

NJC

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



Transition-Metal Free N-Arylation of Cyanamides by Diaryliodonium Triflates in Aqueous Media

Jihui Li, Xinyi Zheng, Wei Li, Wei Zhou, Wen Zhu and Yucang Zhang*

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

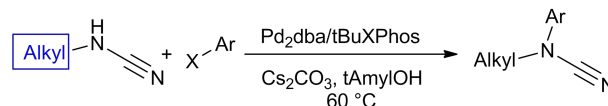
An operationally simple protocol is established for the synthesis of disubstituted cyanamides through the transition-metal free N-arylation of cyanamides by diaryliodonium triflates in aqueous media. Both alkyl and aryl cyanamides are well compatible with the mild reaction conditions. One-pot synthesis of ureas is also possible through sequential arylation and hydrolysis of cyanamides, diaryliodonium triflates and H₂O with good yields.

Cyanamides have attracted considerable attentions as a class of versatile organic molecules. They have a wide range of uses in organic synthetic chemistry¹ and coordination chemistry,² not only can be building blocks for the construction of diverse N-containing compounds but also metal ligands with their unique reactivity and structure of cyanamide unit. Additionally, it has been found that some cyanamide-based compounds show a diversity of interesting bioactivities,³ such as anti-cathepsins K and L,^{3a} inhibition of spontaneous myogenic,^{3d} and peptide activator activities.^{3e} It has also been proved that cyanamide is a natural product present in higher plant even though the distribution is limited.⁴ As a valuable dinitrogen resource, there have been some synthetic methods developed for cyanamides, which can be divided into these two categories: i) Conventional electrophilic substitution and condensation of cyanamide, or nucleophilic substitution of cyanogen bromide;⁵ ii) Transition-metal catalyzed transformations of various starting materials.⁶ The latter method is an alternative approach to making a diversity of complex cyanamides by using easily available starting materials. For example, palladium-catalyzed three component reactions of aryl isocyanides, allyl methyl carbonate, and trimethylsilyl azide were developed for the synthesis of allyl cyanamides and N-cyanoindoles,^{6a,b} a copper-catalyzed cascade reaction of 1-(2-iodoaryl)thioureas and aryl iodides was adopted to build 2-arylsulfanylarylcyanamides.^{6d} A

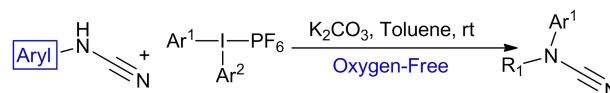
palladium-catalyzed N-arylation of alkyl cyanamides by arylhalides with bidentate phosphane as ligand was developed for the synthesis of disubstituted cyanamides (Figure a).^{6e} Moreover, an N-arylation of aryl cyanamides by diaryliodonium hexafluorophosphates was also developed more recently, and the reaction needed to be performed under oxygen free conditions (Figure b).⁷

Figure 1. N-Arylation of Cyanamides

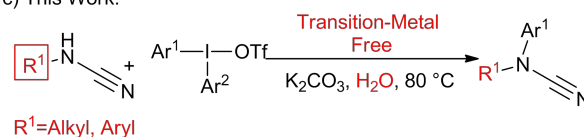
a) Previous Work:^{6e}



b) Previous Work:⁷



c) This Work:



Diaryliodonium salts are popular arylating reagents for construction of C-C, C-O, C-N, C-S, C-Se and C-X (X=halides) bonds with mild reaction conditions in organic synthesis.⁸ For instance, the N-arylations of various N-nucleophiles by diaryliodoniums have been widely used for the construction of C-N bonds. In particular, the transition-metal free transformations which are potentially environmentally benign synthetic methods, are highly pursued in the past decades.^{8c, f, g} Moreover, diaryliodonium salts are easily available, air- and moisture-stable, thermostable, nontoxic and environmentally benign, and the reactions can generate one

^a College of Materials and Chemical Engineering, Hainan University, Haikou, 570228, P. R. China

† Email: zhangyucang88@163.com

Electronic Supplementary Information (ESI) available: Detailed experimental procedures as well as spectral data of all synthesized compounds. See DOI: 10.1039/x0xx00000x

molecular aryl iodide which is also valuable organic intermediate in arylation reactions.

Recently, we have reported a copper-catalyzed three-component reaction of cyanamides, boronic acids and amines for the synthesis of guanidines, where an N-arylation on the terminal nitrogen of cyanamides by arylboronic acids can be realized, and an N-arylation on internal nitrogen of cyanamides was found to be a side reaction.⁹ As a part of our ongoing research in exploiting cyanamides as a dinitrogen resource, here, an N-arylation on the internal nitrogen of both alkyl and aryl cyanamides by diaryliodonium triflates in aqueous media is reported for making disubstituted cyanamides under transition-metal free conditions (Figure 1, c). The arylation of *p*-tolylcyanamide (**1a**) with diphenyliodonium triflate (**2a**) was initially screened in DMF with K₂CO₃ as base at 80 °C without excluding oxygen, producing the cross-coupling product in 82% yield within 2 h (Table 1, Entry 1). Then, higher and lower reaction temperatures were evaluated, inferior yields were all obtained (Table 1, Entries 2-4). Additionally,

Table 1. Reaction Conditions Optimization:^a

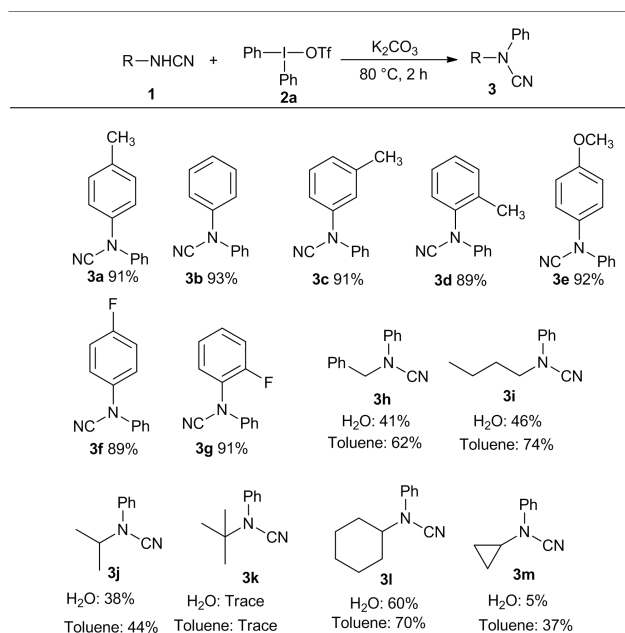
Entry	Base (2 eq)	Solvent	T (°C)	t (h)	Yield ^b (%)
1	K ₂ CO ₃	DMF	80	2	82
2	K ₂ CO ₃	DMF	50	2	55
3	K ₂ CO ₃	DMF	130	2	55
4	K ₂ CO ₃	DMF	rt	24	15
5	----	DMF	50	2	Trace
6	K ₂ CO ₃	H ₂ O	80	2	91
7	K ₂ CO ₃	Toluene	80	2	87
8	K ₂ CO ₃	EtOH	80	2	60
9	K ₂ CO ₃	Dioxane	80	2	84
10	K ₂ CO ₃	DMSO	80	2	77
11	K ₃ PO ₄	H ₂ O	80	2	87
12	Cs ₂ CO ₃	H ₂ O	80	2	58
13	NaOH	H ₂ O	80	2	79
14	Et ₃ N	H ₂ O	80	2	55
15	CH ₃ COONa	H ₂ O	80	2	34

^aReaction Conditions: A mixture of *p*-tolylcyanamide **1a** (0.2 mmol), diphenyliodonium triflate **2a** (0.2 mmol), solvent (1 mL) and base (0.4 mmol) was stirred at identified reaction temperature. ^b Isolated yields.

the reaction only produced trace amount of desired product without base (Table 1, Entry 5). Other solvents including H₂O, toluene, EtOH, and DMSO were further investigated (Table 1, Entries 6-10). Pleasantly, a superior yield was produced in water (Table 1, Entry 6), and the reaction in toluene also afforded comparable yield (Table 1, Entry 7). Different bases such as K₃PO₄, Cs₂CO₃, NaOH, CH₃COONa and Et₃N were finally explored in H₂O, all the reactions provided inferior yields (Table 1, Entries 11-15). Thus, the best reaction conditions were K₂CO₃, H₂O, 80 °C, 2 h (Table 1, Entry 6), and exclusion of oxygen was not required comparing with the reaction between cyanamides and diaryliodonium triflates.⁷

The optimized conditions were subsequently applied to various cyanamides as depicted in scheme 1. *p*-, *m*-, *o*-Tolyl cyanamides all furnished coupling products with comparable yields (**3a**, **3b**, **3c**), indicating the steric hindrance of the aryl cyanamides was not a problem for the reactions. The aryl cyanamides with electron-drawing and -donating groups were both compatible with the reaction conditions with high yields. For example, *p*-methoxyphenyl and *p*-fluorophenyl cyanamides provided 91% (**3e**) and 88% (**3f**) yields respectively. Gratifyingly, although the aliphatic cyanamides can be easily hydrolyzed, the reactions of alkyl cyanamides including linear and cyclic afforded desired products in moderate yields in water (**3h-3j**, **3l**, **3m**); these have not been reported in the reaction with diaryliodonium hexafluorophosphates.⁷ Cyclopropyl cyanamide also produced the corresponding product even only giving 5% yield (**3l**), yet *t*-butyl cyanamide did not produce any arylation product (**3k**). The reactions of alkyl cyanamides were also investigated in toluene for comparison, the results were similar to that in water but higher yields were obtained, and the cyclopropyl cyanamide are well compatible with the mild reaction conditions with moderate yield. It is worth to note that the reaction in a larger scale also provided the desired coupling product in high yield and recovered aryl iodide with good yield under the same reaction conditions.¹⁰

Scheme 1. Phenylation of various cyanamides:^a



^aReaction Conditions: A mixture of cyanamides **1** (0.2 mmol), diphenyliodonium triflate **2a** (0.2 mmol) and K₂CO₃ (0.4 mmol) in H₂O or toluene (1 mL) was stirred at 80 °C for 2 h.

The reaction scope was finally extended to other diaryliodonium salts in the aqueous media. It turned out that both symmetric and unsymmetric diaryliodonium triflates were fully tolerated with the reaction conditions, providing good yields (Table 2). For the

symmetric substrates with electron-rich and -poor aryl groups, the arylation took place smoothly with similar yields (Entries 1-5); and the halogen substituents bromide and chloride which can be further functionalized, were survived under the gentle reaction conditions (Entries 2, 3). The diaryliodonium salts with ortho substituent (**2f**) also produced the corresponding product without reducing the yield (Entry 4). In accordance with other N-nucleophiles,^{8b, c} the aryltransfer of unsymmetric diaryliodonium triflates onto cyanamides generally preferred the electron-poor aryl groups to the electron-rich under transition-metal free conditions, and the selectivities are strongly depended on the gap of the electron density between two aryl groups, which should become better as the gap grows.^{8a, 11} For instance, the electron-poorer phenyl of phenyl(*p*-tolyl)iodonium (**2g**) and phenyl(*p*-acetylamino)iodonium (**2h**) is more easily transferred onto cyanamide rather than the other aryl groups (Entries 6, 7). Acetylamino was well compatible with the mild reaction

Table 2. Arylation of *p*-tolyl cyanamides:^a

Entry	Ar ¹	Ar ²	2	3/4 (Ratio)	Yield ^b (%)
1	4-CH ₃ C ₆ H ₄	4-CH ₃ C ₆ H ₄	2b	3n /- (---)	90
2	4-ClC ₆ H ₄	4-ClC ₆ H ₄	2c	3o /- (---)	97
3	4-BrC ₆ H ₄	4-BrC ₆ H ₄	2d	3p /- (---)	78
4	2,5-(CH ₃) ₂ C ₆ H ₃	2,5-(CH ₃) ₂ C ₆ H ₃	2f	-/ 4a (---)	88
5	4-(<i>t</i> -C ₄ H ₉)C ₆ H ₄	4-(<i>t</i> -C ₄ H ₉)C ₆ H ₄	2e	-/ 4b (---)	89
6	C ₆ H ₅	4-(<i>t</i> -C ₄ H ₉)C ₆ H ₄	2g	3a/4b (2.4/1) ^c	96
7	C ₆ H ₅	4-CH ₃ CONHC ₆ H ₄	2h	3a/4c (6.8/1)	86
8	C ₆ H ₅	4-NO ₂ C ₆ H ₄	2i	3a/4d (<1/20)	97
9	C ₆ H ₅	2-Thienyl	2j	3a/4e (>99/1)	84
10	C ₆ H ₅	4-IC ₆ H ₄	2k	3a/4f (1.5/1) ^c	97
11	C ₆ H ₅	2,5-(CH ₃) ₂ C ₆ H ₃	2l	3a/4a (1.2/1) ^c	89
12 ^d	C ₆ H ₅	2,5-(CH ₃) ₂ C ₆ H ₃	2l	3d/4g (1/1.5) ^c	85

^a Reaction Conditions: A mixture of *p*-tolylcyanamides **1a** (0.2 mmol), diaryliodonium triflate **2** (0.2 mmol) and K₂CO₃ (0.4 mmol) in H₂O (1 mL) was stirred at 80 °C for 2 h.

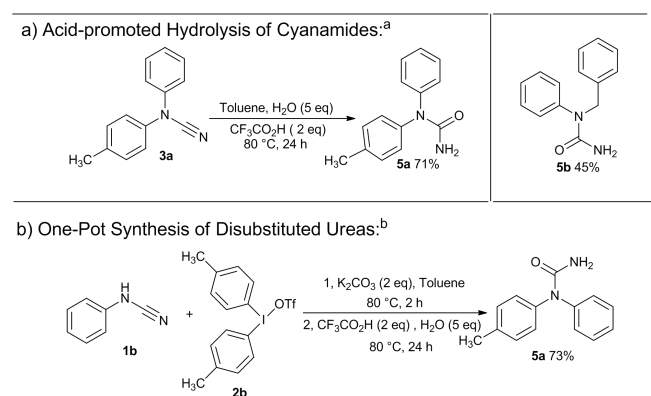
^b Isolated yields. ^c Ratios based on ¹HNMR. ^d *o*-Tolylcyanamide was used.

conditions, as product **4c** and byproduct N-(4-iodophenyl)acetamide were formed. The treatment of *p*-tolylcyanamide by phenyl(*p*-nitrophenyl)iodonium triflate (**2i**) mainly produced the *p*-tolyl(*p*-nitrophenyl)cyanamide (**4d**) in high yield (Entry 8); similarly, phenyl(2-thiophenyl)iodonium triflate (**2j**) afforded an excellent selectivity (Entry 9). Unexpectedly, the electron-poor *p*-iodophenyl of phenyl(*p*-iodophenyl)iodonium triflate (**2k**) is not a preferable transferred group in the reaction (Entry 10), the reason for this discrepancy is unclear at this stage. This indicates that the iodo group is well accommodated with the reaction conditions. Considering the steric hindrance of substrates may be a factor affecting the aryltransfer selectivity.^{8b, 12} The reactions of (2,5-dimethylphenyl)phenyliodonium triflate (**2l**) with both *p*-tolyl and *o*-tolyl cyanamides were evaluated. The treatment of **2l** by *p*-tolylcyanamides provided mixture products with 1.2/1 ratio of phenyl(*p*-tolyl)cyanamide/(2,5-dimethylphenyl)*p*-tolylcyanamides (**3a/4a**) (Entry 11). However, the reaction of **2l** and

o-tolyl cyanamides produced more 2,5-dimethylphenylation product than phenylation product with goods yields, which shows a ortho-effect (**3d/4g**=1/1.5) (Entry 12).^{8c} These results suggest that the steric hindrance of cyanamides plays a significant role on the chemoselectivities for unsymmetric diaryliodonium salts with steric hindrance aryl group, which may due to the accelerated reductive elimination between both bulky cyanamide and bulky aryl groups via a T-shape intermediate.

As ureas are widely distributed in pharmaceutical candidates¹³ and pesticides,¹⁴ the hydrolysis of cyanamides was explored to make ureas. The reaction was briefly investigated as Scheme 2-a, the treatment of the disubstituted cyanamides by water in toluene, which promoted by trifluoroacetic acid, delivered the hydrolysis product ureas with good yields. The phenyl(*p*-tolyl) cyanamide and benzyl(phenyl) cyanamide both afforded desired N,N-disubstituted

Scheme 2. The synthesis of ureas.



ureas which can be the precursors of bioactive benzimidazolones (Scheme 2-a, **5a**, **5b**). One-pot synthesis of ureas can also be easily realized by combination of N-arylation and subsequent hydrolysis with good yield (Scheme 2-b).

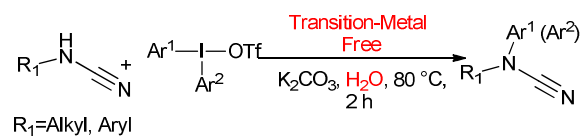
In summary, a transition-metal free N-arylation of cyanamides with diaryliodonium triflates has been developed for the synthesis of disubstituted cyanamides with good yields. The reaction shows a general reaction scope, the aromatic and aliphatic cyanamides are both well compatible with the mild aqueous reaction conditions. Diaryliodonium triflates including symmetric and unsymmetric are all working well, and generally the electron-poorer aryl groups are the preferentially transferred groups for the unsymmetric diaryliodonium triflates, the steric hindrance of both substrates is also an important factor for the reaction chemoselectivities. In addition, the disubstituted cyanamides can be easily hydrolyzed to valuable N,N-disubstituted ureas, and the N-arylation of cyanamides and subsequent hydrolysis can be combined into one-pot procedure with good yields. The mild transition-metal free aqueous conditions and eco-friendly feature of diaryliodonium salts will make this method attractive. Further exploration of N,N-disubstituted ureas for the synthesis of bioactive heterocycles is on progress and will be detailed in the future.

Acknowledgements

The authors thank Hainan innovation and entrepreneurship program for high-tech people, and Hainan international cooperation program (KJHZ 2014-02) for financial support. We also thank Xiaopeng Wu and Jihui Li [from Institute of Tropical Bioscience and Biotechnology (ITBB), Chinese Academy of Tropical Agricultural Sciences (CATAS)] for their excellent technical and analytical support.

Notes and references

- Selected Examples: a) A. Servais, M. Azzouz, D. Lopes, C. Courillon and M. Malacria, *Angew. Chem. Int. Ed.*, 2007, **46**, 576–579; b) M.-H. Larraufie, C. Ollivier, L. Fensterbank, M. Malacria and E. Laocté, *Angew. Chem. Int. Ed.*, 2010, **49**, 2178–2181; c) Z. Pan, S. M. Pound, N. R. Rondla, and C. J. Douglas, *Angew. Chem. Int. Ed.*, 2014, **53**, 5170–5174; d) H. Basavaprabhu and V. V. Sureshbabu, *Org. Biomol. Chem.*, 2012, **10**, 2528–2533; e) V. Panduranga, Basavaprabhu, V. V. Sureshbabu *Tetrahedron Lett.*, 2013, **54**, 975–979; f) S. Kamijo, T. Jin, and Y. Yamamoto *Angew. Chem. Int. Ed.*, 2002, **41**, 1780–1782; g) L. V. R. Boñaga, H.-C. Zhang and B. E. Maryanoff, *Chem. Commun.*, 2004, 2394–2395; h) K. Fukumoto, T. Oya, M. Itazaki, and H. Nakazawa, *J. Am. Chem. Soc.* 2009, **131**, 38–39; i) R. L. Giles, J. D. Sullivan, A. M. Steiner, and R. E. Looper, *Angew. Chem. Int. Ed.* 2009, **48**, 3116–3120; j) S. Guin, S. K. Rout, A. Gogoi, W. Ali, and B. K. Patela, *Adv. Synth. Catal.*, 2014, 356, 2559–2565; k) T. K. Lane, B. R. D'Souza and J. Louie *J. Org. Chem.* 2012, **77**, 7555–7563; l) V. Kumar, M. P. Kaushik, and A. Mazumdar, *Eur. J. Org. Chem.*, 2008, 1910–1916.
- Selected Examples: a) C. J. Adams *J. Chem. Soc., Dalton Trans.*, 1999, 2059–2064; b) A. S. Smirnov, E. S. Butukhanova, N. A. Bokach, G. L. Starova, V. V. Gurzhiy, M. L. Kuznetsov and V. Yu. Kukushkin, *Dalton Trans.*, 2014, **43**, 15798–15811; c) M. Yuan, S. Gao, H.-L. Sun, and G. Su *Inorg. Chem.*, 2004, **43**, 8221–8223.
- a) D. G. Barrett, D. N. Deaton, A. M. Hassell, R. B. McFadyen, A. B. Miller, L. R. Miller, J. A. Payne, L. M. Shewchuk, D. H. Willard, Jr. and L. L. Wright, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3039–3043; b) H.-W. K. Bischofsheim, H.-J. L. Hogheim, J.-R. S. Kelkheim, A. W. Egelsbach, S. F. Idstein, H.-W. J. Niedernhausen, S. P. Frankfurt, U. 6369069B1; c) K. S. Atwal, G. J. Grover, S. Z. Ahmed, P. G. Slep, S. Dzwonczyk, A. J. Baird, and D. E. Normandin, *J. Med. Chem.*, 1995, **38**, 3236–3245; d) P. W. Manley and U. Quast, *J. Med. Chem.*, 1992, **35**, 2327–2334; e) G. Danger, A. Michaut, M. Bucchi, L. Boiteau, J. Canal, R. Plasson, and R. Pascal *Angew. Chem. Int. Ed.* 2013, **52**, 611–614.
- a) T. Kamo, M. Endo, M. Sato, R. Kasahara, H. Yamaya, S. Hiradate, Y. Fujii, N. Hirai and M. Hirota, *Phytochemistry*, 2008, **69**, 1166–1172.
- a) C. Grundmann, In *Methoden der Organischen Chemie (Houben-Weyl)*; J. Falbe, Ed.; Georg Thieme Verlag: Stuttgart, 1985; **Vol. E5**, pp 1611–1658. b) S. R. Sandler, W. Karo, *Organic Functional Group Preparations*; Academic: New York, 1972; **Vol. 3**, p 286–287 and Vol. 2, p174–178.
- Selected transition-metal catalyzed synthesis of cyanamides: a) S. Kamijo, T. Jin, and Y. Yamamoto *J. Am. Chem. Soc.*, 2001, **123**, 9453–9454; b) S. Kamijo and Y. Yamamoto *J. Am. Chem. Soc.* 2002, **124**, 11940–11945; c) S. Kamijo, T. Jin, Y. Yamamoto, *Angew. Chem. Int. Ed.*, 2002, **41**, 1780–1782; d) S. K. Sahoo, L. Jamir, S. Guin, and B. K. Patel *Adv. Synth. Catal.* 2010, **352**, 2538–2548; e) R. M. Stolley, W. Guo, and J. Louie, *org. Lett.*, 2012, **14**, 322–325; f) P. Kumari, R. Nagpal, P. Chauhan, V. Yatindranath and Shive M. Chauhan, *J. Chem. Sci.*, 2015, **127**, 13–18; g) S. Cerezo, J. Cortés, M. Moreno-Mañas, R. Pleixats, A. Roglans, *Tetrahedron*, 1998, **54**, 14869–14884.
- P. Li, G. Cheng, H. Zhang, X. Xu, J. Gao, and X. Cui, *J. Org. Chem.*, 2014, **79**, 8156–8162.
- a) E. A. Merritt and B. Olofsson, *Angew. Chem. Int. Ed.*, 2009, **48**, 9052–9070; b) M. S. Yusubov, A. V. Maskaev, and V.V. Zhdankin, *ARKIVOC*, 2011, 370–409; c) J. Malmgren, S. Santoro, N. Jalalian, F. Himo, and B. Olofsson *Chem. Eur. J.*, 2013, **19**, 10334–10342; d) M. Bielawski, M. Zhu, and B. Olofsson *Adv. Synth. Catal.*, 2007, **349**, 2610–2618; e) Y. Kita, K. Morimoto, M. Ito, C. Ogawa, A. Goto, and T. Dohi, *J. Am. Chem. Soc.*, 2009, **131**, 1668–1669; f) M. A. Carroll, R. A. Wood, *Tetrahedron* 2007, **63**, 11349–11353; g) F. Tinnis, E. Stridfeldt, H. Lundberg, H. Adolfsson, and B. Olofsson, *Org. Lett.*, 2015, **17**, 2688–2691. h) I. P. Beletskaya, D. V. Davydov, M. Moreno-Manas, *Tetrahedron Lett.* 1998, **39**, 5621–5622. i) J. Yan, M. Zhu, Z. Zhou, *Eur. J. Org. Chem.* 2006, 2060–2062.
- J. Li and L. Neuville, *Org. Lett.*, 2013, **15**, 6124–6127.
- The reaction of phenyl cyanamide with di(p-tolyl)iodonium triflate in 1.25 mmol produced 223 mg phenyl(p-tolyl)cyanamide (**3a**, 86% yield) and 196 mg p-tolylidide (72% yield).
- M. Ochiai, Y. Kitagawa, and M. Toyonari, *ARKIVOC*, 2003, 43–48.
- K. M. Lancer and G. H. Wiegand, *J. Org. Chem.*, 1976, **41**, 3360–3364.
- a) B. A.-K. Wulfrath, S. S. Goch, E. K. Hattingen US 2011/0263657; b) C. P. Decicco, J. L. Seng, K. E. Kennedy, M. B. Covington, P. K. Welch, E. C. Arner, R. L. Magolda, D. J. Nelson, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2331–2336; c) J. A. W. Kruijtzter, D. J. Lefeber, R. M. J. Liskamp, *Tetrahedron Lett.* 1997, **38**, 5335–5338; d) A. R. Katritzky, N. Kirichenko, and B. V. Rogovoy, *ARKIVOC*, 2003 (**VIII**), 8–14.
- A. Retnakaran, J. E. Wright, *Chitin and Phenoylphenyl Ureas*, 1987, **38**, 205–282; b) L. Chen, Q. Wand, R. Huang, C. Mao, J. Shang, and F. Bi, *J. Agric. Food Chem.* 2005, **53**, 38–41.



Various disubstituted cyanamides were made through transition-metal free N-arylation of cyanamides by diaryliodonium triflates under aqueous conditions with good yields.