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An Improved Method for the Bromination of Metalated Haloarenes via Lithium, Zinc Transmetalation: A Convenient Synthesis of 1,2-Dibromoarenes

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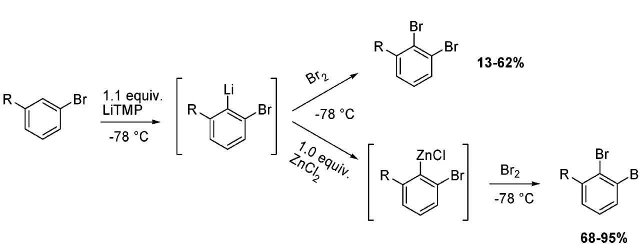

A facile protocol for the synthesis of 1,2-dibromoarenes is described. A standard ortho-lithiation/bromination procedure, when applied to bromoarenes, resulted in poor yields of the corresponding 1,2-dibromoarenes (13−62% yield). However, transmetalation of the transient aryllithium intermediate to an arylzinc species with ZnCl$_2$, followed by bromination, resulted in dramatically improved yields of the synthetically useful 1,2-dibromoarenes (68−95% yield).

Polyhalogenated arenes are ubiquitous target molecules in the field of material science and natural product syntheses.[2] The widespread utility of these subunits necessitates versatile and convenient methods for their preparation. Traditionally, the regioselective preparation of bromoarenes has been accomplished either by using electrophilic bromination[3] or by bromination of lithiated arenes with reagents such as bromine,[4] NBS,[5] $Br_2F_4C_2$,[6] or 1,2-dibromoethane.[7]

While the above methods are commonly used to access a wide array of brominated arenes, there are some limitations to this methodology when applied to the synthesis of 1,2-dibromoarenes. The electrophilic bromination of bromoarenes has afforded mixtures of corresponding 1,4- and 1,2-dibromides.[8] The complimentary ortho-metalation reaction of bromoarenes with LDA or LiTMP[9] has afforded the corresponding ortho-lithiated bromoarenes with high selectivity and yield. However, the subsequent bromination of the ortho-lithiated species furnished 1,2-dibromoarenes in low to moderate yields. A plausible explanation for the poor yields is depicted in Scheme 1.

It is well documented that the original deprotonation of 1,3-bromochlorobenzene (**1a**) with LiTMP affords the lithiated intermediate (**2a**),[10] which is stable at −78 °C. Immediately after bromine addition to this anion is initiated, the reaction mixture contains both the desired product **4a** and unreacted aryllithium (**2a**) (pathway A, Scheme 1). It is our supposition that this yet unreacted anion (**2a**) is basic enough to abstract a proton from the newly generated 1,2-dibromoarene (**4a**).[11] Consequently, the desired 1,2-dibromo-3-chlorobenzene (**4a**) is contaminated with polyhalogenated arene **6**[12] and copious amounts of starting material **1a**.[13] To support our hypothesis, we reacted 0.5 equiv of 3-chloro-1,2-dibromo-3-chlorobenzene (**4a**) with 1.0 equiv of pregenerated aryllithium (**2a**) for 1 h at −78 °C. A sample of the reaction mixture was analyzed by GC/MS after a subsequent quench of the reaction mixture with d_4-acetic acid, which indicated that deuterated **5** was formed.

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(13) All products have been identified by GC/MS.

10.1021/jo052515k CCC: $33.50

SCHEME 1. 1,2-Dibromoarene Formation

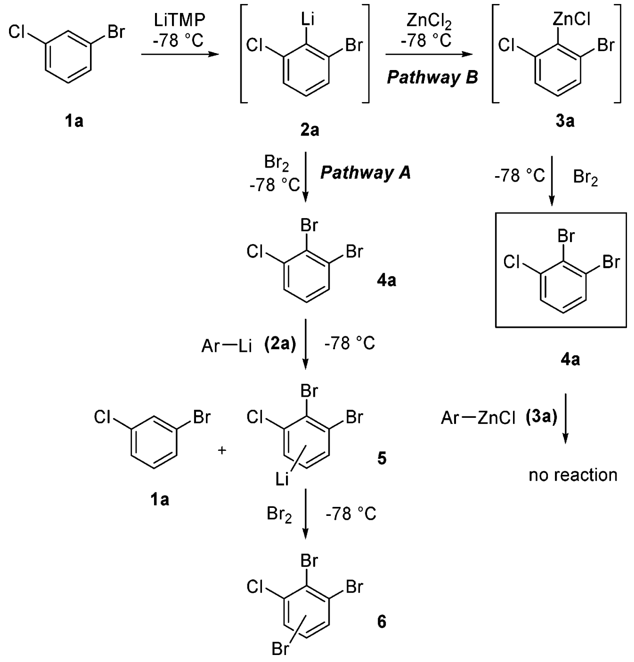

TABLE 1. Variation of Reaction Conditions Following Pathway B in Scheme 1[a]

entry	equiv of $ZnCl_2$	age time[b] [h]	assay yield [%][c] of **4a**
1	0	0.5	58
2	1.0	0.5	95
3	1.0	18[d]	91

[a] Standard reaction conditions: 1.2 equiv of TMP in THF at −78 °C, 1.1 equiv of 1.6 M *n*-BuLi in hexane, 1.0 equiv of 3-bromo-1-chlorobenzene, 2 h age, addition of 1.0 equiv of 1.0 M $ZnCl_2$ in THF, 30 min age, 1.5 equiv of Br_2 at −78 °C. [b] Age time after the addition of $ZnCl_2$ at −78 °C. [c] Assay yield after bromination at −78 °C. [d] 2-Bromo-6-chlorophenylzinc was allowed to warm to room temperature over 18 h followed by the addition of bromine.

To minimize this undesired deprotonation reaction, we envisioned that transmetalation from lithium to a less basic metal like zinc would result in arylzinc (**3a**), which would effectively preclude latent deprotonation of the desired product **4a** after bromination (pathway B, Scheme 1). We were pleased to find that by simply adding an anhydrous zinc chloride solution in THF[14] to 2-bromo-6-chlorophenyllithium (**2a**) followed by bromination afforded 1,2-dibromo-3-chlorobenzene (**4a**) in excellent yield (95% assay yield).[15]

Spectroscopic data confirmed the transmetalation from aryllithium[16] to arylzinc[17] upon the addition of zinc chloride. ^{13}C NMR data recorded on 2-bromo-6-fluorophenyllithium (**2b**)[18] and 2-bromo-6-fluorophenylzinc (**3b**)[19] indicated a high-field chemical shift of the metal-bearing carbon from 170.2 ppm (d, $^{2}J_{CF} = \sim 137$ Hz)[20] to 159.8 ppm (d, $^{2}J_{CF} = 77$ Hz), respectively.[21] Additionally, the $^{2}J_{F-C(ipso)}$ coupling constant reflected the presence of the metal species as compared to 24.2 Hz in **1b**.[22]

The above hypothesis was further substantiated by a series of experiments that are summarized in Table 1.

Only a 58% assay yield of compound **4a** was obtained when the aryllithium species **2a** was brominated with bromine. A dramatically increased assay yield (95%) of **4a** was obtained if aryllithium intermediate **2a** was transmetalated to zinc species **3a** prior to bromination (Scheme 2). A similar assay yield of 1,2-dibromo-3-chlorobenzene (**4a**) was obtained (91%) if the reaction mixture was allowed to warm to room temperature over 18 h prior to the addition of bromine. This result suggested that 2-bromo-6-chlorophenylzinc (**3a**) was much more thermodynamically stable than 2-bromo-6-chlorophenyllithium (**2a**).[23,24] Finally, these transmetalation/bromination conditions with 1.0 equiv of zinc chloride at −78 °C were used to explore the scope of 1,2-dibromoarene formation.

Direct comparisons of aryllithium bromination to arylzinc bromination were made and the data are compiled in Table 2. The direct bromination of the lithiated 1,3-bromohalobenzene derivatives **1a**−**d** gave moderate assay yields (52−62%) of the desired aryl bromides **4a**−**d**; however, each of these reactions contained significant amounts of starting material. In contrast to both the reaction profiles and assay yields of aryllithiums **2a**−**d**, the bromination of the corresponding arylzinc species **3a**−**3d** afforded brominated arenes **4a**−**d** in excellent assay yields (90−95%) and isolated yields (84−93%). In addition, in all of these examples, essentially complete consumption of starting aryl bromides (**1a**−**d**) occurred. The bromination of 1-bromo-2-cyanobenzene (**1e**) via the ortho-lithiated intermediate afforded a low assay yield (45%) of aryl bromide **4e** and occurred with low conversion (39% recovered **1e**). Marked improvements occurred to both the conversion (99%) and yield of dibromide **4e** (93% assay yield, 87% isolated yield) by utilizing the zinc methodology. The bromination of 2- and 3-bromo-1-trifluoromethylbenzene (**1f** and **1h**) once again afforded low assay yields of the two dibromoarenes **4f** and **4h** (32% and 52%, respectively) via the direct bromination of the corresponding aryllithium intermediates. After transmetalation to zinc, the brominated products **4f** and **4h** were formed in 70% and 90% yield, respectively. 3-Bromotrifluoromethylbenzene (**1h**) was selectively deprotonated in the 4-position and afforded 1,2-dibromo-4-trifluoromethylbenzene (**4h**) as a single product after bromination.[25] The sterically demanding bromo and trifluoromethyl substituents prevented the ortho-lithiation in the 2-position with the sterically hindered base LiTMP. Bromination of 2-bromo-3-lithium pyridine (**2i**) afforded 2,3-dibromopyridine

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(14) The anhydrous $ZnCl_2$ solution can be substituted by an anhydrous $ZnBr_2$ solution that afforded 3-chloro-1,2-dibromo-3-chlorobenzene (**4a**) in 94% assay yield.

(15) At the same time only small amounts of side products (**1a** and **6**) according to Scheme 1 were observed.

(16) ^{13}C NMR data confirmed that within 20 min the deprotonation reaction primarily formed the lithiated product **2b**.

(17) For examples of lithium−zinc transmetalation and Negishi-type cross-coupling reactions, see: (a) Karig, G.; Spencer, J. A.; Gallagher, T. *Org. Lett.* **2001**, *3*, 835 and references therein. (b) Examples for the cross-coupling reaction of (2-bromophenyl)(iodo)zinc were described in ref 24.

(18) 1,3-Bromofluorobenzene (**1b**) was chosen for the NMR experiment, because the formation of 2-bromo-6-fluorophenyllithium (**2b**) appeared as a homogeneous reaction mixture under the standard reaction conditions.

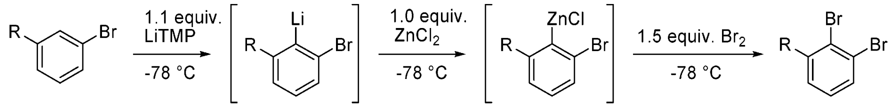
(19) Breitmaier, E.; Voelter, W. *Carbon-13 Spectroscopy of Organic Compounds*; VCH: Weinheim, Germany, 1987; Chapter 5, p 258.

(20) A similar $^{2}J_{F-C(ipso)}$ value was observed for 2-chloro-6-fluorophenyllithium: Ramirez, A.; Candler, J.; Bashore, C. G.; Wirtz, M. C.; Coe, J. W.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 14700.

(21) The same trend as for ^{13}C NMR chemical shifts of aryllithium and arylzinc was reported: Gauthier, D. R., Jr.; Szumigala, R. H.; Dormer, P. G.; Armstrong, J. D., III; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 375.

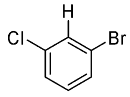
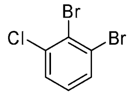
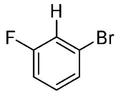
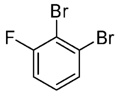
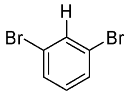
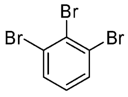
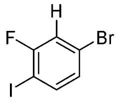
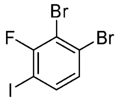
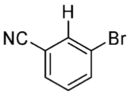
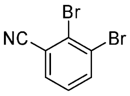
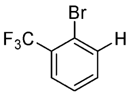
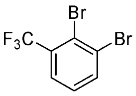
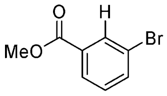
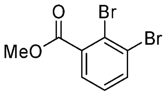
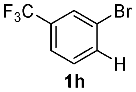
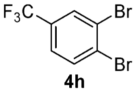
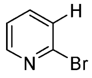
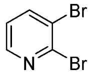
(22) For a discussion about $^{2}J_{C-F}$ values and electronic charges at the ^{13}C atom see: Doddrell, D.; Barfield, M.; Adcock, W.; Aurangzeb, M.; Jordan, D. *J. Chem. Soc., Perkin Trans. 2* **1976**, 402.

SCHEME 2. Arylzinc Pathway to 1,2-Dibromoarenes



1a-g **2a-g** **3a-g** **4a-g**

TABLE 2. Preparation of 1,2-Dibromoarenes

SM[a]	Product	Yield (without $ZnCl_2$)[b]		Yield (with $ZnCl_2$)[d]	
		SM [%][c]	Product [%][c]	SM [%][b]	Product [%][c,e]
 **1a**	 **4a**	32	58	3	95 (93)
 **1b**	 **4b**	16	52	0	93 (93)
 **1c**	 **4c**	28	62	2	90 (85)
 **1d**	 **4d**	11	59	0	93 (84)
 **1e**	 **4e**	39	45	1	93 (87)
 **1f**	 **4f**	10	32	2	70 (61)
 **1g**	 **4g**	18	26	1	68 (43)
 **1h**	 **4h**	24	52	2	90 (77)
 **1i**	 **4i**	62	13	4	90 (77)

[a] Starting material. [b] Reagents and conditions: 1.2 equiv of 2,2,6,6-tetramethylpiperidine, 1.1 equiv of *n*-BuLi, 1.0 equiv.of 3-bromoarene, 2 h age, 1.5 equiv of Br_2, THF, −78 °C. [c] Assay yield by HPLC. [d] Reagents and conditions: 1.2 equiv of 2,2,6,6-tetramethylpiperidine, 1.1 equiv of *n*-BuLi, 1.0 equiv of bromoarene, 2 h age, 1.2 equiv of $ZnCl_2$, 30 min age, 1.5 equiv of Br_2, THF, −78 °C. [e] Isolated yield in parentheses.

(**4i**) in only 13% assay yield, while after transmetalation to zinc the desired product **4i** was formed in 90% yield. Finally, methyl benzoate **4g** was formed in 68% yield via the arylzinc species compared to a 26% assay yield by direct bromination of the aryllithium intermediate.[26]

In conclusion, we have discovered a facile protocol for the synthesis of 1,2-dibromoarenes. When typical ortho-lithiation/bromination conditions were applied to bromoarenes, the corresponding 1,2-dibromoarenes were formed in low to moderate yields. The poor yields were rationalized by a deprotonation pathway. However, transmetalation from aryllithium to the arylzinc species with $ZnCl_2$ effectively suppressed the formation of side products and dramatically improved yields of the synthetically useful 1,2-dibromoarenes.

Experimental Section

To *n*-butyllithium in hexanes (1.95 mL, 1.55 M, 3.02 mmol) at −20 °C was added a solution of 2,2,6,6-tetramethylpiperidine (0.51 mL, 3.02 mmol) in THF (4.75 mL). After aging for 30 min, the solution was cooled to −78 °C and a solution of 3-bromobenzonitrile (0.5 g, 2.7 mmol) in THF (2.8 mL) was added dropwise so as to maintain the temperature at <−70 °C. After 2 h, a 1.0 M solution of $ZnCl_2$ in THF (2.75 mL, 2.75 mmol) was added dropwise and allowed to stir for an additional 30 min. Bromine (0.21 mL, 4.12 mmol) was added dropwise at a rate to keep the temperature below −50 °C. The reaction was monitored by HPLC (typical reaction time <30 min) and the completed reaction was allowed to warm to 25 °C and quenched with H_2O. The product was extracted two times into *tert*-butyl methyl ether and the combined organic layers were washed with 1 M HCl (aq) followed by H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography with hexanes to afford 0.62 g of 2,3-dibromobenzonitrile as a colorless liquid (2.38 mol, 87%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (dd, $J = 8.20$ Hz, 1.40 Hz, 1H), 7.62 (dd, $J = 7.70$ Hz, 1.50 Hz, 1H), 7.29 (t, $J = 8.00$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.7, 133.0, 128.6, 128.0, 126.7, 117.9, 116.8; GC/MS (*m*/*z*) 261, 180, 100, 75; melting point 106.1 °C.

Supporting Information Available: Experimental procedures for the synthesis of compounds **4a**−**i**, as well characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Typically, ortho-lithiated bromoarenes are plagued by low thermodynamic stability, which can lead to debromination via a benzyne pathway: (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (b) Wickham, P. P.; Hazen, K. H.; Guo, H.; Jones, G.; Reuter, K. H.; Scott, W. J. *J. Org. Chem.* **1991**, *56*, 2045. (c) Lecroux, F.; Schlosser, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4272. (d) Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4364. (e) Hickey, M.; Allwein, S. P.; Nelson, T. D.; Kress, M. H.; Sudah, O. S.; Moment, A. J.; Rodgers, S. D.; Kaba, M.; Fernandez, P. *Org. Res. Proc. Dev.* **2005**, *9*, 764.

(24) Okano, M.; Amano, M.; Takagi, K. *Tetrahedron Lett.* **1998**, *39*, 3001.

(25) The same regioselectivity in the deprotonation step with LiTMP has been observed: ref 12(b).

(26) The lithiated methyl-3-bromobenzoate (**2g**) underwent self-condensation as the major side product after bromination was initiated.