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Tetrahedron Letters 46 (2005) 3771–3774
Tetrahedron Letters

Regioselective synthesis of 1-arylindazoles via N-arylation of 3-trimethylsilylindazoles

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Received 9 February 2005; revised 17 March 2005; accepted 18 March 2005
Available online 8 April 2005

Abstract—The copper(II)-catalyzed cross-coupling reaction of 3-trimethylsilylindazoles bearing substituents on the benzene ring with arylboronic acids regioselectively gave the corresponding 1-aryl-3-trimethylsilylindazoles and no 2-aryl isomers were formed at all. Moreover, the trimethylsilyl group of the resulting indazoles was easily removed by treatment with ethanolic KOH to give 1-arylindazoles.

Indazole derivatives have attracted much attention for their pharmaceutical activities, for example, anti-inflammatory, anti-tumor, anti-HIV, anti-depressant, contraceptive activities, etc.[1] Many methods for the synthesis of substituted indazoles have been developed to date.[2] However, it would be difficult to regioselectively introduce a substituent to an indazole nucleus, and for instance, N-arylation of indazoles generally gives a mixture of 1-arylindazoles and its 2-aryl isomers.[3–5] To overcome the problem, recently, Pd-catalyzed cyclization reactions of *N*-aryl-*N*′-(*o*-bromobenzyl)hydrazines[6] and *N*-aryl-*N*′-(*o*-bromophenyl)hydrazones[7] in situ prepared from *o*-bromobenzaldehyde and arylhydrazines giving 1-arylindazoles have been reported. To the best of our knowledge, there is no report concerning regioselective N-arylation of indazoles bearing substituents on the benzene ring.[8,9]

We have already developed various new reactions using trimethylsilyldiazomethane (Me_3SiCHN_2) and its lithium salt ($Me_3SiC(Li)N_2$).[10] For example, recently, we have found a facile, one-pot synthesis of 3-trimethylsilylindazoles by [3+2]cycloaddition reaction of $Me_3SiC(Li)N_2$ with benzynes prepared in situ from halobenzenes.[11] In addition, the resulting 3-trimethylsilylindazole **1** was found to be easily converted to indazoles bearing a hydroxymethyl unit at the 3-position by reaction with aldehydes in the presence of cesium fluoride.[12] We considered that 3-trimethylsilylindazoles would also be useful as substrates for the regioselective N-arylation at the 1-position of an indazole nucleus owing to steric hindrance of the bulky trimethylsilyl group. In this letter, the synthesis of 1-arylindazoles from 3-trimethylsilylindazoles through regioselective N-arylation is described.

As reaction conditions of the N-arylation of trimethylsilylindazoles, we chose a copper(II)-catalyzed cross-coupling reaction with arylboronic acids in consideration of its easy operation and the mild reaction conditions.[3] The results of the reaction are summarized in Table 1.[13,14] As expected, reaction of 3-trimethylsilylindazole **1** with phenylboronic acid at room temperature smoothly proceeded and the desired 1-phenyl-3-trimethylsilylindazole **6a** was obtained in 94% yield (entry 1). In this reaction, no 2-phenyl isomer could be detected. Similarly, the reaction of **1** with various arylboronic acids such as 4-methyl-, 4-methoxy-, 4-bromo-, and 2-methyl-phenyl ones successfully afforded the corresponding 1-arylindazoles **6b–e** in high yields as the sole product, respectively (entries 2–5).[15] 5,6-Dimethyl-3-trimethylsilylindazole **2** also gave the corresponding 1-phenyl derivative **6f** (entry 6). It is presumed that introduction of a substituent to the 7-position of indazole would lead to poor regioselectivity for N-arylation because of the steric hindrance of the substituent. In fact, when 7-methylindazole **7g** was reacted with phenylboronic acid under the same conditions as shown in Table 1, a mixture of 1- and 2-phenylindazoles (**8g** and **9g**) was obtained in 92% yield, in which the 2-phenyl isomer **9g**

Keywords: N-Arylation; Arylboronic acid; Indazoles; Regioselectivity; Silyl compounds.
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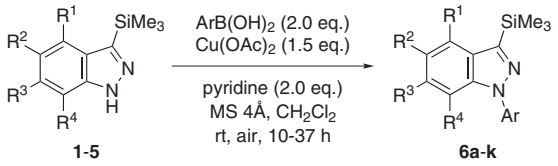
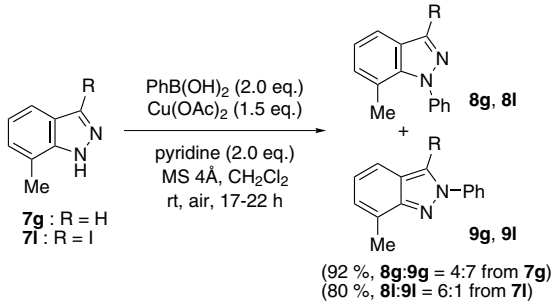
doi:10.1016/j.tetlet.2005.03.157

Table 1. Copper(II)-catalyzed N-arylation of 3-trimethylsilylindazoles[a]



Entry	R^1	R^2	R^3	R^4	Substrate	Ar	Yield (%)[b]
1	H	H	H	H	**1**	Ph	94 (**6a**)
2	H	H	H	H	**1**	4-Tolyl	88 (**6b**)
3	H	H	H	H	**1**	4-MeO–Ph	86 (**6c**)
4	H	H	H	H	**1**	4-Br–Ph	93 (**6d**)
5	H	H	H	H	**1**	2-Tolyl	93 (**6e**)
6	H	Me	Me	H	**2**	Ph	93 (**6f**)
7	H	H	H	Me	**3**	Ph	97 (**6g**)
8	H	H	H	Me	**3**	Ph	84 (**6g**)[c]
9	H	H	H	Me	**3**	4-MeO–Ph	99 (**6h**)
10	H	H	H	Br	**4**	Ph	82 (**6i**)
11	MeO	H	H	MeO	**5**	Ph	98 (**6j**)
12	MeO	H	H	MeO	**5**	4-Br–Ph	95 (**6k**)

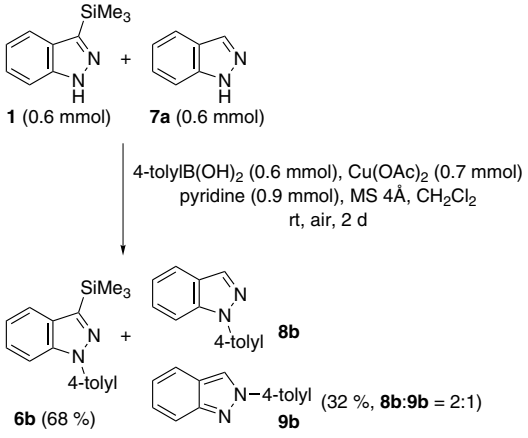
[a] The 2-aryl isomer was not obtained in all cases.
[b] Isolated yield.
[c] $Cu(OAc)_2$ (0.1 equiv) was used. The reaction was carried out under O_2 atmosphere instead of air and the reaction time was 45 h.



Scheme 1.

was predominantly formed (**8g**:**9g** = 4:7) as shown in Scheme 1. Moreover, even N-phenylation of 3-iodo-7-methylindazole **7l** with the bulky substituent at the 3-position gave a mixture of 1- and 2-phenylindazoles (**8l** and **9l**) in 80% yield though the former **8l** was predominant. Thus, examination using 7-substituted 3-trimethylsilylindazoles was carried out (entries 7–12). Surprisingly, the N-arylation of 7-methyl-3-trimethylsilylindazole **3** with arylboronic acids smoothly proceeded to afford only 1-aryl derivatives **6g** and **6h** in high yield, respectively (entries 7 and 9). Similarly, 7-bromo-3-trimethylsilylindazole **4** and 4,7-dimethoxy-3-trimethylsilylindazole **5** also selectively gave the corresponding 1-aryl derivatives **6i**–**k** (entries 10–12). The use of a catalytic amount of copper(II) acetate under O_2 atmosphere was applicable in this reaction, though prolonged reaction time was required (entry 8).

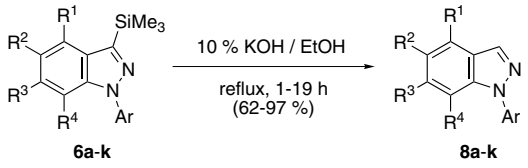
Next, a competitive experiment was carried out to investigate the role of the trimethylsilyl group (Scheme 2). A mixture of 3-trimethylsilylindazole **1** (0.6 mmol) and indazole **7a** (0.6 mmol) was treated with phenylboronic acid (0.6 mmol) in the presence of copper(II) acetate to preferentially give **6b** (68% yield) with a mixture of **8b**



Scheme 2.

and **9b** (32% yield, **8b**:**9b** = 2:1). These results suggest that the trimethylsilyl group may cause not only suppression of N-arylation at the 2-position by its steric hindrance but also acceleration of the reaction rate of N-arylation at the 1-position presumably due to the electronic effect of the silicon atom.

Finally, the trimethylsilyl group of **6** was easily removed by treatment with ethanolic KOH to give 1-arylindazoles **8** in good to high yields (Scheme 3).[16,17]



Scheme 3.

In conclusion, we have found that N-arylation of 3-trimethylsilylindazoles with arylboronic acid proceeds in a completely regioselective fashion and the resulting 1-aryl-3-trimethylsilylindazoles can be easily converted to 1-arylindazoles. Moreover, we have revealed that the trimethylsilyl group at the 3-position of indazoles accelerates the reaction rate of N-arylation at the 1-position.

Acknowledgements

This work was financially supported by a Grant-in-Aid for Scientific Research (KAKENHI) (to T.A.), a Grant-in-Aid from The Fujisawa Foundation (to Y.H.), and a Grant-in-Aid for Research in Nagoya City University (to Y.H.).

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13. Typical procedure. A mixture of **1** (56.7 mg, 0.30 mmol), phenylboronic acid (73.1 mg, 0.60 mmol), copper(II) acetate (81.7 mg, 0.45 mmol), pyridine (48.5 μl, 0.60 mmol), and activated molecular sieves 4 Å (400 mg) in CH_2Cl_2 (2.0 ml) was stirred under air at rt for 28 h. After filtration of the mixture through a pad of Celite®, the filtrate was concentrated in vacuo. The residue was purified by column chromatography (Fuji Silysia, BW-200) using hexane–Et_2O (10:1) as an eluent to give 1-phenyl-3-trimethylsilylindazole **6a** (74.6 mg, 94%). Compound **6a**: mp 52 °C (hexane). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.50 (9H, s), 7.20 (1H, dd, J = 8 and 8 Hz), 7.31–7.42 (2H, m), 7.52 (2H, d, J = 8 Hz), 7.75 (3H, d, J = 8 Hz), 7.87 (1H, d, J = 8 Hz). ^{13}C NMR (68 MHz, $CDCl_3$) δ: −0.6, 110.4, 120.9, 122.0, 122.8, 126.3, 126.4, 129.3, 131.0, 139.0, 140.2, 148.5. IR (nujol) ν: 1504, 1250 cm^{-1}. MS (EI) m/z 266 (M^+), 251. Anal. Calcd for $C_{16}H_{18}N_2Si$: C, 72.13; H, 6.81; N, 10.52. Found: C, 71.99; H, 6.94; N, 10.18.
14. Selected data for the other 1-aryl-3-trimethylsilylindazoles **6b–k**. Compound **6b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.49 (9H, s), 2.42 (3H, s), 7.18 (1H, dd, J = 8 and 8 Hz), 7.30–7.40 (3H, m), 7.61 (2H, d, J = 8 Hz), 7.70 (1H, d, J = 8 Hz), 7.86 (1H, d, J = 8 Hz). Compound **6c**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.48 (9H, s), 3.44 (3H, s), 7.04 (2H, d, J = 8 Hz), 7.18 (1H, dd, J = 8 and 8 Hz), 7.37 (1H, dd, J = 8 and 8 Hz), 7.59–7.65 (3H, m), 7.86 (1H, d, J = 8 Hz). Compound **6d**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.49 (9H, s), 7.21 (1H, dd, J = 8 and 8 Hz), 7.40 (1H, dd, J = 8 and 8 Hz), 7.63 (4H, s), 7.69 (1H, d, J = 8 Hz), 7.86 (1H, d, J = 8 Hz). Compound **6e**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.49 (9H, s), 2.12 (3H, s), 7.15–7.37 (7H, m), 7.88 (1H, d, J = 8 Hz). Compound **6f**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.48 (9H, s), 2.39 (6H, s), 7.31 (1H, dd, J = 8 and 8 Hz), 7.45–7.58 (4H, m), 7.73 (2H, d, J = 8 Hz). Compound **6g**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.47 (9H, s), 2.09 (3H, s), 7.08–7.10 (2H, m), 7.44–7.48 (5H, m), 7.70–7.74 (1H, m). Compound **6h**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.46 (9H, s), 2.09 (3H, s), 3.88 (3H, s), 6.98 (2H, d, J = 9 Hz), 7.06–7.08 (2H, m), 7.38 (2H, d, J = 9 Hz), 7.69–7.70 (1H, m). Compound **6i**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.50 (9H, s), 7.06 (1H, dd, J = 8 and 8 Hz), 7.48–7.52 (5H, m), 7.57 (1H, d, J = 8 Hz), 7.84 (1H, d, J = 8 Hz). Compound **6j**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.41 (9H, s), 3.66 (3H, s), 3.93 (3H, s), 6.38 (1H, d, J = 8.1 Hz), 6.67 (1H, d, J = 8 Hz), 7.32 (1H, dd, J = 8 and 8 Hz), 7.42 (2H, dd, J = 8 and 8 Hz), 7.57 (2H, d, J = 8 Hz). Compound **6k**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.41 (9H, s), 3.71 (3H, s), 3.94 (3H, s), 6.42 (1H, d, J = 8 Hz), 6.70 (1H, d, J = 8 Hz), 7.44–7.56 (4H, m).
15. Under the same reaction conditions as shown in entry 2 of Table 1, the reaction of indazole with 4-tolylboronic acid has been reported to give a mixture of 1- and 2-(4-tolyl)-indazole (9:2) in 88% yield. See Ref. 3.
16. Typical procedure. A solution of 1-phenyl-3-trimethylsilylindazole **6a** (42.8 mg, 0.16 mmol) in 10% ethanolic KOH (1 ml) was refluxed for 6 h. After dilution with H_2O, the mixture was extracted with AcOEt. The organic extracts were washed with 1 N $KHSO_4$, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (Fuji Silysia, BW-200) using hexane–AcOEt (9:1) as an eluent to give 1-phenylindazole **8a** (27.8 mg, 89%). Mp 80 °C (hexane) (lit.[18] mp 78 °C).
17. Selected data for the other 1-arylindazoles **8b–k**. Compound **8b**: Ref. 5. Compound **8c**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 3.87 (3H, s), 7.05 (2H, d, J = 8 Hz), 7.20 (1H, dd, J = 8 and 8 Hz), 7.40 (1H, dd, J = 8 and 8 Hz), 7.58–7.66 (3H, m), 7.79 (1H, d, J = 8 Hz), 8.17 (1H, s). Compound **8d**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 7.21–7.26 (1H, m), 7.40 (1H, dd, J = 8 and 8 Hz), 7.63 (4H, s), 7.69 (1H, d, J = 8 Hz), 7.86 (1H, d, J = 8 Hz), 8.20 (1H, s). Compound **8e**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.12 (3H, s), 7.20–7.25 (2H, m), 7.33–7.40 (5H, m), 7.81 (1H, d, J = 8 Hz), 8.20 (1H, s). Compound **8f**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.38 (3H, s), 2.40 (3H, s), 7.33 (1H, dd, J = 7 and 7 Hz), 7.49–7.55 (4H, m), 7.72 (2H, d, J = 7 Hz), 8.06 (1H, s). Compound **8g**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.12 (3H, s), 7.08–7.13 (2H, m), 7.44–7.48 (5H, m), 7.65 (1H, d, J = 7 Hz), 8.15 (1H, s).

Compound **8h**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.12 (3H, s), 3.89 (3H, s), 6.99 (2H, d, J = 9 Hz), 7.09–7.12 (2H, m), 7.39 (2H, d, J = 9 Hz), 7.63–7.66 (1H, m), 8.13 (1H, s). Compound **8i**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 7.07 (1H, dd, J = 7 and 8 Hz), 7.48–7.52 (5H, m), 7.59 (1H, d, J = 7 Hz), 7.77 (1H, d, J = 8 Hz), 8.20 (1H, s). Compound **8j**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 3.70 (3H, s), 3.94 (3H, s), 6.41 (1H, d, J = 8 Hz), 6.90 (1H, d, J = 8 Hz), 7.35–7.47 (3H, m), 7.56 (2H, d, J = 8 Hz), 8.23 (1H, s). Compound **8k**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 3.73 (3H, s), 3.94 (3H, s), 6.42 (1H, d, J = 8 Hz), 6.70 (1H, d, J = 8 Hz), 7.45 (1H, d, J = 9 Hz), 7.55 (1H, d, J = 9 Hz), 8.22 (1H, s).

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