ORGANIC LETTERS

2009
Vol. 11, No. 15
3382−3385

Acyl-isothiocyanates as Efficient Thiocyanate Transfer Reagents

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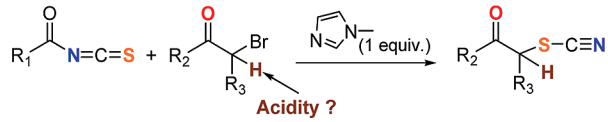
Received June 2, 2009

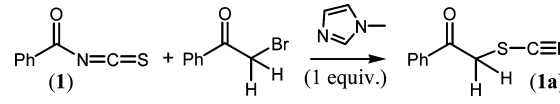
ABSTRACT



An unprecedented transfer of a thiocyanate (−SCN) group from aroyl/acyl isothiocyanate to alkyl or benzylic bromide is observed in the presence of a tertiary amine. This process is most effective when the bromomethyl proton is less acidic, while the presence of a more acidic proton gives 1,3-oxathiol-2-ylidine and other related products.

In biological systems, coenzymes catalyze a variety of reactions including transfer of various functional groups, for example, thiamine pyrophosphate (TPP), coenzyme (CoASH), biotin, and tetrahydrofolate (THF) transfer, two-carbon fragments, acyl groups, carboxyl groups, and one-carbon groups, respectively.[1] Similarly, transfer of various functional groups or a fragment of a molecule from one system to another is well-known in the literature.[2] However, transfer of a thiocyanate group from one molecule to another has not been observed so far. As a continuation of our efforts and interest in developing methods for the synthesis of heterocyclic compounds from thioureas and their analogues,[3] we were prompted to study the reactivity of benzoyl isothiocyanates toward α-bromoketones in the presence of a tertiary amine, where thiocyanation of α-bromoketones was observed. This observation is surprising since a nucleophilic substitution product is formed in the absence of any nucleophilic thiocyanate ion (Scheme 1).

Scheme 1. Formation of α-Thiocyanatoacetophenone **1a**



When benzoyl isothiocyanate (1 equiv) was treated with α-bromoacetophenone (**1**) (1 equiv) in the presence of *N*-methylimidazole (1 equiv) in acetonitrile, both the reactants got consumed giving a new product. Spectroscopic analysis of the product revealed the structure to be α-thiocyanatoacetophenone (**1a**). However, no reaction was observed in the absence of *N*-methylimidazole, suggesting the definite involvement of a tertiary amine in this reaction process.

(1) (a) David, L. N.; Cox, M. M. *Lehninger Principle of Biochemistry*, 3rd ed.; Macmillon, 1982. (b) Bruce, P. Y. *Organic Chemistry*, 3rd ed.; Printice-Hall, Inc.; Pearson Education, 1995.

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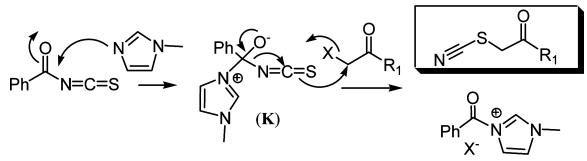
(3) (a) Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *Org. Lett.* **2006**, *8*, 5397. (b) Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *J. Chem. Res.* **2007**, 136. (c) Murru, S.; Singh, C. B.; Kavala, V.; Patel, B. K. *Tetrahedron* **2008**, *64*, 1931. (d) Yella, R.; Ghosh, H.; Patel, B. K. *Green Chem.* **2008**, *10*, 1307. (e) Ghosh, H.; Yella, R.; Nath, J.; Patel, B. K. *Eur. J. Org. Chem.* **2008**, 6189. (f) Ghosh, H.; Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *Tetrahedron Lett.* **2008**, *49*, 2601.

10.1021/ol901561j CCC: $40.75
Published on Web 07/16/2009

The reactivity, i.e., the hard−soft nucleophilic character of thiourea and its analogues toward various α-haloketones, is probably not well understood, thus leading to the proposal of several erroneous mechanisms and structures by various research groups.[4] One common mistake made in these proposed mechanisms is the attack of the thionamidic nitrogen (hard nucleophile) instead of sulfur (soft nucleophile) on a halomethylene carbon of α-haloketone (soft electrophile). Thioureas are *S*-based nucleophiles particularly toward soft electrophiles.[3a−d,4,5] Similar to the acyl transfer reaction mechanism involving alkylimidazole analogues,[2b,l] a mechanism as shown in Scheme 2 can be proposed for

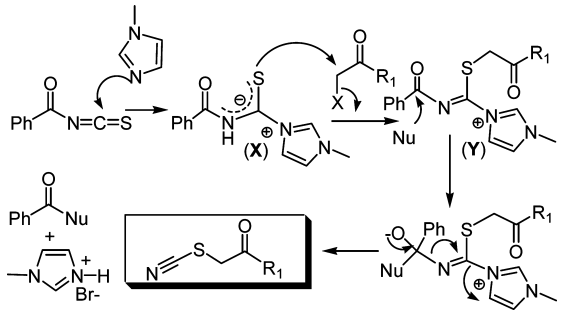
Scheme 2. Proposed Mechanism for Isothiocyanate Transfer



this novel thiocyanate transfer. In this mechanism, the imidazole nitrogen attacks on the carbonyl group forming a tetrahedral negatively charged intermediate (K). The activated intermediate then intramolecularly transfers the NCS group to the α-bromoketone **2** giving the expected product (Scheme 2).

On the basis of the reactivity of thioureas toward α-haloketones and in terms of hard−soft nucleophilic character, the following alternative mechanism can also be envisaged (Scheme 3), which involves the attack of *N*-methylimidazole

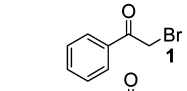
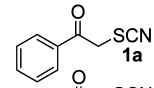
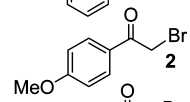
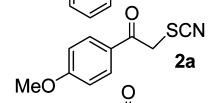
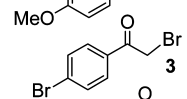
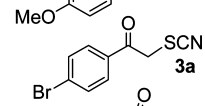
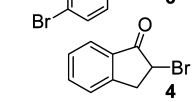
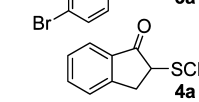
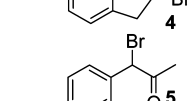
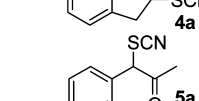
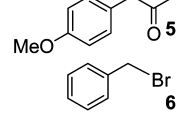
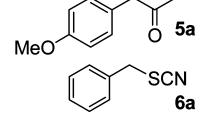
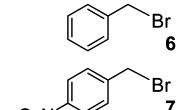
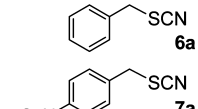
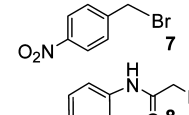
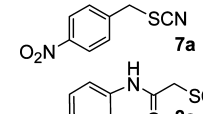
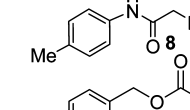
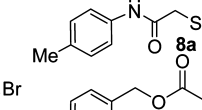
Scheme 3. Alternative Mechanism for Isothiocyanate Transfer



at the cumulated sp-hybridized C-atom of benzoyl isothiocyanate forming an activated thiourea species (X) which reacts with haloketone giving *S*-alkylated product (Y) (soft−soft interaction) and not *N*-alkylated product (hard−soft interaction). The benzoyl carbonyl carbon is susceptible to nucleophilic (*N*-methylimidazole or water from acetonitrile) attack due to the enhanced electrophilicity of the benzoyl carbonyl group, possibly because of the presence of conjugated imidazolium system (Y). This nucleophilic substitution gives rise to a tetrahedral intermediate which then collapses with concomitant departure of *N*-methylimidazole giving the expected thiocyanato product (Scheme 3).

The success of this strategy was subsequently applied to several other α-bromoketones (**1**−**5**) as shown in Table 1.

Table 1. Thiocyanation Using Benzoylisothiocyanate[a]

substrate	product	yield %[b]
 **1**	 **1a**	64
 **2**	 **2a**	81
 **3**	 **3a**	77
 **4**	 **4a**	72
 **5**	 **5a**	85
 **6**	 **6a**	77
 **7**	 **7a**	53
 **8**	 **8a**	83
 **9**	 **9a**	79

[a] Reactions were monitored by TLC. [b] Yields of pure isolated product.

These α-bromoketones on treatment with benzoyl isothiocyante in the presence of *N*-methylimidazole gave good yields of thiocyanato products (**1a**−**5a**). The structure of the product (**2a**) has been confirmed by X-ray crystallography (see Supporting Information). Thus, in these reactions, benzoylisothiocyante is acting as an efficient thiocyanate donor reagent and organic bromides as acceptors.

The reaction of benzyl bromide **6** and *p*-nitrobenzyl bromide **7** gave corresponding thiocyanato products **6a** and **7a**, respectively, proving the fact that benzoylisothiocyanate has the ability to transfer a thiocyanato group to other systems other than α-bromoketones. This methodology is also compatiable in the presence of amides and esters functionality as was tested in substrates **8** and **9** giving the corresponding thiocyanato product **8a** and **9a**, respectively.

However, when 2-bromoethylacetoacetate (**10**) was reacted with benzoylisothiocyanate and *N*-methylimidazole under an

(4) (a) Zeng, R.-S.; Zou, J.-P.; Zhi, S.-J.; Chen, J.; Shen, Q. *Org. Lett.* **2003**, *5*, 1657. (b) Wang, X.-C.; Wang, F.; Quan, Z.-J.; Wang, M.-G.; Li, Z. *J. Chem. Res.* **2005**, 689. (c) Kidwai, M.; Vankatraman, R.; Dave, B. *Green. Chem.* **2001**, *3*, 278.

(5) (a) Manaka, A.; Ishii, T.; Takahashi, K.; Sato, M. *Tetrahedron Lett.* **2005**, *46*, 419. (b) Schmeyers, J.; Kappu, G. *Tetrahedron* **2002**, *58*, 7241.

identical reaction condition, the major product (**10b**) (55% yield) obtained was not the expected thiocyanato product but was found to have a completely different structure (Figure 1). X-ray crystallographic analysis of the product unequivocally revealed the presence of the 1,3-oxathiol-2-ylidine skeleton as shown in Figure 1.

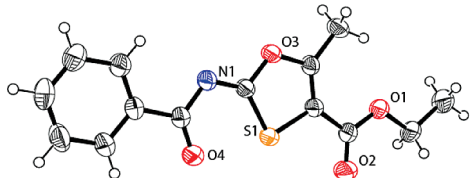
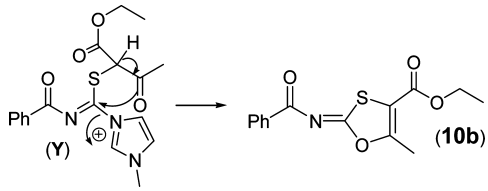


Figure 1. ORTEP view of **10b**.

The only difference between 2-bromoethylacetoacetate (**10**) and the bromo compounds (**1**−**9**) listed in Table 1 is probably the acidity of the bromomethyl proton. The bromomethyl proton in the former (**10**) is more acidic (active methylene) compared to the substrates (**1**−**9**) listed in Table 1. After the initial *S*-alkylation as proposed in Scheme 3, the active methylene proton of 2-bromoethylacetoacetate, flanked by a sulfur and two carbonyl groups, is more susceptible to enolization (Scheme 4). The intramolecular enol attack on the imine carbon displaces 2-methylimidazole giving a product containing a 1,3-oxathiol-2-ylidine skeleton (**10b**) as shown in Scheme 4. Any one of the mechanisms proposed in Scheme 2 and Scheme 3 can account for the formation of isothiocyanate transfer products. However, the formation of the 1,3-oxathiol-2-ylidine can be better explained by the latter mechanism (Schemes 3 and 4), the possibility of multiple mechanisms thus depending on the nature of the substrate.

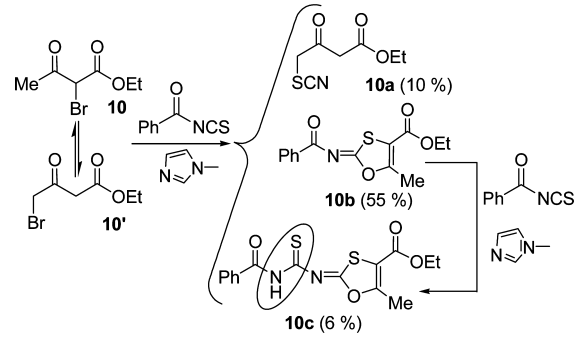
Scheme 4. Proposed Mechanism for the Formation of 1,3-Oxathiol-2-ylidine



In recent literature, the reaction of the in situ generated benzoylisothiocyanate and 2-chloroethylacetatoacetate is reported to give 1,3-oxazolin-2-thione.[6] The reported data (mp, ^{1}H and ^{13}CNMR) are in agreement with our proposed structure (**10b**) confirming the fact that they are infact identical compounds. The interpretation of an incorrect isomeric structure is due to the proposal of an incorrect reaction mechanism.[6]

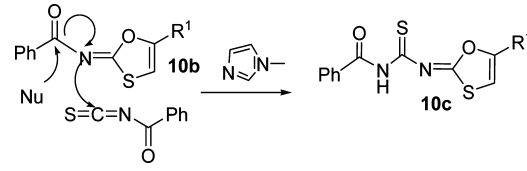
To support the fact that the acidity of the bromomethyl proton dictates whether the product formed will be 1,3-oxathiol-2-ylidene (**10b**) or thiocyanoto product, reaction of 2-bromoacetoacetate (**10**) with benzoyl isothiocyanate in the presence of *N*-methylimidazole (1 equiv) was carried out, and two new products (**10a** and **10c**) were isolated along with the expected product **10b** as shown in Scheme 5.

Scheme 5. Formation of Three Distinct Products



Formation of product (**10b**) has been explained above. The product (**10a**) is obtained by a thiocyanate transfer process from the isomerized 2-bromoethylacetoacetate (**10**) to 4-bromoethylacetoacetate (**10′**). This process of isomerization of **10** to **10′** (Scheme 5) is well-known in the literature.[7] The most surprising result, however, is the formation of product **10c** where an additional NH−C═S moiety is flanked between the benzoyl group and the 1,3-oxathiol-2-ylidine unit (Scheme 5). The formation of product (**10c**) can be explained by the possible attack of nucleophile (such as water or *tert*-amine) on initially formed product **10b** leading to a tetrahedral intermediate, which undergoes debenzoylation and concomitant attack of nucleophilic imine on a second molecule of benzoyl isothiocyanate giving product **10c**, as shown in Scheme 6. When isolated product **10b** was treated with benzoyl isothiocyanate in the presence of *N*-methylimidazole, **10c** was formed thus supporting the proposed mechanism in Scheme 6.

Scheme 6. Proposed Mechanism for the Insertion of the NH−C═S Group



During the course of further investigation, it was observed that the reaction of benzoyl isothiocyanate with 2-bromoethylbenzoacetate (**11**) gave an unclean reaction, from which

(6) Yavari, I.; Hossaini, Z.; Souri, S.; Sabbaghan, M. *Synlett* **2008**, 1287.

(7) Choi, H. Y.; Chi, D. Y. *Org. Lett.* **2003**, *5*, 411.

product **11c** could be isolated in 10% yield. The structure of the product (**11c**) has been confirmed by crystal X-ray crystallography as shown in Figure 2. Formation of product **11c** reconfirms the NH−C═S insertion in this system.

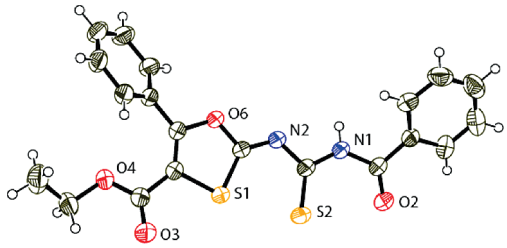


Figure 2. ORTEP view of **11c**.

The significance of the acidity of the bromomethyl proton can be further judged when 3-bromoacetylacetone (**12**) gave the product **12b**, having a 1,3-oxathiol-2-ylidine skeleton (46%). The low isolated yield in most cases is due to the formation of side products which could not be isolated.

In addition to *N*-methylimidazole, other tertiary amines such as triethylamine and DBU were also found to be effective. Acetyl isothiocyanate was found to be an even better thiocyanate transfer agent than benzoyl isothiocyanate. This can be explained in terms of rate of hydrolysis of acetyl and benzoyl amides.[8] In neutral reaction medium, acetamides undergo hydrolysis faster than benzamides.

In conclusion we have demonstrated that three distinct products are obtained from the reactions of aroyl/acyl isothiocyanate with different α-bromoketones in the presence of *N*-methylimidazole. Benzoyl isothiocyanate acts as an efficient thiocyanate (−SCN) transfer reagent, and α-bromoketones or benzylic bromide act as efficient acceptors when the bromomethyl proton is less acidic. When acidity increases, usually a 1,3-oxathiol-2-ylidine skeleton or NH−C═S is inserted, and the 1,3-oxathiol-2-ylidine product is obtained. Further scope and limitation of the process is currently ongoing in our laboratory.

Acknowledgment. We are grateful to the Department of Science and Technology (SR/S1/OC-15/2006) and CSIR [01(2270)/08/EMR-II] for funding. S.M. thanks the CSIR for fellowships. Thanks are also due to CIF, IIT Guwahati for Mass and NMR spectra, and DST-FIST for X-RD facility.

Supporting Information Available: General information, experimental procedures, spectral data, and copies of ^{1}H NMR and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901561J

(8) Smith, C. R.; Yates, K. *Can. J. Org. Chem.* **1972**, *50*, 771.