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A Closer Look at the Bromine–Lithium Exchange with *tert*-Butyllithium in an Aryl Sulfonamide Synthesis

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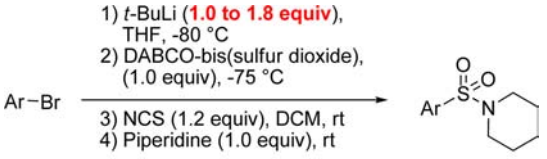
ABSTRACT



Ar included: 7-Azaindolyl, Pyridinyl, Pyrrolyl, Phenyl
8 examples, up to 76% yield

A practical protocol for the one-pot synthesis of various aryl sulfonamides, notably of pyridine-core-substituted 7-azaindolyl sulfonamides, is described. A key step is the well-known bromine–lithium exchange reaction of an aryl bromide with *tert*-butyllithium (*t*-BuLi). Differing from the common practice to use 2 or more equiv of organolithium, the exact amount of *t*-BuLi needed for a sufficient exchange reaction is determined for each aryl bromide in a GC–MS-assisted experiment.

Arene and heteroarene sulfonamides are of major importance in pharmaceuticals, agrochemicals, and other applications.[1] The most straightforward laboratory synthesis involves the reaction of arylsulfonyl chlorides with amines. Within the frame of our ongoing studies of isatin sulfonamides as selective inhibitors of caspases-3 and -7,[2] we were interested in the formation of pyridine-core substituted 7-azaindolyl sulfonamides. The 7-azaindole moiety has attracted considerable attention over the past decades due to its promising potential and proven usefulness in pharmaceuticals[3] as well as its application in coordination chemistry[4] and physicochemical investigations.[5] The chemistry of 7-azaindoles has been reviewed recently.[6] Notably, most transformations to date involve the pyrrolo moiety of 7-azaindole, and only few examples of derivatization at the pyridine core were described in literature.[7]

In an initial attempt to prepare 7-azaindolyl sulfonyl chlorides as precursors for the corresponding sulfonamides, we adapted a reaction sequence starting with *N*-triisopropylsilyl (*N*-TIPS) protected 5-bromo-7-azaindole (**1**) (Table 1).[8] A bromine–lithium exchange reaction was carried out by using 2.0 equiv *t*-BuLi at −80 °C in tetrahydrofuran (THF). The resulting aryllithium was reacted

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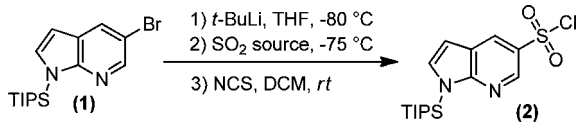
with gaseous SO_2 to yield an arylsulfinate, which subsequently was oxidized to the desired sulfonyl chloride (**2**) with *N*-chlorosuccinimide (NCS) at room temperature in dichloromethane (DCM) (entry 1). In repeating experiments, the product yields varied considerably, and different numbers and amounts of side products were formed, e.g., due to difficult dosing of SO_2, even when the same reaction conditions were applied. The search for an alternative SO_2 source led us to use the known 1,4-diazabicyclo-[2.2.2]octane (DABCO)−bis(sulfur dioxide) (DABSO) (entry 2).[9] The advantages of this bench-stable colorless solid are its excellent usability and a fully controllable dosing of SO_2 equivalents. This enhanced synthetic procedure made it more feasible, but the reproducibility of product yield was still unsatisfying. It is known that an excess of *t*-BuLi in solution can lead to complications in product isolation if an electrophile is added.[10] To avoid any residual *t*-BuLi, we therefore used only 1.0 equiv for the bromine−lithium exchange reaction (entry 3). To our surprise, the starting material was fully converted, the yields were slightly increased, and much better reproducibility of the reaction was achieved.

Table 1. Formation of 7-Azaindolyl Sulfonyl Chlorides

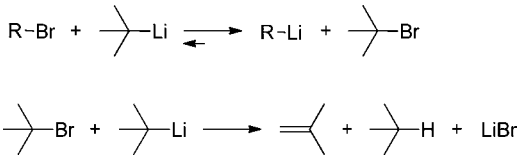


entry	SO_2 source	*t*-BuLi (equiv)	% yield
1	$SO_{2(g)}$[a]	2.0	27−52[b]
2	DABSO	2.0	25−56[b]
3	DABSO	1.0	56−58[c]

[a] Inserted into the reaction mixture via syringe over 10 min. [b] Repeated three times. [c] Repeated two times.

The use of *t*-BuLi in the lithium−halogen exchange reaction has attracted considerable attention since the pioneering works by the groups of Corey and Seebach.[11,12] Since then its applicability and mechanistical details have been further investigated.[13] The reaction is a fast and reversible process leading to an equilibrium mixture favoring the more stable organolithium species.[14] Irreversibility can be achieved by using 2 equiv of *t*-BuLi. The first equivalent is used for the exchange, and the second reacts with the produced *t*-BuBr to form isobutene, isobutane, and lithium bromide (Scheme 1).[12] In addition, *t*-BuBr is

Scheme 1. Bromine−Lithium Exchange Reaction with 2 equiv of *t*-BuLi



prevented from reacting with either the newly formed organolithium or another *t*-BuLi in a putative Wurtz-type coupling. For these reasons, as far as we know, 2 equiv of *t*-BuLi was applied in almost all published syntheses exploiting an bromine−lithium exchange reaction.[7e,8,15] As a result, it has not been investigated so far whether less than 2 equiv of *t*-BuLi might be sufficient for the interconversion with various aryl bromides and if Wurtz-type coupling products are actually formed in those cases.

The bromine−lithium exchange rates of various aryl bromides with varying molar equivalents of *t*-BuLi were determined using a gas chromatography−mass spectrometry (GC−MS) assisted protonation assay. Therefore, the aryl bromides were reacted with 1 or 2 equiv of *t*-BuLi, respectively, and then protonated by addition of methanol. The relative conversion percentages were determined via GC−MS by integrating the peak areas of unreacted aryl bromides (Ar-Br) and aromatics (Ar-H) (Table 2). Initially, we investigated several *N*-protected 7-azaindoles (entries 1 to 4). All of them underwent bromine−lithium exchange with 1.0 equiv of *t*-BuLi with conversion rates >95%. Wurtz-type couplings were not detected between *t*-BuBr and the corresponding aryllithium compounds or between *t*-BuBr and *t*-BuLi under these conditions. To further ensure that the generated *t*-BuBr did not interfere with the reaction, we treated compound **1** with 1.0 equiv of *t*-BuLi at −80 °C in THF and then stirred the reaction mixture for 24 h at room temperature. After addition of methanol, the only product found by analysis with GC−MS and NMR spectroscopy was Ar-H. Therefore, *t*-BuBr seems to not undergo any further reaction which would compromise the outcome of the experiments. To expand the scope to other compound classes, brominated derivatives of pyridine **6**, benzene **7**, and pyrrole **8** (Table 2, entries 5−7) were tested. None of these aryl bromides underwent a complete bromine−lithium exchange with 1.0 equiv of *t*-BuLi. We therefore repeated the experiments by increasing the amount of *t*-BuLi in 0.2 equiv steps until conversions >95% were detected. In the case of the *N*-unprotected 7-azaindole derivative **9** an acidic proton had to be removed by sodium hydride prior to the

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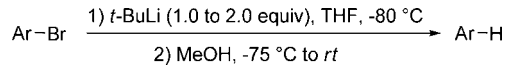
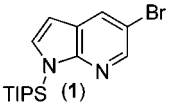
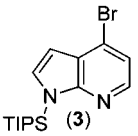
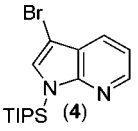
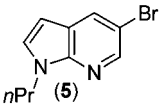
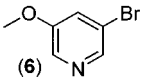
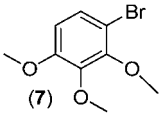
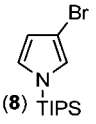
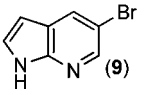
bromine–lithium exchange (Table 2, entry 8).[16] These results show that the use of 2 equiv of *t*-BuLi is not mandatory for complete conversions in bromine–lithium exchange reactions.

Table 2. GC–MS-Assisted Protonation Assay

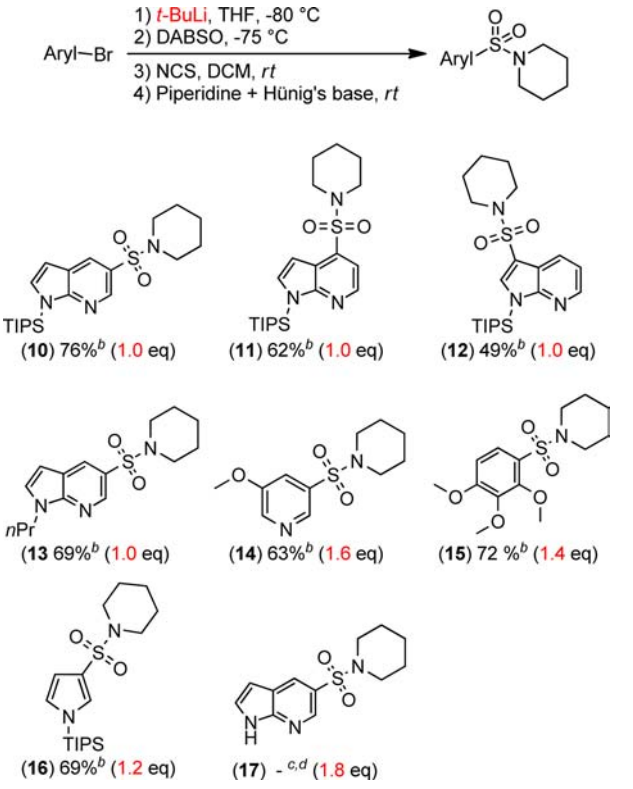


entry	aryl bromide	% conversion[a] *t*-BuLi (equiv) 1.0	1.2	1.4	1.6	1.8	2.0
1[b]		99	-	-	-	-	99
2[b]		100	-	-	-	-	100
3[b]		100	-	-	-	-	100
4[b]		97	-	-	-	-	100
5[b]		72	92	94	96	-	100
6[b]		89	93	100	-	-	100
7[b]		92	99	-	-	-	100
8[c]		71	80	92	93	99	100

[a] Percentage of peak areas of aryl-H compounds and unreacted aryl bromides determined with GC–MS. [b] Reaction conditions: aryl bromides (1 equiv, 0.5 mmol), *t*-BuLi (1–2 equiv), 5 mL of THF, −80 °C, 10 min, MeOH (0.3 mL), −75 °C. [c] Reaction conditions: NaH (1.4 equiv, 0.7 mmol), substrate **9** (1 equiv, 0.5 mmol), 7 mL of THF, 0 °C, 30 min, *t*-BuLi (1–2 equiv), −80 °C, 10 min, AcOH (0.3 mL), −75 °C.

With optimal conditions for the bromine–lithium exchange reaction in hand, we next explored application in the synthesis of aryl sulfonamides. We found that a four-step, one-pot synthesis sequence is the most practical and most rapid way to obtain the desired sulfonamides (Scheme 2). In contrast to our initial plan, the sulfonyl chlorides were reacted in situ with a desired amine. Piperidine turned out to provide high yields and was used as model amine in all cases. To facilitate the coupling reaction, piperidine was deprotonated with an equal amount of Hünig's base prior to addition. Application of the modified bromine–lithium exchange conditions worked well in the reaction sequence delivering the aryl sulfonamides **10** to **16** in fair to good overall yields. Compared to the classical approach using 2 equiv of *t*-BuLi, the reproducibility of the reaction sequence was even improved. Additionally, no Wurtz-type coupling products and few other side products due to excess *t*-BuLi were detected by NMR or GC–MS of the crude product mixture. In the case of compound **17**, we were not able to isolate the pure product in any attempt but could detect it by mass spectrometry and NMR spectroscopy.

Scheme 2. Aryl Sulfonamide Formation Using the Determined Equivalents of *t*-BuLi for the Bromine–lithium Exchange[a]



[a] Isolated yields. [b] Reaction conditions: aryl bromides (1 equiv, 0.5 mmol), *t*-BuLi (1–1.6 equiv), 5 mL of THF, −80 °C, 10 min, DABSO (1 equiv, 0.5 mmol), −75 °C to rt. NCS (1.2 equiv, 0.6 mmol), 10 mL of DCM, rt, 10 min, piperidine (1 equiv, 0.5 mmol), Hünig's base (1 equiv, 0.5 mmol), rt, 10 min. [c] Reaction conditions: NaH (1.4 equiv, 0.7 mmol), substrate **9** (1 equiv, 0.5 mmol), 7 mL of THF, 0 °C, 30 min, *t*-BuLi (1.8 equiv), −80 °C, 10 min, DABSO (1 equiv, 0.5 mmol), −75 °C to rt, NCS (1.2 equiv, 0.6 mmol), 10 mL of DCM, rt, 10 min, piperidine (1 equiv, 0.5 mmol), Hünig's base (1 equiv, 0.5 mmol), rt, 10 min, water (20 mL). [d] Pure product could not be isolated.

In conclusion, this paper describes a facile and reliable one-pot synthesis of pyridine-core substituted 7-azaindolyl as well as other (hetero)aryl sulfonamides. The included bromine–lithium exchange reactions are improved when

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less than 2 equiv of *t*-BuLi is used. The exact molar amount of *t*-BuLi needed was determined in a GC−MS assisted protonation assay for every distinct aryl bromide. Our findings significantly improve the classical protocol using 2 equiv of *t*-BuLi in terms of reproducibility and atom efficiency.

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Supporting Information Available. Experimental, spectroscopic, and GC−MS data for new compounds. This material is available free of charge *via* the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.