7-Alkyl Indole Synthesis via a Convenient Formation/Alkylation of Lithionitrobenzenes and an Improved Bartoli Reaction

Michael C. Pirrung,* Michael Wedel, Yan Zhao

Department of Chemistry, Levine Science Research Center, Duke University, Durham, North Carolina 27708-0317, USA
Fax 1(919)6601591; E-mail: pirrung@chem.duke.edu

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Abstract: A more convenient and efficient method for metalation/alkylation of nitrobenzenes to give 2-substituted nitrobenzenes was developed. Their conversion to 7-alkylindoles using the Bartoli reaction with vinyl magnesium bromide was performed with an improved protocol.

Key words: nitroarenes, lithiation, allylations, alkylations

For a natural product synthetic library, we require a family of 7-alkylindoles. We hoped to gain these compounds from 2-alkylnitrobenzenes using the fascinating Bartoli reaction. Ready access to diverse 2-alkylnitrobenzenes was essential to this plan. A reasonable route to these compounds is via alkylation of a 2-metalated nitrobenzene.

The generation of organometallic derivatives containing nitro groups is challenging. Ready electron transfer reactions to the nitro group preclude generation of Grignard reagents from nitro-containing halides and magnesium. One solution to this problem has been offered by Köbrich and Buck,[1] who reported that 2-bromonitrobenzene undergoes metal-halogen exchange with phenyllithium in THF to yield 2-lithionitrobenzene, which reacts with carbon dioxide as the electrophile. At –100 °C, the 2-lithionitrobenzene is stable (1 h), and the acid is obtained in 97% yield. At even slightly higher temperature (–80 °C), the acid is obtained in only 61% yield due to decomposition of the lithium reagent. The low-temperature reaction conditions can also be applied to 4-bromo-3-nitrotoluene (80%) and 2-bromo-3-nitrotoluene (92%) to obtain the acids. Despite the inconvenience of conducting the reaction at –100 °C, this process has been further used in synthesis,[2] including reactions with other electrophiles: *N*-methyl-4-piperidone (85%),[3] sorbal,[4] and a formyl pyrrole (54%).[5] However, only reactions with carbonyl electrophiles have been reported.

The Bartoli reaction involves a novel mechanism based on addition of a vinyl Grignard to the oxygen of an intermediate nitroso compound.[6] While powerful in that it converts 2-substituted nitrobenzenes directly to 7-substituted indoles, it exhibits variable efficiency. It has generally been performed by adding 3 molar equiv (required by its stoichiometry) of a commercial Grignard reagent solution in THF to a solution of the nitrobenzene at –40 °C. Due to the low solubility of vinyl Grignards in THF at low temperature, this protocol results in heterogeneous reaction mixtures.

This letter reports novel reaction conditions that enable 2-lithionitrobenzene to be generated and used at the much more convenient –78 °C. Alkylation with reactive electrophiles provides the 2-alkylnitrobenzenes in excellent yields. They are converted by excess vinyl magnesium bromide in dimethoxyethane to the indoles in good yields.

Initial experiments were conducted as reported originally by Köbrich and Buck, by addition at –78 °C of phenyllithium in ether to a solution of 2-bromonitrobenzene in THF. The resulting 2-lithionitrobenzene was alkylated after 2 h with prenyl bromide to give 2-prenylnitrobenzene in 48% yield. Simple variation of reaction conditions did not improve this result, so more detailed studies were undertaken. Quenching the reaction (NH_4Cl) after 5 min and capillary gas chromatography analysis showed that metal-halogen exchange is rapid: no starting materials remain, but many products are obtained, including 2-nitrobiphenyl. This product may arise from the reaction of 2-lithionitrobenzene with bromobenzene, suggesting that minimizing their concentrations could improve the reaction. This was accomplished by simultaneous, separate addition of phenyllithium and prenyl bromide in THF to a 2-bromonitrobenzene solution at –78 °C. With this variation, using equimolar amounts of each reagent, the alkylation product is obtained in 63% yield. Superior results were gained by adding the alkyl halide quickly. The limiting reagent was the bromide, as it is the most expensive reactant. Metalation (2 equiv phenyllithium, 2 equiv 2-bromonitrobenzene, 5 min, –78 °C) and alkylation with 1 equiv 1-bromo-3-methyl-2-butene (3 h) proceeds in quantitative yield. Similar reaction conditions were then applied to several other reactive alkyl halides. For 4-bromo-3-nitrotoluene and 2-bromo-3-nitrotoluene, it was necessary to also add TMEDA (2 equiv) to the lithium reagent to obtain the highest yields in the alkylation step. Yields for alkylation products purified by silica gel chromatography are essentially quantitative, as summarized in the Table. These reactions were so successful, alkylation by less reactive alkyl halides was also examined. However, 2-lithionitrobenzene is alkylated with *n*-butyl bromide in only 29% yield.

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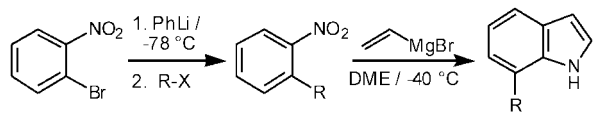
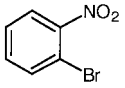
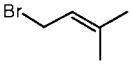
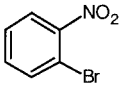
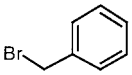
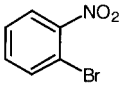
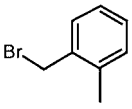
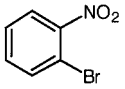
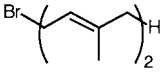
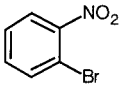
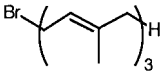
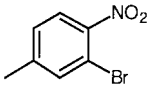
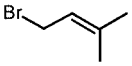
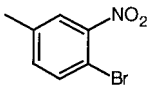
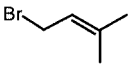
Table Alkylation of Nitrobenzenes



Nitrobenzene	Alkylhalide	Nitrobenzene yield (%)	Indole yield (%)
		100	50[a]
		100[a]	53[a]
		100	57
		100	37
		99	41
		100	43
		100	49

[a] Known compound; unknown compounds characterized by NMR and MS

Under traditional Bartoli reaction conditions, the addition of vinyl magnesium bromide solution to 2-prenyl nitrobenzene produces 7-prenylindole in 50% yield after chromatography. Because of the heterogeneity of these reaction mixtures, the solubility of vinyl Grignard at –40 °C in a variety of ethereal solvents, including diglyme, 1,3-dioxolane, and dimethoxyethane (glyme, DME), was examined. Equal volumes of 1,3-dioxolane and the Grignard/THF solution are required to achieve solubility, whereas only half volumes of either diglyme or DME are required. Because of the volatility of the latter, it was chosen for further study. Two other modifications were made. As the reaction requires a 3 fold excess of the Grignard over the nitrobenzene, the nitrobenzene was added to the Grignard solution in the mixed ethereal solvent to maintain the Grignard in excess throughout the reaction. In classical Grignard chemistry, this would constitute normal addition; inverse addition has become the norm in the modern era when so many reagents are purchased. The Grignard was also used in a 6 fold excess. These modifications make the reaction easier to conduct and give higher yields in several other Bartoli reactions performed in our lab. In this case, they lead to 7-prenylindole in a yield comparable to the original procedure. These reaction conditions were then applied to the 2-substituted nitrobenzenes prepared by earlier alkylation reactions, leading to the desired indoles in 37–57% yields.

The method described here for the production of lithionitrobenzene is much more convenient to conduct than that previously described, encouraging its wider application in organic synthesis. The alkylation of this carbanion proceeds in high yield only with allylic and benzylic halides, however. The use of these 2-alkylnitrobenzenes in the modified Bartoli reaction procedure gives 7-alkylindoles in quite good efficiency and only two reaction steps.

Formation/Alkylation of Lithionitrobenzenes; General Procedure

Phenyllithium (2.3 mmol) was dissolved in THF (25 mL) under argon and the solution cooled to -78 °C [EtOH / N_2(l)]. 2-Bromo-5-methyl-nitrobenzene (2.3 mmol) dissolved in THF (5 mL) was added drop wise via a syringe. After 5 min, prenylbromide (1.15 mmol) was added all at once followed by TMEDA (2.3 mmol). The solution was kept at -78 °C for 3 h. After quenching with saturated NH_4Cl (20 mL) the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined ethereal extracts were filtered through cotton wool and evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexanes–EtOAc, 9:1), yielding 5-methyl-2-prenyl-nitrobenzene as a brown oil (236 mg, 100%). ^{1}H NMR ($CDCl_3$): δ 1.70 (s, 3 H), 1.73 (s, 3 H), 2.38 (s, 3 H), 3.56 (d, *J* = 7.2 Hz, 2 H), 5.23 (m, 1 H), 7.23 (d, *J* = 7.8 Hz, 1 H), 7.30 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.67 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 18.26, 21.01, 26.08, 31.28, 122.14, 124.94, 131.39, 133.64, 133.79, 134.42, 137.20, 149.31. HRMS (EI): $C_{12}H_{15}NO_2$, Calcd.: 205.1102, found: 205.1109.

Bartoli Reaction; Genaral Procedure

Vinyl magnesium bromide (4.8 mmol, 1 M solution in THF) and DME (3 mL) were cooled under argon to -40 °C (EtOH/dry ice). 2-Farnesylnitrobenzene (0.8 mmol) dissolved in THF (2 mL) was added drop wise via a syringe. The solution was kept at -40 °C until TLC and GC showed no remaining starting material (2 h). After quenching with saturated NH_4Cl (20 mL), the aqueous phase was extracted with ether (3 × 20 mL). The combined ethereal extracts were filtered through cotton wool and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexanes–EtOAc, 9:1), yielding 7-farnesylindole as a yellow wax (106 mg, 41%). ^{1}H NMR ($CDCl_3$): δ 1.64 (s, 6 H), 1.72 (d, *J* = 1.2 Hz, 3 H), 1.85 (d, *J* = 1.2 Hz, 3 H), 2.11 (m, 8 H), 3.63 (d, *J* = 6.9 Hz, 2 H), 5.15 (m, 2 H), 5.48 (m, 1 H), 6.59 (dd, *J* = 3.3, 2.1 Hz, 1 H), 7.07 (m, 2 H), 7.19 (dd, *J* = 3.3, 2.7 Hz, 1 H), 7.56 (dd, *J* = 7.5, 0.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 16.47, 16.74, 18.31, 26.12, 26.88, 27.15, 31.15, 40.00, 40.13, 103.16, 118.93, 120.19, 121.73, 122.35, 124.01, 124.12, 124.53, 127.99, 131.57, 135.32, 135.61, 137.27. HRMS (EI): $C_{23}H_{31}N$, Calcd.: 321.2456, found: 321.2456.

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References

(1) (a) Köbrich, G.; Buck, P. *Chem. Ber.* **1970**, *103*, 1412. (b) Buck, P.; Gleiter, R.; Köbrich, G. *Chem. Ber.* **1970**, *103*, 1431.
(2) Parry, R. J.; Li, Y.; Gomez, E. E. *J. Am. Chem. Soc.* **1992**, *114*, 5946.
(3) Berridge, M. S.; Sayre, L. M.; Arora, P. K.; Terris, A. H.; Riachi, N. J.; Harik, S. I. *J. Med. Chem.* **1993**, *36*, 1284.
(4) Pirrung, M. C.; Lee, Y. R.; Park, K.; Springer, J. P. *J. Org. Chem.* **1999**, *64*, 5042.
(5) Wallace, D. M.; Leung, S. H.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1993**, *58*, 7245.
(6) (a) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129. (b) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Palmieri, G.; Marcantoni, E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2757. (c) Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petini, M. *J. Chem. Soc. Perkin Trans. 2* **1991**, 657. (d) Dobson, D. R.; Gilmore, J.; Long, D. A. *Synlett* **1992**, 79. (e) Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron Lett.* **1997**, *38*, 5379. (f) Dobbs, A. P.; Voyle, M.; Whittall, N. *Synlett* **1999**, 1594. (g) Dobbs, A. *J. Org. Chem.* **2001**, *66*, 638.