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A facile synthesis of 1,3,4-trisubstituted isoquinolines

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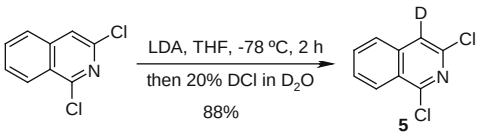
ABSTRACT

A facile and versatile approach to 1,3,4-trisubstituted isoquinoline derivatives from commercially available 1,3-dichloroisoquinoline is described.

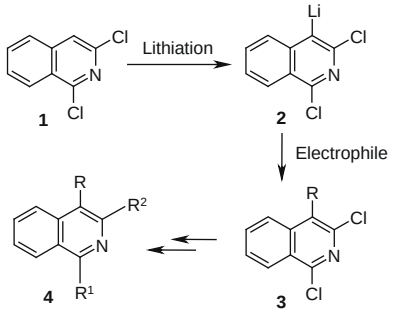
The isoquinoline ring system is frequently found in alkaloids,[1] and it has also been widely used as a scaffold in drug discovery programs.[2] In addition, various isoquinoline derivatives have gained popularity as ligands for transition-metal catalysis.[3] Therefore, the synthesis of isoquinoline derivatives is of considerable interest to synthetic and medicinal chemists.[4]

Although much information concerning the synthesis of isoquinoline and congeners thereof is available in the literature,[5] the generation of 1,3,4-trisubstituted isoquinolines is still a challenging problem. Several approaches to such compounds have been described in the literature,[2b,c,4b,c,6] but the need for highly functionalized intermediates and/or harsh reaction conditions indicates that alternative syntheses of such entities are still required. It occurred to us that the direct C-4 lithiation of commercially available 1,3-dichloroisoquinoline **1** (Scheme 1) ought to be possible,[7] and this, coupled with the well-known difference in reactivity of the chloro groups at C-1 and C-3,[2d,3] in **1** should provide access to a wide variety of 1,3,4-trisubstituted isoquinolines **4**. This work describes the successful realization of such a synthetic strategy.

The first phase of this work involved a study of the lithiation of **1**. Thus, addition of lithium diisopropylamide (LDA) to a THF solution of **1** at −78 °C generated an orange-colored solution. After 2 h at this temperature, the solution was cannulated into 20% DCl in D_2O at room temperature. The monodeuterated compound **5**, determined to contain <5% hydrogen at C-4 by the absence of the δ 7.67 ppm singlet found in the ^{1}H NMR spectrum of **1**, was isolated in high yield.



(1)



Scheme 1. A proposed 1,3,4-trisubstituted isoquinoline synthesis.

The reaction of the 4-lithioisoquinoline derivative **2** with various electrophilic reagents was then examined. Thus, 15 min after the lithiated species had been generated, the solution thereof was cannulated into a THF solution of the electrophilic reagent (3 equiv) at room temperature. Whereas allyl bromide gave only a very minor amount of the desired product **3a**, the much more reactive allyl iodide gave **3a** in nearly 90% yield (Table 1, entries 1 and 2). The homologous compound **3b** was generated equally efficiently from methallyl iodide. In contrast, the reaction with methyl iodide was surprisingly inefficient (entry 4), but it was dramatically improved with methyl triflate, giving **3c** in 90 % yield, even when only 1.1 equiv of the electrophile was used (entry 5). The reaction of the lithiated species **2** with benzoyl chloride, iodine, and benzenesulfonyl chloride was also studied. Whereas the expected products **3d** and **3e** were obtained from benzoyl chloride and iodine, respectively (entries 6 and 7), quenching with benzenesulfonyl chloride gave a complex mixture without even traces of **3f**, as determined by LC–MS analysis.

It is well established for 1,3-dichloroisoquinoline derivatives that both nucleophilic displacement and transition metal-catalyzed cross-coupling reactions occur preferentially at C-1.[2d,3] Therefore, compounds **3a–d** could, in principle, be converted into a variety of 1,3,4-trisubstituted isoquinolines. It appeared to us, however, that the iodo compound **3e** would be an even more

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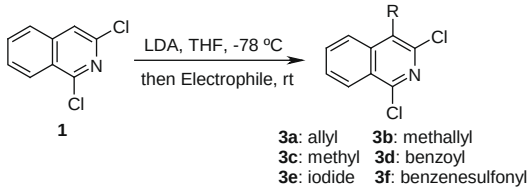
Table 1
Synthesis of 4-substituted-1,3-dichloroisoquinoline via lithiation/electrophilic trapping sequence[a]



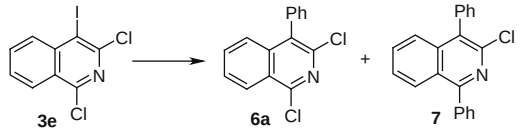
Entry	Electrophile	Conversion[b] (%)	Yield[c] (%)
1	Allyl bromide	5	ND[d]
2	Allyl iodide	87	87[e]
3	Methallyl iodide	87	87[e]
4	Methyl iodide	66	ND[d]
5	Methyl triflate	91	80[e]
6	Benzoyl chloride	100	61
7	Iodine	95	90
8	Benzenesulfonyl chloride	100	0

[a] Reagents and conditions: 1.2 equiv of LDA, THF, −78 °C, 15 min; 3 equiv of electrophile, rt.
[b] Determined by absorption at 240–320 nM range after separation of the crude reaction mixture by LC.
[c] Isolated yield after silica gel chromatography.
[d] ND: not determined.
[e] The product was isolated as a mixture with starting material **1**. The yield was based on the amount of desired product in the mixture.

versatile precursor of 1,3,4-trisubstituted isoquinoline derivatives given that the C-4 iodo group should readily and selectively participate in transition metal-catalyzed cross-coupling reactions. This route to such trisubstituted isoquinoline congeners became even more attractive when it was found that we were unable to gain access to 4-aryl or 4-heteroaryl-1,3-dichloroisoquinlines from the lithio compound **2**.[8]

A series of cross-coupling reactions with **3e** were then carried out and the product mixtures were analyzed by UV spectroscopy in the 240–320 nM region, after separation of the crude reaction mixtures by liquid chromatography on an Xterra C18 column. The Negishi cross-coupling reaction with phenylzinc chloride was the first studied process under the conditions shown in Table 2 (entry 1). Compound **6a** was indeed obtained as the major product (49%), but it was contaminated with significant amounts of the starting material **3e** (18%) and 1,3-dichloroisoquinoline **1** (33%).[9]

Table 2
Optimization of cross-coupling reactions of **3e**



Entry	Conditions[a]	Temp (°C)	Time (min)	Conversion[b] (%)	Ratio[b] (**6a**/**7**/**3e**)
1	A	85[e]	720	82	1.5:0:1
2	B	80[d]	40	100	1.8:1:0
3	B	65[d]	40	100	7:1:0
4	B	60[d]	20	72	1:0:0
5	B[c]	55[e]	720	100	21:1:0

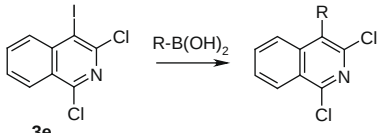
[a] A: phenylzinc chloride (1.8 equiv), $Pd(PPh_3)_4$ (10 mol %), THF. B: phenylboronic acid (1.3 equiv), $PdCl_2$(dppf) (10 mol %), K_2CO_3 (3 equiv), 1,4-dioxane/H_2O (4:1).
[b] Determined from the absorption intensity at 240–320 nM , after separation of the crude reaction mixture by LC.
[c] 1.1 equiv of phenylboronic acid was used.
[d] Microwave heating.
[e] Conventional heating.

Unfortunately, all attempts to prevent the formation of **1** failed (e.g., through rigorous exclusion of moisture). In addition, separation of **6a** and **1** by silica gel chromatography was not successful. Therefore, further study of the Negishi coupling was curtailed. The Suzuki cross-coupling with phenylboronic acid in aqueous dioxane (4:1) was then studied (reagent quantities shown in Table 2), examining the effect of the reaction temperature and time on the course of the reaction. Thus, after 40 min of microwave irradiation at 80 °C, the reaction ceased, but the product consisted of a 1.8:1 mixture of **6a** and the bis-coupling product **7** (entry 2). Effecting the reaction at lower temperatures had a pronounced effect on the **6a**/**7** ratio. For example, at 65 °C it improved to 7:1 (entry 3), and at 60 °C, and at a 20-min reaction period, only **6a** was formed, but consumption of the starting material was not complete (entry 4). The optimum cross-coupling conditions turned out to involve conventional heating at 55 °C for 12 h, which resulted in complete consumption of the starting material and a 21:1 ratio of **6a**/**7a** (entry 5).

The scope of the Suzuki cross-coupling reaction with several aryl- and heteroarylboronic acids was then examined (Table 3). Phenylboronic acids bearing electron donating or accepting substituents at the *meta* or *para* positions gave good to excellent results, both in terms of product yields and mono:bis coupling product ratios. The coupling reaction failed with *o*-methoxyphenylboronic acid (entry 4). Satisfactory results were also obtained with 3-furyl- and 4-pyridylboronic acids, although a higher reaction temperature (up to 75 °C) was required (entries 7 and 8, respectively). No coupling occurred with 2-furlyboronic acid at 75 °C, and at 95 °C an inseparable 3:1 mixture of the desired product **6i** and **l** was obtained (entry 9).

The utility of the processes and intermediates described herein was demonstrated by the synthesis of climiqualine **8**[6c] (Scheme 2), a compound with hypolipemic and hypoglycemic activities in rats and rabbits, from **6a** and the sodium salt of imidazole. Furthermore, under the conditions reported by Buchwald,[10] compound **8**

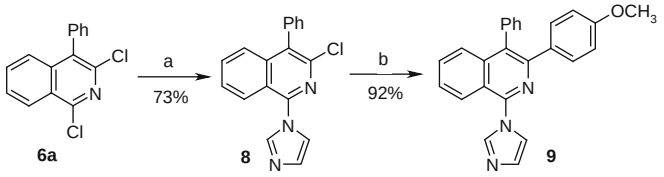
Table 3
Substrate scope for the Suzuki cross-coupling reaction of **4e**[a]



6a: phenyl **6b**: 4-$MeOC_6H_4$
6c: 3,4,5-tri$MeOC_6H_2$ **6d**: 2-$MeOC_6H_4$
6e: 4-FC_6H_4 **6f**: 4-NCC_6H_4
6g: 3-furanyl **6h**: 4-pyridyl
6i: 2-furanyl

Entry	R–$B(OH)_2$	Prod.	Ratio[b] (mono/bis)	Yield (%)
1	Ph	**6a**	21/1	87
2	4-$MeOC_6H$[4]	**6b**	32/1	93[c]
3	3,4,5-tri$MeOC_6H_2$	**6c**	[d]	89
4	2-$MeOC_6H_4$	**6d**	ND[e]	Trace
5	4-FC_6H_4	**6e**	11/1	97
6	4-NCC_6H_4	**6f**	[d]	92
7	3-Furanyl	**6g**	20/1	89[f]
8	4-Pyridyl	**6h**	[d]	71[g]
9	2-Furanyl	**6i**	[d]	40%[f,h]

[a] Reagents and conditions: R–$B(OH)_2$ (1.1 equiv), K_2CO_3 (3 equiv), $PdCl_2$(dppf) (10 mol %), 1,4-dioxane/H_2O (4/1), 55 °C, 12 h.
[b] Mono//bis-coupling product ratio was determined from the absorption at 240–320 nM , after separation of the crude reaction mixture by LC.
[c] Isolated as a mixture with **6** by silica gel chromatography.
[d] Bis-coupling product was not observed.
[e] ND: not determined.
[f] Performed at 75 °C.
[g] Performed at 70 °C.
[h] An inseparable 3:1 mixture of **6i**/**1**.



Scheme 2. Synthesis of climiqualine **8** and its derivative. Reagents and conditions: (a) NaH, imidazole, DMF, 60 °C; (b) $Pd(OAc)_2$, XPHOS, K_3PO_4, 4-methoxyphenylboronic acid, THF, 85 °C.

readily participated in Suzuki cross-coupling reaction with 4-methoxyphenyl boronic acid to afford **9** in excellent yield (92%). Similarly, this nucleophilic aromatic substitution/Suzuki cross-coupling sequence could be applied to **3a**–**d**, **6a**–**c**, and **6e**–**h** to prepare a variety of other 1,3,4-trisubstituted isoquinolines.

In summary, we report a facile route to 1,3,4-trisubstituted isoquinolines from commercially available 1,3-dichloroisoquinoline **1**. A key step in the process is the direct lithiation of **1** at C-4, and the reaction of the so-produced lithium species **2** with various electrophilic reagents to produce diverse 4-substituted-1,3-dichloroisoquinolines.[11] The 4-iodo compound **3e** obtained in this way, readily participated in Suzuki cross-coupling reactions to produce various 4-aryl-1,3-dichloroisoquinolines,[12] which could be transformed into 4-aryl-isoquinoline derivatives bearing different substituents at C-1 and C-3.

Acknowledgments

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References and notes

1. Bentley, K. W.. In *The Isoqunoline Alkaloids*; Hardwood Academic: Amsterdam, 1998; Vol. 1.
2. For recent examples, see: (a) Vasdev, N.; LaRonde, F. J.; Woodgett, J. R.; Garcia, A.; Rubie, E. A.; Meyer, J. H.; Houle, S.; Wilson, A. A. *Bioorg. Med. Chem.* **2008**, *16*, 5277–5284; (b) Yoon, T.; De Lombaert, S.; Brodbeck, R.; Gulianello, M.; Chandrasekhar, J.; Horvath, R. F.; Ge, P.; Kershaw, M. T.; Krause, J. E.; Kehne, J.; Hoffman, D.; Doller, D.; Hodgetts, K. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 891–896; (c) Trotter, B. W.; Nanda, K. K.; Kett, N. R.; Regan, C. P.; Lynch, J. J.; Stump, G. L.; Kiss, L.; Wang, J.; Spencer, R. H.; Kane, S. A.; White, R. B.; Zhang, R.; Anderson, K. D.; Liverton, N. J.; McIntyre, C. J.; Beshore, D. C.; Hartman, G. D.; Dinsmore, C. J. *J. Med. Chem.* **2006**, *49*, 6954–6957; (d) Örtqvist, P.; Peterson, S. D.; Åkerblom, E.; Gossas, T.; Sabnis, Y. A.; Fransson, R.; Lindeberg, G.; Danielson, U. H.; Karlén, A.; Sandström, A. *Bioorg. Med. Chem.* **2007**, *15*, 1448–1474.
3. (a) Durola, F.; Sauvage, J. P.; Wenger, O. S. *Chem. Commun.* **2006**, 171–173; (b) Sweetman, B. A.; Müller, H.; Guiry, P. J. *Tetrahedron Lett.* **2005**, *46*, 4643–4646; (c) Ford, A.; Sinn, E.; Woodward, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 927–934.
4. For recent examples, see: (a) Yang, Y.-Y.; Shou, W.-G.; Chen, Z.-B.; Hong, D.; Wang, Y.-G. *J. Org. Chem.* **2008**, *73*, 3928–3930; (b) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558–1559; (c) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4764–4766; (d) Korivi, R. P.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 5179–5182.
5. Alvarez, M.; Joule, J. A. *Sci. Synth.* **2005**, *15*, 661–838.
6. (a) Bartmann, W.; Konz, E.; Rueger, W. *Synthesis* **1988**, *9*, 680–683; (b) Renger, B.; Konz, E.; Rueger, W. *Synthesis* **1988**, *9*, 683–685; (c) Lerch, U.; Granzer, E. Ger. Offen. DE 2314985, Mar 26, 1973; *Chem. Abstr.* **1975**, *82*, 16836.
7. For an excellent review on lithiation of halogenated aryl and heteroaryl compounds, see: Schlosser, M. *Eur. J. Org. Chem.* **2001**, *21*, 3975–3984.
8. Palladium catalyzed cross-coupling reactions of **2**, or its zinc derivative, with iodobenzene were not successful.
9. The identity of the major product was confirmed by comparison with an authentic sample of **4a**.
10. Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819.
11. *A representative procedure*—The preparation of compound **3e**: To a solution of 1,3-dichloroisoquinoline **1** (5 g, 25.3 mmol) in THF (400 mL) at −78 °C was added LDA (1 M in THF, 27.5 mL, 27.5 mmol) drop-wise. The resulting orange solution was stirred at −78 °C for 15 min and quenched by cannulating to a solution of iodine (12.7 g, 50 mmol) in THF (100 mL) at room temperature. The reaction mixture was stirred at room temperature overnight and then quenched with 10% aqueous $Na_2S_2O_3$. The mixture was further diluted with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in CH_2Cl_2, filtered through a short pad of silica gel with 25% EtOAc in hexane as eluent to give crude **3e** as a pale yellow powder, which upon trituration from CH_2Cl_2/hexane afforded 7.3 g of **3e** (containing about 5% of **1**, 85% yield,) as a off-white powder. The product was further purified by recrystallization from 8/1 hexane/CH_2Cl_2 to give an analytically pure sample. Mp: 129–131 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.27 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.83 (t, J = 7.0 Hz, 1H), 7.72 (t, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.4, 148.1, 141.2, 133.6, 132.5, 129.4, 127.1, 125.7, 97.2; IR (KBr film): 3431, 1609, 1535, 1478, 1432, 1349, 1297, 1248, 1183, 1150, 1128, 1035, 982, 897, 848, 769, 757, 713, 649, 616 cm^{-1}; HRMS calcd for $C_9H_5Cl_2IN$ [M+H]+: 323.8838. Found: 323.8835. Anal. Calcd for $C_9H_4Cl_2IN$: C, 33.37; H, 1.24; N, 4.32. Found: C, 33.61; H, 1.15; N, 4.27.
12. *Selected spectroscopic data*—Compound **6a**: Mp: 93–95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.40–8.35 (m, 1H), 7.70–7.64 (m, 2H), 7.57–7.46 (m, 4H), 7.36–7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.9, 142.0, 138.9, 134.9, 131.9, 131.4, 130.1, 128.7, 128.5, 128.3, 126.5, 126.0, 125.8; IR (KBr film): 3430, 1653, 1615, 1560, 1547, 1502, 1436, 1384, 1322, 1265, 1146, 1117, 984, 861, 771, 703, 631, 620 cm^{-1}; MS calcd for $C_{15}H_9Cl_2N$ [M+H]$^+$: 274. Found: 274. Compound **8**: Mp: 166–169 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.14 (t, J = 1 Hz, 1H), 8.11–8.07 (m, 1H), 7.72–7.51 (m, 7H), 7.40–7.37 (m, 2H), 7.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.1, 142.4, 139.9, 137.8, 135.0, 131.9, 131.8, 130.1, 128.8, 128.6, 128.4, 126.3, 124.5, 121.3, 120.3; IR (KBr film): 3138, 1614, 1552, 1503, 1480, 1414, 1333, 1259, 1235, 1172, 1144, 1103, 1074, 1035, 972, 863, 828, 764, 702, 684, 672, 660, 615 cm^{-1}; HRMS calcd for $C_{18}H_{13}ClN_3$ [M+H]$^+$: 306.0793. Found: 306.0790; Anal. Calcd for $C_{18}H_{12}ClN_3$: C, 70.71; H, 3.96; N, 13.74. Found: C, 70.05; H, 3.87; N, 13.68. Compound **9**: Mp: 170–172 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.33 (t, J = 1.1 Hz, 1H), 7.99 (d, J = 7.2 Hz, 1H), 7.87 (t, J = 1.2 Hz, 1H), 7.85–7.72 (m, 2H), 7.59 (d, J = 7.6 Hz, 1H), 7.52–7.43 (m, 3H), 7.34–7.30 (m, 4H), 7.25 (t, J = 1.0 Hz, 1H), 6.80–6.74 (m 2H), 3.60 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 158.7, 147.7, 147.0, 138.1, 138.0, 136.5, 131.6, 131.5, 131.4, 130.8, 130.2, 129.0, 128.7, 128.3, 127.8, 125.5, 124.2, 121.0, 120.6, 113.0, 55.0; IR (KBr film): 3052, 1607, 1569, 1515, 1471, 1409, 1331, 1297, 1248, 1176, 1072, 1033, 968, 839, 774, 707, 672 cm^{-1}; HRMS calcd for $C_{25}H_{20}N_3O$ [M+H]$^+$: 378.1601. Found: 378.1595. Anal. Calcd for $C_{25}H_{19}N_3O$: C, 79.55; H, 5.07; N, 11.13. Found: C, 79.22; H, 5.00; N, 11.16.