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(2-Ethylhexyl)sodium: A Hexane-Soluble Reagent for Br/Na-Exchanges and Directed Metalations in Continuous Flow

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Dedicated to Prof. Dr. Dieter Seebach in recognition to his seminal contributions in chemistry



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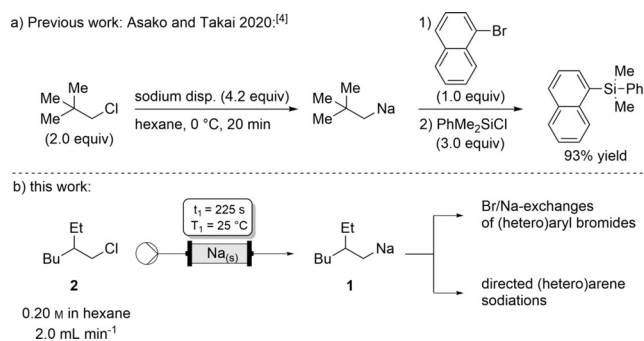
Abstract: We report the on-demand generation of hexane-soluble (2-ethylhexyl)sodium (**1**) from 3-(chloromethyl)heptane (**2**) using a sodium-packed-bed reactor under continuous flow conditions. Thus, the resulting solution of **1** is free of elemental sodium and therefore suited for a range of synthetic applications. This new procedure avoids the storage of an alkylsodium and limits the handling of metallic sodium to a minimum. (2-Ethylhexyl)sodium (**1**) proved to be a very useful reagent and undergoes in-line Br/Na-exchanges as well as directed sodiations. The resulting arylsodium intermediates are subsequently trapped in batch with various electrophiles such as ketones, aldehydes, Weinreb-amides, imines, allyl bromides, disulfides and alkyl iodides. A reaction scale-up of the Br/Na-exchange using an in-line electrophile quench was also reported.

Organosodium reagents are highly reactive organometallics towards various electrophiles due to the very ionic character of the C–Na bond.^[1] Despite the appealing chemical properties and the low price, high abundance and low toxicity of sodium, these compounds have seldomly found applications in organic syntheses.^[2] Dimethylethylamine soluble NaDA (sodium diisopropylamide) was prepared by Collum and co-workers as an alternative to the frequently used LDA (lithium diisopropylamide).^[3] Recently, Asako and Takai have reported a new method for the preparation of arylsodiums via a Br/Na-exchange using neopentylsodium, which was prepared by the reaction of neopentyl chloride with sodium dispersion (Scheme 1a). This procedure seems to limit the trapping of the resulting arylsodium to R₃SiCl, D₂O and transmetalation reactions.^[4] The presence of residual sodium dispersion may hamper the use of more complex electrophiles. In contrast to well established lithium chemistry,^[5] the use of organosodium reagents remains underexploited in continuous flow due to their poor solubility.^[6] We have reported the generation of organosodium and -potassium derivatives in continuous flow using Na- and K-amide bases.^[7] In the course of this work, we envisioned a new procedure for generating soluble alkylsodiums in continuous flow expanding pioneering work of Alcázar,^[8] Ley,^[9] McQuade^[8a] and others,^[10] which established the use of metal-packed-bed reactors for the direct preparation of Mg or Zn organometallics in continuous flow. Herein, we report a new sodium-packed-bed reactor for on-demand generation of the hexane-soluble sodium reagent (2-ethylhexyl)sodium (**1**)^[11] from readily available 3-(chloromethyl)heptane (**2**), which was

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Scheme 1. a) Generation of neopentylsodium in batch and its use in halogen/sodium-exchange reactions. b) On-demand continuous flow generation of (2-ethylhexyl)sodium (**1**) and subsequent in-line Br/Na-exchange and directed metalation.

used for performing in-line Br/Na-exchanges as well as directed metalations (Scheme 1b) in continuous flow.

To prepare the packed-bed reactor, we charged a glass column (7.5 mL) with sodium particles (3.4 mL, Ø ca. 1 mm).^[12,13] The resulting mixed-bed reactor^[14] was flushed with dry hexane and was activated using a 0.1 M solution of *i*-PrOH in hexane. Pumping alkyl chloride **2** (0.2 M in hexane, 2.0 mL min⁻¹, 25 °C) through the reactor afforded a slightly yellow solution of **1** in hexane (ca. 0.15 M).^[15] This soluble alkylsodium species^[16] was free of metallic sodium and was directly used for in-line Br/Na-exchanges as well as directed sodiations. Collected aliquots of **1** prepared in continuous flow showed moderate stability (Figure 1), demonstrating the importance of the direct use of the sodium species. This on-demand procedure avoids storage problems of instable **1** and considerably limits hazards of working with metallic sodium. Whereas preparation of **1** in batch led to a dark solution over metallic sodium, the flow procedure resulted in a slightly yellow solution of **1** free of elemental sodium (Figure 1).

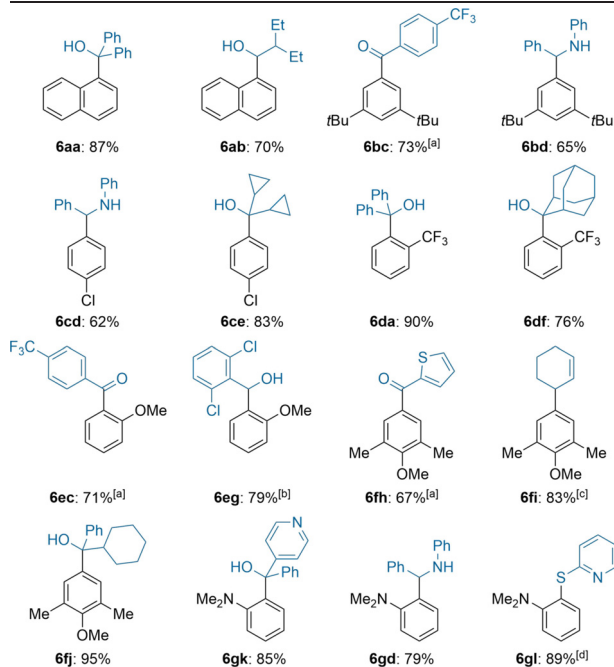
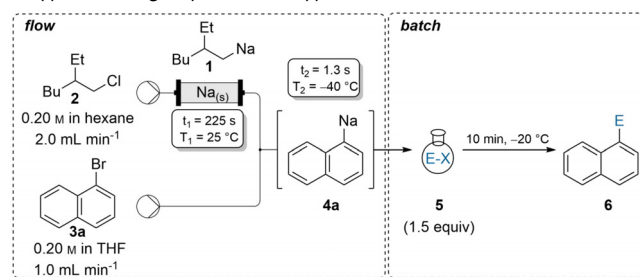


Figure 1. From left to right: (2-Ethylhexyl)sodium (**1**) in hexane prepared in batch over metallic sodium, 5 min after addition of **2**. (2-Ethylhexyl)sodium (**1**) in hexane prepared via a sodium-packed-bed reactor, 5 min after collecting. (2-Ethylhexyl)sodium (**1**) in hexane prepared via a packed-bed sodium reactor, 18 h after collecting.

The sodium-packed-bed reactor was used without clogging for ca. 1 h pumping a 0.2 M solution of **2** in hexane with a flow rate of 2.0 mL min⁻¹. The soluble organosodium **1** was directly used for Br/Na-exchanges with various aryl bromides of type **3**. Thus, mixing a THF-solution of 1-bromonaphthalene (**3a**, 0.2 M, 1.0 mL min⁻¹) with (2-ethylhexyl)sodium (**1**, 0.2 M, 2.0 mL min⁻¹) in a T-shaped mixer gave 1-naphthylsodium (**4a**) (−40 °C, 1.3 s).^[17]

Subsequent batch-quench of **4a** with benzophenone (**5a**) or enolisable 2-ethylbutyaldehyde (**5b**) afforded the desired alcohols (**6aa–6ab**) in 70–87% yield (Table 1). The resulting arylsodiums reacted instantly with various electrophiles such as ketones, aldehydes, Weinreb-amides, imines, allyl bromides, disulfides and alkyl iodides. Weinreb-amide **5c** and imine **5d** gave the expected products **6bc** and **6bd** in 65–73% yield upon Br/Na-exchange on 1-bromo-3,5-di-*tert*-butylbenzene (**3b**). Halogen- and trifluoromethyl-substituted aryl bromides such as **3c** and **3d** furnished after batch quenching the functionalized arenes **6cd**, **6ce**, **6da** and **6df** in 62–90% yield.

Table 1: On-demand preparation of alkylsodium reagent **1** from alkyl chloride **2** followed by Br/Na-exchange on aryl bromides of type **3** leading to arylsodiums of type **4** and subsequent batch quench with electrophiles of type **5** leading to products of type **6**.

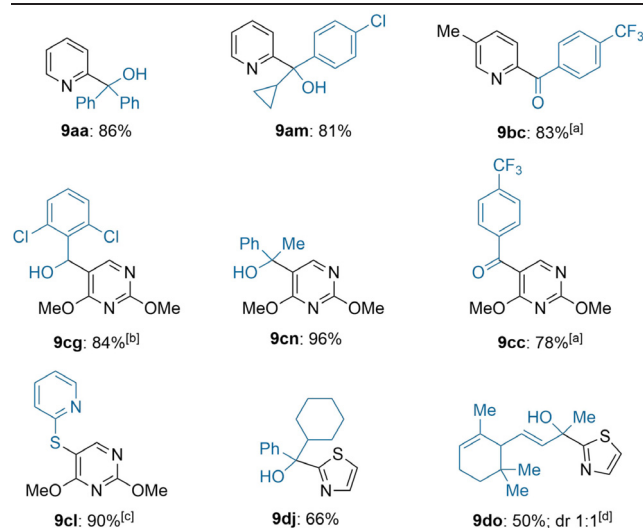
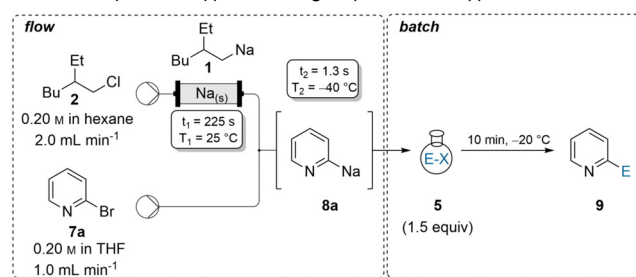


Yields of analytically pure products. [a] From the Weinreb-amide [b] 2.0 equiv E-X were used. [c] From the allyl bromide with addition of 50 mol% CuCN·2 LiCl. [d] From the disulfide.

yield. Electron-rich bromoarenes were well suited for such a Br/Na-exchange in continuous flow affording the polyfunctionalized arenes **6ec**, **6eg**, **6fh**, **6fi**, **6fj**, **6gk**, **6gd** and **6gl** in 67–95% yield.

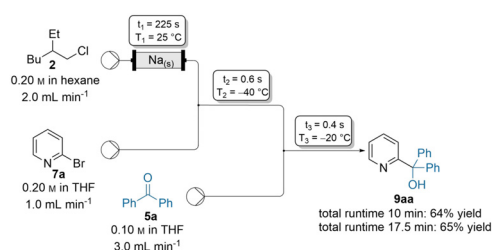
Nitrogen containing heterocycles are important building blocks in pharmaceutical and agricultural chemistry.^[18] Therefore, the functionalization of those scaffolds is an ongoing task in synthetic chemistry.^[19] The exchange procedure was extended towards heterocyclic bromides using the optimized reaction conditions. Br/Na-exchange on 2-bromopyridine (**7a**) at −40 °C using a combined flow rate of 3.0 mL min⁻¹ led to the desired aryl-sodium **8a**, which was subsequently quenched in batch with ketones **5a** and **5m** affording the tertiary alcohols **9aa** and **9am** in 81–86% yield (Table 2). Similarly, 5-methyl-2-bromopyridine (**7b**) and highly substituted bromopyrimidine **7c** underwent Br/Na-exchanges. Batch quenching using various electrophiles of type **5** led to the functionalized *N*-heterocycles **9bc**, **9cg**, **9cn**, **9cc** and **9cl** in 78–96% yield. Furthermore, 2-bromothiazole (**7d**) was converted into the corresponding sodium species **8d**, which was quenched with ketone **5j** resulting in **9dj** (66% yield). Trapping **8d** with a racemic mixture of α -ionone (**5o**) gave the 1,2-addition product **9do** (50% yield, *dr* 1:1).

Table 2: On-demand preparation of alkylsodium reagent **1** from alkyl chloride **2** followed by Br/Na-exchange on heteroaryl bromides of type **7** leading to heteroarylsodiums of type **8** and subsequent batch quench with electrophiles of type **5** leading to products of type **9**.



Yields of analytically pure products. [a] From the Weinreb-amide. [b] 2.0 equiv E-X were used. [c] From the disulfide. [d] From racemic α -ionone.

To demonstrate the scalability^[20] of the Br/Na-exchange reaction, an in-line electrophile quench was set up. Thus, pumping a solution of **2** (0.2 M, 2.0 mL min⁻¹) through the sodium-packed reactor resulted in the sodium exchange reagent **1**. 2-Bromopyridine (**7a**, 0.2 M, 1.0 mL min⁻¹) was mixed with the solution of **1** in a T-shaped mixer. After passing through a micro-reactor (0.6 s, -40 °C, combined flow rate: 3.0 mL min⁻¹), the pyridylsodium **8a** was trapped in-line with a solution of benzophenone (**5a**, 0.1 M, 3.0 mL min⁻¹). Increasing the runtime 10- or 17.5-fold (2.0 or 3.5 mmol) led to the functionalized pyridine **9aa** in 64–65% isolated yield (Scheme 2).

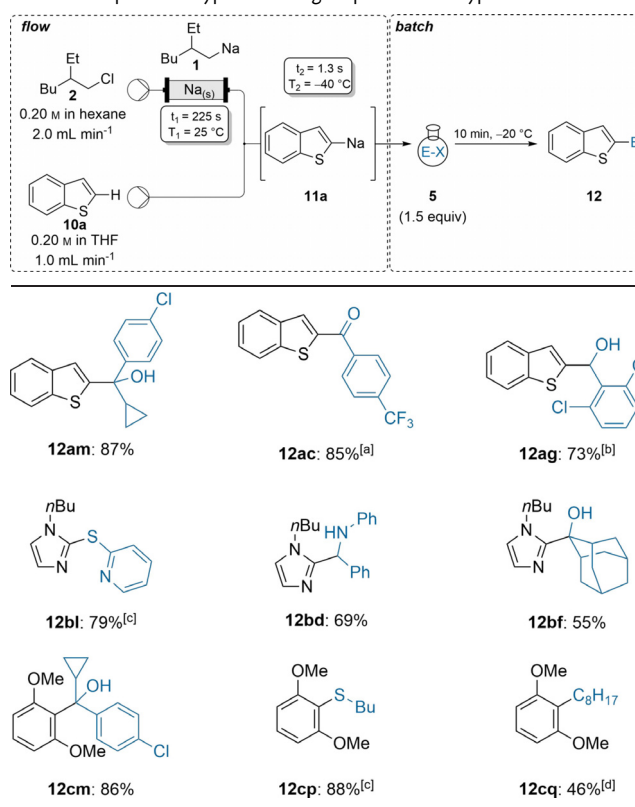


Scheme 2. Scale-up of the Br/Na-exchange reaction using 2-bromopyridine (**7a**), (2-ethylhexyl)sodium (**1**) as exchange reagent and benzophenone (**5a**) as electrophile, applying in-line quenching conditions.

Apart from halogen/lithium-exchanges, alkyllithiums are frequently used in directed metalations converting readily available arene starting materials into highly reactive aryllithiums, therefore allowing the functionalization of previously unreactive aromatic C–H bonds.^[21] We expected **1** to behave similarly, and indeed without changing the set-up of the continuous flow procedure, (2-ethylhexyl)sodium (**1**) was able to metalate benzothiophene (**10a**) resulting in the corresponding sodium species **11a**.^[22] Quenching with carbonyl electrophiles **5m**, **5c**, and **5g** gave the expected products **12am**, **12ac** and **12ag** in 73–87% yield (Table 3). Imidazole **10b** was metalated similarly and subsequent batch quench gave the products **12bl**, **12bd** and **12bf** in 55–79% isolated yield. The electron rich 1,3-dimethoxybenzene (**10c**) was converted to the arylsodium **11c**. Trapping with ketone **5m** or disulfide **5p** gave the desired products **12cm** and **12cp** in 86–88% yield. Additionally, transition metal free Wurtz-type coupling,^[23] with iodoctane (**5q**) gave the alkylated product **12cq** in 46% yield.

In summary, we have reported the on-demand generation of sodium metal free, hexane-soluble (2-ethylhexyl)sodium from 3-(chloromethyl)heptane using a sodium-packed-bed reactor in a commercially available continuous flow set-up. The procedure avoids storage of alkyllithium species and limits the handling of metallic sodium to a minimum. (2-Ethylhexyl)sodium was used for in-line sodiations and Br/Na-exchange reactions. The resulting arylsodiums were subsequently trapped with various electrophiles such as ketones, aldehydes, Weinreb-amides, imines, allyl bromides, disulfides and alkyl iodides. A reaction scale-up of the Br/Na-exchange using an in-line electrophile quench was reported. Further

Table 3: On-demand preparation of alkyllithium reagent **1** from alkyl chloride **2** followed by directed metalation of (hetero)arenes of type **10** leading to (hetero)arylsodiums of type **11** and subsequent batch quench with electrophiles of type **5** leading to products of type **12**.



Yields of analytically pure products. [a] From the Weinreb-amide. [b] 2.0 equiv E-X were used [c] From the disulfide. [d] From the alkyl iodide.

investigations on the use of alkyllithium reagents are currently under way in our laboratories.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Br/Na-exchange · directed sodiation · flow chemistry · packed-bed reactor · sodium

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