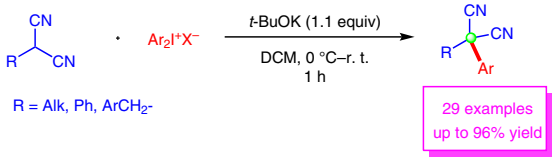
Synlett J. Han et al. Letter

Potassium *tert*-Butoxide Mediated Arylation of 2-Substituted Malononitriles Using Diaryliodonium Salts

Jianwei Han[*a,b]
Xiaofei Qian[a]
Bowen Xu[a]
Limin Wang[*a]

[a] Key Laboratory for Advanced Materials, Institute of Fine Chemicals, School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, P. R. of China
jianweihan@ecust.edu.cn
wanglimin@ecust.edu.cn
[b] Shanghai-Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, 345 Ling Ling Road, Shanghai 200237, P. R. of China



Received: 24.04.2017
Accepted after revision: 22.05.2017
Published online: 06.07.2017
DOI: 10.1055/s-0036-1589061; Art ID: st-2017-u0285-l

Abstract Direct arylation of 2-substituted malononitriles using diaryliodonium salts without involving transition-metal catalysts was developed. By using potassium *tert*-butoxide as a promoter, the desired 2-substituted α-arylmalononitriles derivatives were synthesized in good to excellent yields of 55–96%. This synthetic method provided an efficient way to prepare a variety of 2-substituted arylmalononitriles which were useful in agrochemicals.

Key words arylation, diaryliodonium salts, metal-free, arylmalononitriles, agrochemicals

α-Arylmalononitriles were demonstrated to be important compounds in organic functional materials as well as chemical intermediates for the preparation of useful bioactive agents.[1–3] For examples, dicyanomethylphenyl scaffold was well-studied in organic radicals because of their simplicity in formation of radicals via a dimerization equilibrium (**A**, Figure 1).[1] In light of their utilization in organic synthesis, pinoxaden, the active ingredient of the herbicide for the postemergence control of grass weeds in cereals, was prepared with 2,4,6-trialkylaryl malononitrile as starting material (**B**, Figure 1).[2] Aminopyrazolopyrimidine derivatives as promising drug leads for treatment of myeloproliferative disorders was also synthesized from arylmalononitriles (**C**, Figure 1).[3] Therefore, an efficient access to the family of α-arylmalononitriles is still highly desirable. A survey of the literature showed that several catalytic systems involving transition-metal complexes (copper, palladium, or nickel) afforded α-arylmalonates in good yields with cross-coupling of aryl halides with malononitrile.[4] However, the construction of quaternary carbon center by direct arylation of 2-substituted malononitriles is very rare, one reported example by Ciufolini et al. is the intramolecular arylation of dicyanomethylphenyl substrate in the presence of palladium catalyst and NaH in DMF at high temperature of 130–140 °C.[4e] The intermolecular variant of arylation of 2-substituted malononitriles is still unknown to date, one concern is that the sterically hindered reactive site by substituent and dicyano groups may be problematic. Of note, many compounds of 2-aryl alkylmalonoitriles bearing a quaternary carbon center was used to protect crops from infestation by animal pests.[5] Recently, we reported a method of direct arylation of ethyl 2-cyanobutanoate derivatives by using diaryliodonium salts under transition-metal-free conditions.[6] It is worth to mention that construction of C–C bonds by metal-free arylations of active methylene substrates using diaryliodonium salts was attracted much attention in the recent decades.[7] As a part of our ongoing research on the development of metal-free arylations,[8] herein we presented a direct arylation of 2-substituted malononitriles with diaryliodonium salts mediated by potassium *tert*-butoxide.

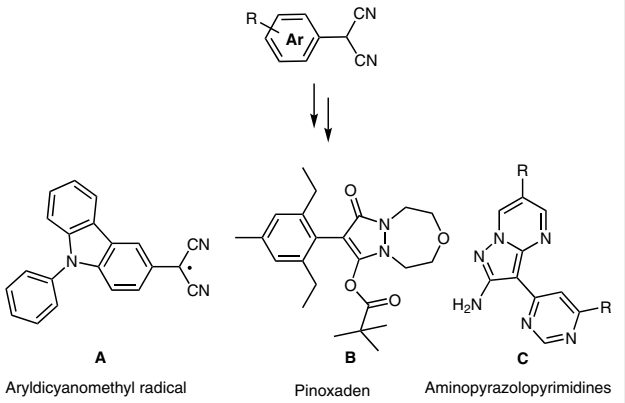
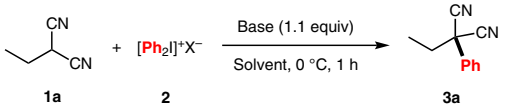


Figure 1 Selective examples of useful compounds from α-arylmalonates

Inspired by our previous work,[6] we initiated this study using diphenyliodonium triflate (**2a**) with 2-ethylmalononitrile (**1a**) to optimize the conditions (Table 1, entries 1–10). It was pleased to find that the reaction gave the arylated product of ethyl 2-phenyl-2-ethylmalononitrile (**3a**) in an excellent yield of 96% by using 1.1 equivalents potassium *tert*-butoxide as the base in dichloromethane at 0 °C. As shown in Table 1, we examined the impact of bases on the reaction, it was shown that potassium hydroxide resulted in an identical yield of 89% (Table 1, entry 3) while organic bases of Et_3N and DMAP gave no product or low yield, respectively. After examining several solvents, it is found that the solvents showed significant effect on this reaction. The reaction also worked well in toluene, which gave **3a** in high yield of 84% (Table 1, entry 7), while the solvents MeCN, THF, and DMF gave only a trace amount of the desired products (Table 1, entries 6, 9, and 10). When DCE was used as the solvent, it gave **3a** in 30% yield. Next, we evaluated different anions of diphenyliodonium salts. A negligible influence was observed on the yield of **3a** (Table 1, entries 11–14). In the optimization process, it revealed that the previous reported conditions of strong base of potassium *tert*-butoxide in DCM was still the most efficient in delivering the desired product of **3a**.[6]

Table 1 Screening of Reaction Conditions for Arylation of Ethyl 2-Methylcyanoacetate[a]



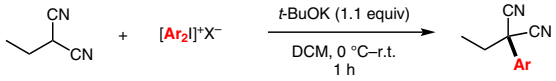
1a 2 3a

Entry	X[b]	Base	Solvent	Yield (%)[c]
1	OTf	*t*-BuOK	DCM	96
2	OTf	K_2CO_3	DCM	82
3	OTf	KOH	DCM	89
4	OTf	Et_3N	DCM	trace
5	OTf	DMAP	DCM	23
6	OTf	*t*-BuOK	MeCN	trace
7	OTf	*t*-BuOK	toluene	84
8	OTf	*t*-BuOK	DCE	30
9	OTf	*t*-BuOK	THF	trace
10	OTf	*t*-BuOK	DMF	trace
11	OTs	*t*-BuOK	DCM	78
12	Br	*t*-BuOK	DCM	70
13	BF_4	*t*-BuOK	DCM	85
14	PF_6	*t*-BuOK	DCM	88

[a] Reaction conditions (unless otherwise specified): **1a** (0.5 mmol), **2** (0.55 mmol, 1.1 equiv), base (0.55 mmol, 1.1 equiv), and solvent (2 mL); 0 °C; 1 h under nitrogen.
[b] OTf = trifluoromethansulfonate; OTs = 4-toluenesulfonate.
[c] Isolated yield.

With the optimized reaction condition in hand, we then investigated the substrate scope of various diaryliodonium salts as arylation partners. The results are shown in Table 2, the reaction system was suitable for most functional groups on the diphenyliodonium salts, and the reactions were finished in one hour at 0 °C as determined by thin-layer chromatography. It was found that the results were significantly affected by the electronic nature of the aromatic rings (Table 2, entries 1–12). The electron-donating substituents on the benzene ring, such as methoxy and alkyl, gave the relative higher yields. While the electron-withdrawing nitro groups led to decomposition of the diaryliodonium salts, no desired product was observed in this procedure (Table 2, entry 12). Moreover, the steric factor also affected the reactivity of this reaction, for example, double substituted diaryliodonium salts only gave moderate yields of the desired product **3** in comparison with their corresponding monosubstituted diaryliodonium salts (Table 2, entries 5, 6, and 11 vs. entries 1 and 8, respectively).

Table 2 Scope of Iodonium Salts in Arylation of 2-Ethylmalononitrile[a]

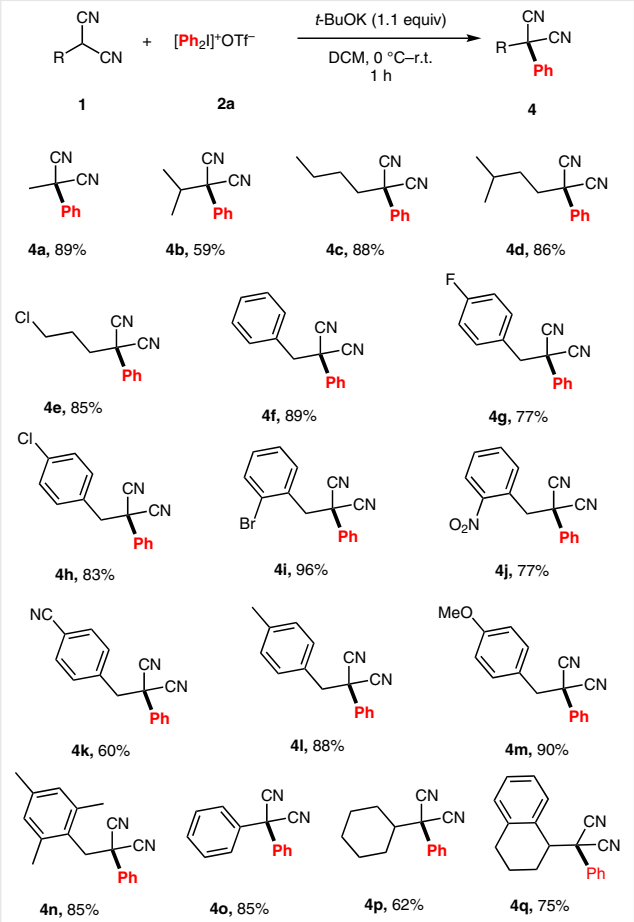


1a 2 3

Entry	Ar	X[b]	Product	Yield (%)[c]
1	$(4\text{-}MeC_6H_4)_2$	OTf	**3b**	86
2	$(4\text{-}t\text{-}BuC_6H_4)_2$	OTf	**3c**	88
3	$(4\text{-}MeOC_6H_4)_2$	OTf	**3d**	90
4	$(3\text{-}MeC_6H_4)_2$	OTf	**3e**	85
5	$(2,4\text{-}Me_2C_6H_3)_2$	OTf	**3f**	55
6	$(2,5\text{-}Me_2C_6H_3)_2$	PF_6	**3g**	65
7	$(4\text{-}FC_6H_4)_2$	OTf	**3h**	61
8	$(4\text{-}ClC_6H_4)_2$	OTf	**3i**	65
9	$(4\text{-}BrC_6H_4)_2$	OTf	**3j**	72
10	$(4\text{-}CF_3C_6H_4)_2$	OTf	**3k**	62
11	$(3,4\text{-}Cl_2C_6H_3)_2$	BF_4	**3l**	62
12	$(3\text{-}O_2NC_6H_4)_2$	PF_6	**3m**	0

[a] Reaction conditions (unless otherwise specified): **1a** (0.5 mmol), iodonium salt (0.55 mmol, 1.1 equiv), *t*-BuOK (0.55 mmol, 1.1 equiv), and DCM (2 mL); 0 °C to r.t.; 1 h; under nitrogen.
[b] OTf = trifluoromethansulfonate; OTs = 4-toluenesulfonate.
[c] Isolated yield.

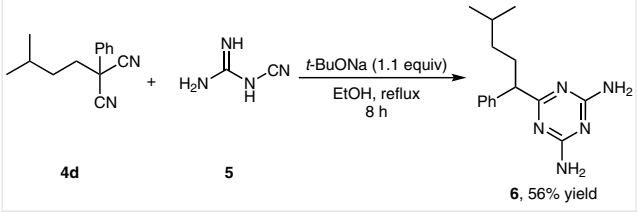
To further investigate the scope of this reaction, a wide variety of 2-substituted malononitrile derivatives were phenylated into the corresponding dicyanomethylphenyl products **4** in the presence of potassium *tert*-butoxide in dichloromethane. This reaction procedure was proved to be efficient in the phenylation as shown in Scheme 1. 2-Alkyl 2-phenylmalononitriles **4** were obtained in good to excel-



Scheme 1 Arylation of 2-substituted malononitriles **1**.[a,b] [a] Reaction conditions (unless otherwise specified): **1a** (0.5 mmol), iodonium salt (0.55 mmol, 1.1 equiv), *t*-BuOK (0.55 mmol, 1.1 equiv), and DCM (2 mL); 0 °C to r.t.; 1 h; under nitrogen.[b] Isolated yield.

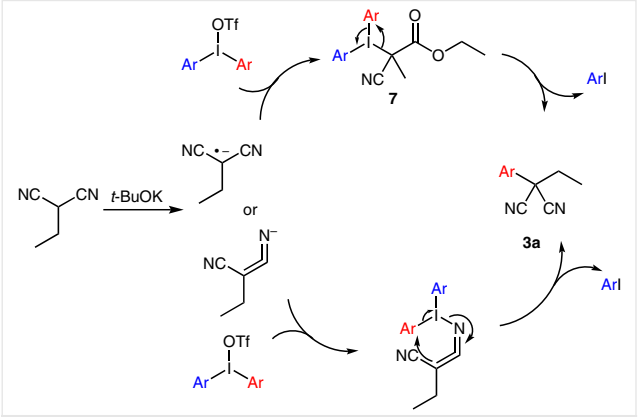
lent yields of 80–92% (Scheme 1, **4a–e**). Among them (R = chloroalkyl) **4e** was furnished in good yield of 85% without hydrolysis of the alkyl halide under the standard conditions. Moreover, the desired products were obtained in good yields of 60–96% when R of **1** is benzyl or substituted benzyl groups. 4-Fluoro, 4-chloro, 2-bromo, 2-nitro, 4-cyano, 4-methyl, 4-methoxyl, and 2,4,6-trimethyl groups substituted on the 2-benzyl group regardless of their electronic nature or steric effect were well accommodated in this reaction (Scheme 1, **4f–n**). Dicyanomethyl substrates **1** bearing a phenyl group were employed, 2,2-diphenylmalononitrile **4o** were readily prepared in 85% yield. In addition, when R of **1** is cyclohexyl or 1-tetralin, the phenylation products **4p** and **4q** were provided in a yield of 62% and 75%, respectively.

Moreover, 2-isopentyl-2-phenylmalononitrile (**4d**) was employed for one further transformation. As shown in Scheme 2, one cyano group of **4d** underwent cyclization with dicyandiamide to produce triazine **6** in 56% yield with sodium *tert*-butoxide under reflux in ethanol,[9] the other cyano group of **4d** was cleaved off under these conditions as determined by NMR and MS spectra. The triazines are promising hetercyclic compounds for the development of bioactive agents in pharmaceutical industry.[3,9]



Scheme 2 Related transformation with **4d**

Regarding the mechanism of this reaction, the previous reports on metal-free arylation by diaryliodonium salts were believed to proceeded though ligand exchange with nucleophiles by associative or dissociative mechanism.[10] The ligand-coupling pathway by reductive elimination affords the product along with releasing loss of ArI. Nucleophilic aromatic substitution (S_NAr) or single-electron-transfer reaction (SET) were discussed with special cases and conditions.[10b] At this stage it is premature to draw a conclusive mechanism of this reaction, however, based on the mechanistic insights on the arylation involving hypervalent iodine, a plausible mechanism of this reaction was proposed as shown in Scheme 3.



Scheme 3 Proposed mechanism for the formation of α-arylmalonates

In summary, we have succeeded in the development of an approach for direct arylation of 2-substituted malononitriles using diaryliodonium salts without the use of transition-metal catalysts.[11] Various 2-substituted 2-arylmalononitrile were prepared in good yields, which are valuable chemical intermediates in agrochemical or medical research. Current studies are focused on further transformation of these dicyanomethylaryl products into useful heterocycles and synthetic utility of this arylation method in our laboratories.

Funding Information

The work was supported by the National Nature Science Foundation of China (NSFC 21472213, 21272069), National Key Program (2016YFA0200302, Study on application and preparation of aroma nanocomposites), and the Fundamental Research Funds for the Central Universities.

Supporting Information

Supporting information for this article is available online at https://doi.org /10.1055/s-0036-1589061.

References and Notes

(1) (a) Kobashi, T.; Sakamaki, D.; Seki, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 8634. (b) Görner, H.; Mrozek, T.; Daub, J. *Chem. Eur. J.* **2002**, *8*, 4008. (c) Hartzler, H. D. *J. Org. Chem.* **1966**, *31*, 2654.

(2) (a) Lamberth, C.; Jeanmart, S.; Luksch, T.; Plant, A. *Science* **2013**, *341*, 742. (b) Schnyder, A.; Indolese, A. F.; Maetzke, T.; Wenger, J.; Blaser, H.-U. *Synlett* **2006**, 3167.

(3) (a) Ledeboer, M. W.; Pierce, A. C.; Duffy, J. P.; Gao, H.; Messersmith, D.; Salituro, F. G.; Nanthakumar, S.; Come, J.; Zuccola, H. J.; Swenson, L.; Shlyakter, D.; Mahajan, S.; Hoock, T.; Fan, B.; Tsai, W. J.; Kolaczkowski, E.; Carrier, S.; Hogan, J. K.; Zessis, R.; Pazhanisamy, S.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6529. (b) Meyers, M. J.; Sun, J.; Carlson, K. E.; Marriner, G. A.; Benita, S.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2001**, *44*, 4230.

(4) (a) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607. (b) Gao, C.; Tao, X.; Qian, Y.; Huang, J. *Chem. Commun.* **2003**, 1444. (c) Cristau, H. J.; Vogel, R.; Taillefer, M.; Gadras, A. *Tetrahedron Lett.* **2000**, *41*, 8457. (d) Todorovic, N.; Awuah, E.; Albu, S.; Ozimok, C.; Capretta, A. *Org. Lett.* **2011**, *13*, 6180. (e) Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4151.

(5) Meng, C.; Miculka, C.; Soll, M.; Paulini, R.; Pohlman, M.; Sorgel, S.; Bastiaanns, H. M. M.; Thompson, S.; Ebuenga, D. C.; Malveda, U. A.; Suiza, C. R.; Palmer, C.; Hokama, T. WO 2015161224, **2015**.

(6) Qian, X.; Han, J.; Wang, L. *Adv. Synth. Catal.* **2016**, *358*, 940.

(7) (a) Chai, Z.; Wang, B.; Chen, J.-N.; Yang, G. *Adv. Synth. Catal.* **2014**, *356*, 2714. (b) Monastyrskyi, A.; Namelikonda, N. K.; Manetsch, R. *J. Org. Chem.* **2015**, *80*, 2513. (c) Dey, C.; Lindstedt, E.; Oloffson, B. *Org. Lett.* **2015**, *17*, 4554.

(8) (a) Guo, F.; Wang, L.; Wang, P.; Yu, J.; Han, J. *Asian J. Org. Chem.* **2012**, *1*, 218. (b) Mao, S.; Geng, X.; Yang, Y.; Qian, X.; Wu, S.; Han, J.; Wang, L. *RSC Adv.* **2015**, *5*, 36390. (c) Zhang, Y.; Han, J.; Liu, Z. -J. *Synlett* **2015**, *26*, 2593. (d) Qian, X.; Han, J.; Wang, L. *RSC Adv.* **2016**, *6*, 89234. (e) Yang, Y.; Wu, X.; Han, J.; Mao, S.; Qian, X.; Wang, L. *Eur. J. Org. Chem.* **2014**, 6854.

(9) Li, M.-B.; Li, H.; Wang, J.; Liu, C.-R.; Tian, S.-K. *Chem. Commun.* **2013**, *49*, 8190.

(10) (a) Beaulieu, S.; Legault, C. Y. *Chem. Eur. J.* **2015**, *21*, 11206. (b) Norrby, P-O.; Petersen, T. B.; Bielawski, M.; Olofsson, B. *Chem. Eur. J.* **2010**, *16*, 8251.

(11) **General Procedure for the Synthesis of 3 and 4**

An oven-dried Schlenk tube was charged with 2-substituted malononitriles (0.5 mmol, 1 equiv), the tube was evacuated and charged with nitrogen, then 2 mL anhydrous DCM and *t*-BuOK (61.7 mg, 0.55 mmol, 1.1 equiv) were added, and the mixture was stirred at 0 °C for 5 min. The solution of diaryliodonium salts (0.55 mmol, 1.1 equiv) in 2 mL anhydrous DCM was added through a syringe subsequently for 5 min. The reaction was stirred for another 1 h, and the reaction temperature was elevated to r.t. The reaction mixture was quenched with 20 mL water, then the mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and filtered. After the solvent was removed under vacuum, and the residue was purified by flash chromatography to give the desired product. Analytical data for representative sample **3a** is provided below.

2-Ethyl-2-phenylmalononitrile (3a)

81.7 mg (96% yield), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.53 (m, 2 H), 7.52–7.45 (m, 3 H), 2.29 (q, *J* = 7.4 Hz, 2 H), 1.23 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 132.0, 129.9, 129.7, 125.8, 115.0, 43.2, 36.6, 10.0. HRMS (EI): *m/z* calcd for $C_{11}H_{10}N_2$ [M]$^+$: 170.0844; found: 170.0843.