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Iodine-Mediated Diastereoselective Cyclopropanation of Arylidene Malononotriles by 2,6-Dimethylquinoline

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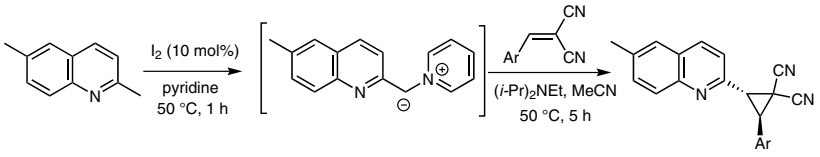

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Abstract A novel iodine-mediated reaction of 2,6-dimethylquinoline with Knoevenagel condensation products of malononitrile with benzaldehydes, leading to a facile, one-pot synthesis of 2-aryl-3-(6-methylquinolin-2-yl)cyclopropane-1,1-dicarbonitriles, in moderate to good yields, is described.

Keywords diastereoselective reactions, cyclopropanation, small rings, iodine, N-heterocycles

Cyclopropane and its derivatives are versatile molecules with numerous applications in organic synthesis.[1] Because of their rigid structure and inherent reactivity, cyclopropane rings can constitute key components in the synthesis of complex molecules.[2] Functionalized arylcyclopropylnitriles have found utility in organic synthesis as precursors for a wide variety of natural products,[3] bioactive compounds,[4] and general synthetic targets.[5] Moreover, considerable research efforts have been devoted to the stereoselective construction of three-membered carbocyclic rings over the last few decades.[6] The most common methods for the synthesis of functionalized cyclopropanes are metal-catalyzed decomposition of α-diazocarbonyl compounds in the presence of alkenes[7] and reaction of electron-deficient olefins with sulfur ylides.[8]

As part of our current studies on the development of new routes to carbocyclic and heterocyclic systems,[9] we report herein a transition-metal-free protocol in which a nitrogen ylide generated in situ combines with the Knoevenagel condensation products of malononitrile with benzaldehydes to afford 2-aryl-3-(6-methylquinolin-2-yl)cyclopropane-1,1-dicarbonitriles.[10]

Initially, the reaction between 2,6-dimethylquinoline (**1**), 4-bromobenzaldehyde (**2a**), malononitrile (**3**), and pyridine in the presence of *N*,*N*-diisopropylethylamine was studied as a model reaction; the results are shown in Table 1. In all cases, the zwitterionic intermediates, generated from **1**, Lewis acids, and pyridine were reacted with arylidene malononitrile, generated from condensation of **3** and **2a**, in the presence of *N*,*N*-diisopropylethylamine at room temperature in different solvents.

As shown in Table 1 (entries 1–7), copper salts such as CuBr, CuI, $Cu(OAc)_2$, and AgOAc were found to be less effective catalysts for this transformation. Lewis acids such as $AlCl_3$ and $BF_3{\cdot}Et_2O$ did not promote the desired reaction. Furthermore, the presence of CuBr and CuI in combination with 1,10-phenanthroline promoted the reaction only slightly (< 10%).

Iodine (30 mol%), was found to be an effective catalyst, affording 2-(4-bromophenyl)-3-(6-methylquinolin-2-yl)cyclopropane-1,1-dicarbonitrile (**4a**) in 15% yield (Table 1, entry 10). The use of THF or MeCN as solvent, led to improved yields (Table 1, entries 11 and 12). These results encouraged us to optimize the reaction conditions with iodine. The conversion proceeded in better yield (46%) with 50 mol% iodine. In the presence of stoichiometric amounts of iodine, the reaction was complete after 12 h with up to 60% yield of isolated material (Table 1, entries 13 and 14).

With the optimized reaction conditions in hand, we prepared a range of 2-(6-methylquinolin-2-yl)-3-arylcyclopropane-1,1-dicarbonitriles **4** from **1**, pyridine, benzaldehydes **2**, and malononitrile in the presence of iodine as Lewis acid and *N*,*N*-diisopropylethylamine as Lewis base (Table 2). Both electron-donating and electron-withdrawing substituents on the benzaldehyde ring were well-tolerated, affording the desired products in 52 to 73% yields (Table 2).

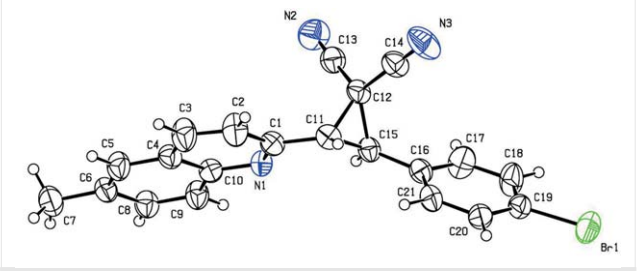
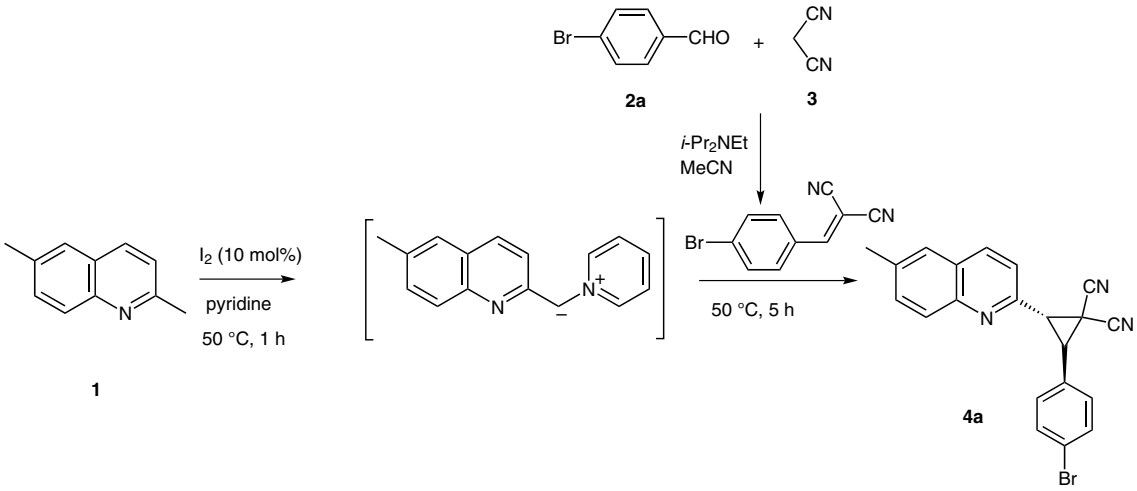


Figure 1 ORTEP diagram of **4a**

Table 1 Optimization of the Reaction Conditions for the Preparation of 2-(4-Bromophenyl)-3-(6-methylquinolin-2-yl)cyclopropane-1,1-dicarbonitrile (**4a**)[a]



Entry	Cat. (30 mol%)	Ligand (10 mol%)	Solvent	Yield [%][b]
1	CuBr	none	DMF	no reaction
2	CuBr	1,10-phenanthroline	DMF	< 10
3	CuI	none	DMF	no reaction
4	CuI	1,10-phenanthroline	DMF	< 10
5	$Cu(OAc)_2$	none	DMF	no reaction
6	$Cu(OAc)_2$	1,10-phenanthroline	DMF	no reaction
7	AgOAc	none	DMF	no reaction
8	$AlCl_3$	none	DMF	no reaction
9	$BF_3{\cdot}Et_2O$	none	DMF	no reaction
10	I_2	none	DMF	15
11	I_2	none	THF	23
12	I_2	none	MeCN	38
13	I_2 (50 mol%)	none	MeCN	46
14	I_2 (100 mol%)	none	MeCN	60
15	I_2 (120 mol%)	none	MeCN	56

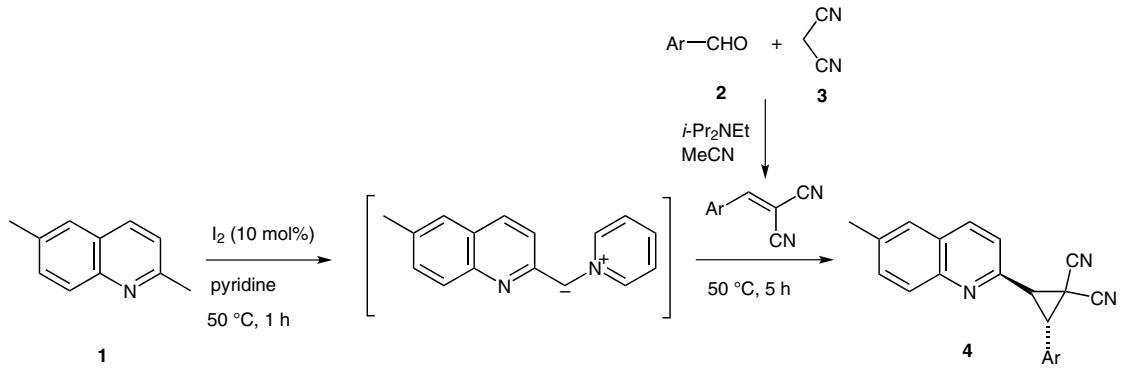
[a] Reaction conditions: (i) **1** (0.157 g, 1.0 mmol), pyridine (0.158 g, 2.0 mmol), Lewis acid, 50 °C, 1 h; (ii) arylidene malononitrlile, produced from **2a** (0.106 g, 1.0 mmol) and **3** (0.066 g, 1.0 mmol), solvent (3.0 mL), $(i\text{-Pr})_2NEt$ (0.284 g, 2.2 mmol).
[b] Isolated yield after column chromatography.

Unambiguous evidence for the structure and stereochemistry of **4a** was obtained from single-crystal X-ray analysis. An ORTEP[11] diagram of **4a** is shown in Figure 1. The structure deduced from the crystallographic experiment, can be applied by analogy to the other products on account of their similar NMR spectra.

The ^1H NMR spectrum of product **4a** exhibited two sharp doublets (δ = 4.50 and 3.76 ppm, $^3J_{H-H}$ = 8.2 Hz) for the methine protons of the cyclopropane. The ^1H-decoupled ^{13}C NMR spectrum of **4a** showed 19 distinct resonances, in agreement with the proposed structure. The ^1H and ^{13}C NMR spectra of products **4b**–**l** were similar to those of **4a**, except for the aryl moieties, which exhibited characteristic signals with appropriate chemical shifts.

A mechanistic rationalization for the formation of products **4** is given in Scheme 1. Presumably, the initial event is activation of 2-methylquinoline by coordination to iodine, which leads to 1,2-dihydro-1-iodo-2-methylenequinoline intermediate **5**. This intermediate is attacked by pyridine to afford alkylpyridinium salt **6**, which is converted into nitro-

Table 2 Iodine-Mediated Synthesis of Substituted 2-Aryl-3-(6-methylquinolin-2-yl)cyclopropane-1,1-dicarbonitriles **4**[a]



Entry	Product	Ar	Yield [%][b]
1	**4a**	4-BrC_6H_4	60
2	**4b**	Ph	52
3	**4c**	4-ClC_6H_4	73
4	**4d**	4-MeC_6H_4	54
5	**4e**	3-$O_2NC_6H_4$	73
6	**4f**	4-$MeOC_6H_4$	68
7	**4g**	2-BrC_6H_4	48
8	**4h**	3-ClC_6H_4	64
9	**4i**	1-naphthyl	67
10	**4j**	4-HOC_6H_4	52
11	**4k**	4-$O_2NC_6H_4$	68
12	**4l**	2-MeC_6H_4	53

[a] Reaction conditions: (i) **1** (0.157 g, 1.0 mmol), pyridine (0.158 g, 2.0 mmol), I_2 (0.253 g, 1.0 mmol), 50 °C, 1 h; (ii) arylidene malononitrile, produced from **2** (0.106 g, 1.0 mmol) and **3** (0.066 g, 1.0 mmol), MeCN (3.0 mL), $(i\text{-Pr})_2NEt$ (0.284 g, 2.2 mmol).
[b] Isolated yield after column chromatography.

gen ylide **7** by *N*,*N*-diisopropylethylamine. Conjugate attack of ylide **7** with arylidene malononitrile derivatives generated in situ, affords intermediate **8**, which undergoes cyclization via intermediate **9** to generate **4**.

In summary, we have described a novel synthesis of 2-aryl-3-(6-methylquinolin-2-yl)cyclopropane-1,1-dicarbonitriles from the reaction of pyridinium ylides, generated from iodine-mediated reaction of 2,6-dimethylquinoline and pyridine, with Knoevenagel condensation products of benzaldehydes with malononitrile, in moderate to good yields.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379496.

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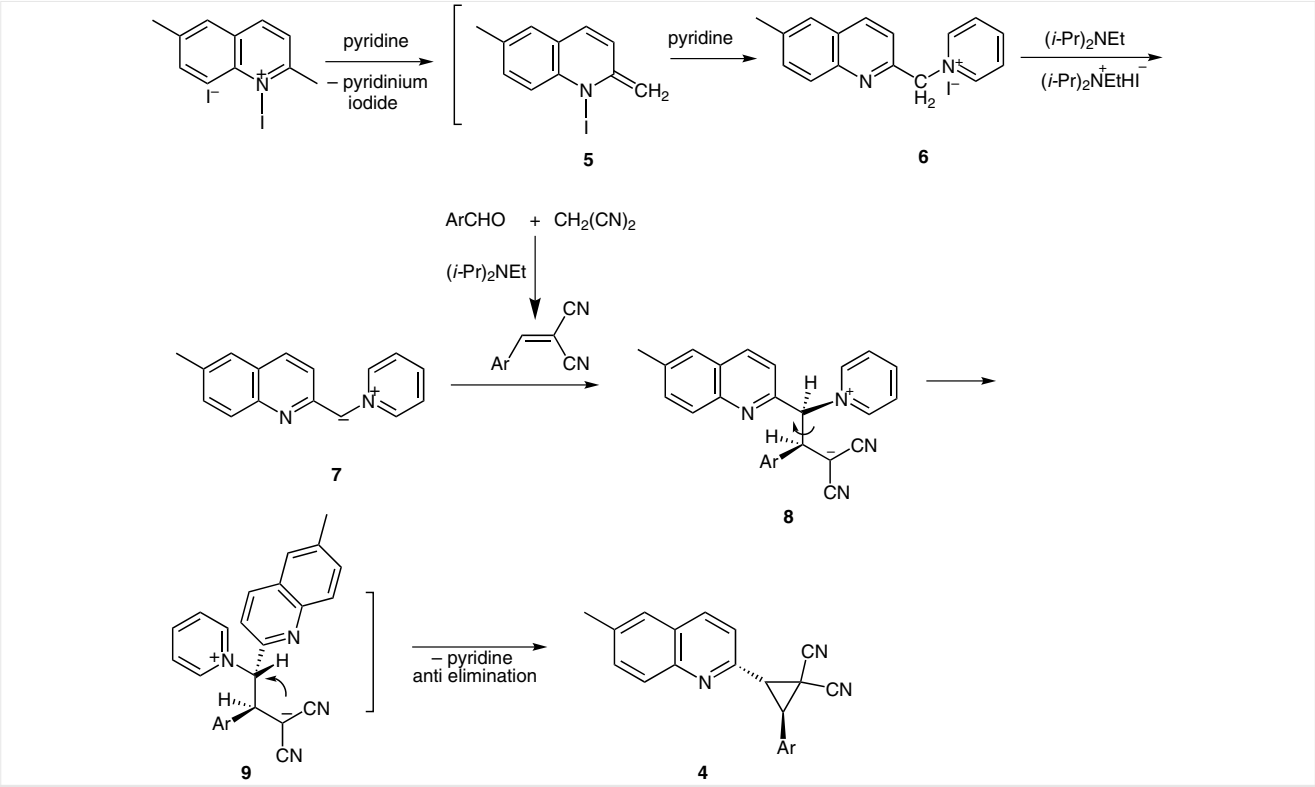

Scheme 1 Mechanistic rationalization for the formation of product **4**

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(10) **Diastereoselective Synthesis of 4; General Procedure:** A mixture of 2,6-dimethylquinoline (0.157 g, 1 mmol), pyridine (0.158 g, 2 mmol), and I_2 (0.253 g, 1 mmol) was warmed to 50 °C for 1 h. A solution of aryl aldehyde (1 mmol), malononitrile, and (*i*-Pr)$_2$NEt (0.284 g, 2.2 mmol) in MeCN (3 mL) was then added and the reaction mixture was stirred for 5 h. Upon completion of reaction, as evidenced by TLC, solvent was removed in vacuo, and the residue was diluted with $CHCl_3$ (20 mL), and washed with saturated K_2CO_3 solution (3 × 10 mL), and H_2O (3 × 10 mL). The organic layer was evaporated to give the crude product, which was purified by silica gel (Merck 230–240 mesh) column chromatography (gradient hexane–EtOAc) to afford **4**.

2-(4-Bromophenyl)-3-(6-methylquinolin-2-yl)cyclopropane-1,1-dicarbonitrile (4a): Yield: 0.23 g (60%); colorless powder; mp 200–202 °C. R_f = 0.71 (hexane–EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.2 Hz, 1 H), 8.01 (d, *J* = 8.7 Hz, 1 H), 7.65–7.56 (m, 5 H), 7.36 (d, *J* = 8.2 Hz, 2 H), 4.50 (d, *J* = 8.2 Hz, 1 H), 3.76 (d, *J* = 8.2 Hz, 1 H), 2.58 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3 (C), 146.2 (C), 137.6 (C), 136.8 (CH), 132.8 (CH), 132.4 (2 CH), 130.2 (2 CH), 129.9 (C), 129.1 (CH), 127.9 (C), 126.5 (CH), 123.7 (C), 121.7 (CH), 113.1 (CN), 112.3 (CN), 38.9 (CH), 37.3 (CH), 21.7 (Me), 16.0 [C(CN)$_2$]. IR (KBr): 2244, 1590, 1490 cm^{-1}. MS (EI): *m*/*z* (%) = 387 (5) [M]$^+$, 360 (10), 353 (7), 307 (15), 282 (10), 266 (5), 242 (12), 232 (15), 207 (10), 182 (100), 157 (13), 142 (46), 127 (11), 115 (48), 101 (8), 89 (27), 75 (18), 63 (25), 51 (24). Anal. Calcd for $C_{21}H_{14}BrN_3$: C, 64.96; H, 3.63; N, 10.82. Found: C, 64.98; H, 3.67; N, 10.78.

X-ray Crystal-Structure Determination of 4a: Formula: $C_{21}H_{14}BrN_3$; M_r 388.26; monoclinic; space group P21/n; *a* = 9.844(1), *b* = 14.911(1), *c* = 12.959(1) Å; Z = 4; V = 1828.1(3) Å^3; $D_{calc.}$ = 1.411 Mg/m^3; Mo K_α radiation (0.71073 Å), *T* = 293(2) K; 3644 reflections collected on a Bruker P4 diffractometer, 3179 unique (R_{int} = 0.0670), 1555 unique reflections with $I > 2\sigma(I)$. All non-hydrogen atoms have been located by difference Fourier maps and refined anisotropi-

cally. The hydrogen atoms have been placed on calculated positions and refined isotropically by using the Riding model. Final indices [$I > 2\sigma(I)$]: $R1 = 0.0556$, $wR2 = 0.0999$, GOF = 0.979. The crystallographic data of **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-976608. Copies of the data can be obtained, free of charge, via the internet (http://www.ccdc.cam.ac.uk/data_request/cif), e-mail: data_request@ccdc.cam.ac.uk, or fax: +44(1223)336033.

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