Synthesis of Nitriles via the Iodine-Mediated Dehydrosulfurization of Thioamides

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Received March 11, 2020; accepted April 1, 2020

A simple general method for the synthesis of nitriles using the inexpensive and easy to handle iodine (I2) is described herein. The reaction of thioamides with I2 in the presence of triethylamine at room temperature under aerobic conditions afforded various nitriles bearing aryl, vinyl, and alkyl groups in good-to-excellent yields. This method was also effective for conversion from thioureas to cyanamides.

Key words iodine; thioamide; nitrile; cyanamide; dehydrosulfurization

Introduction

Nitriles are important compounds in organic chemistry and widely used as precursors to obtain various functional groups, such as amines, amides, aldehydes, tetrazoles, and amidines. In addition, the nitrile group is present in a range of natural products, pharmaceuticals, and functional materials, and so numerous methods have been developed for their preparation. For example, the nuclophilic displacement reaction of diazonium salts or aryl halides with bodiimides is one example of a common protocol. Furthermore, alternative methods for the synthesis of aryl nitriles that do not require cyanide sources have been reported, for example, the dehydration of amidines or aldazines, the oxidative coupling of alcohols with ammonia, the conversion of carboxylic acids to nitriles, and the dehydrosulfurization of thioamides. The last of these examples is a particularly efficient approach, and involves the treatment of thioamides with diverse desulfurizing agents such as the transition metal reagents MnO2, AgOAc, Hg(OAc)2, and Cu(OAc)2, heavier main group reagents such as nBu3SnO, a combination of Zn(OTf)2 and AgOAc, Hg(OAc)2, and Cu(OAc)2, triphenylbismuth dichloride, or gold nanoparticles has been recently reported by Doris and colleagues, respectively. However, these reactions present disadvantages, such as high costs and toxicities, long reaction times or harsh reaction conditions. In addition, hypervalent iodine reagents such as diacetoxyiodobenzene (PIDA) and 2-iodoxybenzoic acid (IBX) have been reported to act as oxidative desulfurization agents, converting dithiocarbamate salts and thioureas into isothiocyanates, cyanamides, and carbodiimides. However, iodine (I2) is an inexpensive and less toxic reagent compared to the above hypervalent iodine compounds, and so has also been used as a mild desulfurization agent. For example, Patel and colleagues reported the I2-mediated synthesis of cyanamides and isothiocyanates from dithiocarbamate salts, while Nembenna and colleagues carried out the synthesis of bulky N,N'-diaryl carbodiimides by reacting the corresponding thioureas with I2. Furthermore, Ning and colleagues developed the synthesis of guanidines via the I2-mediated desulfurization of N,N'-di tert-butoxy carbonyl (Boc)-thioureas. Synthesis of nitriles into thioamides is also possible, and interconversion reaction be-

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Table 1. Screening of Reaction Conditions

| Entry | Reagent | Et3N (eq) | Solvent | Time (h) | Yield (%) |
|-------|---------|-----------|---------|---------|-----------|
| 1     | I2      | 3         | CH2Cl2  | 0.5     | 99        |
| 2     | PhI(OAc)2 | 3       | CH2Cl2  | 2       | 99        |
| 3     | IBX   | 3         | CH2Cl2  | 0.5     | 88        |
| 4     | TBAI   | 3         | CH2Cl2  | 1       | 48 (39)   |
| 5     | Ph3Bi(OAc)2 | 3 | CH2Cl2  | 2       | 93        |
| 6     | Ph3Sb(OAc)2 | 3 | CH2Cl2  | 2       | 73        |
| 7     | Ph3SbCl2 | 3         | CH2Cl2  | 1       | 76        |
| 8     | I2      | 3         | DCE     | 1       | 95        |
| 9     | I2      | 3         | Toluene | 2       | 71        |
| 10    | I2      | 3         | THF     | 2       | 84        |
| 11    | I2      | 3         | CH3CN   | 1       | 90        |
| 12    | I2      | 3         | MeOH    | 0.5     | 85        |
| 13    | I2      | 3         | DMF     | 1       | 94        |
| 14    | I2      | 3         | CH2Cl2  | 0.5     | 91        |
| 15*   | I2      | 3         | CH2Cl2  | 2       | 27 (68)   |
| 16    | I2      | 2         | CH2Cl2  | 2       | 80        |
| 17    | I2      | —         | CH2Cl2  | 24      | 11 (69)   |
| 18    | —       | 3         | CH2Cl2  | 24      | 85 (57)   |
| 19*   | I2      | 3         | CH2Cl2  | 1       | 82        |

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Vol. 68, No. 7 679
Chem. Pharm. Bull. 68, 679–681 (2020) 679

Note

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between thioamide and nitrile is one of the important reactions in the field of organic synthesis. Inspired by the aforementioned reports, we herein present the facile dehydrosulfurization of thioamides using I$_2$ for the synthesis of aryl nitriles under mild reaction conditions.

**Results and Discussion**

We initially focused our attention on determination of the optimal conditions for the dehydrosulfurization of benzothioamide 1a. The standard reaction conditions involved the use of various reagents containing I$_2$, antimony, and bismuth in the presence of triethylamine as a base at room temperature under aerobic conditions. The reagent and solvent screening results for the synthesis of benzonitrile 2a from 1a are summarized in Table 1. Initially, the reaction of 1a with various reagents was carried out in CH$_2$Cl$_2$ to compare their reactivity (entries 1–7). All reagents gave the expected benzonitrile 2a in good-to-excellent yields. Among them, I$_2$ was found to be the best reagent for this dehydrosulfurization process, producing 2a in 99% yield. Subsequent solvent screening showed that the reaction took place effectively in all solvents examined, among which CH$_2$Cl$_2$ gave the optimal results in terms of the yield and reaction time (entries 8–13). Using diisopropylethylamine instead of triethylamine as a base also gave 2a in high yield (entry 14). This reaction was found to be stoichiometric, and as an example, decreasing the loading of I$_2$ to 0.3 eq significantly reduced the yield of 2a (entries 1 and 15). Furthermore, the use of triethylamine as a base gave superior results when 3 equivalents were employed (entries 1 and 16). Moreover, it was found that I$_2$ and triethylamine were essential for the reaction, 2a was hardly obtained without these reagents. (entries 17 and 18). When the reaction did not proceed smoothly, by-products were not obtained and a considerable amount of thioamide 1a was recovered (entries 4, 15, 17, 18). This dehydrosulfurization process was also successfully scale-up to 30 mmol to give 2a in good yields of up to 82%, and generating up to 2.54 g of the desired product (entry 19). The Gram-scale reaction was found to exotherm during the reaction at room temperature, and the yield of 2a was reduced to 52% yield. Therefore, this reaction was operated under cooling at −20°C. When benzamide was used instead of benzothioamide, the starting material was recovered, and the corresponding nitrile was not obtained.

To demonstrate the efficiency and generality of the above-mentioned protocol, the reactions of various thioamides 1 (2 mmol) and I$_2$ (2 mmol) were investigated under the optimized conditions, and the results are summarized in Table 2. The reaction of aryl thioamides 1b–1i bearing electron-donating and electron-withdrawing substituents on the benzene ring afforded the corresponding aryl nitriles 2b–2i in good-to-excellent yields. The electronic nature (electron-rich or electron poor) of the substituents in the p-position did not affect the outcome of the reaction. The dehydrosulfurization reaction of phenol 1c using Ph$_3$BiCl$_2$ reported by Doris and colleagues gave a complex mixture. In contrast, the smooth progress of this reaction using I$_2$ indicates the superiority of this method. In addition, phenol derivative 1c gave a complex mixture when the dehydrosulfurizing agent was changed from I$_2$ to Ph$_3$BiCl$_2$, suggesting the superiority of the described protocol. Furthermore, sterically hindered ortho-substituted thioamides reacted to give the corresponding nitriles 2j and

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**Table 2. Dehydrosulfurization of Thioamides with I$_2$**

| Entry | Substrate | Time (h) | Product | Yield (%) | Entry | Substrate | Time (h) | Product | Yield (%) |
|-------|-----------|----------|---------|-----------|-------|-----------|----------|---------|-----------|
| 1     | 1b        | 0.5      | 2b: 88  |           | 11    | 1h        | 0.5      | 2h: 76  |           |
| 2     | 1e        | 0.5      | 2e: 80  |           | 12    | 1m        | 0.5      | 2m: 97  |           |
| 3     | 1d        | 0.5      | 2d: 92  |           | 13    | 1m        | 1        | 2m: 94  |           |
| 4     | 1e        | 0.5      | 2e: 82  |           | 14    | 1o        | 1        | 2o: 90  |           |
| 5     | 1f        | 0.5      | 2f: 87  |           | 15    | 1p        | 1        | 2p: 81  |           |
| 6     | 1g        | 0.5      | 2g: 94  |           | 16    | 1q        | 1        | 2q: 86  |           |
| 7     | 1h        | 0.5      | 2h: 72  |           | 17    | 1r        | 1        | 2r: 72  |           |
| 8     | 1i        | 0.5      | 2i: 94  |           | 18    | 1s        | 1        | 2s: 71  |           |
| 9     | 1j        | 0.5      | 2j: 76  |           | 19    | 1u        | 1        | 2u: 70  |           |
| 10    | 1k        | 0.5      | 2k: 93  |           |       |           |          |         |           |

*a) 1 (2 mmol), I$_2$ (2 mmol), Et$_3$N (6 mmol). b) Isolated yield. c) −20°C.
2k without any difficulty. The reaction proceeded smoothly even when 11 and 1m, bearing electron-rich heteroaromatic rings (e.g., thiophene), and 1n–1p, bearing electron-deficient heteroaromatic rings (e.g., pyridine and pyrazine) to give the corresponding nitriles 2l–2p. This reaction advanced not only with thioamides but also with thioamides 1q and 1r bearing vinyl groups and alkyl side chains to afford cinnamnitrite 2q and 2-phenylacetaminitril 2r, respectively. Furthermore, it should be noted that the reactions of thioureas 1s–1u with I2 required a lower temperature of −20°C, but the corresponding cyanamides 2s–2u were obtained in moderate yields. When thioureas 1s–1u was reacted at room temperature, cyanamides 2s–2u gave in low yields (13–43%).

A possible mechanism for the present dehydrosulfurization process is presented in Chart 1. In this mechanism, the initial step involves the generation of intermediate A from the reaction of thioamide 1 with I2, through attack of the sulfur atom of 1 to I2. The subsequent reductive elimination of sulfur from intermediate A gives the desired nitrile 2 and triethylamine salt.

![Chart 1. Possible Mechanism](image)

**Conclusion**

In conclusion, we demonstrated a simple method for the synthesis of nitriles from thioamides via dehydrosulfurization using I2 in the presence of triethylamine. In this system, I2 acted as mild and convenient reagent, and gave the corresponding products efficiently and in good yields. This protocol is characterized by its simple operation at room temperature under aerobic conditions, the absence of by-products, and short reaction times. Since I2 is an inexpensive and low-toxic reagent, studies into expanding the desulfurization reaction to other substrates are currently in progress, and the results will be reported in due course.

**Conflict of Interest** The authors declare no conflict of interest.

**Supplementary Materials** The online version of this article contains supplementary materials (detailed experimental procedure, physical data, and NMR spectra of isolated products).

**References**

1) Larock R. C., “Comprehensive Organic Transformation: A Guide to Functional Group Preparations,” 2nd ed., Wiley, New York, 1999.

2) Scheuer P. J., Acc. Chem. Res., 25, 432–439 (1992).

3) Fleming F. F., Fleming F. F., Nat. Prod. Rep., 16, 597–606 (1999).

4) Fleming F. F., Yao L., Ravikumar P. C., Funk L., Shook B. C., J. Med. Chem., 53, 7902–7917 (2010).

5) Cao X., Zhang D., Zhang S., Tao Y., Huang W., J. Mater. Chem. C, 5, 7699–7714 (2017).

6) Yan G., Zhang Y., Wang J., Adv. Synth. Catal., 359, 4068–4105 (2017).

7) Bisserset P., Duret G., Blanchard N., Org. Chem. Front., 1, 825–833 (2014).

8) Wang T., Jiao N., Acc. Chem. Res., 47, 1137–1145 (2014).

9) Kim J., Kim H. J., Chang S., Angew. Chem. Int. Ed., 51, 11948–11959 (2012).

10) Ellis G. P., Romney-Alexander T. M., Chem. Rev., 87, 779–794 (1987).

11) Nauth A. M., Opatrz T., Org. Biomol. Chem., 17, 11–23 (2019).

12) Enthaler S., Eur. J. Org. Chem., 2011, 4760–4763 (2011).

13) Enthaler S., Inoue S., Chem. Asian J., 7, 169–175 (2012).

14) Singh M. K., Lakshman M. K., J. Org. Chem., 74, 3079–3084 (2009).

15) Preger Y., Root T. W., Stahl S. S., ACS Omega, 3, 6091–6096 (2018).

16) Televkar V. N., Rane R. A., Tetrahedron, 48, 6051–6053 (2007).

17) Yamaguchi K., Yajima K., Mizuno N., Chem. Commun., 48, 11247–11249 (2012).

18) Avalos M., Babiano R., Cintas P., Durán C. J., Higes F. J., Jiménez J. L., Lopez J., Palacios J. C., Tetrahedron, 53, 14463–14480 (1997).

19) Avalos M., Babiano R., Durán C. J., Jiménez J. L., Palacios J. C., Tetrahedron Lett., 35, 477–480 (1994).

20) Bose D. S., Jayalakshmi B., Goud P. R., Synthesis, 1999, 1724–1726 (1999).

21) Lim M., Ren W. Y., Klein R. S., J. Org. Chem., 47, 4594–4595 (1982).

22) Suzuki H., Tani H., Takeuchi S., Bull. Chem. Soc. Jpn., 58, 2421–2422 (1985).

23) Hu N. X., Aso Y., Otsubo T., Ogura F., Bull. Chem. Soc. Jpn., 59, 879–884 (1986).

24) Fukushima T., Matsuishi T., Hu N. X., Ion, Z., Otsubo T., Ogura F., Chem. Lett., 19, 2269–2272 (1990).

25) Hu N. X., Aso Y., Otsubo T., Ogura F., Tetrahedron Lett., 27, 6099–6102 (1986).

26) Mineno T., Takebe Y., Tanaka C., Mashimo S., Int. J. Org. Chem., 4, 169–173 (2014).

27) Sato R., Itoh K., Ishikawa K., Ishida H., Goto T., Saito M., Chem. Lett., 13, 1913–1916 (1984).

28) Bose D. S., Narasiah A. V., Synthesis, 2001, 373–375 (2001).

29) Bose D. S., Sunder K. S., Synth. Commun., 29, 4235–4239 (1999).

30) Liebscher J., Synthesis, 1982, 1084–1086 (1982).

31) Gopi E., Gravel E., Doris E., Eur. J. Org. Chem., 2019, 4043–4045 (2019).

32) Gopi E., Geertsen V., Gravel E., Doris E., ChemCatChem, 11, 5758–5761 (2019).

33) Ghosh H., Yella R., Nath J., Patel B. K., Eur. J. Org. Chem., 2008, 6189–6196 (2008).

34) Ghosh H., Yella R., Ali A. R., Sahoo S. K., Patel B. K., Tetrahedron Lett., 50, 2407–2410 (2009).

35) Chaudhari P. S., Danzate P. S., Akamanchi K. G., Synlett, 2010, 3065–3067 (2010).

36) Nath J., Patel B. K., Janmil L., Sinha U. B., Satyanarayana K. V. V., Green Chem., 11, 1503–1506 (2009).

37) Nath J., Janmil L., Patel B. K., Green Chem. Lett. Rev., 4, 1–34 (2011).

38) Peddara T., Baishya A., Barman M. K., Kumar A., Nembenna S., New J. Chem., 40, 7627–7636 (2016).

39) Rong H.-J., Yang C.-F., Chen T., Wang Y-Q., Ning B-K., Tetrahedron Lett., 60, 150970 (2019).