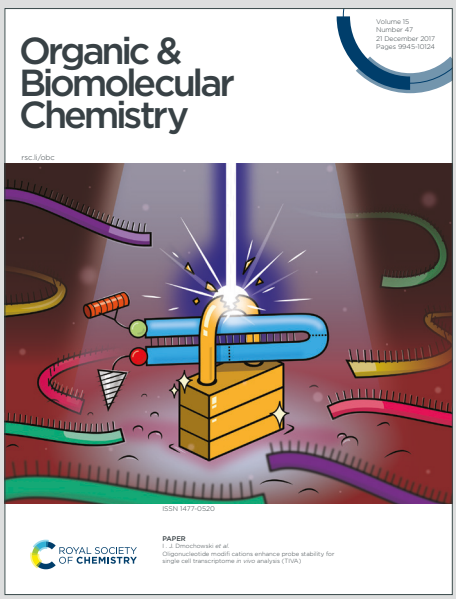
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: C. Li, P. Long, H. Wu, H. Yin and F. Chen, *Org. Biomol. Chem.*, 2019, DOI: 10.1039/C9OB01340G.



ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C9OB01340G

COMMUNICATION

N-Thiocyanato-dibenzenesulfonimide: A New Electrophilic Thiocyanating Reagent with Enhanced Reactivity

Chengqiu Li,[a] Pingliang Long,[a] Haopeng Wu,[a] Hongquan Yin[a] and Fu-Xue Chen[a]*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

A novel electrophilic thiocyanating reagent, *N*-thiocyanato-dibenzenesulfonimide was prepared and exhibited enhanced electrophilicity with a wide scope of substrates. Thus, it reacted with activated aromatics such as phenols, indoles, anilines and anisoles whithout catalyst giving the corresponding thicyanate derivatives in high yields, while TfOH for unactivated arenes and hetero aromatics and $Zn(OTf)_2$ for ketones was used as the catalyst respectively. Notewothy, internal alkenes and styrenes were bifunctionalized giving 1,2-amino thiocyanates in high yields.

Recently, we have being interested in the chemistry of electrophilic substitution reactions to introduce cyano (-CN)[1] and thiocyanato (-SCN) groups[2] by using cationic reagents such as cyanohyperiodine,[3] cyanate,[4] and N-thiocyanato imide.[5] Among the varying electrophilic thiocyanato reagents (Fig. 1), N-thiocyanato imides showed increasing reactivity in the order from **R-1** to **R-2** to **R-3** and **R-4** for activated substrates such as β-keto esters and electron-rich aromatics. To improve the activity of this type thiocyanato reagent, we envisioned that

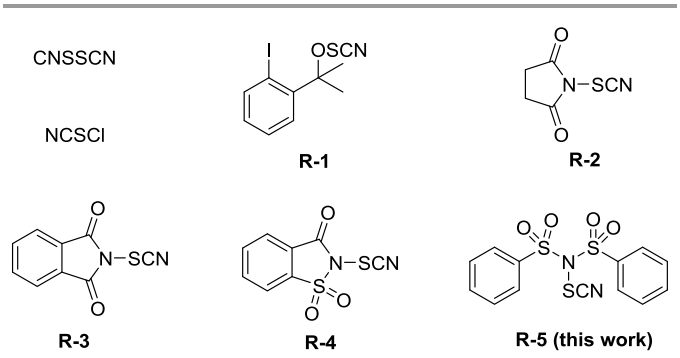
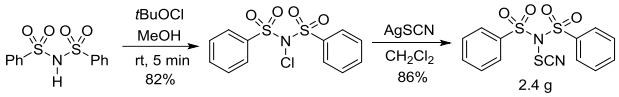


Fig. 1 Electrophilic thiocyanating reagents.

N-thiocyanatodibenzenesulfonimide (**R-5**) should have improved reactivity as the result of double strong electron-withdrawing sulfonyl groups.

Following our previously reported procedure,[4b-c] **R-5** was readily prepared in overall yield of 71% by sequentially treatment of bis(phenylsulfonyl)imide with *tert*-butyl hypochlorite and AgSCN (Scheme 1) on gram scale (see ESI), The structure of reagent **R-5** was determined by IR, HRMS, ^1H and ^{13}C NMR together with X-ray single crystal diffraction (Fig. 2, CCDC 1919695). It is a white solid, not sensitive to air and moisture, but slightly sensitive to light. So, we suggest to store it in the dark and at low temperatures.

Scheme 1 Synthesis of reagent **R-5**



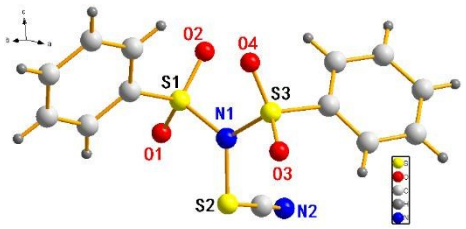


Fig.2 Single crystal structure of **R-5**.

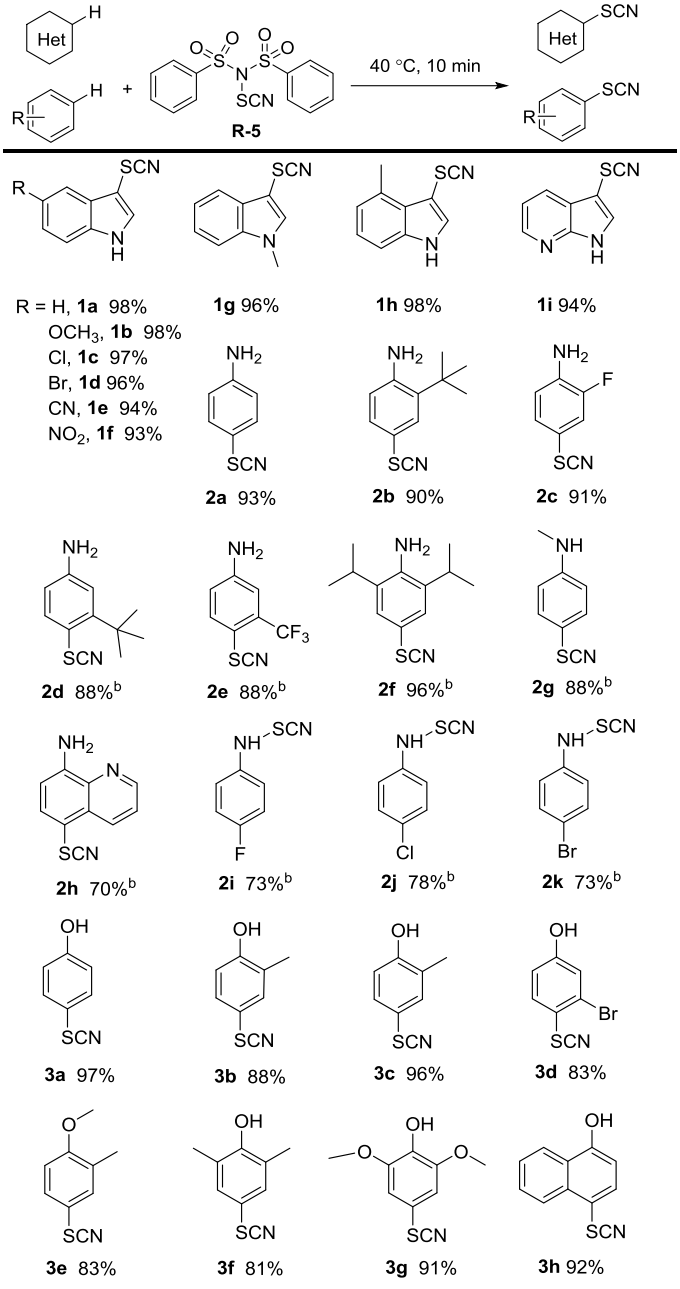
With **R-5** in hand, we explored its reactivity with nucleophiles. As shown in Table 1, without any catalysts or additives, indoles, anilines, phenols, and anisole derivatives bearing electron-donating or electron-withdrawing group were converted into corresponding thiocyanated products **1-3** in high yields within 10 min at room temperature. Therefore, the reactions of indoles completed quickly and cleanly in excellent yields in CH_3CN, where electron-deficient indole derivatives (**1e-f**) had lower yields than those with electron-donating groups (**1a-d, 1g-i**). Similarly, thiocyanated aniline derivatives **2a-k** were accomplished in high yields but in CH_2Cl_2. The thiocyanation exclusively took place at the *para*-position to the amino group

[a] *School of Chemistry & Chemical Engineering, Beijing Institute of Technology (Liangxiang Campus). No. 8 Liangxiang East Road, Fangshan District, Beijing 102488, China.*
e-mail: fuxue.chen@bit.edu.cn

Electronic Supplementary Information (ESI) available: details of reaction procedures, characteristic data of all new compounds, copies of NMR spectra. See DOI:10.1039/x0xx00000x

(**2a-h**), while N-substitution reaction instead at the amino group in the case of halogenated anilines (**2i-k**). Comparing to previous study, thiocyanantion of anilines completed in 10 min using **R-5** rather than 12 h using **R-4**,[4c] indicating the activity of this reagent **R-5** was greatly enhanced. However, for the thiocyanation of anilines with bulky and electron-withdrawing groups, however, slow down the reaction in lower yield (**2d**, and **2c, 2h-k**). Moreover, the electrophilic thiocyanation of phenols and anisoles with **R-5** were investigated. As shown in **Table 1**, the reaction of phenols and anisoles gave the corresponding products (**3a-h**) in high yields. Performing the reaction on gram scale **2f** was isolated in 84% yield (see ESI).

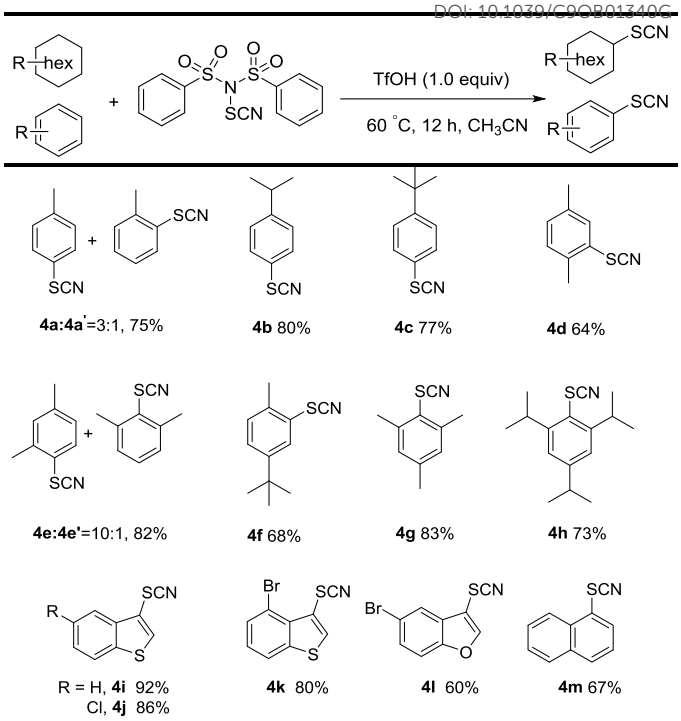
Table 1 Thiocyanation reaction of indoles, anilines, phenols, and anisole derivatives.[a]



[a] Reaction conditions: indoles, anilines, phenols, and anisoles (0.20 mmol), **R-5** (92 mg, 0.26 mmol, 1.3 equiv), CH_3CN (1.0 mL). [b] CH_2Cl_2, 1.0 mL, room temperature, 10 min.

Table 2 Thiocyanation reaction of unactivated arenes and heteroaromatics

View Article Online
DOI: 10.1039/C9OB01340C



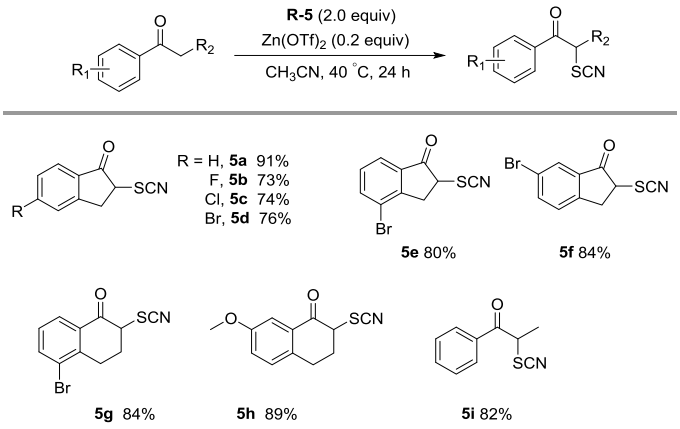
[a] Reaction conditions: arenes and heteroaromatics (0.20mmol), **R-5** (92 mg, 0.26 mmol, 1.3 equiv), CH_3CN (1.0 mL), 60 °C, 12 h, TfOH (30 mg, 0.20 mmol, 1.0 equiv).

The efficient thiocyanation of indoles, anilines, phenols and anisoles with **R-5** encouraged us to pay attention to a various of unactivated alkyl arenes[6] and heteroaromatics,[7] to the best of knowledge, which are unsuitable substrates to date for such electrophilic thiocyanation reactions. As shown in Table 2, a variety of alkyl arenes reacted with **R-5** giving the corresponding thiocyanated products in moderate yields when TfOH was used as the catalyst at 60 °C for 12 h. Therefore, toluene was transformed into a mixture of *ortho* and *para*-products **4a** and **4a'** in ratio 3:1 determined by ^{1}H NMR, while there is no *ortho*-substituted product for bulky *iso*-propylbenzene and *tert*-butylbenzene (**4b**-**c**). Moreover, 1,4-dialkyl and 1,3,5-trialkylbenzene (**4c-d**, **4f-h**) were exclusively mono thiocyanated in moderate to high yields. However, the reaction of 1,3-dimethylbenzene gave a mixture of 2,4-dimethylthiocyanato-benzene (**4e**) and 2,6-dimethylthiocyanatobenzene (**4e'**) in a ratio of 10:1. Moreover, under the same reaction condition heteroaromatics such as benzothiophene (**4j-k**) and benzofurane (**4l**) reacted with **R-5** smoothly in moderate to high yields. Notably, reaction of sluggish naphthalene produced corresponding products (**4m**) in 67% yield.

To further extend the synthetic utility of **R-5**, we studied the thiocyanation of ketones.[8] After brief screening of the reaction conditions, the optimal reaction parameters were found to be in CH_3CN at 40 °C with $Zn(OTf)_2$ as the catalyst. As shown in Table 3, a variety of 1-indanone derivatives with different substituent were thus efficiently thiocyanated with 73-91% yield (**5a**-**5f**). Moreover, other ketones like 5-bromo-1-tetralone and 7-methoxyl-1-teralone produced the corresponding

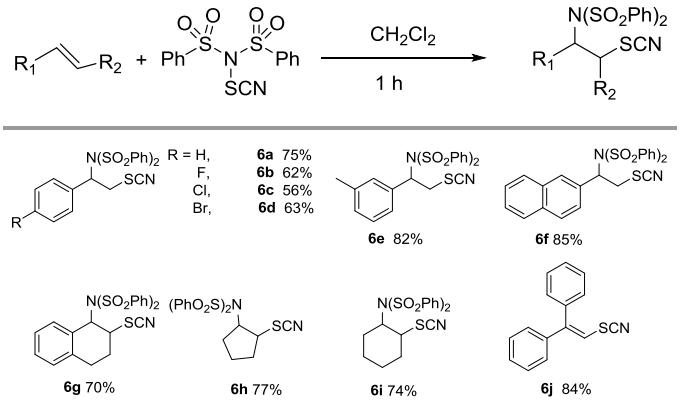
products (**5g-5h**) in high yields. In addition, reaction of propiophenone with **R-5** took place giving 1-phenyl-2-thiocyanatopropan-1-one (**5i**) in 82% yield.

Table 3 Thiocyanation reaction of ketones derivatives



[a] Reaction conditions: ketones (0.20 mmol), **R-5** (141 mg, 0.4 mmol, 2.0 equiv), $Zn(OTf)_2$ (14.5 mg, 0.04 mmol, 0.2 equiv), CH_3CN (1.0 mL), 40 °C, 24 h.

Table 4 Thiocyanation reaction of Alkenes.[a]



[a] Reaction conditions: alkenes (0.20 mmol), **R-5** (92 mg, 0.26 mmol, 1.3 equiv), CH_2Cl_2 (1.0 mL), room temperature, 1 h.

The good reactivity and wide substrate scope promoted us to explore the reaction of **R-5** with alkenes.[9] Strikingly, we discovered that the styrene was smoothly difunctionalized to afford the corresponding amino thiocyanato product **6a** in 75% yield in CH_2Cl_2 at room temperature after 1 h. As shown in Table 3, other styrene derivatives with electron-donating groups (**6e-f**) achieved higher yields than those with electron-withdrawing ones (**6b-d**). Furthermore, 1,2-disubstituted cyclic alkenes reacted with **R-5** to give corresponding amino thiocyanato products (**6g-6i**) in good yields. However, this protocol of difunctionalization was not suitable to 1,1-disubstituted terminal alkene, e.g. 1,1-diphenyl-ethene afforded the eliminated product **6j** exclusively.[10]

Conclusions

DOI: 10.1039/C9OB01340G

In summary, we successfully prepared a new electrophilic thiocyanating reagent **R-5** and demonstrated the anticipated enhanced reactivity. In absence of any catalysts and additives **R-5** readily reacted with a variety of phenols, indoles, anilines, anisoles, hetero aromatics, and alkenes in high yields under mild reaction conditions. In presence of TfOH and Lewis acid, reactions of unactivated arenes and electron-deficient heterocycle with **R-5**, and ketones afforded thiocyanation products in good yields, respectively. The reaction of terminal alkenes and asymmetric variant was under way in our group.

Conflicts of interest

There are no conflicts to declare

Acknowledgement

The authors thank NSFC financial support (201572020).

References

1 (a) P. G. Karmaker, J. S. Qiu, D. Wu, M. M. Reng, Z. Yang, H. Q. Yin and F.-X. Chen, *Org. Biomol. Chem.,* 2017, **15**, 7753–7757; (b) N. Kurono and T. Ohkuma, *ACS Catal*., 2016, **6**, 989-1023; (c) H. Pellissier, *Adv. Synth. Catal.*, 2015, **357**, 857-882; (d) M. North, D. L. Usanov and C. Young, *Chem. Rev.*, 2008, **108**, 5146-5226; (d) Y.F. Wang, W. Zeng, M. Sohail, J. Guo, S. Wu and F.-X. Chen, *Eur. J. Org. Chem.,* 2013, 4624-2633.

2 (a) K. D. Jones, D. J. Power, D. Bierer, K. M. Gericke and S. G. Stewart, *Org. Lett*., 2012, **20**, 208-211; (b) D. A. Boyd, *Angew. Chem. Int. Ed*., 2016, **55**, 15486-15502; (c) G. A. Patani and E. J. LaVoie, *Chem. Rev.,* 1996, **96**, 3147-3176; (d) P. F. Yuan, Q. B. Zhang, X. L. Jin, W. L. Lei, L. Z. Wu and Q. Liu, *Green Chem*., 2018, **20**, 5464-5468; (e) M. Noikham and S. Yotphan, *Eur. J. Org. Chem*., 2019, 2759-2766.

3 (a) E. V. Vinogradova, P. Műller, S. L. Buchwald, *Angew. Chem. Int*. *Ed.*, 2014, **53**, 3125–3128; (b) X. X. Shao, X. Q. Wang, T. Yang, L. Lu, Q. L. Shen, *Angew. Chem. Int. Ed.,* 2013, **52**, 3457–3460; (c) J. P. Brand, D. F. González, S. Nicolai and J. Waser, *Chem. Commun*., 2011, **47**, 102–105; (d) B. Liu, C. H. Lim, and G. M. Miyake, *J. Am. Chem. Soc*., 2017, **139**, 13616−13619; (e) X. Wang, T. Yang, X. Cheng, Q. Shen, *Angew. Chem. Int. Ed*., 2013, **52,** 12860–12864; (f) K. Niedermann, N. Früh, E.Vinogradova, M. S. Wiehn, A. Moreno, A. Togni, *Angew. Chem. Int. Ed*., 2011, **50**, 1059–1063.

4 (a) R. G. R. Bacon and R. G. Guy, *J. Chem. Soc*., 1960, 318-324; (b) C J. Burchell, P, Kilian, A. M. Z. Slawin, J. D. Woollins, K. Tersago, C. V. Alsenoy and F. Blockhuys, *Inorg. Chem*., 2006, **45**, 710-715; (c) H. F. Jiang, W. T. Yu, X. D. Tang, J. X. Li and W. Q. Wu, *J. Org. Chem*., 2017, **82**, 9312-9320; (d) N. Zhu, F. Wang, P. H. Chen, J. X. Ye and G. X. Liu, *Org. Lett*., 2015, **17**, 3580-3583; (e) M. C. Gao, K. J. Zhou and B. Xu, *Adv. Synth. Catal.*, 2019, **361**, 2031-2036.

5 (a) J. R. Falck, S. H. Gao, R. N. Prasad, and S. R. Koduru, *Bioorg. Med. Chem. Lett.,* 2008, **18**, 1768-1771; (b) J. S. Qiu, D. Wu, P. G. Karmaker, H. Q. Yin and F.-X. Chen, *Org. Lett*., 2018, **20**, 1600−1603; (c) D. Wu, J. S. Qiu, P. G. Karmaker, H. Q. Yin and F.-X. Chen, *J. Org. Chem.,* 2018, **83,** 1576−1583; (d) J. Y. See, Y. Zhao., *Org. Lett*., 2018, **20**, 7433−7436; (e) J. Qiu, D. Wu, L. Yuan, P. Long, H. Yin, and F.-X. Chen, *J. Org. Chem.* 2019, **84**,

View Article Online
DOI: 10.1039/C9OB01340G

7917−7926; f) Most similar but independent work published online during this revision, A.-H. Ye, Y. Zhang, Y.-Y. Xie, H.-Y. Luo, J.-W. Dong, X.-D. Liu, X.-F. Song, T.-M. Ding and Z.-M. Chen, *Org. Lett.* 2019, DOI: 10.1021/acs.orglett.9b01706.

6 (a) A. Khazaei, A. Alizadeh and R. G. Vaghei, *Molecules*, 2001, **6,** 253-257; (b) W. Guo, W. Tan, M. M. Zhao, L. Y. Zheng, K. L. Tao and D. L. Chen, *J. Org. Chem*., 2018, **83**, 6580−6588; (c) P. P. Zhang, M. Li, X. S. Xue, C. F. Xu, Q. C. Zhao, Y. F. Liu, H. Y Wang, Y. L. Guo, L. Lu and Q. L. Shen, *J. Org. Chem.,* 2016, **81**, 7486−7509.

7 (a) S. Mitra, M. Ghosh, S. Mishra, and A. Hajra, *J. Org. Chem.,* 2015, **80**, 8275−8281; (b) B. Bayarmagnai, C. Matheis, K. Jouvin, and L. J. Goossen, *Angew. Chem. Int*. *Ed*., 2015, **54**, 5753–5756; (c) B. Exner, B. Bayarmagnai, F. Jia, and L. J. Goossen, *Chem. Eur. J*., 2015, **21**, 17220–17223.

8 (a) L. Yu, X. Y. Wu, M. J. Kim, V. Vaithiyanathan, Y. D. Liu, Y. Tan, W. L. Qin, C. E. Song and H. L. Yan, *Adv. Synth. Catal*., 2017, **359**, 1879–1891; (b) S. Liang, C. C. Zeng, H. Y. Tian, B. G. Sun, X. G. Luo and F. Z. Ren., *Adv. Synth. Catal*., 2018, **360**, 1444–1452; (c) G. M. Nan and H. l. Yue, *Synlett.*, 2018, **29**, 1340-1345; (d) F. R. Bisogno, A. Cuetos, I. Lavandera and V. Gotor, *Green Chem.,* 2009, **11**, 452–454; (e) K. Nikoofar and S. Gorj. *J. Sulfur Chem.*, 2016, **37**, 80-88.

9 (a) G. B. Jiang, C. L. Zhu, J. X. Li, W. Q. Wu and H. F. Jiang, *Adv. Synth. Catal.,* 2017, **359**, 1208–1212; (b) S. M. Yang, T. J. He, D. Z. Lin and J. M. Huang, *Org. Lett.,* 2019, **21**, 1958−1962; (c) K. K. Laali, G. C. Nandi and S. D. Bunge, *Tetrahedron Lett*., 2014, **55**, 2401-2405; (d) A. S. Reddy and K. K. Laali, *Beilstein J. Org. Chem*., 2015, **11**, 1641-1648; (e) Z. Liang, F. Wang, P. Chen and G. Liu, *Org. Lett*., 2015, **17**, 2438-2441; (f) S. M. Yang, T. J. He, D. Z. Lin and J. M. Huang, *Org. Lett*., 2019, **21**, 1958−1962; (g) S. E. Denmark, D. J. P. Kornfilt, and T. Vogler, *J. Am. Chem. Soc.,* 2011, **133**, 15308–15311; (h) S. E. Denmark, E. Hartmann, D. J. P. Kornfilt and H. Wang, *Nat. Chem.* 2014, **6**, 1056-1064.

10 (a) Q. Chen, Y. J. Lei, Y. F. Wang, C. Wang, Y. A. Wang, Z. Q Xu, H. Wang and R. Wang, *Org. Chem. Front*., 2017, **4**, 369–372; (b) A. Levy and J. Y. Becker, *Electrochim. Acta*, 2015, **178**, 294-302.

DOI: 10.1039/C9OB01340G

N-Thiocyanato-dibenzenesulfonimide: A new electrophilic thiocyanating reagent was readily prepared and exhibited enhanced reactivity with a wide scope of substrates.