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# Iodine catalyzed desulphurization strategy: The synthesis of 2-halo aromatic isothiocyanates.

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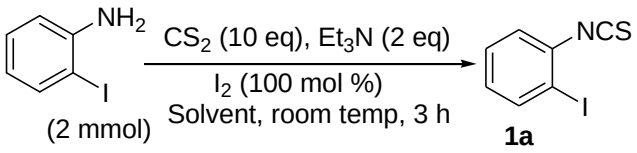
***Abstract – 2-Haloaromatic isothiocyanates could be obtained from 2-halo amines using cheap and readily available Iodine catalyst under mild reaction conditions. It is a highly efficient and simple protocol. All the reactions carried out under moderate reaction conditions to give their target products in good to excellent yields.***

## Introduction

In recent years, isothiocyanates have been used as versatile important synthetic intermediates for the synthesis of number of natural products and hetero cycles, such as thiohydantoins, benzothiozole, benzimidazoles, benzoxazoles, thiopyrimidones, thioqui-nazolones, merca-ptoimidizoles, thio-amidazolones, pyrid-inethiones, pyrrolidine and benzothiazine.1 In addition, the functional group isothiocyanate is a ubiquity structural functional class in many biological and pharmaceutical active compounds such as antimicrobial,2 antiproliferatives,3 antitumor,4 enzyme inhibitors for the HIV virus5 and reagent in Edman peptide sequencing,6 and other biological assays of DNA and protein.7 For this reason, much effort has been devoted to develop efficient methods for the synthesis of isothiocyanates and their derivatives. Isothiocyantes can be obtained from different starting materials such as tert-alcohols,8 amines,9 nitrile oxides,10 isocyanides,11 and isocyanates.12 Due to broad resource and versatility of amines, these are usually selected to obtain isothiocyanates. In long decades thiophosagene was mostly well known reagent for the synthesis of isothiocyanates.13 Due to the high toxicity of thiophosgene, it was replaced by other "thiocarbonayl transfer" reagents, such as thiocarbonylditriazole, thiocarbonyldiimid-azole, bis-(trichlorome-thyl) carbonate, trichloromethylformats, di-2-pyridyl thionocarbonate and bis-(trichloromethyl) pentat-hiocarbonate.14 However, most of them are not readily available and often do not work as desired due to the formation of thiourea as a side product. On the other hand, isothiocyanates can also be synthesized by the desulfurization of dithiocarbomates, which is formed from the reaction between amine and carbondisulphide in the presence of base, with diverse reagents, including uranium and phosphonium-based peptide coupling reagents,15 triphenylphosphine dibromide,16 tosyl chloride,17 dialkyl dicarbonates,18 hydrogen peroxide,19 iodine,20 diacetoxyiodobenzene, other harsh reagents,21 using chlorosilanes such as Me3SiCl, Me2SiCl2, MeSiCl3, and SiCl4.22 and other mild methods are known.23 In recent years, halo isothiocyanates were also prepared by Pengfe,24 Sebastieni25 and Krzysztof.26 The reported methods are really efficient enough, but most of them possess drawbacks such as rigorous or hazardous conditions, intractable side reactions, evolved toxic gases. Thus, there is still need for a commercially available and environmentally acceptable methodology for the preparation of isothiocyanates. In this connection to overcome the above mentioned disadvantages we would like to demonstrate a facile method for the synthesis of 2-haloaryl isothiocyanates having excellent functional group compatibility, operational simplicity, inexpensive and readily available Molecular Iodine catalyst. The optimization of the reaction conditions was carried out with 2-iodoaniline as model substrate using different bases, solvents and Iodine as catalyst at varied temperatures (Table 1). The best result was obtained when the reaction was pursued at room temperature using 50 mol % of the Iodine catalyst and Et3N base in the presence of DMSO affording the 2-iodophenyl isothiocyanate 1a in 95% conversion (Conversion was confirmed by TLC as well as GC also). Firstly, the reaction was checked in the presence of different solvents. Among

them DMSO could give target product in excellent yield. Polar protic solvents such as EtOH, MeOH and Acetone showed less effect. (Table 1, entries 1-3). Other polar solvents like ethyl acetate gave final product 1a in 80% yield (Table 1, entry 6). In continuous of our solvent optimization, we have also examined non polar solvents like n-Hexane and n-Heptane and we could find no target product (Table 1, entry 4-5). Inorder to increase the yield of the reaction, we have tested the reaction in the presence of DMSO and DMF. Very fortunately, DMSO could give target product 1a in excellent yield (Table 1, entry 7), where as DMF gave target product in moderate yield (Table 1, entry 8). Unfortunately the grenary solvent H2O couldn't give target product. Very interestingly, no recation was occurred in the absence of solvent and the starting material was recovered intact (Table 1, entry 10).

**Table 1. Solvent optimization**[a]

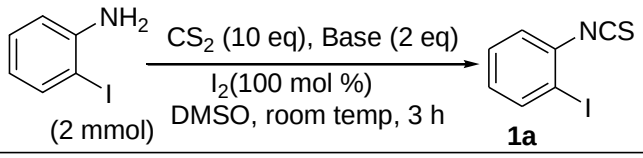



| Entry | Solvent | Conversion (%)[b] (**1a**) |
|---|---|---|
| 1 | Ethanol | 50 |
| 2 | MeOH | 30 |
| 3 | Acetone | 40 |
| 4 | n-Hexane | ND |
| 5 | n-Heptane | ND |
| 6 | Ethyl acetate | 80 |
| 7 | DMSO | >95 |
| 8 | DMF | 70 |
| 9 | $H_2O$ | ND |
| 10 | - | ND |

a Reaction conditions: 2-Iodo aniline (2 mmol), CS2 (10 eq), Et3N (2 eq), I2 (100 mol %) respective solvent (4 ml), rt, 3 h. b Conversion was confirmed by GC analysis

The reaction with other orgnaic base pyridine could give expected product 1a in less yield (Table 3, entry 2). Later, the inorganic bases sodiumbicarbonate, sodium acetate and sodium hydroxide activity was also checked. In among them sodium acetate is the best for this reaction and it could give target product 1a in 75% yield (Table 3, entry 3). The organic bsae Et3N could show better effect than inorganic bases.

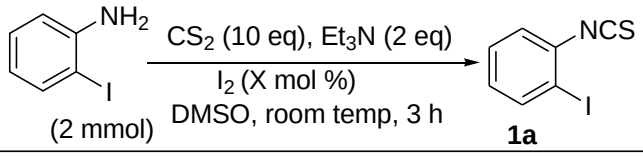
**Table 2. Base standardization for the synthesis of 2-iodophenyl isothiocyanate**[a]




| entry | Base | conversion (%)[b] |
|---|---|---|
| 1 | $Et_3N$ | >95 |
| 2 | Pyridine | 20 |
| 3 | NaOAc | 75 |
| 4 | NaOH | 60 |
| 5 | $NaHCO_3$ | 70 |

a Reaction conditions: 2-Iodo aniline (2 mmol), CS2 (10 eq), Base (2 eq), I2 (100 mol %), DMSO (4 ml), rt, 3 h. b Conversion was confirmed by GC analysis.

**Table 3. Amount of catalyst optimization for the construction of 2-iodophenyl isothiocyanate**




| entry | X mol % | conversion (%)[b] |
|---|---|---|
| 1 | 100 | >95 |
| 2 | 50 | >95 |
| 3 | 25 | 60 |
| 4 | 10 | 10 |
| 5 | - | ND |

a Reaction conditions: 2-Iodo aniline (2 mmol), CS2 (10 eq), Et3N (2 eq), I2 (X mol %), DMSO (4 ml), rt, 3 h. b Conversion was confirmed by GC analysis.

Finally, various amount of iodine effect was also conducted. Both 100 mol% and 50 mol % iodine could give traget product in excellent yield. Where as 25 mol % Iodine could give target product in moderate yield and 10 mol % Iodine gave final product in less yield. Similarly, lowering of the reaction temperature (10 °C) or base (1 equiv) led to the formation of a target product. The control experiment confirmed that in the



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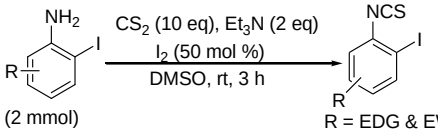
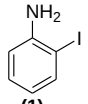
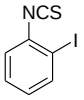
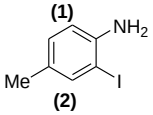
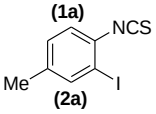
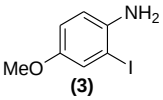
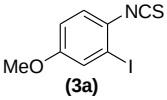
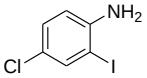
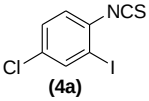
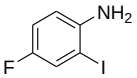
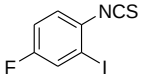
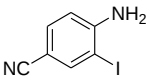
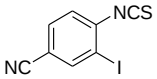
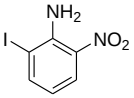
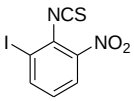
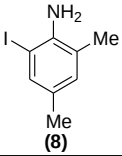
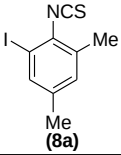
absence of Iodine catalyst and no reaction was occurred and the starting material was recovered intact.

**Table 4. Substrate scope for the synthesis of 2-iodoaromatic isothiocyanates[a]**



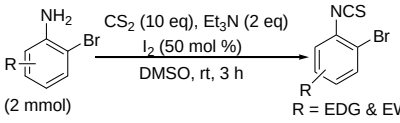

(2 mmol) R = EDG & EWG

| Entry | Substrate | Product | Isolated yield (%)[b] |
|---|---|---|---|
| 1 |  **(1)** |  **(1a)** | 95 |
| 2 |  **(2)** |  **(2a)** | 95 |
| 3 |  **(3)** |  **(3a)** | 90 |
| 4 |  **(4)** |  **(4a)** | 90 |
| 5 |  **(5)** |  **(5a)** | 85 |
| 6 |  **(6)** |  **(6a)** | 60 |
| 7 |  **(7)** |  **(7a)** | 60 |
| 8 |  **(8)** |  **(8a)** | 90 |

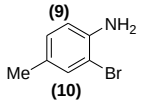
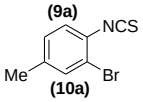
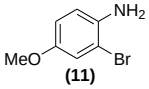
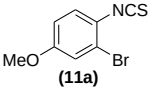
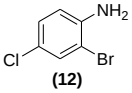
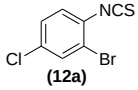
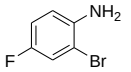
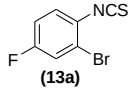
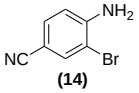
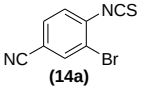
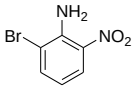
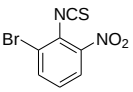
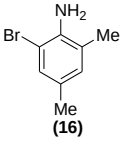
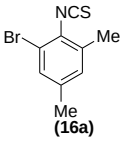
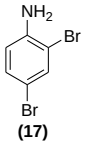
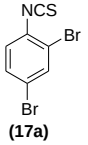
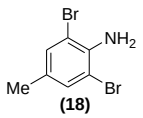
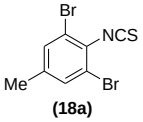
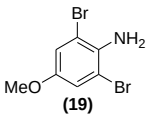
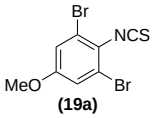
a Reaction conditions: 2-Iodo amine (2 mmol), CS2 (10 eq), Et3N (2 eq), I2 (50 mol %), DMSO (4 ml), rt, 3 h. b Isolated yield.

Having the optimal conditions in hand, we explored the scope of this procedure for the substrates having electron donating and electron withdrawing substituents on the aryl rings. In this connection, the various substrates bearing electron donating and electron withdrawing groups were examined under the standard reaction conditions (Table 4). The phenyl ring having electron donating groups such as 4-methyl (2), 4-methoxy (3) could give their respective aromatic iodoisothiocyanates (2a and 3a; Table 4, entries 2-3) in high yield. The unsubstited

**Table 5. Substrate scope for the construction of mono and dibromo aromatic isothiocyanates[a]**




(2 mmol) R = EDG & EWG

| Entry | Substrate | Product | Isolated yield (%)[b] |
|---|---|---|---|
| 1 |  **(9)** |  **(9a)** | 90 |
| 2 |  **(10)** |  **(10a)** | 90 |
| 3 |  **(11)** |  **(11a)** | 80 |
| 4 |  **(12)** |  **(12a)** | 55 |
| 5 |  **(13)** |  **(13a)** | 60 |
| 6 |  **(14)** |  **(14a)** | 45 |
| 7 |  **(15)** |  **(15a)** | 50 |
| 8 |  **(16)** |  **(16a)** | 90 |
| 9 |  **(17)** |  **(17a)** | 80 |
| 10 |  **(18)** |  **(18a)** | 70 |
| 11 |  **(19)** |  **(19a)** | 80 |
| 12 |  **(20)** |  **(20a)** | 55 |
| 13 |  **(21)** |  **(21a)** | 60 |

[a]Reaction conditions: 2-Bromo amine (2 mmol), $CS_2$ (10 eq), $Et_3N$ (2 eq), $I_2$ (50 mol %), DMSO (4 ml), rt, 3 h. [b] Isolated yield.



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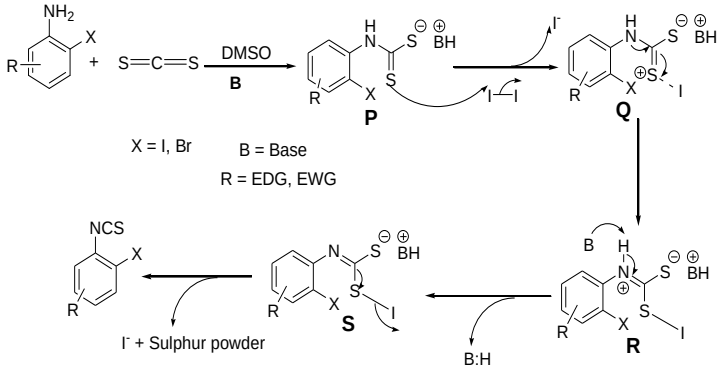
phenyl ring (**1)** also gave target product in 95% yield (**1a**; table 4, entry 1). Electron withdrawing groups such as 4-fluoro (**5**), 4-chloro (**4**), 4-cyano **(6)** and 2-nitro **(7)** substituent's could give their respective final products **5a, 4a, 6a** and **7a** in 60-90% yields (Table 4, entries 4-7). Aryl ring having disubstituted methyl group **(8)** gave expected product **(8a)** in good yield. Soon after successfully finish the synthesis of 2-iodoaromatic isothiocyanates, we became interested to develop the construction of bromo aromatic isothiocyanates. In this connection various substituted monobromo and dibromo aromatic isothiocyanates have been constructed under below shown reaction conditions (Table 5). All the reactions were carried out under optimized conditions and could obtain their final products **9a-21a** in 45-90% yields.The mechanism of formation for 2-halophenyl isothiocyante from 2-haloanilines is shown in below Scheme 1. The experimental evidence and from the literature reports the mechanism is proposed. As we shown in scheme 1, 2-haloaniline (**1**) reacts with carbondisulphide in the presence of base ($Et_3N$) and respective solvent to give thiocarbomate salt **P**. It may co-ordinate with iodonium and followed by remove the proton to afford the intermediate **S** via intermediate complexes **Q** and **R**. The intermediate **S** may give the target product along with byproduct sulphur powder.




**Scheme 1: Proposed mechanism**

## Conclusion

We have developed neat, clean and efficient methodology for the synthesis of 2-halo aromatic isothiocyanates. During the reaction process we couldn't observe any other byproducts (no other products could observe except isothiocyanate only). The reactions are rapid and facile and accomplished under mild reaction conditions. All the substrates could obtain their target products in good to excellent yields.

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