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Authors: Niels Weidmann, Marthe Ketels, and Paul Knochel

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Sodiation of Arenes and Heteroarenes in Continuous Flow

Niels Weidmann⁺, Marthe Ketels⁺, and Paul Knochel^{*}

Dedicated to Professor Dieter Seebach

Abstract: We report the first sodiations of (hetero)arenes in continuous flow using NaDA (sodium diisopropylamide) in Me₂EtN. This flow-procedure enables sodiation of functionalized arenes and heteroarenes that decompose under batch-sodiation conditions. The resulting sodiated (hetero)arenes react instantly with various electrophiles, such as ketones, aldehydes, isocyanates, alkyl bromides and disulfides affording polyfunctionalized (hetero)arenes in high yields. A scale-up is possible without further optimization.

The functionalization of aromatics and heteroaromatics is an important synthetic task especially for the elaboration of pharmaceuticals and agrochemicals.^[1] Lithium bases have been extensively used for the metalation of (hetero)arenes.^[2] In addition, other milder magnesium and zinc bases have been developed in order to achieve a higher functional group tolerance allowing the preparation of polyfunctional aromatics.^[3] In the course of these studies, it was realized by Yoshida,^[4] Ley,^[5] Buchwald,^[6] Organ^[7] and others^[8] that a high compatibility with sensitive functional groups can be achieved by performing these reactions under flow conditions. Such flow set-ups have multiple advantages, such as mild reaction conditions (ambient temperature metalations), short reaction times and scale-ups without the need of further optimization.^[9] In contrast to lithium bases, corresponding sodium bases have received little attention due to the high reactivity of the ionic C-Na bond and poor solubility. Since sodium is ca. 1500 times more abundant than lithium in the earth crust and lithium demand and prices are increasing in recent years,^[10] the use of sodium compounds is certainly underexploited in organic synthesis. Already, Schlosser, Mordini,^[11] Mulvey^[12] and Mioskowski^[13] have demonstrated the high potential of sodium organometallic chemistry.^[14] Recently, Collum^[15] reported sodiations of aromatic and heterocyclic substrates using sodium diisopropylamide (NaDA) as a soluble highly reactive base in dimethylethylamine (DMEA) at cryogenic temperatures.

Herein, we wish to report the first sodiation of (hetero)arenes of type **1** in a microflow reactor set-up producing a broad range of (hetero)aryl-sodium intermediates of type **2**. These organosodium reagents react instantly in batch with various electrophiles (**3**, E-X) forming functionalized arenes and heteroarenes of type **4** (Scheme 1). The scope of this sodiation in flow is significantly broader compared to batch reactions. The sodium base NaDA was prepared according to a slightly optimized procedure by Collum using less equivalents of sodium in DMEA and diluted to a 0.2 M solution.^[15a,16] This concentration was ideal for sodiation performed in flow avoiding any precipitation.^[17] The reaction conditions were optimized with 1,3-dichlorobenzene (**1a**) as a

[*] N. Weidmann⁺, M. Ketels⁺, Prof. Dr. P. Knochel Ludwig-Maximilians-Universität München, Department Chemie Butenandtstrasse 5-13, Haus F, 81377 München (Germany) E-mail: <u>paul.knochel@cup.uni-muenchen.de</u> substrate. Using a flow rate of 10 mL/min, it was possible to achieve full sodiation of **1a** within 0.5 s at -20 °C, compared to batch sodiation at -78 °C.^[15a]



Scheme 1. General set-up for the sodiation of (hetero)arenes of type 1 with NaDA in a microflow reactor and subsequent trapping with electrophiles in batch.

The resulting 2,6-dichlorophenylsodium (2a) was quenched in batch with iodine at 0 °C providing aryl iodide (4a) in 84% isolated yield (Table 1, entry 1). Similarly, 2a was quenched in batch with benzaldehyde (3b), PPh₂Cl (3c, followed by the addition of sulfur), phenylisocyanate (3d) and S-(4-fluorophenyl)benzenesulfonothioate (3e) affording the expected products 4b-e in 64-95% yield (entries 2-5). Remarkably, no benzyne formation was observed under these flow conditions.

Table 1. Sodiation of 1,3-dichlorobenzene (1a) using a microflow reactor and subsequent batch quench of the intermediate organosodium 2a with various electrophiles of type 3 leading to functionalized dichlorobenzenes of type 4.



^{[&}lt;sup>+</sup>] These authors contributed equally to this work.

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We have then examined substitution reactions (*Wurtz-Fittig*couplings).^[18] Whereas the use of an allylic bromide such as cyclohexenyl bromide (**3f**) required copper-catalysis,^[19] methyl iodide (**3g**) and *n*butyl bromide (**3h**) reacted instantly at -40 °C in the absence of any transition metal catalyst with the in flow generated arylsodium **2a** affording the cross-coupling products **4f-h** in 53-75% yield (entries 6-8).

Table 2. Sodiation of (hetero)arenes of type 1 leading via intermediate organosodiums of type 2 to polyfunctional (hetero)arenes of type 4.



[a] Yield of analytically pure isolated product. [b] 1.5 equiv E-X. [c] 2.5 equiv E-X.

Furthermore, related arenes bearing chloro-, iodo-, fluoro- or trifluoromethyl-substituents were subjected to the optimized flow conditions. Thus, 1,3-difluorobenzene (1b) was sodiated at -40 °C providing the corresponding arylsodium 2b which was subsequently quenched in batch with aldehyde 3i providing alcohol 4i in 88% yield (Table 2, entry 1). Alternatively, arylsodium 2b was trapped with benzoyl chloride (3j) in the absence of any transition metal catalyst leading to benzophenone derivate 4j in 71% yield (entry 2). Flow-sodiation of 2fluoroiodobenzene (1c) and subsequent quench with aldrithiol (3k) led to the corresponding thioether 4k in 62% yield (entry 3). In addition, trifluoromethyl-substituted arene 1d was sodiated at -40 °C and quenched with aldehyde 3I leading to alcohol 4I in 85% yield (entry 4). Furthermore, the optimized flow conditions were applied to the sodiation of heteroarenes. Thus, 2chloropyridine (1e) was sodiated in flow at convenient conditions (-20 °C, 0.5 s at a flow rate of 10 mL/min; compared to -78 °C in batch^[15a]) and the intermediate 2-chloro-3-pyridyl sodium (2e) was subsequently trapped with iodine (3a) and dibutyl disulfide (3m) leading to the functionalized pyridines 4m and 4n in 53-89% yield (entries 5-6). Trifluoromethyl-substituted pyridine 1f was sodiated in flow and trapped with aldehyde **3n** yielding the secondary alcohol **4o** in 68% yield (entry 7).



Scheme 2. Sodiation of sensitive heteroarene 2-chloropyrazine (**1g**) in a microflow reactor and under batch conditions and subsequent trapping with iodine leading to functionalized heteroarene **4p** or decomposition.

This flow sodiation procedure extends considerably the reaction scope of such metalations and applies to sensitive substrates that decompose under batch sodiation conditions.^[20,15a] Thus, for example, 2-chloropyrazine (**1g**) cannot be sodiated in batch with NaDA at -78 °C, however under our optimized conditions (-78 °C, 0.5 s using a flow rate of 10 mL/min) a complete consumption of the starting material takes place affording after iodolysis the pyrazine **4p** in 65% yield (Scheme 2).

Table 3. Sodiation of sensitive (hetero)arenes of type 1 leading via intermediate
organosodiums of type 2 to polyfunctional (hetero)arenes of type 4.



[a] Yield of analytically pure isolated product. [b] 1.5 equiv E-X. [c] 5 mol% CuCN-2LiCl, 2.5 equiv E-X. [d] 2.5 equiv E-X.

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In addition to 2-chloropyrazine (**1g**), 2-fluoropyrazine (**1h**) and substituted pyridines **1i** and **1j** that decompose upon batchsodiation were successfully sodiated under flow conditions and trapped with aldehydes yielding functionalized heteroarenes **4q-t** in 65-97% yield (Table 3, entries 1-4). Copper-catalyzed^[19] batch allylation under flow-conditions of sodiated 2-iodothiophene (**1k**) led to functionalized thiophene **4u** in 76% yield (entry 5). At -60 °C it was possible to sodiate 2-bromofluorbenzene (**1l**) without aryne-formation. Instant reaction of the sodiated intermediate **2l** with dimethyl disulfide (**3s**) or benzaldehydes **3t** and **3b** furnished functionalized arenes **4v-x** in 70-81% yield (entries 6-8).



Scheme 3. Sodiation of (hetero)arenes of type **1** and subsequent batch quench with ketones of type **5** leading to tertiary alcohols of type **6**.

Addition of organometallics to ketones is always subject to side reactions.^[21] In particular, sterically hindered ketones are prone to undergo reduction instead of addition reactions using alkyllithium or-magnesium species.^[22] Remarkably, the in flow generated sodium derivatives of type **2** underwent reactions with ketones of type **5**, leading to tertiary alcohols of type **6**. Thus, polyfunctional arenes and heteroarenes **6a-I** were obtained in up to 91% yield (Scheme 3).



Scheme 4. Sodiation of highly sensitive 4-fluorobenzonitrile (7) and subsequent batch quench with electrophiles yielding functionalized benzonitriles **9a-c**.

Noteworthy, sodiation of 4-fluorobenzonitrile at -78 °C led to the desired sodium arene **8** without the attack at the nitrile functionality.^[23] Batch quench of sodiated intermediate **8** with benzaldehyde (**3b**), ketone **5n** and disulfide **3k** led instantly to functionalized benzonitriles **9a-c** in 75-81% yield (Scheme 4). Additionally, a scale-up^[24] was possible without any further optimization by simply extending the running time. Thus, a scaleup by factor 30 was conducted and functionalized benzonitrile **9a** was obtained in 76% yield on a gram scale (Scheme 4).

In summary, we have reported the first sodiation of (hetero)arenes containing sensitive functional groups using a flow set-up. The procedure could be scaled up without any further optimization. Further investigations of flow-sodiations are currently under way in our laboratories.

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Keywords: flow chemistry • sodium • metalation • NaDA • pyrazine

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Layout 2:

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Taming Sodium: Sodium is an abundant, non-toxic metal, however the high ionic character of the C-Na-bond precludes many applications in synthesis. Using flow chemistry, we report the first sodiation of arenes and heteroarenes under flow conditions using the soluble base NaDA (sodium diisopropylamide) allowing sodiation of (hetero)arenes containing sensitive functional groups that decompose under batch-sodiation conditions. The resulting sodiated (hetero)arenes react instantly with various electrophiles yielding polyfunctionalized (hetero)arenes in high yields.

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