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Convenient Method for the 3-Functionalization of Isoindazoles

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Abstract: The C-3 position of isoindazoles is readily functionalized by metalation with lithium diisopropylamide followed by reaction with a variety of electrophiles.

Keywords: Deprotonation, functionalization, 2*H*-indazoles, isoindazoles

We recently needed a general method for functionalization of the C-3 position of isoindazoles (also called 2*H*-indazoles). A perusal of the literature revealed that this position can be metalated with alkyllithium reagents, and the resulting organolithium species then reacted with electrophiles.[1] This method appeared to us to be the most suitable of the limited number of examples that we found (For a review on the chemistry of indazoles and isoindazoles, see).[2] However, the use of alkyllithium reagents was incompatibile with some of our requisite substrates. We wondered if the same transformation could be effected with other bases and found that lithium diisopropylamide is an effective base for this purpose.

Addition of 2-methylisoindazole 1 to a solution of freshly prepared lithium diisopropylamide, followed by stirring at 0–5°C for 15 min, resulted in a clean generation of presumed 3-lithio-2-methylisoindazole, which was quenched by methyl iodide at −78°C to afford 2,3-dimethylisoindazole **1a**

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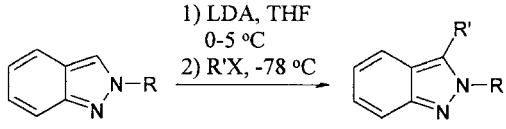
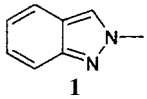
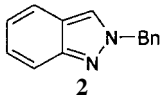
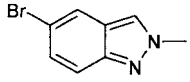
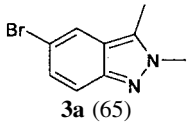
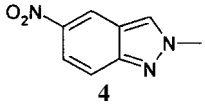
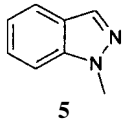
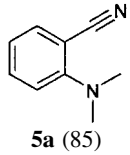
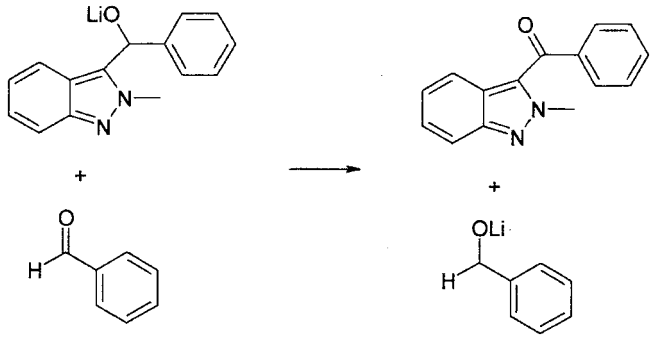
in 82% yield. The same reaction could be performed using commercially available lithium diisopropylamide solution (2.0 M in heptane/tetrahydrofuran/ethylbenzene, Aldrich), but the yields were slightly lower (73%). The same generated anion could be quenched with a variety of electrophiles, in good to excellent yields (Table 1).

When benzaldehyde was used as the electrophile (to generate alcohol **1f**), a significant side product was also isolated, ketone **1g**. This ketone was presumably generated by Oppenauer oxidation of the expected intermediate

Table 1. Preparation of 3-substituted isoindazoles



Substrate	Electrophile R′X	Product (yield, %)
 **1**	MeI	**1a**, R′ = Me (82)
1	I_2	**1b**, R′ = I (80)
1	TMSCl	**1c**, R′ = TMS (65)
1	$ClCO_2Me$	**1d**, R′ = CO_2Me (86)
1	PhSSPh	**1e**, R′ = SPh (79)
1	PhCHO	**1f**,R′ = CHOHPh (59) **1g**, R′ = COPh (24)
 **2**	MeI	—
 **3**	MeI	 **3a** (65)
 **4**	MeI	—
 **5**	MeI	 **5a** (85)

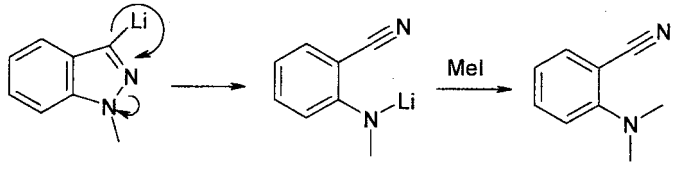


Scheme 1.

lithium alkoxide, with concomitant reduction of benzaldehyde to benzyl alcohol (Scheme 1). Although this type of reaction is generally associated with aluminum alkoxides, examples are known for other metal alkoxides, including those of lithium.[3]

We further investigated the scope of this 3-functionalization with the attempted methylations of the additional substrates shown in Table 1. We obtained a good yield for the methylation of 2-methyl-5-bromoisoindazole **3**. This result is particularly noteworthy because it demonstrates the compatibility of our method with halide substituents. The method was, however, unsatisfactory for 2-benzylisoindazole **2** and for 2-methyl-5-nitroisoindazole **4**. In both cases, multiple products were evident by TLC analysis, and the reactions were not investigated further.

We also attempted to methylate 1-methylindazole **5** using the same conditions used to methylate 2-methylisoindazole **1**, and we observed a clean reaction, but it did not give the desired 1,3-dimethylindazole product. Instead, we isolated 2-dimethylaminobenzonitrile **5a** in 85% yield. A probable mechanism for this transformation is shown in Scheme 2. Initial formation of the expected 3-lithioindazole could be followed by a Kemp-type elimination reaction,[4] with concomitant *N-N* bond cleavage, to form an intermediate 2-lithioamidobenzonitrile. This species would be the one quenched by methyl iodide to form the observed product. A closely related reaction has been reported in which 1-substituted indazoles yield



Scheme 2.

2-aminobenzophenones upon treatment with organolithiums[5a] (for a related reaction involving pyrazolo[4,3-*d*]pyrimidines, see Ref.[5b]).

Our original literature search for methods of functionalizing the 3-position of isoindazoles yielded only a few additional hits.[2] Uff and coworkers have reported a multistep methylation sequence, and Boucher and coworkers have reported an amination reaction applicable to nitroindazoles. There are also reports of electrophilic brominations. With the exception of some brominations, the reactions tend to be low yielding, and all are of limited scope. The simple metalation–electrophilic quench sequence described here is therefore a particularly attractive route to this class of compound.

EXPERIMENTAL

General

All reactions were run under nitrogen in oven-dried glassware. Preparations of 2-methylindazole **1**,[1d,6] 2-benzylisoindazole **2**,[7] 2-methyl-5-bromo-isoindazole **3**,[8] and 1-methylindazole **5**[1d] are known in the literature. All other reagents were commercially available and were used as received. Anhydrous tetrahydrofuran was purchased from Aldrich Chemical Company and used as received. Melting points recorded are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75.40 MHz respectively using a Bruker AMX300 instrument using $CDCl_3$ or DMSO-d^6 as solvent, with tetramethylsilane as the internal standard. Some of the products have been previously prepared by alternative methods (2,3-dimethylisoindazole **1a**,[2b] 3-iodo-2-methylisoindazole **1b**,[1c] 3-methoxycarbonyl-2-methylisoindazole **1d**,[9] 3-(1-hydroxybenzyl)-2-methylisoindazole **1f**,[1b] and 2-dimethylaminobenzonitrile **5a**[10]).

General Procedure for the Preparation of Isoindazoles 1(a–g)

A 1.6 M solution of *n*-butyl lithium hexanes (0.59 mL, 0.94 mmol) was added to a solution of diisopropylethylamine (0.13 mL, 0.93 mmol) in 3 mL of tetrahydrofuran at − 78°C. The solution was stirred at 0–5 °C for 10 min and then rechilled to −78°C. Isoindazole **1** (0.761 mmol) was added, and the resulting solution was stirred at 0–5°C for 10–15 min and then rechilled to −78°C. The appropriate electrophile was then added all at once. Further details for each compound are described next.

2,3-Dimethylisoindazole (**1a**)

After addition of iodomethane (0.060 mL, 0.96 mmol), the solution was stirred at −78°C for 2 h. A saturated aqueous NH_4Cl solution (5 mL) was added, and

the mixture was extracted with three 5 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to an orange oil, which was further purified by silica-gel chromatography ($0 \rightarrow 50\%$ EtOAc/hexanes) to afford 0.092 g (82%) of 2,3-dimethylisoindazole as a white solid: mp 76–78°C; IR (KBr) 3046, 2921, 1629, 1502, 1437, 1367, 1286 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60–7.64 (m, 1 H), 7.53–7.56 (m, 1 H), 7.23–7.28 (m, 2 H), 4.10 (s, 3 H), 2.61 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 148.1, 131.6, 126.4, 121.5, 120.8, 119.9, 117.2, 37.7, 10.3; ESI-MS m/z 147 (M + 1) 100%. Anal. calc. for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.17. Found: C, 73.98; H, 6.86; N, 19.16.

3-Iodo-2-methylisoindazole (**1b**)

After addition of iodine (0.230 g, 0.906 mmol), the solution was stirred at −78°C for 2 h. A 10% aqueous sodium thiosulfate solution (5 mL) was added, and the mixture was extracted with three 5 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to an orange solid, which was further purified by silica-gel chromatography ($0 \rightarrow 50\%$ EtOAc/hexanes) to afford 0.197 g (80%) of 3-iodo-2-methylisoindazole as a white solid: mp 151–152°C; IR (KBr) 3056, 3025, 2935, 1620, 1545, 1497, 1397, 1278, 1232 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64–7.67 (m, 1 H), 7.37–7.41 (m, 1 H), 7.29–7.34 (m, 1 H), 7.10–7.15 (m, 1 H), 4.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.2, 128.3, 127.7, 123.3, 121.2, 118.6, 76.6, 41.8; ESI-MS m/z 259 (M + 1) 100%. Anal. calc. for $C_8H_{17}IN_2$: C, 37.23; H, 2.73; N, 10.86. Found: C, 37.63; H, 2.72; N, 10.66.

2-Methyl-3-trimethylsilylisoindazole (**1c**)

After addition of chlorotrimethylsilane (0.115 mL, 0.909 mmol), the solution was stirred at −78°C for 2 h. A saturated aqueous NH_4Cl solution (5 mL) was added, and the mixture was extracted with three 5-mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to a yellow oil, which was further purified by silica-gel chromatography ($0 \rightarrow 50\%$ EtOAc/hexanes) to afford 0.101 g (65%) of 2-methyl-3-trimethylsilylisoindazole as a white solid: mp 50–51°C; IR (KBr) 3046, 2956, 1543, 1457, 1421, 1367, 1339, 1280, 1249 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72–7.78 (m, 2 H), 7.25–7.30 (m, 1 H), 7.04–7.09 (m, 1 H), 4.29 (s, 3 H), 0.53 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 148.2, 135.2, 129.7, 125.4, 121.4, 121.2, 117.1, 41.3, 0.0; ESI-MS m/z 205 (M + 1) 100%. Anal. calc. for $C_{11}H_{16}N_2Si$: C, 64.66; H, 7.89; N, 13.71. Found: C, 64.56; H, 7.83; N, 13.54.

3-Methoxycarbonyl-2-methylisoindazole (**1d**)

After addition of methyl chloroformate (0.07 mL, 0.91 mmol), the solution was stirred overnight and allowed to slowly warm to room temperature.

A saturated aqueous NH_4Cl solution (5 mL) was added, and the mixture was extracted with three 5-mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to an orange liquid, which was further purified by silica-gel chromatography ($0 \rightarrow 50\%$ EtOAc/hexanes) to afford 0.123 g (86%) of 3-methoxycarbonyl-2-methylisoindazole as a pale yellow solid: mp 61–62°C; IR (KBr) 2956, 1712, 1508, 1477, 1454, 1438, 1402, 1369, 1285, 1211 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00–8.03 (m, 1 H), 7.76–7.79 (m, 1 H), 7.28–7.38 (m, 2 H), 4.53 (m, 3 H), 4.04 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.9, 147.3, 126.3, 125.0, 124.1, 123.5, 121.2, 118.1, 52.0, 41.4; ESI-MS m/z 191 (M + 1) 100%. Anal. calc. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.31; H, 5.28; N, 14.63.

2-Methyl-3-thiophenylisoindazole (**1e**)

After addition of diphenyl disulfide (0.198 g, 0.907 mmol), the solution was stirred at −78°C for 3 h. A 10% aqueous NaOH solution (5 mL) was added, and the mixture was extracted with three 5-mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to a yellow-orange liquid, which was further purified by silic-gel chromatography ($0 \rightarrow 50\%$ EtOAc/hexanes) to afford 0.143 g (79%) of 2-methyl-3-thiophenylisoindazole as a yellow liquid: IR (KBr) 3057, 2943, 1626, 1582, 1502, 1478, 1286, 1241 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74–7.78 (m, 1 H), 7.65–7.69 (m, 1 H), 7.32–7.38 (m, 1 H), 7.12–7.25 (m, 4 H), 6.98–7.06 (m, 2 H), 4.21 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 148.5, 135.7, 129.8, 127.4, 127.0, 126.9, 126.7, 123.6, 123.5, 120.2, 118.3, 38.5; ESI-MS m/z 241 (M + 1) 100%. Anal. calc. for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66. Found: C, 70.11; H, 4.99; N, 11.55.

3-(1-Hydroxybenzyl)-2-methylisoindazole (1f) and 2-Methyl-3-phenylcarbonylisoindazole (**1g**)

After addition of benzaldehyde (0.09 mL, 0.88 mmol), the solution was stirred overnight and allowed to slowly warm to room temperature. A saturated aqueous NH_4Cl solution (5 mL) was added, and the mixture was extracted with three 5-mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to a yellow oil, which was further purified by silica-gel chromatography ($0 \rightarrow 50\%$ EtOAc/hexanes) to afford two products: 2-Methyl-3-phenylcarbonylisoindazole (**1g**) eluted first (0.043 g, 24%) as a yellow oil: IR (KBr) 3056, 2952, 1639, 1597, 1578, 1453, 1405, 1361, 1279, 1226 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79–7.88 (m, 3 H), 7.65–7.70 (m, 1 H), 7.51–7.56 (m, 2 H), 7.29–7.34 (m, 1 H), 7.04–7.13 (m, 2 H), 4.52 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 186.6, 147.8, 139.1, 133.6, 131.9, 130.1, 129.0, 126.5, 125.0, 123.9, 120.9, 118.6, 41.8; ESI-MS m/z 237 (M + l), 100%. Anal. calc. for $C_{15}H_{12}N_2O$: C, 76.25;

H, 5.12; N, 11.86. Found: C, 76.18; H, 5.02; N, 11.65. 3-(1-Hydroxybenzyl)-2-methylisoindazole (**1f**) eluted second (0.195 g, 59%) as a pale yellow solid: mp 115°C; IR (KBr) 3386, 3059, 2923, 2852, 2645, 1623, 1496, 1451, 1432, 1403, 1384, 1288 cm^{-1}; ^1H NMR (CDC_{13}) δ 7.51–7.54 (m, 1 H), 7.22–7.30 (m, 6 H), 7.16–7.21 (m, 1 H), 6.89–6.95 (m, 1 H), 6.29 (s, 1 H), 3.87 (s, 3 H), 3.42–3.64 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 147.5, 140.5, 136.5, 129.1, 128.5, 126.8, 126.6, 122.2, 121.1, 120.4, 117.1, 68.2, 39.0; ESI-MS m/z 239 (M + 1) 100%. Anal. calc. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.28; H, 5.88; N, 11.61.

5-Bromo-2,3-dimethylisoindazole (**3a**)

A 1.6 M solution of *n*-butyl lithium in hexanes (0.37 mL, 0.60 mmol) was added to a solution of diisopropylethylamine (0.080 mL, 0.57 mmol) in 3 mL of tetrahydrofuran at −78°C. The solution was stirred at 0–5°C for 10 min and then rechilled to −78°C. 5-Bromo-2-methylisoindazole **3** (0.100 g, 0.476 mmol) was added; the solution was stirred at 0–5°C for 15 min and then rechilled to −78°C. Iodomethane (0.035 mL, 0.57 mmol) was added, and the solution was stirred overnight, allowing it to slowly warm to room temperature. A saturated aqueous NH_4Cl solution (5 mL) was added, and the mixture was extracted with three 5-mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to an orange solid, which was further purified by silica-gel chromatography (0 → 50% EtOAc/hexanes) to afford 0.069 g (65%) of 5-bromo-2,3-dimethylisoindazole as a white solid: mp 110–113°C; IR (KBr) 2919, 2852, 1624, 1495, 1443, 1328, 1261 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.94 (d, $J = 1.9$ Hz, 1 H), 7.47 (d, $J = 9.1$ Hz, 1 H), 7.26 (dd, $J = 9.1$ Hz, 1.9 Hz, 1H), 4.04 (s, 3 H), 2.58 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 145.5, 132.2, 128.8, 122.8, 122.4, 119.1, 112.4, 37.8, 9.7; ESI-MS m/z 225 (M + 1) 100%, 145 (M-Br) 25%. Anal. calc. for $C_9H_9BrN_2$: C, 48.03; H, 4.03; N, 12.45. Found: C, 48.07; H, 3.91; N, 12.35.

2-Dimethylaminobenzonitrile (**5a**)

A 1.6 M solution of *n*-butyl lithium in hexanes (0.59 mL, 0.94 mmol) was added to a solution of diisopropylamine (0.13 mL, 0.93 mmol) in 3 mL of tetrahydrofuran at −78°C. The solution was stirred at 0–5°C for 10 min and then rechilled to −78°C. 1-Methyl indazole **5** (0.101 g; 0.764 mmol) was added; the solution was stirred at 0–5°C for 15 min and then rechilled to −78°C. Iodomethane (0.060 mL, 0.96 mmol) was added, and the solution was stirred overnight, allowing it to slowly warm to room temperature. A saturated aqueous NH_4Cl solution (5 mL) was added, and the mixture was extracted with three 5-mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to an oily, orange solid, which was further purified by silica-gel chromatography (0 → 50%

EtOAc/hexanes) to afford 0.095 g (85%) of 2-dimethylaminobenzonitrile as a colorless liquid: IR (KBr) 3018, 2917, 2216, 1599, 1502, 1433, 1342, 1216 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49–7.52 (m, 1 H), 7.38–7.44 (m, 1 H), 6.88–6.90 (m, 1 H), 6.81–6.86 (m, 1 H), 3.05 (appar s, 6 H) [lit. ($CDCl_3$, 60 MHz) δ 7.20–7.56 (m, 2 H), 6.68–6.93 (m, 2 H), 2.90 (s, 6 H)[10b]; ^{13}C NMR ($CDCl_3$) δ 155.7, 135.4, 133.8, 120.1, 119.5, 117.1, 101.7, 43.4 [lit. ($CDCl_3$, 400 MHz) δ 155.7, 135.4, 133.9, 120.1, 119.6, 117.2, 101.7, 43.5[10c]; ESI-MS m/z 147 (M + 1), 100%.

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