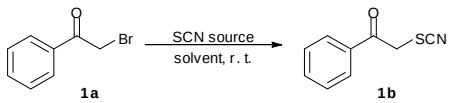
A simple preparation on gram-scale of thiocyanate derivatives *via* nucleophilic substitution of halogenated compounds with SCN salts at high substrate concentrations in a few minutes and excellent yields was successfully accomplished in hydroalcoholic media. The obtained compounds were employed for the efficient synthesis of valuable 5-aryl-2-imino-1,3-oxathiolane derivatives (a one-pot approach is also presented).

In the last few years, sustainable processes are highly demanded in the chemical industry.[1] The "process efficiency" concept is not only related to a high chemical yield, but also to the minimised use of large amounts of harmful organic solvents and production of chemical waste.[2] The choice of an appropriate solvent is not a simple issue.[3-5] From an environmental point of view, aqueous solvents are often an attractive option.[6,7] Consequently a number of organic processes are designed to be carried out either in pure water or in aqueous mixtures.[8,9]

Thiocyanate compounds have attracted great attention as interesting intermediates due to its easy transformation into highly valuable molecules applied to both organosulfur and heterocyclic chemistry. These compounds possess a broad range of bioactivities and applications as anticancer agents, insecticides, antiasthmatic drugs, DNA topoisomerase inhibitors, etc.[10-13] Several routes to prepare alkyl thiocyanate derivatives have been reported including the oxidative thiocyanation of silyl enol ethers with hypervalent iodine-lead(II) thiocyanate reagents[10] and S_N2 reactions using task-specific ionic liquids containing SCN as counterion[11,12] or in organic solvents employing KSCN[14,15] or TMSNCS.[16] Also the α-thiocyanation of ketones using I_2[17] or $FeCl_3$[18] with NH_4SCN or the transformation of thiols employing a $Ph_3P/Br_2/NH_4SCN$ mixture[19] or alkenes with CAN/NH_4SCN[20] have been shown. Finally, the formation of β-hydroxy thiocyanates *via* oxirane ring-opening with NH_4SCN has been described.[21] In most cases, several reagents, organic solvents and high temperatures were employed, and therefore purification by chromatography was necessary. This is in contrast with the optimum conditions to synthesise these compounds since the isomerisation thiocyanate-isothiocyanate can occur in solution at temperatures above 50ºC and/or acidic conditions.[10,16,22] For these reasons, the development of new procedures for the easy and rapid synthesis of thiocyanate derivatives in high yields is required.

Herein we report our efforts in the preparation of versatile thiocyanate compounds in aqueous mixtures at high substrate concentrations and further conversion into the interesting heterocyclic 2-imino-1,3-oxathiolane system employing mild reaction conditions and cheap reagents.

Table 1. Optimisation of the model reaction[a]



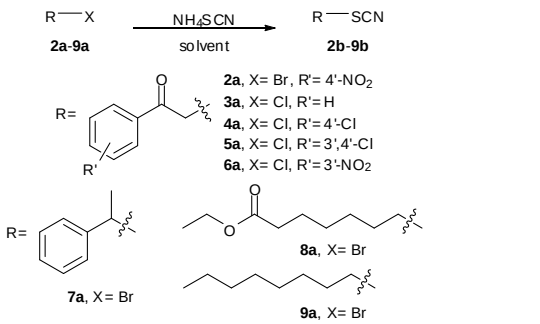
entry	solvent	time (min)	SCN source	yield (%)[b]
1	MeCN	4	NH_4SCN	95
2	MeOH	4	NH_4SCN	90
3	MeOH/H_2O 1:1	10	NH_4SCN	94
4	MeOH	25	KSCN	87
5	MeOH/H_2O 1:1	20	KSCN	68
6	EtOH	3	NH_4SCN	93
7	EtOH/H_2O 1:1	8	NH_4SCN	96
8	^{i}PrOH	3	NH_4SCN	96
9	^{i}PrOH/H_2O 1:1	3	NH_4SCN	96

[a] Substrate concentration: 1.25 M. For reaction conditions, see ESI. [b] Isolated yields.

In a first set of experiments, we carried out the reactions using α-bromoacetophenone (**1a**) as the model substrate at a very high substrate concentration and room temperature (Table 1). MeCN and MeOH were chosen as solvents for the first approach since they could solubilise the SCN salt (entries 1 and 2). The reactions took place homogeneously and were accomplished very quick but a tedious and inconvenient work-up was necessary: evaporation of the water-miscible solvent at low temperature to avoid the isomerisation of the thiocyanate group, redisolution of the crude reaction in a suitable solvent (for instance, CH_2Cl_2), wash with water several times to eliminate the remaining salts, and reevaporation of the organic solvent at low temperature. Bearing this in mind, we speculated that whether the reaction took place heterogeneously in an aqueous mixture and the desired product would precipitate, a simpler and more effective work-up could be applied. In this way, when a MeOH/H_2O 1:1 (v v^{-1}) mixture was employed (entry 3), a solid was quickly formed, then filtered off and washed with water, obtaining to our delight an excellent yield of the pure desired product **1b**. Regarding to the SCN source, the ammonium salt provided shorter reaction times as compared with the potassium one (entries 4 and 5), and therefore was chosen for the subsequent experiments. We extended this procedure to other alcohols such as EtOH and 2-propanol, these reactions were either homogeneous (entries 6 and 8) or heterogeneous (entries 7 and 9). For the homogenous one, we modified the work-up of the reactions. Once the process was complete, water (five-fold

volume) was added to the crude, precipitating the final compound with very high yields. As can be noticed, water/organic solvent combinations also afforded excellent yields in a very short time.

Table 2. S_N2 reaction with different types of alkyl halides (**2a-9a**)[a]



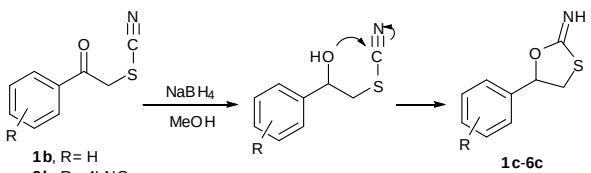
entry[a]	substrate	product	time	T (ºC)	solvent	yield %[b] (conv.)[c]
1	**2a**	**2b**	4 min	r. t.	^{i}PrOH/H_2O 1:1	97
2	**3a**	**1b**	24 h	r. t.	^{i}PrOH/H_2O 1:1	82
3	**4a**	**4b**	27 h	r. t.	^{i}PrOH/H_2O 1:1	96
4	**5a**	**5b**	27 h	r. t.	^{i}PrOH/H_2O 1:1	95
5	**6a**	**6b**	25 h	r. t.	^{i}PrOH/H_2O 1:1	94
6	**7a**	**7b**	5 h	r. t.	^{i}PrOH	16[d] (65)
7	**8a**	**8b**	3.3 h	50	EtOH	95
8[e]	**9a**	**9b**	3 h	50	^{i}PrOH/H_2O 1:1	30[d] (88)

[a] Substrate concentration: 1.25 M. For reaction conditions, see ESI. [b] Isolated yields. [c] Conversions calculated by ^{1}H-NMR. [d] After *flash* chromatography on silica gel. [e] Substrate concentration: 0.26 M

Due to the simplicity of the reaction conditions and the excellent yields obtained when using the mixture ^{i}PrOH/H_2O, we tested it as medium with different alkyl halides **2a-9a** (Table 2). From the results obtained, several interesting features can be highlighted. An important reactivity difference was noticed depending on the halide (compare Table 1, entry 9 with Table 2, entries 1-5) since the reaction with α-bromo ketones **1a-2a** took a few minutes while several hours for α-chloro derivatives **3a-6a** although excellent yields were also obtained. This fact can be explained due to the better ability of Br over Cl as leaving group. Such a big difference makes this method suitable to chemoselectively substitute bromide rather than chloride by careful control of the SCN equivalents and the reaction time. It is important to remark that these reactions were performed on gram-scale, showing the robustness of this methodology. On the other hand, it was noteworthy the different reactivity of activated substrates such α-carbonyl or benzylic halides (**2a-7a**, entries 1-6) in contrast to the non-activated ones (**8a-9a**, entries 7 and 8). In the case of compound **7a**, the solvent used was ^{i}PrOH due to the fact that in the aqueous solution a complex mixture of products was obtained. For bromides **8a** and **9a**, no conversions were detected even after long reaction time when reactions were performed at room temperature, but good to excellent conversions were reached at 50ºC. To synthesise **8b**, ethanol was employed as solvent to avoid the transesterification reaction. The final product appeared as a second phase which could easily be separated as the pure derivative. When *flash* chromatography was used to isolate the final compounds **7b** and **9b** (entries 6 and 8), yields substantially dropped emphasising the relevance of avoiding this separation technique.

With the aim to demonstrate the applicability of this class of compounds we envisaged the possibility of synthesising several 2-imino-1,3-oxathiolane derivatives starting from α-thiocyanate ketones **1b-6b**. There are only a few reports concerning the synthesis of this valuable motif, either by [4+1] cycloaddition reactions employing harsh conditions (100ºC, sealed tube) in argon atmosphere[23] or by Cu(I)-catalysed coupling of *o*-iodophenols and aryl isothiocyanates under nitrogen atmosphere at 80ºC.[24] The 2-imino-1,3-oxathiolane core is present in compounds with potential bioactivities.[23,25] With this in mind, we designed a strategy where by simple reduction of the carbonyl moiety plus further addition of a suitable base and/or adjuvant such as crown ether or phase transfer catalyst,[21] it would be possible to obtain the desired heterocycle. Thus, the standard reduction of **1b** with $NaBH_4$ in MeOH was assayed (Table 3, entry 1). After three minutes, we were pleased to find out that the formed product was not the expected hydroxy thiocyanate intermediate but the 2-imino-1,3-oxathiolane derivative **1c**. This finding may be rationalised by considering the high pH (~9, see ESI) due to the presence of hydride and methoxide species which deprotonate the OH group of the hydroxy thiocyanate intermediate. Those deprotonated species could act as suitable bases to catalyse the cyclisation step. Likewise, this procedure was successfully extended to other similar substrates obtaining the desired products **2c-6c** with high isolated yields in three minutes (entries 2-5).

Table 3. Preparation of 5-aryl-2-imino-1,3-oxathiolanes **1c-6c**[a]



1b, R= H
2b, R= 4'-NO2
4b, R= 4'-Cl
5b, R= 3',4'-Cl
6b, R= 3'-NO2

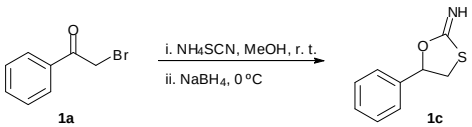
entry	substrate	product	time (min)	yield (%)[b]
1	**1b**	**1c**	3	95
2	**2b**	**2c**	3	71
3	**4b**	**4c**	3	84
4	**5b**	**5c**	3	90
5	**6b**	**6c**	3	95

[a] For reaction conditions, see ESI. [b] Isolated yields.

In order to corroborate the proposed reaction pathway, we followed the formation of the desired heterocycle **1c** through ^{1}H-NMR. Thus, the α-thiocyanate ketone **1b** was dissolved in d_4-MeOH and the corresponding amount of $NaBH_4$ was added in the NMR tube, but unfortunately we were not able to detect any intermediate since the reaction proceeded extremely fast. We employed instead a mixture of d_8-THF:d_4-MeOH 90:10% v v^{-1} to decelerate the process, thus detecting the hydroxy thiocyanate derivative. These results are in agreement with the accepted mechanism for the epoxide-thiirane conversion.[21,26-28]

Encouraged by these results and since the S_N2 reaction and

the subsequent reduction/cyclisation process occurred under similar conditions, a one-pot three-step procedure starting from the α-bromo ketone **1a** to obtain 2-imino-5-phenyl-1,3-oxathiolane **1c** on gram-scale was carried out as depicted in Scheme 1. We were satisfied to find out that this process smoothly proceeded, furnishing the desired product in 88% overall yield in a few minutes.



1a **1c**

Scheme 1. One-pot synthesis of 2-imino-5-phenyl-1,3-oxathiolane from α-bromoacetophenone.

In summary, it has been developed an efficient protocol to easily obtain in hydroalcoholic media valuable α-thiocyanate ketones on gram-scale with excellent yields at high substrate concentrations and very short reaction times. On the other hand, it has been demonstrated that in a one-pot three-step procedure was possible to efficiently access to the promising 2-imino-1,3-oxathiolane core using readily available starting materials and inexpensive reagents (NH_4SCN, $NaBH_4$) producing a minimal amount of waste with high atom economy.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [General experimental procedures as well as compound characterisation of **1c**, **2c**, **4c**, **5c**, and **6c** are described]. See DOI: 10.1039/b000000x/

‡ Compounds **1b**,[10,18] **2b**,[13,29] **4b**,[20,29] **5b**,[29] **6b**,[30,31] **7b**,[16,32] **8b**[33] and **9b**[34] have previously been described and their physical properties were in agreement with those reported.

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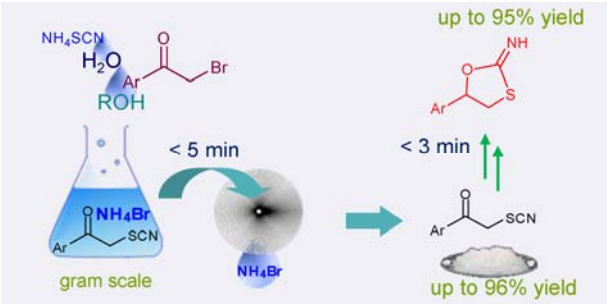
Graphical Contents Entry



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