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To cite this article: Xinyun Liu, Hang Li & Xiaogang Yin (2021): NaOH-promoted one-pot aryl isothiocyanate synthesis under mild benchtop conditions, Phosphorus, Sulfur, and Silicon and the Related Elements, DOI: [10.1080/10426507.2021.1927031](https://doi.org/10.1080/10426507.2021.1927031)

To link to this article: <https://doi.org/10.1080/10426507.2021.1927031>



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SHORT COMMUNICATION



NaOH-promoted one-pot aryl isothiocyanate synthesis under mild benchtop conditions

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ABSTRACT

In this work, we have established a green synthesis of aryl isothiocyanates promoted by the low-cost and readily available NaOH from aryl amines and carbon disulfide in a one-pot procedure. The developed protocol features no extra desulfurating reagents and mild benchtop conditions, in which NaOH serves as both the base and the desulfurating reagent to decompose the dithiocarbamate intermediate. Fourteen examples of aryl amines bearing electronic neutral, rich and poor substituents, as well as benzylamine, have proved to be compatible substrates in the developed method to furnish the corresponding isothiocyanates. The reaction has been performed on a gram scale to further demonstrate its synthetic utility. Compared to the reported base-promoted synthesis of aryl isothiocyanates that requires the use of special equipment, such as the ball mill or the microwave reactor, the simplicity in operation and scalability enables this method to efficiently access a variety of aryl isothiocyanates.

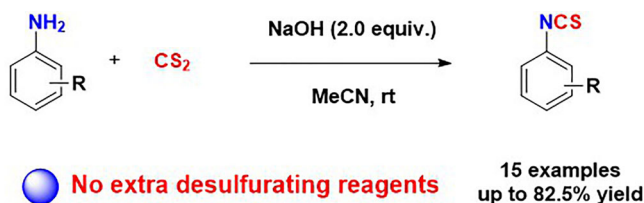
ARTICLE HISTORY

Received 15 January 2021
Accepted 4 May 2021

KEYWORDS

Isothiocyanates; benchtop synthesis; sodium hydroxide; aryl amines; desulfurating reagents

GRAPHICAL ABSTRACT



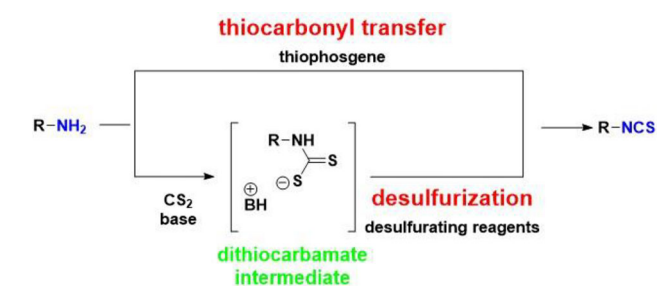
Introduction

Naturally found in Brassicaceae vegetables, isothiocyanates (ITCs) possess a wide range of biological activities such as anticancer,^[1] antibacterial,^[2] anti-inflammatory.^[3] Even ITCs bearing simple phenyl and benzyl groups are identified as effective anticancer agents.^[4] In organic synthesis, aryl ITCs are versatile synthetic intermediates for the synthesis of thioureas and a variety of nitrogen- and sulfur-containing heterocycles,^[5] including benzimidazoles,^[6] benzoxazoles,^[7] thiohydantoins.^[8]

Arising from the importance of aryl ITCs to synthetic and medicinal chemistry, a number of methods that mainly utilize readily available amines as starting materials have been established to synthesize ITCs. In general, two approaches are exploited to prepare ITCs from amines (Scheme 1). In the “thiocarbonyl transfer” approach, amines react with thiophosgene, or its less toxic alternatives, to directly deliver ITC products via thiocarbonylation. Although efficient, high toxicity and difficult preparation of the thiocarbonyl transfer reagents remarkably limit the synthetic

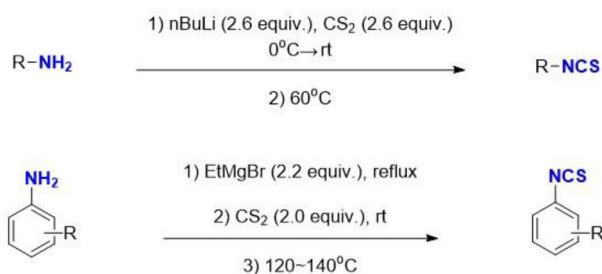
utility of this approach. Alternatively, the “dithiocarbamate desulfurization” approach is a two-step process: the amine starting material is first treated with carbon disulfide in the presence of a base to afford a dithiocarbamate intermediate, which then decomposes to provide the ITC product via desulfurization. A plethora of diverse desulfurating reagents have been developed, including uronium and phosphonium-based peptide coupling reagents,^[9] tosyl chloride,^[10] iodine,^[11] di-tert-butyl dicarbonate,^[12] copper salts,^[13] iron salts,^[14] persulfate salts,^[15] the phase transfer catalyst Triton B,^[16] and recently reported organofluorides.^[17]

Despite the wide variety, the use of extra desulfurating reagents, mostly in stoichiometric amounts, unavoidably impairs eco-friendliness and complicates reaction conditions. Therefore, greener and operationally simpler protocols for ITC preparation are expected to eliminate the need of extra desulfurating reagents. So far, very few reports have investigated base-promoted ITC synthesis from amines without extra desulfurating reagents (Scheme 2). In the mid-1970s, Sakai and coworkers reported a stepwise ITC synthesis from



Scheme 1. Two general approaches to ITC synthesis.

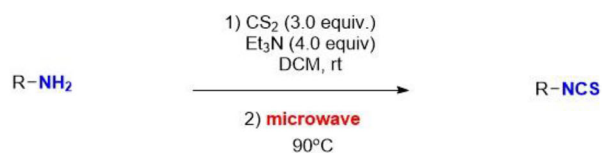
Sakai, 1970s



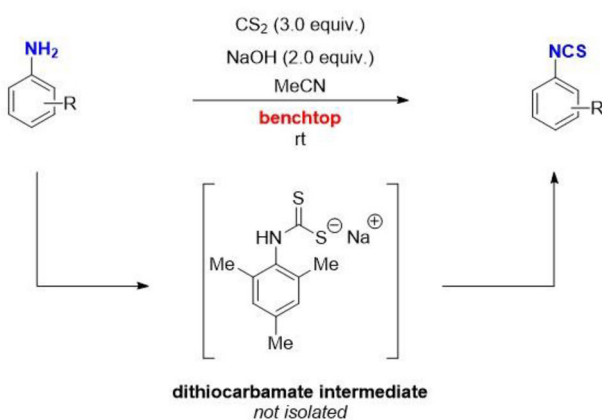
Zhang, 2013



Gajda, 2019

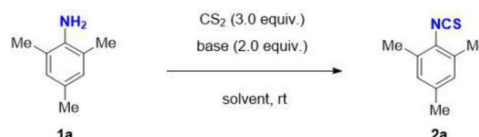


This work:



Scheme 2. Base-promoted ITC synthesis.

Table 1. Optimization of NaOH-promoted synthesis of mesityl ITC from 2,4,6-trimethylaniline.



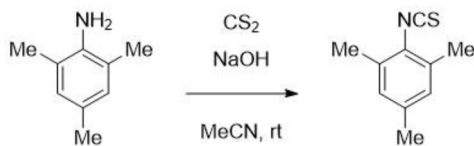
Entry	Base	Solvent	Time (h)	Yield ^a
1	Et_3N	MeCN	3	45%
2	K_2CO_3	MeCN	3	33%
3	NaHCO_3	MeCN	3	14%
4	NaOAc	MeCN	3	16%
5	NaOH	MeCN	3	66%
6	KOH	MeCN	3	64%
7	NaOH	dried MeCN	3	58%
8	NaOH	$\text{MeCN}:\text{H}_2\text{O} = 9:1$	3	50%
9	NaOH	H_2O	3	15%
10	NaOH	EtOAc	3	10%
11	NaOH	DCM	3	7%
12	NaOH	THF	3	22%
13	NaOH	DMSO	3	36%
14	NaOH	MeOH	3	50%
15	NaOH	EtOH	3	21%
16	NaOH	MeCN	6	73%
17	NaOH	MeCN	9	81%
18	NaOH	MeCN	12	62%

^aIsolated yields.

primary amines promoted by *n*-butyllithium^[18] and a Grignard reagent.^[19] Although the strongly basic organolithium and organomagnesium reagents effectively desulfurate the dithiocarbamate intermediate, the very forcing conditions have severely restricted the substrate scope and limited its synthetic utility. One-pot base-promoted preparation of ITCs has not been disclosed until within the last decade. In 2013, Zhang and coworkers reported KOH-promoted aryl ITC synthesis under mechanical ball milling conditions. Employing KOH as both the base and the desulfurating reagent, a series of aryl ITCs were prepared at room temperature.^[20] More recently, Gajda and coworkers studied microwave-assisted ITC synthesis promoted by triethylamine at 90°C .^[21] In both cases, special equipment, a ball mill or a microwave reactor together with sealed vessels, is required for the implementation of the reactions. To our knowledge, benchtop base-promoted ITC synthesis has not been disclosed. Herein, we report NaOH-promoted synthesis of ITCs under mild benchtop conditions in the absence of extra desulfurating reagents. In this method, ITCs are synthesized via the dithiocarbamate desulfurization approach, wherein the dithiocarbamate intermediate undergoes decomposition with the low-cost and readily available NaOH serving as the base as well as the desulfurating reagent. Various aryl and benzyl ITCs are prepared at room temperature without special equipment.

Results and discussion

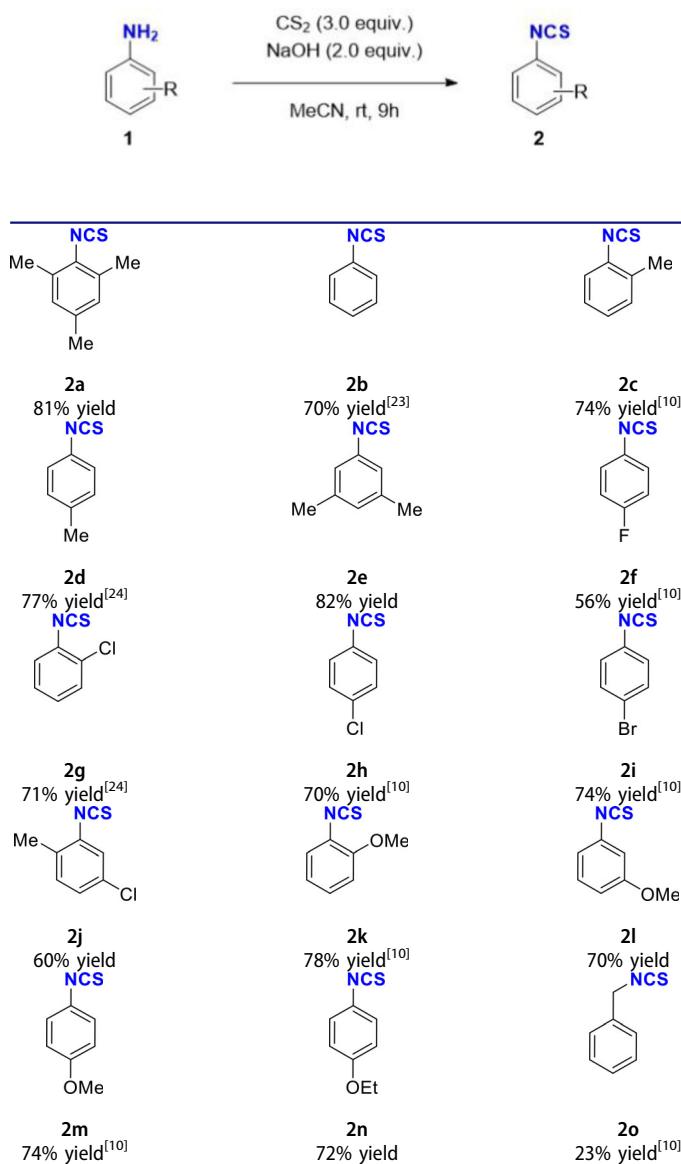
We commenced our investigation by screening a series of bases for the desired benchtop synthesis of mesityl ITC **2a** (Table 1). When the organic base triethylamine was employed as reported by Gajda,^[21] **2a** was obtained in 45% yield (entry 1). Switching to weak inorganic bases failed to

Table 2. Optimization of carbon disulfide and NaOH loading.

Entry	NaOH (equiv.)	CS ₂ (equiv.)	Time (h)	Yield ^a
1	1.0	3.0	3	48%
2	2.0	3.0	3	66%
3	3.0	3.0	3	65%
4	2.0	1.0	9	24%
5	2.0	2.0	9	77%
6	2.0	3.0	9	81%
7	2.0	4.0	9	76%

^aIsolated yields.

provide comparable yields (entry 2–4, 14%–33% yield). The strong inorganic bases NaOH (entry 5) and KOH (entry 6) furnished the product in 66% and 64% yield, respectively. These results were surprising in that NaOH and KOH are known to hydrolyze the solvent acetonitrile, but yet they afforded the target ITC in the highest yields. It was evident that such difference in reaction yields unlikely resulted from the hydrolysis of acetonitrile, since the reaction with the hydrolysis product (in the case of NaOH), NaOAc, afforded the product in only 16% yield (entry 4). These findings motivated us to perform a detailed solvent study using NaOH as the base. In our attempt to probe the effect of the potential hydrolysis of acetonitrile, both dried and wet acetonitrile were subjected to the reaction conditions, but no superior yields were achieved (entry 7 and 8, 58% and 50% yield, respectively). In addition, water was tested as the sole solvent for the reaction to give the target ITC in 15% yield (entry 9), indicating that an organic solvent was necessary for dissolving the 2,4,6-trimethylaniline starting material. A recent study suggested that the hydrolysis of acetonitrile by NaOH required the presence of a significant amount of water as well as remarkably higher temperature than room temperature.^[22] Herein, with entry 5 as an example, we postulated that the trace amount of water in the solvent would not cause considerable hydrolysis of acetonitrile under basic conditions at room temperature, but to the contrary, increased the solubility of NaOH in the reaction mixture for improved reaction efficiency. Next, a series of aprotic solvents were screened. To our disappointment, only poor yields were obtained (entry 10–13, 7%–36% yield). Alcohols were also tested in the solvent study. While the reaction with methanol was promising (entry 14, 50% yield), much reduced yield was observed with ethanol (entry 15, 21% yield). With NaOH as the base and acetonitrile as the solvent, extending the reaction time to 6 h improved the yield to 73% (Table 1, entry 16). Further extending the reaction time to 9 h, to our satisfaction, **2a** was obtained in 81% yield (entry 17). However, a decrease in reaction efficiency was observed when the substrates were allowed to react for 12 h (entry 18, 62% yield).

Table 3. The substrate scope of aryl amines.^[10,23,24]

Note: Isolated yields.

The effect of carbon disulfide and NaOH loading on the reaction was also examined and the results are summarized in Table 2.

With optimized reaction conditions in hand, we set out to explore the substrate scope of the developed ITC synthesis. A variety of aryl amines were subjected to the developed conditions (Table 3). With unsubstituted aniline provided **2b** in 70% yield, introducing methyl groups at the ortho (**2c**) and the para (**2d**) positions increased the yield to 74% and 77%, respectively. Submitting the disubstituted 3,5-dimethylaniline to the reaction conditions afforded **2e** in excellent yield. Apparently, the steric effect did not play a significant role in the cases of the mono- and di-methyl substituted anilines tested. Substrates containing electron-

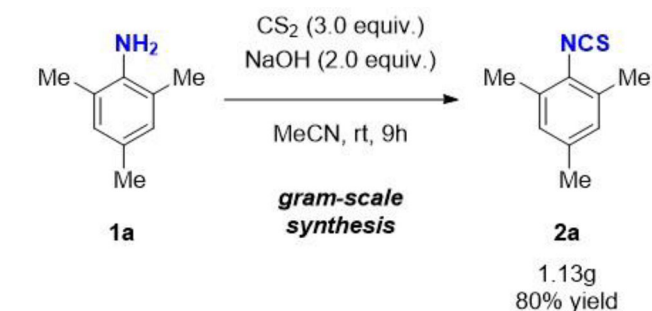
withdrawing groups were also tolerated. Notable electronic effects were observed in fluorine to bromine substitution (**2f–2i**, 56%–74% yield), which was consistent with the increased nucleophilicity of the corresponding aryl amines. Quite unexpectedly, 5-chloro-2-methylaniline delivered the product **2j** with much diminished reaction efficiency. Electron-sufficient aryl amines proved to be compatible substrates as well. Ortho, meta and para-methoxy anilines afforded the targeted ITCs in generally good yields (**2k–2m**, 70%–78% yield). The para-substituted aniline bearing an ethoxy group provided ITC **2n** in 72% yield. Once again, steric hindrance did not exhibit obvious effects in the cases of aryl amines possessing electron-donating groups. Finally,

when benzylamine was subjected to the reaction conditions, benzyl ITC **2o** was furnished notwithstanding that the yield was not ideal. Aryl amines with strongly electron-withdrawing groups, such as 4-nitroaniline, and aliphatic primary amines were also subjected to the optimal conditions, but unfortunately, they failed to provide respective ITC products.

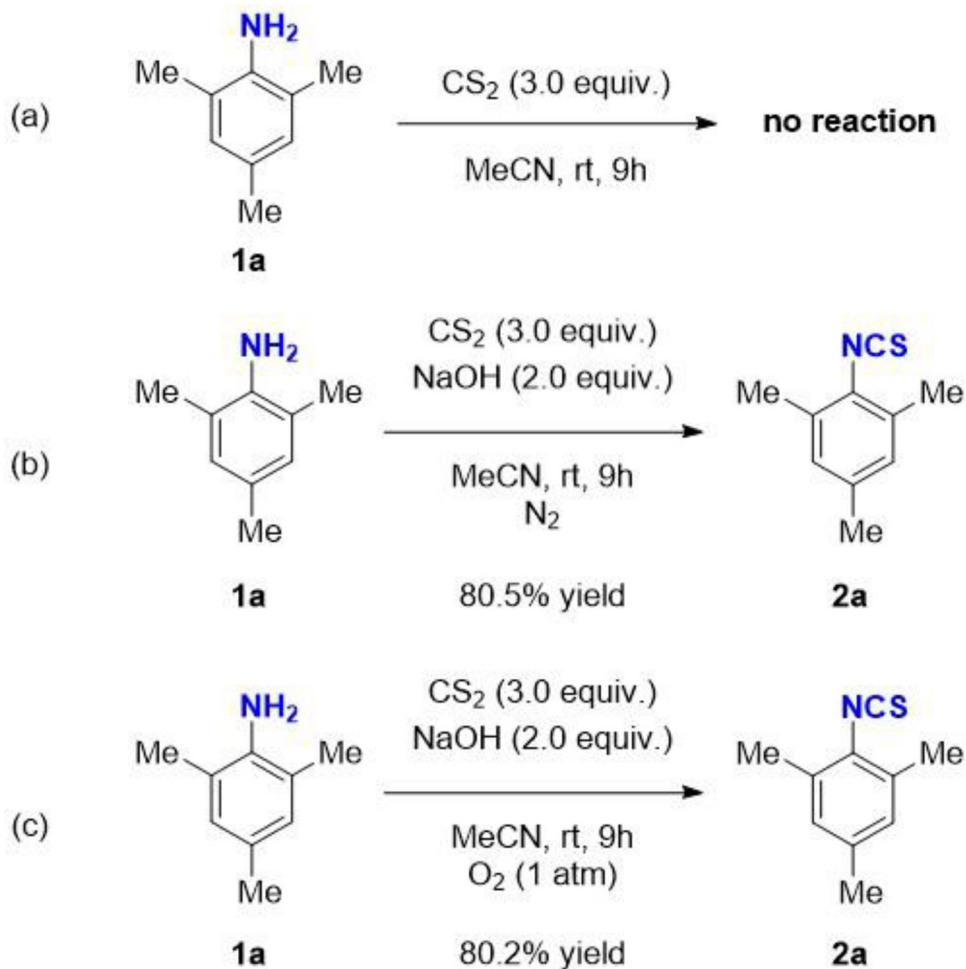
In order to further demonstrate the synthetic utility of the developed method, we performed a gram-scale synthesis of the mesityl ITC **2a** (Scheme 3). To our delight, the reaction remained efficient at large scale.

Proposed mechanism

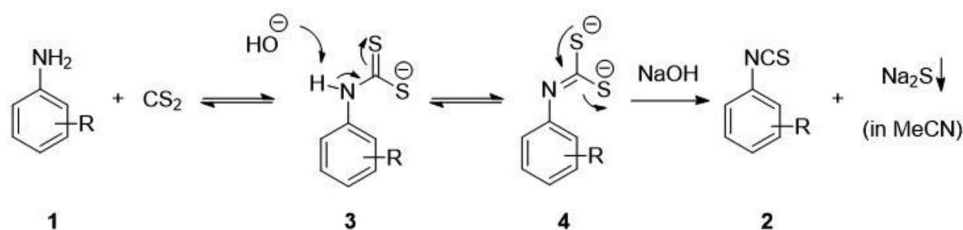
Control experiments were performed to propose a mechanism for the developed ITC synthesis (Scheme 4). In the absence of NaOH, the reaction from 2,4,6-trimethylaniline **1a** to ITC **2a** did not proceed (Scheme 4a), suggesting that NaOH was necessary for the reaction to take place. The insignificant effect of atmosphere (oxygen and nitrogen) on reaction efficiency (Scheme 4b and 4c, respectively) indicated that the dithiocarbamate desulfurization was unlikely an oxidative decomposition promoted by the oxygen in air or the dissolved oxygen in the solvent.



Scheme 3. Gram-scale synthesis of mesityl ITC.



Scheme 4. Control experiments.



Scheme 5. Proposed mechanism.

Given the above results, the proposed mechanism (Scheme 5) is based on literature precedents^[14b,21,25] and supported by the formation of sodium sulfide, which was observed during the reaction course as a yellow precipitate in acetonitrile, but well soluble in water. It is proposed that aniline derivative **1** first reacts with carbon disulfide to provide the key dithiocarbamate intermediate **3**. Under the alkaline conditions, **3** undergoes deprotonation to form the dianion **4**. Finally, in the presence of NaOH, the dianion **4** decomposes, expelling a sulfide anion to produce the sodium sulfide precipitate, whose formation serves as a plausible driving force for the reaction.

Conclusion

In conclusion, we have developed an operationally-simple, economical and environmentally-friendly protocol for ITC synthesis under benchtop conditions at room temperature. Notably this is the first benchtop ITC synthesis promoted solely by a base. The readily available NaOH functioned both as a base and a desulfurating reagent. Sterically and electronically diverse aryl amines and benzylamine were tolerated under the reaction conditions. Future work in our laboratory will focus on the detailed mechanistic study of NaOH-promoted desulfurating decomposition of the dithiocarbamate intermediate.

Experimental

General procedure of isothiocyanate synthesis

To an 8 mL vial were added CH₃CN (1.5 mL), powder sodium hydroxide (40.0 mg, 1 mmol), primary amines (0.5 mmol) and carbon disulfide (114.2 mg, 1.5 mmol) subsequently. The mixture was allowed to stir for 9 h at room temperature and slightly yellow solids were observed to precipitate at the bottom of the reaction vials. Then the reaction mixture was centrifuged for 3 min at 6000 rpm. The upper clear solution was collected and concentrated by rotavap. Flash chromatography on silica gel (eluent: petroleum ether) provided the desired isothiocyanates.

The supplemental materials contain experimental details and spectroscopic characterization data of **2a** – **2o** (Figures S1–S5).

Acknowledgment

We thank Qiong Yang from Guizhou Medical University for her assistance in preparing samples for compound characterization.

Disclosure statement

The authors declare no potential conflict of interest.

Funding

This work was supported by Guizhou Provincial Natural Science Foundation under Grant [2020]1Y030; Guizhou Medical University Ph.D. Research Foundation under Grant J[2019]007.

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