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COMMUNICATION

Oxygen–sulfur rearrangement in the reaction of thiocarbamate imidazolium ylide with arylaldehyde†

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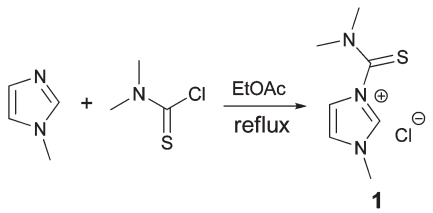
The nucleophilic addition of thiocarbamate imidazolium ylide to aldehyde triggered sequential intramolecular *N* to *O* migration of thiocarbonyl amide group and reversible oxygen–sulfur rearrangement to afford 2-imidazolium alkylcarbamothioate. The *ortho* group on phenyl of aldehyde strongly affects the balance of the *O*- to *S*-rearrangement.

The rearrangement of *O*-aryl or *O*-alkyl thiocarbamates into their corresponding *S*-isomers is a practical way for the preparation of thiophenols or thiols from phenols or alcohols. Among many reactions belonging to this group, the O_{Ar} to S_{Ar} migration in aryl thiocarbamates which is commonly referred to as the Newman–Kwart Rearrangement (NKR) has been extensively studied.[1] Due to the importance of alkyl thiocarbamates[2] in its applications in medicine[3] and pesticide syntheses,[4] the chemistry of intermolecular or intramolecular rearrangement of *O*-alkyl thiocarbamates has also been an important research topic.[5] However, achieving these transformations often requires harsh thermal conditions,[6] special catalysts,[7] photochemical activation,[8] or existence of special groups on the substrate structure.[9]

In conjunction with the project on the study of functionalized imidazolium salts ongoing in our laboratory, some of which were known as ionic liquids,[10] we were interested in discovering whether some special chemical properties could be exhibited when thiocarbonyl was introduced to their molecular structure as a functional group, and the chemistry of *N*-thiocarbonyl imidazolium salts was the focus of our study. To the best of our knowledge, no prior reports of these compounds could be found in the literature and only a few mentioned that thiocarbonyl imidazolide was used as a protective group for alcohols.[11]

Firstly, 1-methylimidazole was allowed to react with dimethylthiocarbamate chloride to prepare *N*-thiocarbamate imidazolium salt **1** as light yellow crystals (Scheme 1). It is known that imidazolium salts easily lose a proton at the 2-position.[12]



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Scheme 1 Preparation of *N*-thiocarbamate imidazolium salt **1**.

Previous literature showed that an *N*-aroyl imidazolium ylide[13] or *N*-carbamate imidazolium ylide[14] can be generated *in situ* by treating the corresponding imidazolium salts with base, which subsequently can be trapped by electrophiles to afford 2-substituted imidazoles, although the reactions for *N*-aroyl imidazolium ylide are not easy to control and for *N*-carbamate imidazolium ylide, a carbamate group of small size is needed.

We assumed that salt **1** would be deprotonated in the presence of an amine base to form *N*-thiocarbamate imidazolium ylide which could be trapped by electrophile benzaldehyde (**2a**), producing 2-substituted-1-benzylimidazole. The initial experiment of this project was carried out in DMF at room temperature. After the reaction, the only product was isolated and recrystallized.

X-ray diffraction analysis[15] revealed that its structure (**3a**) contains a carbonyl group instead of a thiocarbonyl group, indicating that oxygen–sulfur interchange has occurred at some stage during the process (Scheme 2).

Scheme 3 shows the presumed reaction process which includes deprotonation of imidazolium salt **1** to generate the *N*-thiocarbamate imidazolium ylide, nucleophilic addition to benzaldehyde to afford a zwitterionic intermediate, intramolecular nucleophilic attack on the thiocarbonyl to form *O*-(imidazolium)-(phenyl) methyl thiocarbamate, and the final oxygen–sulfur rearrangement.

To study the influence of conditions on this new reaction, initially, the model reaction was carried out in different solvents (Table 1). We found that the transformation was accelerated in polar aprotic solvents. In the presence of Et_3N and using DMF as solvent, an isolated yield of 95% was obtained (entry 3). DMSO and acetonitrile also appeared to be good solvents (entries 1 and 2), but the protic solvent methanol was not

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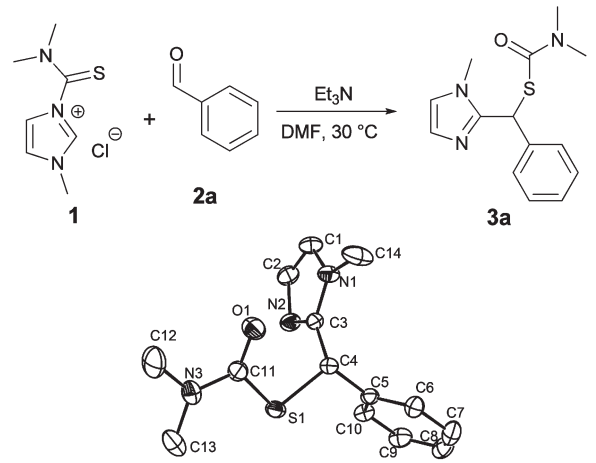
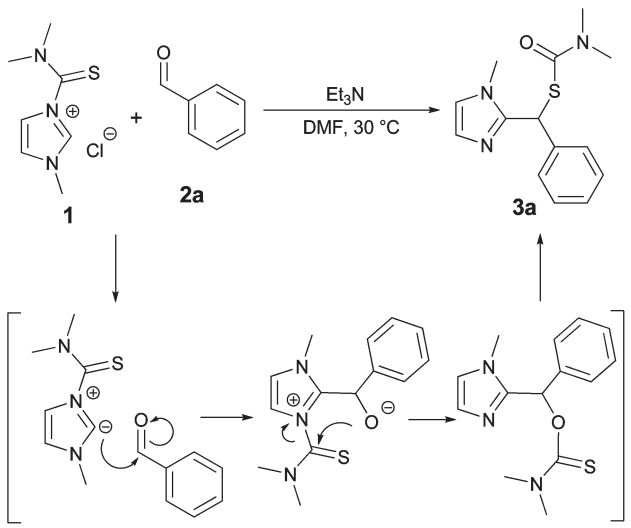
†Electronic supplementary information (ESI) available: Experimental detail for the reaction of imidazolium salt with arylaldehydes; characterization data including ^{1}H NMR spectra, ^{13}C NMR spectra, HRMS, and X-ray crystallographic data. CCDC 880883. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26520f



Scheme 2 Reaction of *N*-thiocarbamate imidazolium salt **1** with benzaldehyde **2a** and the ORTEP illustration for the product **3a** (hydrogen atoms were omitted for clarity).



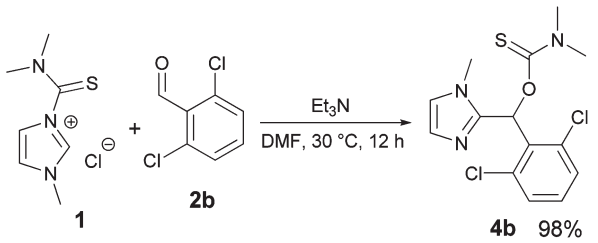
Scheme 3 Proposed mechanism.

Table 1 Reaction of imidazolium salt **1** with benzaldehyde **2a**[a]

Entry	Solvent	Base	Yield[b] (%)
1	DMSO	Et_3N	91
2	MeCN	Et_3N	88
3	**DMF**	**Et_3N**	**95**
4	THF	Et_3N	26
5	MeOH	Et_3N	57
6	Dioxane	Et_3N	61
7	DMF	Cs_2CO_3	84
8	DMF	NaOH	83
9	DMF	KOAc	29
10	DMF	Et_2NH	76
11	DMF	Pyridine	Trace

[a] Imidazolium salt (**1**, 5.0 mmol), benzaldehyde (**2a**, 5.0 mmol), base (6.0 mmol), solvent (2.0 mL), reactions were carried out at 30 °C for 12 h. [b] Isolated yield.

efficient (entry 5). Solvent effects have proved that this reaction may proceed *via* an ionic-type process.



Scheme 4 Reaction of thiocarbamate imidazolium ylide **1** with 2,6-dichlorobenzaldehyde **2b**.

Although the widely used Et_3N was successful for deprotonation of the imidazolium salt **1** to form carbamothioate, various other bases were also tested. High yields of product were also achieved when using strong inorganic bases such as Cs_2CO_3 and NaOH (Table 1, entries 7 and 8). However, in the presence of a weak base such as KOAc, the reaction proceeded extremely slowly (Table 1, entry 9) and the use of pyridine led to nearly no product (Table 1, entry 11).

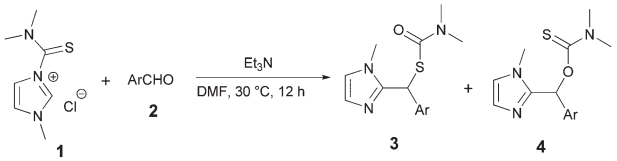
To further extend the scope of this protocol, the thiocarbamate imidazolium ylide was allowed to react with other substituted arylaldehydes. To our surprise, treatment of 2,6-dichlorobenzaldehyde **2b** with the imidazolium salt **1** at room temperature gave the corresponding *O*-alkyl thiocarbamate **4b**[16] in quantitative yield instead of the rearranged product carbamothioate **3b** (Scheme 4). This means the *O*–*S* exchange had not happened for this substrate at the standard reaction conditions.

Based on this interesting finding, we then decided to subject a wide range of arylaldehydes to these reaction conditions to study the substituent effect in detail. The reactions were carried out under standard conditions and the results are illustrated in Table 2.

Most of these aryl aldehydes tested here exhibited high reaction activities (>80% yield) at room temperature but the selectivity of rearrangement product was dependent on the structure of the aldehyde. Firstly, all the aryl aldehydes with electron-donating substituent on the phenyl ring (**2c**–**2h**) gave complete rearrangement products (**3**) which were determined by ^1H NMR, whether the substituent group was on the *ortho*, *meta*, or *para* position. Other electron-rich aryl aldehydes such as 1-naphthyl aldehyde **2u** and 2-fural aldehyde **2v** also led to the corresponding carbamothioates **3**. However, the product distribution for electron-withdrawing aldehydes was unpredictable. 2-Pyridinecarboxaldehyde **2w** and paraformaldehyde **2x** afforded only *O*-thiocarbamates **4**. For other aryl aldehydes it seems that the presence of electron-withdrawing groups on the *meta*, or *para* position (**2j**, **2k**, **2m**, **2n**, **2p**, **2q**, **2s**, **2t**) did not influence the *O* to *S* rearrangement, but the treatment of *ortho*-substituted aromatic aldehydes **2i**, **2l** and **2r** with imidazolium ylide **1** resulted in the formation of a mixture of carbamothioates **3** and their structural isomers, non-rearranged *O*-alkyl partners **4**. The only exception is the reaction of 2-fluorobenzaldehyde **2o**, which only gave rearranged product **3o**.

These results indicate that this thermal *O* to *S* rearrangement is very sensitive to the electron effects as well as the steric hindrance of the substituent on the phenyl ring. This phenomenon is consistent with the widely accepted mechanism for NKR-like reactions stating that the *O* to *S* rearrangement proceeds *via* a

Table 2 Reaction of imidazolium salt **1** with arylaldehyde at room temperature[a]



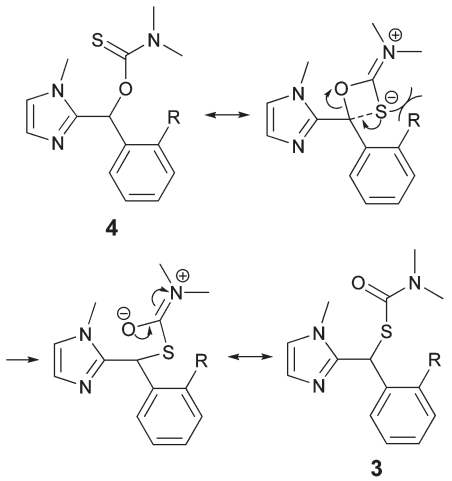
Entry	Ar (**2**)	**3** : **4**[b]	Total yield[c] (%)
1	2-MeC_6H_4 (**2c**)	>20 : 1	80
2	3-MeC_6H_4 (**2d**)	>20 : 1	89
3	4-MeC_6H_4 (**2e**)	>20 : 1	86
4	2-$MeOC_6H_4$ (**2f**)	>20 : 1	76
5	3-$MeOC_6H_4$ (**2g**)	>20 : 1	91
6	4-$MeOC_6H_4$ (**2h**)	>20 : 1	48
7	2-ClC_6H_4 (**2i**)	1 : 1	94
8	3-ClC_6H_4 (**2j**)	>20 : 1	94
9	4-ClC_6H_4 (**2k**)	>20 : 1	98
10	2-BrC_6H_4 (**2l**)	1.5 : 1	84
11	3-BrC_6H_4 (**2m**)	>20 : 1	91
12	4-BrC_6H_4 (**2n**)	>20 : 1	90
13	2-FC_6H_4 (**2o**)	>20 : 1	88
14	3-FC_6H_4 (**2p**)	>20 : 1	89
15	4-FC_6H_4 (**2q**)	>20 : 1	85
16	2-$NO_2C_6H_4$ (**2r**)	1 : 6	89
17	3-$NO_2C_6H_4$ (**2s**)	>20 : 1	98
18	4-$NO_2C_6H_4$ (**2t**)	>20 : 1	86
19	1-Naphthyl (**2u**)	>20 : 1	81
20	2-Fural (**2v**)	>20 : 1	84
21	2-Pyridine (**2w**)	<1 : 20	85
22[d]	H (**2x**)	<1 : 20	94

[a] Imidazolium salt (**1**, 5.0 mmol), aldehyde (**2**, 5.0 mmol), Et_3N (6.0 mmol), DMF (2.0 mL). [b] Determined by ^1H NMR. [c] Isolated yield. [d] Paraformaldehyde was used as the substrate.

four-membered 1,3-oxathietane transition state.[17] In contrast with the classic NKR of aryl groups, which is activated by electron-withdrawing substituents at the aromatic nucleus, the alkyl-like version shows an inverse electronic situation.

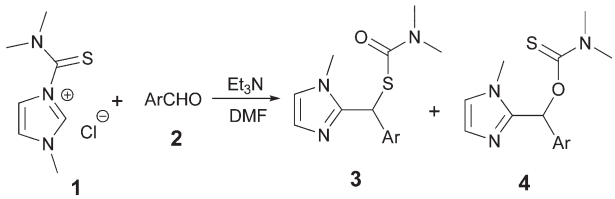
The transformation of **4** to **3** at room temperature was strongly dependent on the electron property of the substrates. Electron-rich aryl aldehydes possess higher electron density on the aryl ring so that the intramolecular *O* to *S* displacement on the sp^3 carbon was thermodynamically beneficial (Scheme 5), making this transformation easy so that the substituent on the *ortho* position did not affect the product distribution. For the electron-deficient aryl aldehydes, the energy barrier of this step was higher. The steric resistance could be significant when a relatively large electron-withdrawing substituent such as Cl, Br, or NO_2 was in the *ortho* position. The fluorine atom is too small to form a steric barrier for the addition of nucleophilic thiocarbonyl to the sp^3 carbon.

Based on the discussion above, we conclude that in order to selectively obtain *S*-thiocarbamate **3**, additional energy, for example in the form of heat, to conquer this energy barrier is needed. The reactions of 2,6-dichlorobenzaldehyde with the imidazolium ylide at higher temperatures were then carried out (Table 3). The results indicated that the equilibrium between **3** and **4** moved when the reaction temperature was increased. In the case of 2,6-dichlorobenzaldehyde **2b**, the ratio of the rearranged product **3b** to unrearranged product **4b** was up to 2.5



Scheme 5 The *O* to *S* rearrangement.

Table 3 Reaction of aldehydes with imidazolium ylide **1** at different temperatures[a]



Entry	Ar (**2**)	*T* (°C)	*t* (h)	Total yield[b] (%)	**3** : **4**[c]
1	2,6-$Cl_2C_6H_3$ (**2b**)	30	12	98	<1 : 20
2	2,6-$Cl_2C_6H_3$ (**2b**)	60	48	94	2.5 : 1[d]
3	2,6-$Cl_2C_6H_3$ (**2b**)	100	12	64	>20 : 1
4	2-ClC_6H_4 (**2i**)	60	24	82	>20 : 1
5	2-BrC_6H_4 (**2l**)	60	24	83	>20 : 1
6	2-$NO_2C_6H_4$ (**2r**)	60	24	79	>20 : 1

[a] Imidazolium salt (**1**, 5.0 mmol), aldehydes (**2**, 5.0 mmol), Et_3N (6.0 mmol), DMF (2.0 mL). [b] Isolated yield. [c] Determined by ^1H NMR. [d] Based on isolated products.

when the reaction was carried out at 60 °C (Table 3, entry 2). Further increasing the temperature to 100 °C led to almost 100% selectivity for **3b**, although the yield was relatively low probably because of product decomposition at such high temperature (Table 3, entry 3). A similar phenomenon could also be observed when other aldehydes **2i**, **2l** and **2r**, with an electron-withdrawing substituent in the *ortho* position of the phenyl ring, were used as substrates. Given the property of mono-substitution, the corresponding energy barriers for them could be easier to overcome compared to that of 2,6-dichlorobenzaldehyde. Thus, complete rearranged products were observed when the reactions were carried out at 60 °C. These results show that selectivity control of this reaction is possible.

In conclusion, we have developed a new reaction between *N*-thiocarbamate imidazolium ylide and arylaldehyde to afford 2-imidazolium alkylcarbamothioate bearing a wide diversity of substitution patterns. The crucial step, oxygen to sulfur rearrangement was strongly affected by the *ortho*-substitution on

the aromatic aldehyde, but the control of reaction temperature could selectively achieve *S*-thiocarbamate as the only product. Further extension of this reaction to other heterocycle substrates and the application of this methodology are underway.

Acknowledgements

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