Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201901103

Link to VoR: http://dx.doi.org/10.1002/adsc.201901103

10.1002/adsc.201901103

FULL PAPER

DOI: 10.1002/adsc.201

Regioselective Cyanation of Six-Membered *N*-Heteroaromatic Compounds Under Metal-, Activator-, Base- and Solvent-Free Conditions

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Received:

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201

Abstract. A regioselective cyanation of heteroaromatic *N*-oxides with trimethylsilyl cyanide has been developed to obtain 2-substituted *N*-heteroaromatic nitrile without the requirement of any external activator-, metal-, base-, and solvent. The present protocol is a straightforward, one-pot heteroaromatic C−H cyanation process, and proceeds smoothly in conventional heating but also under microwave irradiation with shorter reaction times. This approach now allows access to a broad class of quinoline *N*-oxides and other heteroarene *N*-oxides with high to good yields and can also be scaled up to obtain gram quantities. Further application of this process was observed and utilized in late-stage cyanation of the anti-malarial drug quinine as well as transformation of the 2-cyanoazines to a series of biologically important molecules. Based on the experimental observations, a plausible mechanism has also been proposed highlighting the dual role of trimethylsilyl cyanide as a nitrile source and as an activating agent.

Keywords: activator-free; base-free; solvent-free; cyanation; microwave; regioselective; trimethylsilyl cyanide; heteroaromatic *N*-oxide, bio-active heteroaromatic nitrile.

Introduction

Heterocyclic compounds, especially *N*-containing heterocycles, represent a highly important class of compounds that exhibit diverse pharmacological and therapeutic effects.[1] However, the therapeutic effect of the *N*-heterocyclic scaffolds (such as the quinoline moiety) is often detoxified in the body due to the hydroxylation at the C-2 position, thereby resulting in the decline of the aforementioned therapeutic effect.[2] To block this detoxification, a vast majority of research is aimed towards functionalization at the C-2 position in fused azine systems for the construction of new C−C bonds.[3] Among them, functionalization with a nitrile group is an important methodology as it plays a key role in chemistry, biology, and medicine.[4] The nitrile group itself acts as a good hydrogen bond acceptor promoting binding to the protein backbone. It can also serve as an isostere to the carboxyl or hydroxyl moiety because of its strong dipole nature.[4a] In addition, the nitrile can easily be converted to various other functional groups such as amide, amine, ketone, carboxylic acid, etc. as well as other pharmaceutically relevant heterocyclic compounds.[5]

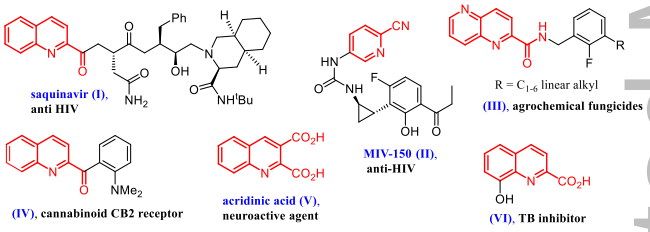
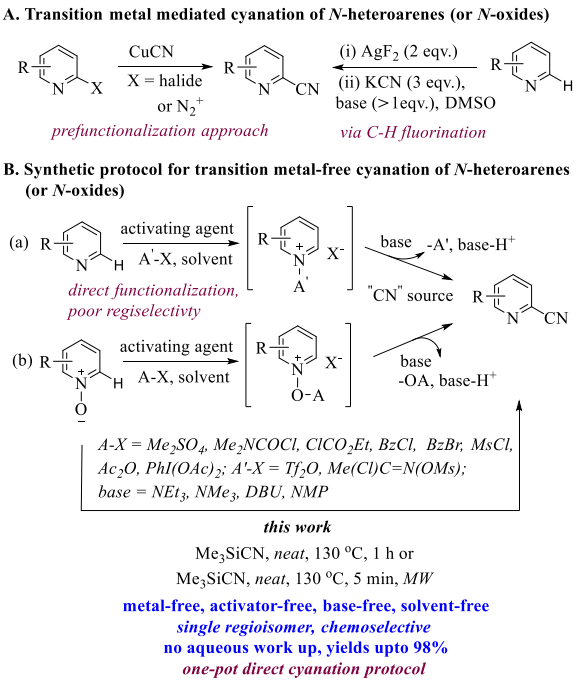


Figure 1. Selected bio-active compounds with *N*-containing 2-cyano heteroaromatic derivatives.

The nitrile containing derivative of *N*- heteroarenes are widely used in pharmaceutical and agrochemical industries and for the total synthesis of natural products. These include the anti HIV and anti AIDS drug saquinavir (I),[6] anti HIV drug MIV-150 (II),[7] agrochemical fungicides (III),[8] cannabinoid CB2 receptor (IV),[9] neuroactive agent acridinic acid (V),[10] and TB inhibitor (VI)[11] (Figure 1). As a result, a considerable effort has been devoted to developing an efficient synthetic protocol that gives facile access to the 2-cyano heterocyclic scaffolds.



Scheme 1. Synthetic strategies for C-2 cyanation of 6-ring *N*-containing heteroaromatics.

Earlier research to incorporate the nitrile group into the *N*-heteroaromatic system included transition-metal-mediated pathways either through the Pd-catalyzed cyanation approach [12] or *via* the Sandmeyer and Rosenmund-von Braun reaction[13]. The latter requires the prefunctionalization of the heterocyclic ring and the use of copper cyanide as a cyanide source. To avoid the prefunctionalization approach, Hartwig and coworkers[14] introduced direct functionalization of pyridines at the C-2 position *via* silver fluoride mediated sequential C–H fluorination and subsequent nucleophilic displacement of the fluoride in the presence of a base (Scheme 1). Though it provided a diverse range of nucleophiles, there are still some disadvantages. These include (a) the use of expensive and super stoichiometric metals and (b) late-stage removal of the trace metal contamination in the final product, which can be difficult. Because of this, the applications of this methodology have been limited from the pharmaceutical point of view, therefore a transition metal-free cyanation approach is highly desirable.

In general, the transition metal-free approach for the cyanation of *N*-heteroarenes (or *N*-oxides) often involves two steps: (1) activation of the heteroaromatic ring by a suitable electrophilic activator and (2) the nucleophilic addition of the cyanide ion immediately followed by the associated base mediated elimination and rearomatization to generate the cyanated heteroaromatic compounds. Two encouraging reports appeared in the recent literature one each by the groups of Fier[15] and Paton[16] describing the transition metal-free direct cyanation approach. However, both methodologies have limitations. For instance, the Fier group used toxic NaCN as a cyano group source and the super stoichiometric base was exploited to facilitate the complete conversion. And although the Paton group used triflic anhydride (Tf_2O) as an activating agent with NMM as a base and Me_3SiCN as the cyanide source, ultimately it suffered from poor regioselectivity. (Scheme 1).

The heteroaromatic *N*-oxide class would seemingly be a suitable alternative to overcome the issue of selectivity, as the electrophilic character at the C-2 position is enhanced by the coordination of an activating agent to the *N*-oxide. Various reagents like dimethyl sulphate,[17] *N*,*N*-dimethylcarbamoyl chloride,[18] ethyl chloroformate,[19] benzoyl halides,[20] acetic anhydrides,[21] and MsCl,[22] have been used as activators for this purpose [more recently, Sun and co-workers used hypervalent iodine (III)[23] as an activating agent]. Despite considerable progress, these protocols suffer from several limitations such as longer reaction times and excess use of reagents or activators. In addition, these reagents are often hazardous, toxic, and sensitive towards air and moisture, which stiffen easy handling. In many cases the competing additions of the activator counter-ion also become problematic.[23,24] And bases are generally required[21,25] with a super-stoichiometric amount to facilitate the full conversion at the final re-aromatization step.[15,16,25] Therefore, it is apparent that these particular methodologies need not only high cost but have environmental issues. However, the greatest and most obvious drawback in most of these cases is the lack of regioselectivity[15,16,21,25c,26,27]

In today's pursuit of sustainable chemistry, the use of solvents, particularly halogenated solvents, should be avoided wherever possible.[28,29] Following the axiom of Sheldon that the "best catalyst is no catalyst" and the "best solvent is no solvent",[30] we were interested in designing a methodology which is devoid of any catalyst or solvent. Herein, we report the first example of an operationally simple, one-pot heteroaromatic C−H cyanation system that proceeds without the need for metals, catalysts, activators, base, and solvent with excellent regioselectivity at the C-2 position.

Results and Discussion

We began our study by measuring the cyanation of *N*-heteroaromatic compounds under metal-free, activator-free, and base-free conditions. 1 equiv. of quinoline *N*-oxide was added to 3 equiv. of trimethylsilyl cyanide in dichloroethane (DCE) at room temperature. We observed no conversion after refluxing overnight (Table 1, entries 1 and 2) which was consistent with the reported literature.[23] However, when dimethylformamide (DMF) was employed as the solvent rather than DCE, the conversion was slightly improved and the desired product was obtained with a modest 12% yield (entry 3). But when we performed the reaction under

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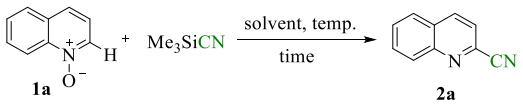
solvent-free conditions with the same stoichiometry of Me_3SiCN (3 equiv.) at 80 °C, substrate **1a** was completely consumed and quinoline-2-carbonitrile was obtained with a 90% yield within 6 hours. In addition, we found that increasing the reaction temperatures even more resulted in shorter reaction times. This suggested that the reaction temperature plays a significant role in the reaction outcome. To investigate the influence of the concentration of Me_3SiCN, we examined different equivalents of trimethylsilyl cyanide and the results revealed that 3 equiv. of Me_3SiCN gave the same conversion that was achieved while employing 2.2 equiv. However, lowering the equivalents from 2.2 led to a decrease in conversion (entries 10 and 11). We then decided to try the reaction under microwave irradiation (μw). This method is emerging as an alternative to conventional heating practice and leads to accelerated reaction rates.[31] Gratifyingly, we have found that our optimized reactions using microwave irradiation complete within five minutes and give quantitative yields at 130 °C (entry 15).

Table 1. Optimization of C-H cyanation of heterocyclic *N*-oxides[a,b]



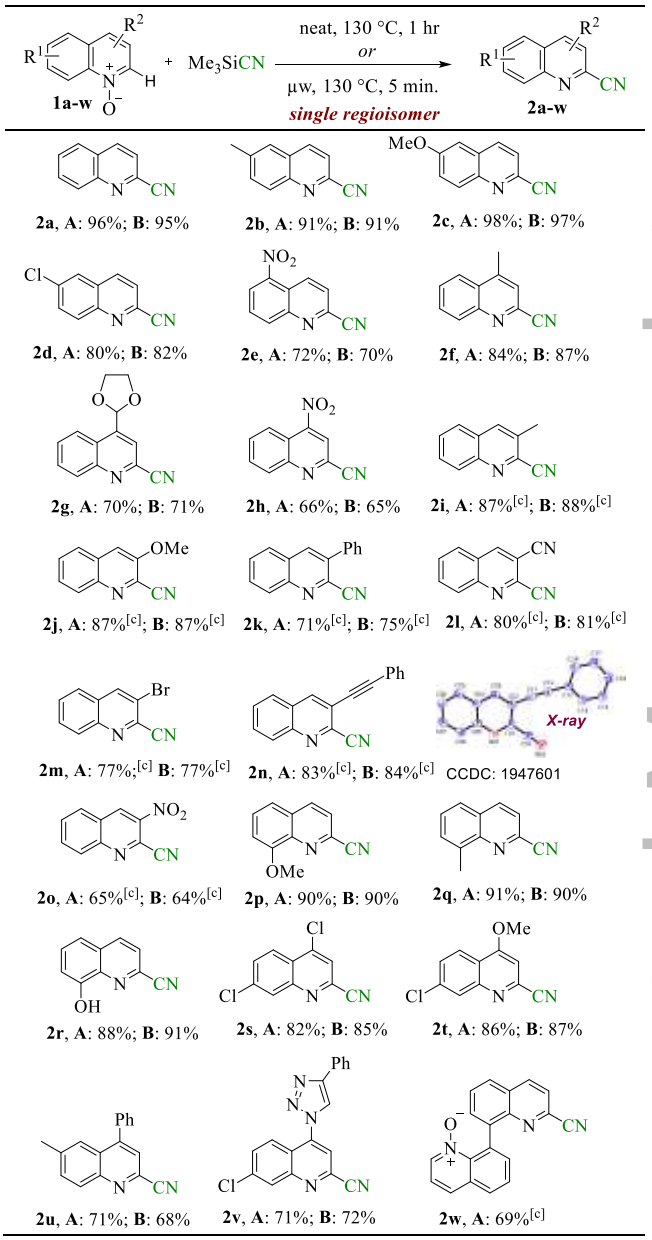
1a **2a**

entry	cyanide source (equiv.)	temperature	solvent	time	yield (%)
1	Me_3SiCN (3)	rt	DCE	15 h	n.d.
2	Me_3SiCN (3)	reflux	DCE	15 h	n.d.
3	Me_3SiCN (3)	130 °C	DMF	15 h	12
4	Me_3SiCN (3)	rt	neat	15 h	n.d.
5	Me_3SiCN (3)	60 °C	neat	15 h	10
6	Me_3SiCN (3)	80 °C	neat	6 h	90
7	Me_3SiCN (3)	100 °C	neat	2 h	92
8	Me_3SiCN (3)	130 °C	neat	1 h	96
9	Me_3SiCN (2.2)	130 °C	neat	1 h	96
10	Me_3SiCN (1.5)	130 °C	neat	15 h	60
11	Me_3SiCN (1)	130 °C	neat	15 h	45
12	PhCOCN (3)	130 °C	neat	15 h	19
13	$K_4Fe(CN)_6$ (3)	130 °C	neat	15 h	n.d.
14	Me_3SiCN (3)	80 °C, μw	neat	1 h	76
15	Me_3SiCN (2.2)	130 °C, μw	neat	5 m	95

[a] Reaction was carried out using 0.6 mmol of quinoline *N*-oxide under argon atmosphere. [b] Isolated yield after column chromatography. n.d. = not detected.

With the optimized conditions in hand, the scope of the cyanation reaction was explored between various quinoline *N*-oxide derivatives (**1a-w**) and the trimethylsilyl cyanide nucleophile. The reaction seems to be fairly effective for a wide pool of substrates with high to good yields of the cyanation product at the C-2 position. This was observed for both electron-donating as well as electron-withdrawing substituents (such as −Me, −Ph, −OH, −OMe, −Cl, −Br, −CN, −C≡C–Ph and –NO_2) at the quinoline scaffold. Notably, the electron-donating substituents (Table 2, products **2b**, **2c**) led to the desired products with higher yields compared to electron-withdrawing substituents (product **2d**). Retaining halogen functional groups can be beneficial as it allows for further functionalization. In our study, the halogen substituents remained intact giving desired nitrile compounds in excellent yields. In the case of 4,7-dichloroquinoline *N*-oxide, the C-4-substituted chloro group is susceptible to nucleophilic attack. Despite this, we were able to obtain only C-2 cyanated single regioisomer with 85% yield. It should be noted that the introduction of aliphatic groups at various positions was explored (products **2b**, **2f**, **2i**

Table 2. Substrate scope for the cyanation of quinoline *N*-oxides[a,b]



[a] Reaction conditions: substrate (0.6 mmol), Me_3SiCN (1.32 mmol), neat, under argon atmosphere, at 130 °C; Method-**A**. The reaction was performed under conventional heating method at 130 °C for 1 h. Method-**B**. The reaction was performed under microwave (power 50 W) at 130 °C for 5 to 15 min. [b] Isolated yields are reported. [c] 4.2 equiv. Me_3SiCN was used.

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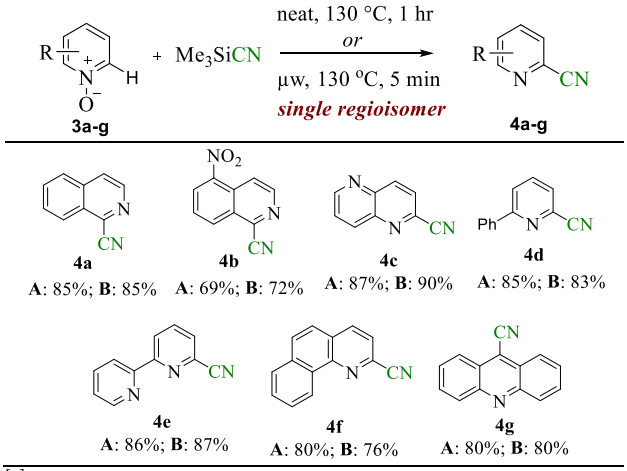
and **2q**) and very good yields were obtained in all of our cases. We decided next to synthesize various polysubstituted quinoline *N*-oxide derivatives and found that the desired products were obtained in modest to good yields (products **2s-v**). C-3 and C-8 functionalized quinoline *N*-oxides were also employed in cyanation providing the products **2i-o** and **2p-r** with good yields. To our delight, the current protocol is not sensitive to the steric effect and shows excellent regioselectivity for all of our cases. However, complete conversion for the substituents at the C-3 position required an additional two equivalents of the nucleophile. Interestingly, the hydroxy functional group survived under the current protocol (product **2r**) and we also found that the cyano group can be installed selectively at the 2-position in 8,8'-biquinolyl *N*,*N*'-dioxide (**1w**) moiety with a 69% yield. The entity of the quinoline moiety and substitution of the nitrile unit at the C-2 position was confirmed by X-ray crystallography (**2n** in Figure S2).[32]

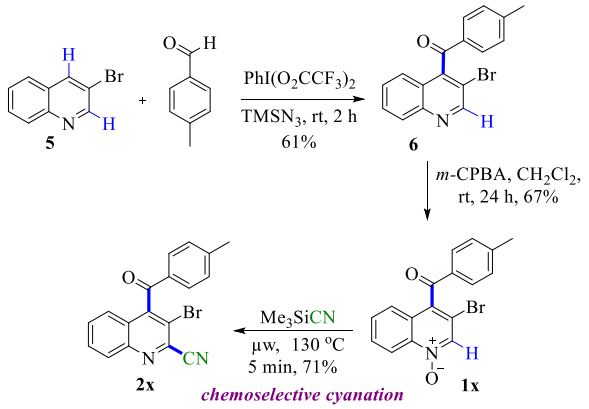
Table 3. Substrate scope for the cyanation of other heterocyclic *N*-oxides with Me_3SiCN [a,b]



[a] Reaction conditions: substrate (0.6 mmol), Me_3SiCN (1.32 mmol), neat, under argon atmosphere, at 130 °C. [b] Isolated yield are reported. Method-**A**. The reaction was performed under conventional heating method at 130 °C for 1 h. Method-**B**. The reaction was performed under microwave (power 50 W) at 130 °C for 5 min.

After successfully obtaining quinoline *N*-oxide derivatives using our protocol, we then turned our attention to the isoquinoline systems as it is an important scaffold in medicinal chemistry. We were again able to successfully apply our protocol to substituted isoquinoline leading to the isoquinoline-1-carbonitrile derivatives with good yields up to 85% (Table 3, products **4a**, **4b**). However, the scope of the present synthetic protocol is not just limited to quinoline and isoquinoline scaffolds, but proceeds readily to other *N*-heteroarenes such as 5-naphthyridine, benzo[*h*]quinoline and acridine (products **4c**, **4f**, **4g**), as well as the pyridine *N*-oxide derivatives (**3d**) and 2, 2′-bipyridine-*N*-oxide (**3e**).

Our methodology was further applied to the selective substitution of nitrogenous heterocycles.[33] Stepwise C−H bond functionalization of 3-bromoquinoline was carried out using cross-dehydrogenative coupling followed by *N*-oxidation and cyanation. This resulted in the formation of **2x** in 71% yield (Scheme 2), thus demonstrating that the sequential C−C bond formation at C-2 and C-4 positions with different substituents could be obtained without the need for metal-containing reagents. Interestingly, the carbonyl group remained intact during the cyanation process, suggesting the chemoselective nature of the developed protocol.[34]



Scheme 2. Metal-free regioselective sequential C-H bond functionalization of 3-bromoquinoline.

The current methodology was also used for the late-stage functionalization of the anti-malarial drug quinine **2y** and (±)-α-tocopherol modified quinoline derivative **2z**. Both were obtained in good yields (Figure 2).

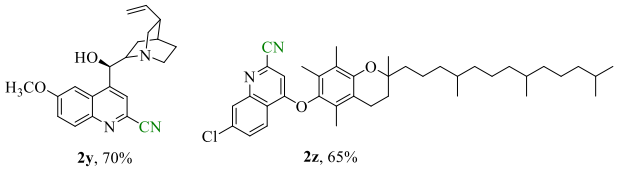


Figure 2. Late-stage functionalization of anti-malarial drug quinine and (±)-α-tocopherol modified quinoline derivative.

We studied the efficiency of this process by scaling up the reaction in a gram scale for bulk utilization. First, we attempted to synthesize 2-cyanoquinoline (**2a**) from 1 g of quinoline *N*-oxide using standard conditions and found that **2a** could be obtained in 86% yield (Scheme 3a). We also discovered that the final compound was easily isolable through sublimation (sublimated yield for **2a**, 76%), thereby evading any aqueous workup (which is often required to remove the promoters, additives, bases, and side products in the traditional cyanation of *N*-heteroarenes). Hence, the process is overall very efficient from a practical perspective.

We then attempted the reaction with 4,7-dichloroquinoline. The compound effectively

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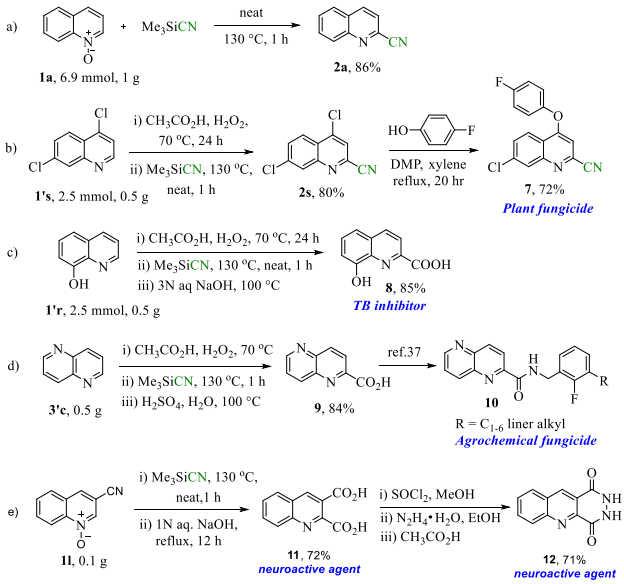
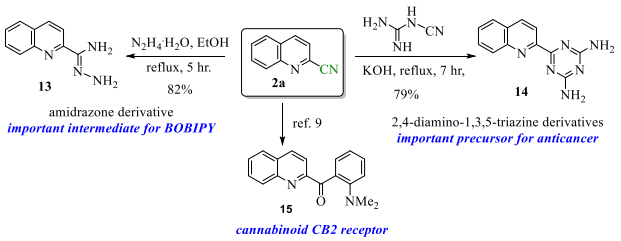
underwent one-pot oxidation and cyanation, yielding compound **2s**. **2s** represents an important reaction intermediate for MRK-8-29,[35] a specific *in vivo* agent for mGlu2 negative allosteric modulator. The resulting **2s** could then be simply transformed into the potent plant fungicide derivative **7** in 72% yield (Scheme 3b).[36] Our protocol was also extended to the synthesis of the TB inhibitor **8**[11] and plant fungicide precursor **9**[37], obtaining both in high yields (Scheme 3c and 3d). We discovered that several neuroactive agents can easily be accessed by simple hydrolysis of **2l**, leading to acridinic acid (**11**)[38] and it's the derivative of 2,3-dihydropyridazino [4,5-*b*] quinoline-1,4-dione (**12**)[39] in 72% and 71% yield, respectively (Scheme 3e).



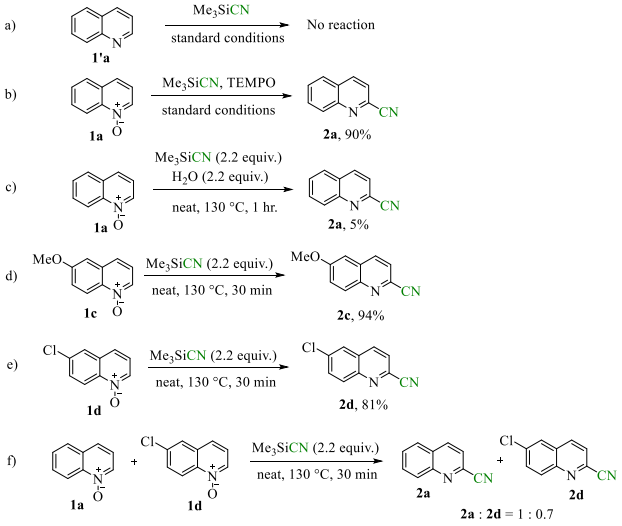
Scheme 3. Gram-scale synthesis, one-pot transformation and application of synthesized 2-cyanoheterocyclic derivatives.

The limits of using 2-cyanoquinoline as a substrate were explored in the synthesis of amidrazone derivative **13**, which is an important building block for biological imaging studies.[40] **13** was readily obtainable and could be easily converted to the 2,4-diamino-1,3,5-triazine derivative **14**, an important precursor for anticancer activity.[41] In addition, carbonitrile **2a** can be easily transformed into the quinolinyl aryl ketone, which is used as a novel agonist for the cannabinoid CB2 receptor[9] (Scheme 4).

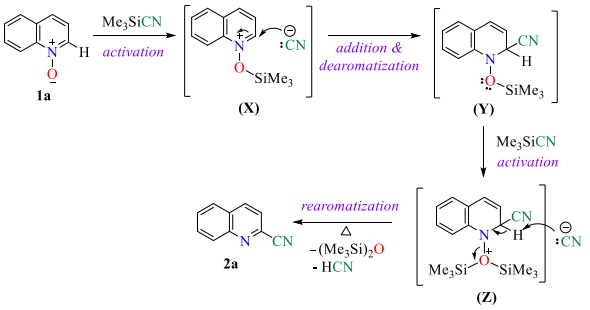


Scheme 4. The synthetic utility of 2-position-substituted heteroaromatic nitriles.

To gain insight into the reaction pathway, we have performed a series of control experiments. For example, when quinoline was treated with trimethylsilyl cyanide, the desired 2-cyanoquinoline product was not observed, suggesting the important role of the *N*-O group in this transformation (Scheme 5a). Further, by using radical scavenger TEMPO in the reaction mixture, the expected product was formed without any change in the reaction conditions which ruled out any radical mechanism pathway. In addition, the cyanation of quinoline *N*-oxide was ineffective with water, which implied that the present transformation may not occur *via* the hydrogen cyanide pathway. We have demonstrated the reaction independently with 6-methoxyquinoline *N*-oxide and 6-chloroquinoline *N*-oxide with trimethylsilyl cyanide at 130 ˚C for half an hour. While 94% desired product was observed for the former, 81% product was obtained in the latter case (Scheme 5d, and 5e). The intermolecular competition reaction between quinoline *N*-oxide and 6-chloroquinoline *N*-oxide with trimethylsilyl cyanide yielded the desired products **2a** and **2d** in a 10:7 ratio. Both these experiments suggested that electron-donating substituents have a favourable impact on the reaction rate compared to electron-withdrawing substituents (Scheme 5f).



Scheme 5. Control experiments for the reaction mechanism.



Scheme 6. Plausible reaction mechanism.

Based on earlier reports[25a] and our experimental findings a plausible reaction mechanism has been proposed in Scheme 6. The quinoline *N*-oxide is activated by trimethylsilyl cyanide releasing the cyanide anion. In the next step, the nucleophilic addition at the C-2 position of the activated ring takes place, resulting in the dearomatized intermediate **Y**. The latter is further activated by an additional equivalent of trimethylsilyl cyanide generating the ionic species **Z**. Subsequent rearomatization gives the final compound **2a** with concomitant release of hexamethyldisiloxane [$(Me_3Si)_2O$] as the byproduct.[42,43] This was detected in the GC-MS (*m/z* = 147.06 $[Me_5Si_2O]^+$)[44] and confirmed by ^{29}Si NMR spectroscopy (δ = 7.31 ppm).[45] The formation of proposed intermediate **Z** (for the product **2c**) is supported by the appearance of the respective peak in the crude NMR at different interval times (see ESI in detail). This plausible pathway explains the dual role of trimethylsilyl cyanide as a cyanide source for the cyanation reaction as well as an activating agent for the *N*-oxides to produce the target heterocycles.

Conclusion

In summary, we have demonstrated the cyanation of heteroaromatic *N*-oxides with trimethylsilyl cyanide in the absence of metals, external activators, base and solvent with excellent regioselectivity at the C-2 position. To the best of our knowledge, this is the first example of an efficient incorporation of a nitrile moiety into the C−H bond of *N*-heteroaromatic compounds in the absence of any external activator and base. The present protocol proceeds smoothly in conventional heating but also microwave irradiation with shorter reaction times. The synthetic utility of the C-2-substituted heteroaromatic nitriles is further demonstrated by the synthesis of several bioactive molecules, including late-stage functionalization of anti-malarial drug quinine and the (±)-α-tocopherol modified quinoline derivative. Preliminary mechanistic data highlights the dual role of trimethylsilyl cyanide, which can act as a cyanide source as well as an activating agent. From an industrial perspective, this method is promising as it is (a) operationally simple, (b) highly efficient, (c) economically viable, and (d) easy to scale-up. Further utilization of this simple trimethylsilyl cyanide in other cyanation reactions under solvent-free conditions is underway.

Experimental Section

General procedure for cyanation of heterocyclic *N*-oxides (A): Heterocyclic *N*-oxides (0.6 mmol, 1 equiv.) and trimethylsilyl cyanide (1.32 mmol, 2.2 equiv.) were added successively to an oven-dried 15 mL-vial containing a stirring bar. Then the tube was flushed with argon and sealed with screw-cap. The resulting solution was heated at 130 °C for 1 hour. After the reaction was completed as determined from TLC, the reaction mixture was dried under reduced pressure. The crude product was purified through SiO_2-gel column chromatography to afford analytically pure cyanoheterocyclic compounds.

General procedure for cyanation of heterocyclic *N*-oxides (B): Heterocyclic *N*-oxides (0.6 mmol, 1 equiv.) and trimethylsilyl cyanide (131 mg, 1.32 mmol, 2.2 equiv.) were added successively to an oven-dried microwave reaction tube containing a stirring bar. The tube was then flushed with argon and sealed with screw-cap. The resulting solution was heated at 130 °C for 5 min under microwave irradiation (50 W). The reaction mixture was then cooled to room temperature. After the reaction was completed as determined from TLC, the reaction mixture was dried under reduced pressure. The crude product was purified through SiO_2-gel column chromatography to afford analytically pure cyanoheterocyclic compounds.

Acknowledgements

A.D gratefully acknowledges the SERB, DST (ECR/2016/001459) and DST-INSPIRE (IFA-14-CH-135) for financial support. We would like to thank the Department of Chemistry and the CIF, IITG for instrumental support and a start-up grant. B.S., M.K., D.B., and P.A. would also like to thank IITG for their research fellowship. We are thankful to Dr. Muhammed Yousufuddin for his kind help. We are also thankful to the reviewer for useful suggestions.

References

[1] a) X. F. Shang, S. L. Morris-Natschke, Y. Q. Liu, X. Gou, X. S. Xu, M. Goto, J. C. Yang, K. H. Lee, *Med. Res. Rev.* **2018**, *38*, 775–828; b) R. A. Hughes, C. J. Moody, *Angew. Chem. Int. Ed.* **2007**, *46*, 7930–7954, *Angew. Chem.* **2007**, *119*, 8076–8101; c) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274; d) T. E. Wellems, *Science.* **2002**, *298*, 124–126; e) R. G. Ridley, *Nature.* **2002**, *415*, 686–693; f) M. Paolino, A. Choidas, S. Wallner, B, Pranjic, I. Uribesalgo, S. Loeser, A. M. Jamieson, W. Y. Langdon F. Ikeda, J. P. Fededa, S. J. Cronin, R. Nitsch, C. Schultz-Fademrecht, J. Eickhoff, S. Menninger, A. Unger, R. Torka, T. Gruber, R. Hinterleitner, G. Baier, D. Wolf, A. Ullrich, B. M. Klebl, J. M. Penninger, *Nature.* **2014**, *507*, 508–512; g) S. J. Foote, J. K. Thompson, A. F. Cowman, D. J. Kemp, *Cell* **1989**, *57*, 921–930.

[2] a) F. E. Keisey, E. M. K. Geiling, F. K. Oldham, E. Dearborn, *J. Pharmacol. Exp. Therap.* **1944**, *80*, 391–392; b) W.-Z. Bi, K. Sun, C. Qu, X.-L. Chen, L.-B. Qu S.-H. Zhu, X. Li, H.-T. Wu, L.-K. Duan, Y.-F. Zhao, *Org. Chem. Front.* **2017**, *4*, 1595–1600.

[3] a) S. Han, P. Chakrasali, J. Park, H. Oh, S. Kim, K. Kim, A. K. Pandey, S. H. Han, S. B. Han, I. S. Kim, *Angew. Chem. Int. Ed.* **2018**, *57*, 12737–12740; *Angew. Chem.* **2018**, *130*, 12919–12922; b) M. Puthanveedu, V. Polychronidou, A. P. Antonchick, *Org. Lett.* **2019**, *21*, 3407–3411; c) L. Bering, A. P. Antonchick, *Org. Lett.* **2015**, *17*, 3134−3137; d) R. Kumar, R. Kumar, A. K. Dhiman, U. Sharma, *Asian J. Org. Chem.* **2017**, *6*, 1043–1053; e) R. Kumar, I. Kumar, R. Sharma, U. Sharma, *Org. Biomol. Chem.* **2016**, *14*, 2613–2617; f)

Z. Zhang, C. Pi, H. Tong, X. Cui, Y. Wu, *Org. Lett.* **2017**, *19*, 440–443; g) X. Chen, X. Cui, F. Yang, Y. Wu, *Org. Lett.* **2015**, *17*, 1445–1448; h) S. B. Wagh, R. R. Singh, R. L. Sahani, R.-S. Liu, *Org. Lett.* **2019**, *21*, 2755–2758; i) S. Du, C. Pi, T. Wan, Y. Wu, X. Cui, *Adv. Synth. Catal.* **2019**, *361*, 1766–1770; j) X. Zhang, A. Xia, H. Chen, Y. Liu, *Org. Lett.* **2017**, *19*, 2118–2121; k) Y. Han, X. Li, X. Zhu, M. Li, L. Zhou, X. Song, Y. Liang, *J. Org. Chem.* **2017**, *82*, 1697–1704; l) G. E. M. Crisenza, E. M. Dauncey, J. F. Bower, *Org. Biomol. Chem.* **2016**, *14*, 5820–5825; j) A. K. Jha, N. Jain, *Chem. Commun.* **2016**, *52*, 1831–1834; k) C. Sen, S. C. Ghosh, *Adv. Synth. Catal*. **2018**, *360*, 905–910.

[4] a) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902–7917; b) J. P. Ferris, in: *The Chemistry of the Cyano Group*, (Eds.:), John Wiley & Sons Ltd, New York, 1970, pp. 718–739; c) D. T. Mowry, *Chem. Rev.* **1948**, *42*, 189–283; d) B. M. Trost, I. Fleming, in: *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, U.K., **1991**.

[5] a) R. C. Larock, T. Yao, in: *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, (Eds.:), John Wiley & Sons, New York, **1989**, pp 819–995; b) A. J. Fatiadi, in: *Triple-Bonded Functional Groups, 1st ed*., *Vol. 2* (Eds.: S. Patai, Z, Rapporoport), John Wiley & Sons Ltd, *Chichester*, **1983**, pp. 1057–1303.

[6] a) K. E. B. Parkes, D. J. Bushnell, P. H. Crackett, S. J. Dunsdon, A. C. Freeman, M. P. Gunn, R. A. Hopkins, R. W. Lambert, J. A. Martin, J. H. Merrett, S. Redshaw, W. C. Spurden and G. J. Thomas, *J. Org. Chem.* **1994**, *59*, 3656–3664; b) M. R. Sampson, K. Y. Cao, P. L. Gish, K. Hyon, P. Mishra, W. Tauber, P. Zhao, E. H. Zhou, I. R. Younis, *J. Clin. Pharmacol.* **2019**, *59*, 500–509.

[7] a) G. Villegas, G. Calenda, S. Zhang, O. Mizenina, K. Kleinbeck, M. L. Cooney, C. J. Hoesley, G. W. Creasy, B. Friedland, J. A. Fernandez-Romero, *Antimicrob. Agents Chemother.* **2016**, *60*, 5459–5466; b) S. Cai, M. Dimitroff, T. McKennon, M. Reider, L. Robarge, D. Ryckman, X. Shang, J. Therrien, *Org. Process Res. Dev.* **2004**, *8*, 353–359.

[8] a) Y. Kando, H. Sakaguchi, M. Kubota, Patent JP 2009173593, **2009**; b) M. Kubota, H. Sakaguchi, Y. Kandoh, Patent WO2009093640 (A1), **2009**.

[9] B. Reux, T. Nevalainen, K. H. Raitio, A. M. P. Koskinen, *Bioorg. Med. Chem.* **2009**, *17*, 4441–4447.

[10] K. Curry, D. S. Magnuson, H. McLennan, M. J. Peet, *Neurosci. Lett.* **1986**, *66*, 101–105.

[11] a) Y. N. Song, H. Xu, W. Chen, P. Zhan, X. Liu, *MedChemComm* **2015**, *6*, 61–74; b) G. C. Capodagli, W. G. Sedhom, M. Jackson, K. A. Ahrendt, S. D. Pegan, *Biochemistry*. **2014**, *53*, 202–213.

[12] Y. Tagawa, Y. Higuchi, K. Yamagata, K. Shibata, D. Teshima, *Hetrocycles.* **2004**, *63*, 2859–2862.

[13] a) T. Sandmeyer, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633–1635; b) T. Sandmeyer, *Chem. Ber.* **1884**, *17*, 2650– 2653; c) K. W. Rosenmund, E. Struck, *Chem. Ber.* **1919**, *2*, 1749–1756; d) J. Almaliti, A. A. Al-Hamashi, A. T. Negmeldin, C. L. Hanigan, L. Perera, M. K. Pflum, R. A. Casero, Jr., L. M. Tillekeratne, *J. Med. Chem.* **2016**, *59*, 10642–10660.

[14] P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 10139–10147.

[15] P. S. Fier, *J. Am. Chem. Soc.* **2017**, *139*, 9499–9502.

[16] B. L. Elbert, A. J. M. Farley, T. W. Gorman, T. C. Johnson, C. Genicot, B. Lallemand, P. Pasau, J. Flasz, J. L. Castro, M. MacCoss, R. S. Paton, C. J. Schofield, M. D. Smith, M. C. Willis, D. J. Dixon, *Chem. -Eur. J.* **2017**, *23*, 14733–14737.

[17] a) W. E. Feely, G. Evanega, E. M. Beavers, *Org. Synth.* **1962**, *42*, 30–33; b) I.V. Rudenko, A. A. Kucherak, A. A. Tolmachev, O.V. Hordiyenko, *Chem Heterocycle Com.* **2011**, *47*, 964–969; c) W. D. Shrader, J. Celebuski, S. J. Kline, D. Johnson, *Tetrahedron Lett.* **1988**, *29*, 1351–1354.

[18] a) W. K. Fife, *J. Org. Chem.* **1983**, *48*, 1375–1377; b) W. Baratta, M. Ballico, S. Baldino, G. Chelucci, E. Herdtweck, K. Siega, S. Magnolia and P. Rigo, *Chem. -Eur. J.* 2008, **14**, 9148–9160; c) A. V. Malkov, J. B. Hand, P. Kočovský, *Chem. Commun.* **2003**, 1948–1949; d) Z. Huo, T. Kosugi, Y. Yamamoto, *Tetrahedron Lett.* **2008**, *49*, 4369–4371.

[19] A. Veerareddy, G. Surendrareddy, P. K. Dubey, *J. Heterocyclic Chem.* **2011**, *48*, 961– 964.

[20] a) J. R. Quinn, S. C. Zimmerman, *J. Org. Chem.* **2005**, *70*, 7459–7467; b) J. I. van der Vlugt, S. Demeshko, S. Dechert, F. Meyer, *Inorg. Chem.* **2008**, *47*, 1576–1585.

[21] A. Ashimori, T. Ono, T. Uchida, Y. Ohtaki, C. Fukaya, M. Watanabe, K. Yokoyama, *Chem. Pharm. Bull.***1990**, *38*, 2446–2458.

[22] H. Bernard, G. Bülow, U. E. W. Lange, H. Mack, T. Pfeiffer, B. Schäfer, W. Seitz, T. Zierke, *Synthesis* **2004**, *14*, 2367–2375

[23] F. Xu, Y. Li, X. Huang, X. Fang, Z. Li, H. Jiang, J. Qiao, W. Chu, Z. Sun, *Adv. Synth. Catal.* **2019**, *361*, 520–525.

[24] S. E. Wengryniuk, A. Weickgenannt, C. Reiher, N. A. Strotman, K. Chen, M. D. Eastgate, P. S. Baran, *Org. Lett.* **2013**, *15*, 4792–795.

[25] a) Miyashita, T. Kawashima, C. Iijima, T. Higashino, *Heterocycles.* **1992**, *33*, 211–218; b) Z. Huo, H.Tomeba, Y. Yamamoto, *Tetrahedron Lett.* **2008**, *49*, 5531–5533; c) T. Sakamoto, S. Kaneda, S. Nishimura, H. Yamanaka, *Chem. Pharm. Bull.***1985**, *33*, 565–571.

[26] a) V. Cerrada, M. P. Matía-Martín, J. L. Novella, J. Alvarez-Builla, *ARKIVOC* **2005**, *9*, 200−206; b) J. Mehnert, J. Schnekenburger, *Arch. Pharm.* **1988**, *321*, 891−896.

[27] L.-Y. Xie, S. Peng, F. Liu, J.-Y. Yia, M. Wang, Z.-L. Tang, X.-H. Xi, W.-M. He, *Adv. Synth. Catal.* **2018**, *360*, 4259–4264.

[28] D. Prat, O. Pardigon, H.- W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani and P. Hosek, *Org. Process Res. Dev.* **2013**, *17*, 1517–1525.

[29] a) A. Sarkar, S. Santra, K. Kundu, A. Hajra, G. V. Zyryanov, O. N. Chupakhin, V. N. Charushin, A. Majee, *Green Chem.* **2016**, *18*, 4475–4525; b) M. B. Gawande, V. D. B. Bonifacio, R. Luque, P. S. Branco, R. S. Varma, *ChemSusChem* **2014**, *7*, 24–44; c) W. Wang, M. Luo, W. Yao, M. Ma, S. A. Pullarkat, L. Xu, P.

Leung, *ACS Sustainable Chem. Eng.* **2019**, ***7***, 1718–1722; d) H. Stachowiak, J. Kaźmierczak, K. Kuciński, G. Hreczycho, *Green Chem.* **2018**, *20*, 1738–1742; e) A. Harinath , J. Bhattacharjee, T. K. Panda, *Chem. Commun.* **2019**, ***55***, 1386–1389.

[30] R. A. Sheldon, *Chem. Commun.* **2008**, 3352–3365.

[31] a) V. Polshettiwar, R. S. Varma, *Acc. Chem. Res.* **2008**, *41*, 629–639; b) R. S. Varma, *J. Heterocycl. Chem.* **1999**, *36*, 1565–1571; c) R. S. Varma, *Pure Appl. Chem.* **2001**, *73*, 193–198; d) D. Gangrade, SD Lad, AL Mehta, *Int. J. Res. Pharm. Sci.* **2015**, *5*, 37–42. e) C. R. Strauss, R. S. Varma, in: *Microwave Methods in Organic Synthesis*, Vol. 266 (Eds.: M. Larhed, K. Olofsson), Springer, Heidelberg, **2006**, pp. 199–231.

[32] CCDC-1947601 contains the supplementary crystallographic data for the compound **2n**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) *via* www.ccdc.cam.ac.uk/data_request/cif.

[33] L. Bering, A. P. Antonchick, *Org. Lett.* **2015**, *17*, 3134−3137.

[34] H. Iida, H. Hamana, K. Matsumoto, *Synth. Commun.* **2007**, 37, 1801-1805.

[35] A. G. Walker, C. J. Wenthur, Z. Xiang, J. M. Rook, K. A. Emmitte, C. M. Niswender, C. W. Lindsley, P. J. Conn, *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 1196–1201.

[36] M. J. Coghlan, E. V. Krumkalns, B. A. Caley, H. R. Hall, W. R. Arnold, in: *Synthesis and Chemistry of Agrochemicals II* (Ed.: W. K. Moberg), ACS Symposium Series, American Chemical Society, Washington DC, **1991**, *443*, pp. 538-552.

[37] a) Y. Kando, H. Sakaguchi, M. Kubota, (Jpn. Kokai Tokkyo Koho) Patent JP 2009173589, **2009**; b) M. Kubota, H. Sakaguchi, Y. Kandoh, Patent WO2009093640 (A1), **2009**.

[38] K. Curry, D. S. Magnuson, H. McLennan, M. J. Peet, *Neurosci. Lett.* **1986**, *66*, 101–105.

[39] E. Rozhkov, I. Piskunova, M. Gol'd, I. Kalvin'sh, *Chem. Heterocycl. Compd.* **1998**, *34*, 77–91.

[40] S. P. J. T. Bachollet, D. Volz, B. Fiser, S. Münch, F. Rönicke, J. Carrillo, H. Adams, U. Schepers, E. Gómez-Bengoa, S. Bräse, J. P. A. Harrity, *Chem. - Eur. J.* **2016**, *22*, 12430–12438.

[41] a) Z. Brzozowski, F. Sączewski, M. Gdaniec, *Eur. J. Med. Chem.* **2000**, *35*, 1053-1064; b) X. Chen, P. Zhan, X. Liu, Z. Cheng, C. Meng, S. Shao, C. Pannecouque, E. D. Clercq, X. Liu, *Bioorg. Med. Chem.* **2012**, *20*, 3856–3864.

[42] Hydrogen cyanide is also evolved as the another byproduct and the same can be trapped by proton sponge; see the ESI for further details.

[43] The evolved hydrogen cyanide can be detoxified by oxidation using an aqueous solution of hydrogen peroxide in the presence of a catalytic amount of copper sulphate; see references, a) M. Kitis, A. Akcil, E. Karakaya, N. O. Yigit, *Miner. Eng.* **2005**, *18*, 353–362; b) A. Khodadadi, M. Abdolahi, P. Teimoury, *Iran. J. Environ. Health. Sci. Eng.* **2005**, *2*, 177–182.

[44] S. Carles, J. L. Le Garrec, J. B. A. Mitchell, *J. Chem. Phys.* **2007**, *127*, 144308.

[45] K. Chulsky, R. Dobrovetsky, *Org. Lett.* **2018**, *20*, 6804–6807.

10.1002/adsc.201901103

FULL PAPER

Regioselective Cyanation of Six-Membered *N*-Heteroaromatic Compounds Under Metal-, Activator-, Base- and Solvent-Free Conditions

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