# The thiocarbonyl 'S' is softer than thiolate 'S': A catalyst-free one-pot synthesis of isothiocyanates in water†

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Treatment of the preformed or the *in situ* generated aryl/alkyl dithiocarbamates triethylammonium salt ($ArNHCSS^-.Et_3NH^+$) with methyl acrylate in an aqueous medium gave solely arylisothiocyanate (ArNCS), whereas the *in situ* generated aryl dithiocarbamic acid ($ArNHCSS^-.H^+$) yielded exclusively the *thia*-Michael adduct ($ArNHCSSCH_2CH_2COOMe$). This differential reactivity can be explained by two alternative mechanisms which is dependent both on the nature of the counter cation and on the pH of the reaction medium. Irrespective of the counter cations, the thiocarbonyl sulfur (=S) atom, having large orbital-coefficient, is softer compared to the thiol/thiolate sulfur (-SH/$S^-$) in a dithiocarbamate salt and the former adds to the Michael acceptor by a 1,4-addition.

## Introduction

Organic isothiocyanates are important synthetic intermediates often encountered in natural products and have various biological activities such as antifungal, antiproliferatives, antitumor, enzyme inhibitors for the HIV virus[1] and reagent in Edman peptide sequencing[2] and other biological assays of DNA and protein.[3] Isothiocyanates are also key intermediates specially for the preparation of both nitrogen and sulfur containing heterocycles.[4] The classical method for the preparation involves the reaction of toxic thiophosgene with amine.[5] Subsequently, 'thiocarbonyl transfer' reagents such as thiocarbonylditriazole,[6] thiocarbonyldiimidazole,[7] bis-(trichloromethyl) carbonate (BTC), trichloromethyl chloroformates (TFC),[1] di-2-pyridyl thionocarbonate (DPT)[8] and bis(trichloromethyl) pentathiodiperoxycarbonate[9] were used instead of toxic thiophosgene. However, most of these reagents are not readily available and formation of thiourea byproduct limits the scope of these methodologies. In an alternative strategy, isothiocyanates have been synthesised by the desulfurization of dithiocarbamic acid salts[10,14,15] with various reagents such as uronium- and phosphonium-based peptide coupling reagents,[11] di-*tert*-butyl dicarbonate,[12] ethyl chlorocarbonate,[13] hydrogen peroxide[14] and tosyl chloride.[15]

Recently, we reported environmentally benign methods for the preparation of heterocumulenes such as isothiocyanate and cyanamide and synthesised heterocycles using hypervalent iodine/molecular iodine by an oxidative desulfurization strategy.[16] Initially, we speculated that the desulfurization could only be achieved using hypervalent iodine diacetoxyiodobenzene (DIB) reagent,[16c] but subsequently it was revealed that the hypervalency of the iodine is not really essential and molecular iodine was found to be equally effective for these transformations.[16d]

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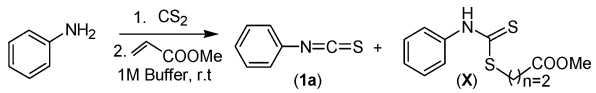
## Results and discussion

In one of our ongoing projects, we wished to prepare *thia*-Michael adduct (**X**) by treating dithiocarbamate triethylammonium salt ($ArNHCSS^-.Et_3NH^+$) (**1**) with methyl acrylate in water but surprisingly no traces of *thia*-Michael adduct (**X**) was observed, rather, phenyl isothiocyanate (PhNCS) was isolated as the major product (82%) within 0.5 h. This is in sharp contrast to the observation made by Saidi *et al.*[17] where exclusively *thia*-Michael adducts were obtained for arylamines (5–18 h). The only difference between Saidi *et al.* and ours is, in the former, the dithiocarbamate salt is generated *in situ* having $H^+$ as its counter cation whereas in our case the isolated dithiocarbamate salt has triethylammonium as its counter cation. Is this due to the effect of the counter cations or the change in pH of the medium caused by the counter cations or the effect of both? When the reaction was performed under the Saidi *et al.* condition,[17] the observed pH (after adding all the reactants) was ~6 which rose to ~7 after completion of the reaction (2 h). On the other hand, the corresponding pH observed using preformed phenyl dithiocarbamates triethylammonium salt ($PhNHCSS^-.Et_3NH^+$) was ~9 at the beginning and ~10.5 at the end of the reaction. Thus, the pH of the medium seems to be one of the major differences between the two reactions. Thus, there is a possibility that the *thia*-Michael adduct under basic condition (> pH 10) perhaps yields isothiocyanate. However, when the isolated *thia*-Michael adduct (**X**) was treated with three equivalents of triethylamine in water (pH ~11.5), the formation of isothicyanate was extremely slow, only 50% conversions after 5 h, thus ruling out the possibility of isothiocyanate formation *via* a *thia*-Michael adduct route. We therefore reasoned that the high basicity of the medium caused due to triethylamine (pKa 10.75) is not essentially the factor for the efficient formation of isothiocyanate. To further prove this fact, when the dithiocarbamic acid ($ArNHCSS^-.H^+$) was generated *in situ* at pH 6, 7, 8, 9 and 10 buffer ($K_2HPO_4$ + $KH_2PO_4$, 1M, 5 mL) and treated with methyl acrylate, the *thia*-Michael adduct was obtained as the major product in the entire range of pH investigated as shown in Table 1. As can be seen from Table 1, the buffering capacity of the buffer was nearly maintained during the experiment. Thus, with hard

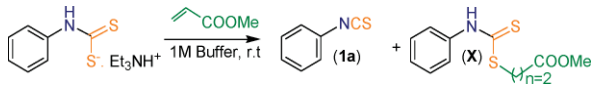
**Table 1** Reaction of *in situ* generated dithiocarbamate salt with methyl acrylate in aqueous buffer at different pH[a]




| Buffer | Initial pH | Final pH | % **1a** | % **X**[a] |
|---|---|---|---|---|
| $K_2HPO_4 + KH_2PO_4$ (1M) | 6.0 | 6.15 | Nil | 91 |
| | 7.0 | 7.20 | Nil | 93 |
| | 8.0 | 8.04 | Nil | 92 |
| | 9.0 | 8.94 | Nil | 89 |
| | 10.0 | 9.85 | Nil | 91 |

[a] Isolated yield.

**Table 2** Reaction of dithiocarbamate triethylammonium salt with methyl acrylate in aqueous buffer at different pH




| Buffer | Initial pH | Final pH | % **1a**[a] | % **X**[a] |
|---|---|---|---|---|
| $K_2HPO_4 + KH_2PO_4$ (1M) | 6.0 | 6.45 | Nil | 91 |
| | 7.0 | 7.44 | 5 | 88 |
| | 8.0 | 8.84 | 15 | 77 |
| | 9.0 | 9.45 | 65 | 22 |
| | 10.0 | 10.18 | 82 | 08 |

[a] Isolated yield.

counter cations ($H^+$ or $K^+$), irrespective of the pH of the medium, *thia*-Michael was the main product and no traces of isothiocyanate was observed in the pH range of 6 to 10 within 0.5 h.

From the above experiment, it is clear that not only the pH of the medium but also the presence of triethylammonium as its counter cation seems to be essential for the isothiocyanate formation (**1a**). To ascertain the role of triethylammonium as counter cation, the above experiment *i.e.* generation of dithiocarbamic acid ($ArNHCSS^-.H^+$) was carried out at pH 8 buffer (1M) but in the presence of two equivalents of triethylammonium hydrochloride salt. In this reaction, along with the *thia*-Michael adduct (**X**) (75%), isothiocyanate (**1a**) was isolated in 15% yield. Thus, in spite of the high concentration of $K^+$ counter cation present in the medium, formation of isothiocyanate is observed proving the definite role of triethylammonium counter cation in this transformation at alkaline pH 8 and above.

Next, we wished to investigate the optimum pH of the reaction medium for isothiocyanate formation when triethylammonium is the counter cation. To scrutinise this, phenyldithiocarbamate triethylammonium salt (1 mmol) was treated with methyl acrylate (1.5 mmol) at pH 6, 7, 8, 9 and 10 buffer ($K_2HPO_4 + KH_2PO_4$, 1M, 5 mL). As can be seen from Table 2, the *thia*-Michael adduct (**X**) was the major product below pH 8 and isothiocyanate (**1a**), the main product above pH 9. In this experiment, the pH of the buffer increased towards basic pH which however is not expected to affect the final conclusion drawn.

Dithiocarbamate triethylammonium ($ArNHCSS^-.Et_3NH^+$) even when generated *in situ*, gives isothiocyanate exclusively (80%) along with the *thia*-Michael adduct (**X**) (<8%) in 0.5 h. Instead of triethylamine (pKa 10.75), when pyridine, a weak base (pKa 5.25) was used, the *thia*-Michael adduct was observed exclusively in the first 0.5 h and isothiocyanate was formed very slowly at the expense of the *thia*-Michael adduct at longer reaction time. When a strong base DBU (estimated pKa = 12)[20a] was used for the *in situ* generation of dithiocarbamate salt and treated with methyl acrylate, *thia*-Michael adduct (**X**) was isolated in 86% yield (0.5 h) and no traces of isothiocyanate were observed within 0.5 h. This result was rather unexpected since DBU is more basic as compared to triethylamine and hence anticipated to give isothiocyanate. Surprisingly, the measured pH of the reaction medium was found to be 8.4, 11.5 and 9.2 respectively, when DBU, triethylamine and pyridine were used for the *in situ* generation of dithiocarbamate salt.

Reactivity based on the principle of HSAB is well known, a hard acid prefers to bond to a hard base, and a soft acid prefers to bond to a soft base.[18] The effect of the counter cation on the nucleophilicity of the anion is well documented in the literature.[19] It is established that due to the weak ion pair or more dissociation, the sodium or potassium enolates are better nucleophiles towards thermodynamically controlled conjugated addition compared to its hard lithium analogues.[20b] Again, formations of kinetic *vs.* thermodynamic enolates are strongly dependent on the types of countercations. In addition, selective N/C, O/C, O/S, N/S , N/O alkylations are well known, which at times depends on the nature of the nucleophiles and at times on the nature of the counter cations.[20b] So far, these processes have been mainly demonstrated for hard nucleophiles such as O and N. However, the effect of counter cations on the reactivity of soft sulfur nucleophile has not been noticed so far.

In continuation to our quest to find out the differential reactivity of dithiocarbamate salt, it is further found that irrespective of the countercations, $H^+$ (**I**), $Et_3NH^+$ (**II**) or $PyH^+$ (**III**) present in the dithiocarbamate salt (Fig. 1) (see ESI†), the HOMO of thiocarbonyl sulfur (=S) atom having large orbital-coefficient is softer compared to the thiol/thiolate sulfur (-SH/$S^-$). Again, in methyl acrylate, in the LUMO (**IV**) (Fig. 1), the largest co-efficient is on the β-carbon of this α,β-unsaturated carbonyl compound and it is here that the soft nucleophile attacks. It may be mentioned here that this reaction is also equally successful with other Michael acceptors such as acrylonitrile, ethyl acrylate, methyl methacrylate *etc*.

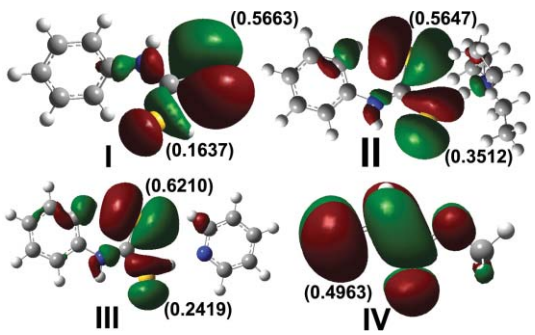
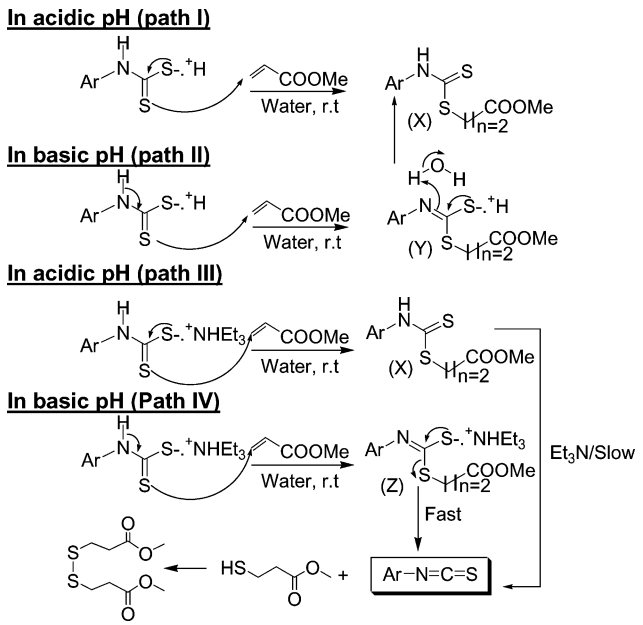



**Fig. 1** Co-efficient of molecular orbitals calculated using gaussian 03W.

Based on the above experimental results and from the molecular orbital coefficients, also keeping in mind that soft–soft interactions are orbital controlled rather than charge controlled, mechanisms as shown in Scheme 1 is proposed. The HOMO of thiocarbonyl

sulfur (=S) atom having large orbital coefficient attacks on the β-carbon of the methyl acrylate having largest coefficient in its LUMO (**IV**) (Fig. 1, Scheme 1). Sulfur being a soft nucleophile has lesser affinity for hard acid like proton ($H^+$) or $K^+$. When $H^+$ is the counter cation in an acidic or a neutral pH, the thiocarbonyl sulfur attacks on the Michel acceptor directly giving *thia*-Michael adduct (**X**) (Scheme 1, path I). In basic medium, it follows a deprotonative path as shown in Scheme 1, path II. The stable neutral intermediate (**Y**) then picks up a proton from the medium giving the *thia*-Michael adduct (**X**). On the other hand, with triethylammonium as the counter cation at lower pH (below 8), the attack is similar to $H^+$ as the counter cation (Scheme 1, path III) directly giving *thia*-Michael adduct. In basic pH, again a deprotonative path is proposed forming an unstable anionic intermediate (**Z**) which then rapidly loses a thiolate (mercapto-propionic acid methyl ester) giving isothiocyanate (path IV). Despite the high pH of the medium (pH 9.2), when pyridine (pKa 5.25) was used for the *in situ* generation of dithiocarbamate salt, no isothiocyanate formation was observed within 0.5 h. Possibly, in this case, it follows the path II, similar to that when $H^+$ is the counter cation. A similar deprotonative path (path II) is anticipated when DBU (pKa=12, pH=8.5) is the counter cation for the *in situ* generation of dithiocarbamate salt to account for the exclusive formation of *thia*-Michael adduct.

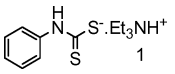
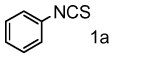
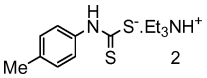
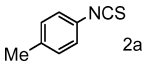
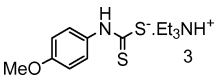
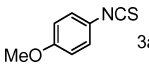
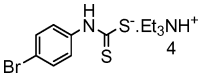
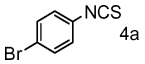
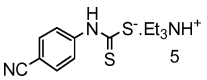
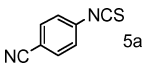
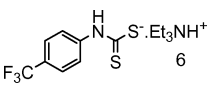
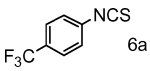
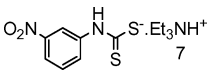
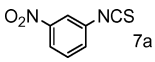
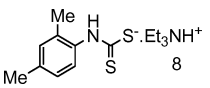
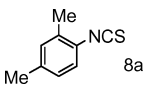
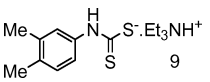
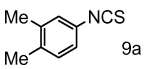
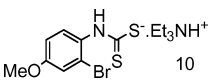
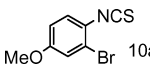
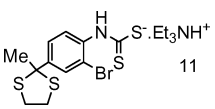
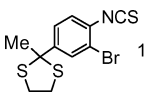
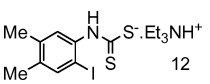
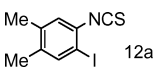
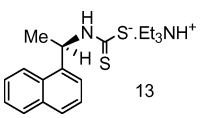
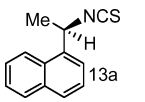
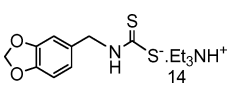
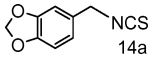
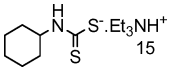
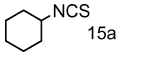
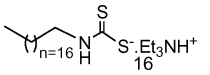
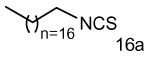



**Scheme 1** Proposed mechanism for the formation of isothiocyanate and *thia*-Michael adduct.

Irrespective of the mechanism involved, this is one of the efficient and cost effective methods for preparing isothiocyanates. Several isothiocyanates (Table 3) were successfully prepared in good to excellent yields by employing this protocol. As can be seen from Table 3, aromatic substrates containing weakly (**2**) as well as strongly (**3**) activating groups reacts efficiently giving isothiocyanates (**2a**) and (**3a**) in good yields.

This methodology is equally successful for substrates containing weakly (**4**) and strongly (**5–7**) deactivating substituents giving isothiocyanates (**4a–7a**) in excellent yields. Through this strategy,

**Table 3** Preparation of isothiocyanates from dithiocarbamate salts and methyl acrylate in water[a]

| Substrate | Product[b] | Yield (%)[c] |
|---|---|---|
|  1 |  1a | 82% |
|  2 |  2a | 89% |
|  3 |  3a | 91% |
|  4 |  4a | 85% |
|  5 |  5a | 82% |
|  6 |  6a | 75% |
|  7 |  7a | 67% |
|  8 |  8a | 84% |
|  9 |  9a | 84% |
|  10 |  10a | 78% |
|  11 |  11a | 70% |
|  12 |  12a | 70% |
|  13 |  13a | 72%[d] |
|  14 |  14a | 76%[d] |
|  15 |  15a | 71%[d] |
|  16 |  16a | 73%[d] |

[a] Reactions were monitored by TLC. [b] Confirmed by IR, $^1$H NMR and $^{13}$C NMR spectroscopy. [c] Isolated yields. [d] Reactions were carried out in dioxane to which three equivalent of NaOH was added.

we were able to obtain excellent yields of arylisothiocyanates (**8a–12a**) having various di- and tri- substitutions. Aliphatic amines (**15** and **16**) including benzylamines (**13** and **14**) yielded *thia*-Michael adducts as the major product along with traces of isothiocyanate (<5%). This may be due to the higher basic character of aliphatic amines (**13–16**) compared to aromatic amines (**1–12**) listed in Table 3. Due to the higher basic character of these amines, they prefer path III and not the deprotonative path IV proposed for aryl amines. The isolated *thia*-Michael adduct of these dithiocarbamate salts, when treated with three equivalents of NaOH in dioxane gave corresponding isothiocyanates **13a**, **14a**, **15a** and **16a** respectively in good yields (Table 3). Thus, from synthetic utility, reactions of aliphatic dithiocarbamate salts **13–16** were carried out in dioxane solvent and upon formation of *thia*-Michael adduct (0.5 h) was treated with 3 equivalents of NaOH to give isothiocyanate in good yields (4.5 h).

## Conclusion

In summary, an aryldithiocarbamate salt having triethylammonium as its counter cation, when treated with a Michael acceptor, methyl acrylate, in an aqueous alkaline medium (above 8.5) the major product obtained is an arylisothiocyanate. However for the same reaction when the counter cation is a proton ($H^+$), the only product obtained is *thia*-Michael adduct, irrespective of the pH (6–10) of the medium. The thiocarbonyl sulfur (=S) atom having large orbital-coefficient is softer and attacks on the β-carbon of the Michael acceptor compared to the thiol/thiolate sulfur (-SH/$S^-$) which is/was generally believed to be the nucleophile in a dithiocarbamate salt for these kind of reactions. The difference in product formation with change in the counter cation can be accounted by two different kinds of mechanisms. This method gives an easy access to the preparation of various isothiocyanates and is perhaps one of the simplest and cost effective method.

## Experimental

### General remarks

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Reaction progress was monitored by TLC using Merck silica gel 60 $F_{254}$ (0.25 mm) with detection by UV or iodine. Chromatography was performed using Merck silica gel (60–120) mesh size with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Varian FT-400 MHz instrument using TMS as an internal standard. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, b = broad, appt = apparent triplet), coupling constant *J* (Hz). Elemental analyses were carried out on a Perkin–Elmer 2400 automatic carbon, hydrogen, and nitrogen analyzer. Melting points were recorded on Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer. Mass data were obtained with a WATERS MS system, Q-tof premier and data analyzed using Mass Lynx4.1.

### General experimental procedure

**General procedure for the preparation of phenyl isothiocyanate from its dithiocarbamate triethylammonium salt.** To a solution/suspension of the phenyl dithiocarbamate triethylammonium salt **1** (5 mmol) in water (10 mL) was added methyl acrylate (8 mmol). The heterogeneous reaction mixture was stirred at room temperature for 1.5 h. The resultant isothiocyanate (**1a**) was extracted with hexane (2 × 10 mL) and the hexane layer was dried over anhydrous $Na_2SO_4$. The crude isothiocyanate so obtained was purified over a short column of silica gel using 100% hexane as the eluent to give product **1a** in 82%. Oily; $^1$H NMR (400 MHz, $CDCl_3$):$\delta$ (ppm) 7.21–7.37 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$):$\delta$ (ppm) 125.8, 127.4, 129.6, 131.3, 135.3; IR (KBr): 3064, 2164, 2063, 1591, 1489, 1474, 1451, 1070, 927, 905, 749, 684 $cm^{-1}$.

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