Continuous Flow Sodiation of Substituted Acrylonitriles, Alkenyl Sulfides and Acrylates

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Abstract: The sodiation of substituted acrylonitriles and alkenyl sulfides in a continuous flow set-up using NaDA (sodium diisopropylamide) in EtNMMe₂ or NaTMP (sodium 2,2,6,6-tetramethylpiperidide)-TMEDA in n-hexane provides derivatized acrylonitriles and alkenyl sulfides, which are subsequently trapped in batch with various electrophiles such as aldehydes, ketones, disulfides and allylic bromides affording functionalized acrylonitriles and alkenyl sulfides. This flow procedure was successfully extended to other acrylates by using Barbier-type conditions.

The metalation of unsaturated nitriles and sulfides is an important synthetic procedure. After quenching with various electrophiles, highly functionalized unsaturated products are obtained, which may be useful building blocks for biologically active heterocycles and natural products. The batch-metalation of alkynyl nitriles or sulfides with lithium or potassium amides may avoid such limitations. However, the use of stronger, more polar bases like sodium or potassium amides may avoid such limitations. Moreover, the use of sodium organometallics is much less convenient bases for the regioselective flow-metalation of various unsaturated compounds is much less explored. The use of sodium organoaluminates is of high interest due to the low price, high abundancy and low toxicity of sodium salts. Recently, aryllithium compounds have been prepared by Collum using NaDA (sodium diisopropylamide) as deprotonating agent and by Asako and Takai, who have investigated the utility of aryllithiums in catalytic cross-couplings. Yoshida, Ley, Organ and others have demonstrated a high functional group tolerance performing challenging metalations in a continuous flow set-up. Based on these studies, we have extended the Collum procedure to the preparation of sodiated aryl and heteroaryl derivatives which are difficult to generate otherwise and decompose upon batch-sodiation. KDA-TMEDA (potassium diisopropylamide-N,N,N',N'-tetramethylethylenediamine) in n-hexane was used in continuous flow for similar metalations. Herein, we wish to report that NaDA and NaTMP (TMPh = 2,2,6,6-tetramethylpiperidine) were efficient bases for the regioselective flow-metalation of various substituted acrylonitriles and alkenyl sulfides. In first experiments, we have optimized the sodiation of cinnamoni- trile (1a) and have found that metatalation with NaDA (0.24 m in DMEA (dimethyl ethylamine), 1.2 equiv) at −78°C using a combined flow-rate of 10 mL min⁻¹ and a 0.02 mL reactor proceeded best with a residence time of 0.12 s affording organosodium 2a. Subsequent trapping with electrophiles of type 3 such as aldehydes, ketones, disulfides and allylic bromides afforded 2-substituted cinnamimotrienes of type 4 with usually high E/Z ratios (Table 1, entries 1–10). Thus, for a quenching with aromatic aldehydes, we obtained the Z-product of type 4 as major product, whereas for more sterically hindered ketones the E-product was formed.

The diastereoselectivity of products of type 4 obtained after the addition to a carbonyl electrophile was tentatively explained by assuming that the sodiated nitrile 2a reacted fast with an aldehyde (RCHO) according to pathway A leading to the allylic alcohol Z-4. In contrast, by using ketones, an equilibration to the cummulene form 2a' may occur and the cyclic transition state B would be disfavoured due to steric hindrance. E/Z isomerization of the cummulene structure 2a' occurred affording the E-product via transition state B (Scheme 1).

We have then extended this flow procedure to various functionalized arylacronitriles of type 5. Electron-rich cinnamimotriene derivatives (5a–5d) were selectively metalated in 2-position using NaDA in a continuous flow set-up within 0.12 s at −78°C. The resulting organosodiums (6a–d) were trapped in batch with various carbonyl electrophiles, such as m-anisaldehyde (3k), cyclohexanecarboxaldehyde (3i) or cyclohexanone (3m), and with 3-bromocyclohexene.
Table 1: Sodiation of cinnamonitrile (1a) using a microflow reactor and subsequent batch quench of the intermediate sodium organometallic 2a with various electrophiles of type 3 leading to functionalized cinnamonitriles of type 4.

| # | electrophile | product[^a] | # | electrophile | product[^a] |
|---|--------------|-------------|---|--------------|-------------|
| 1 | 3a           | 4aa: 95%, Z/E > 99/1[^b] | 6 | 3f           | nBu₂S₂       |
| 2 | 3b           | 4ab: 92%, Z/E > 99/1[^b] | 7 | 3g           | 4ag: 82%, E/Z > 99/1[^b] |
| 3 | 3c           | 4ac: 74%, Z/E = 89/1[^b] | 8 | 3h           | 4ah: 82%, E/Z > 99/1[^b] |
| 4 | 3d           | 4ad: 93%, Z/E > 99/1[^b] | 9 | 3i           | 4ai: 78%, E/Z > 99/1[^b] |
| 5 | 3e[^i]       | 4ae: 93%, E/Z = 9/1[^b]   | 10| 3j           | 4aj: 87%, E/Z > 99/1[^b] |

[^a] Yield of analytically pure product.  
[^b] The E- or Z-diastereoselectivity was assigned in analogy to related products, for which X-ray data were obtained.  
[^c] The diastereoselectivity was determined by crystal structure analyses, see Supporting Information.  
[^d] 10 mol % CuCN·2LiCl.

(3e) using 10 mol % CuCN·2LiCl as catalyst, affording the desired alcohols (7ak, 7bk, 7cl and 7dm) and an allylated cinnamonitrile derivative (7de) in 57–97% yield with diastereomeric ratios up to > 99/1 (Table 2, entries 1–5). Similarly, regioselective sodiation of electron-deficient 3-(4-(trifluoromethyl)phenyl)acrylonitrile (5e) followed by copper-catalyzed allylation with 3-bromocyclohexene (3e) led to the functionalized phenacylnitrile (7ee) in 66% yield with an E/Z ratio > 99/1. Furthermore, an extension to methoxy- and ethoxyacrylonitriles (5f and 5g) was possible resulting in secondary alcohols (7fn, 7fd, 7gc and 7gl) after batch-quench with aliphatic aldehydes (3c, 3d and 3n), and aliphatic aldehyde (3l) in 91–98% and Z/E ratios > 99/1 (entries 7–10). An alkenyl sulfide such as phenyl-(styrly)sulfane (5h) provided the sodium derivative (6h) upon metalation with NaDA, which after trapping with sterically demanding ketones such as adamantanone (3o) and benzophenone (3g) gave tertiary alcohols (7ho and 7hg) in 85–95% yield and comparable E/Z ratios to the starting material 5h (entries 11–12).

Extension to alkyl-substituted acrylonitriles such as geranyl nitrile (8a, E/Z = 50/50) and the related nitrile 8b (E/Z = 65/35) was possible under the standard sodiation conditions providing after electrophilic quench the desired functionalized nitriles (10ap, 10al, 10aq, 10br) in 60–98% yield as E/Z mixtures (Table 3, entries 1–4). Interestingly, starting from the diastereomERIC ally substituted acrylonitrile 8c (E/Z > 99/1) the desired product 10ca was obtained in 67% yield (Z/E = 58/42) after quench with α-tetralone (3q) (entry 5) showing the prevalence of the cumulene structure of the sodiated nitrile (see 2a’ in Table 1). However, the methoxy-substituted acrylonitrile 8d (E/Z = 80/20) afforded after continuous flow sodiation and quenching with α-anisaldehyde (3k) the allylic alcohol 10dk as single diastereoisomer in 58% yield (Z/E > 99/1) showing the importance of the methoxy group for controlling the stereochemistry of the intermediate sodiated nitrile (entry 6). Also, the dienyl nitrile 8e was sodiated in flow and trapping with an allylic bromide (3e) or an aldehyde (3k) furnished the functionalized dienyl nitriles (10ee and 10ek) in 74–82% yield (entries 7–8).

Recently, Takai and Asako published a straightforward synthesis of lithium-free sodium 2,2,6,6-tetramethylpiperidine (NaTMP) in n-hexane by using sodium dispersion, TMPH, TMEDA and isopropene.[12] This method would allow us to avoid the use of the amine DMEA as solvent and therefore making our method more practical. Using the Takai procedure, we have prepared hexane-soluble NaTMP-TMEDA[13] and have performed an efficient continuous flow sodiation of cinnamonitrile (1a) selectively in 2-position within 0.12 s at −78°C. A subsequent batch trapping of 2a’ with various ketones of type 3 afforded the desired tertiary alcohols of type 4 in 58–83% yield as single regioisomers (Scheme 2). Similarly, ethoxyacrylonitrile 5g gave, after batch quench with α-anisaldehyde (3k) and benzophenone (3g), the allylic alcohols (7gk and 7gg) in 65–78% yield (Z/E > 99/1). Further, geranyl nitrile (8a) provided the organosodium 9a upon metalation with NaTMP-TMEDA, which after a copper-catalyzed allylation using 3-bromocyclohexene (3e) led to the desired product (10ae) in 54% yield with an E/Z ratio of 52/48.

However, the sodiation of other acrylics still remained challenging. Applying our standard sodiation method to ethyl cinnamate (11a) afforded solely the condensation product 13a showing that the sodiation of 11a was possible, but difficult to control. Thus, the intermediate organosodium 12a reacted instantaneously with another molecule of 11a before the desired electrophile quench proceeded (Scheme 3a). To prevent this self-condensation reaction, sterically hindered tert-butyl cinnamate (11b) was used affording organosodium 12b after continuous flow sodiation. A copper-catalyzed batch allylation with 3-bromocyclohexene (3e) gave the desired product 13be in 61% yield with an E/Z ratio > 99/1 (Scheme 3b). To overcome the need of sterically hindered esters, we envisioned a Barbier-type in situ trapping[14] of the
highly reactive organosodiums of type 12. Interestingly, ethyl cinnamate (11a), which underwent self-condensation side reactions applying our standard flow conditions (Scheme 3a), was sodiated at $-78^\circ$C under Barbier-conditions and afforded organosodium 12a, which was instantaneously trapped by adamantanone (3o), outcompeting self-condensation and resulting in the tertiary alcohol 13ao in 66% yield ($E/Z > 99/1$). Similarly, methyl-3-methoxyacrylate (11c) was sodiated in 3-position in the presence of adamantanone (3o) using NaDA (1.2 equiv) affording the spirolactone 13co in 58% yield (Scheme 3c).

In summary, we have reported the sodiation of substituted acrylonitriles and alkenyl sulfides in a continuous flow set-up using NaDA (sodium diisopropylamide) in EtNMe$_2$ (DMEA) and NaTMP (sodium 2,2,6,6-tetramethylpiperidide)-TMEDA.

Table 2: Sodiation of substituted acrylonitriles and alkenyl sulfides of type 5 using a microflow reactor and subsequent batch quench of the intermediate sodium organometallics of type 6 with various electrophiles of type 3 leading to functionalized phenylacrylonitriles and alkenyl sulfides of type 7.

| # | SM product$^a$ | # | SM product$^a$ |
|---|---|---|---|
| 1 | 5a E/Z = 76/24 | 7 | 5f E/Z = 83/17 |
| 2 | 5b E/Z = 79/21 | 8 | 5f E/Z = 83/17 |
| 3 | 5c E/Z = 83/17 | 9 | 5g E/Z = 68/32 |
| 4 | 5d E/Z = 79/21 | 10 | 5g E/Z = 68/32 |
| 5 | 5d$^b$ E/Z = 79/21 | 11 | 5h E/Z = 71/29 |

[a] Yield of analytically pure product. [b] The $E$- or $Z$- diastereoselectivity was assigned in analogy to related products, for which X-ray data were obtained. [c] The diastereoselectivity was determined by crystal structure analyses, see Supporting Information. [d] 10 mol% CuCN·2LiCl.
The resulting sodiated acrylonitriles and alkenyl sulfides were subsequently trapped in batch with various electrophiles of type 3 leading to functionalized alkyl- and alkenyl-substituted acrylonitriles of type 10.

### Table 3: Sodiation of alkyl- and alkenyl-substituted acrylonitriles of type 8 using a microflow reactor and subsequent batch quench of the intermediate sodium organometallics of type 9 with various electrophiles of type 3 leading to functionalized alkyl- and alkenyl-substituted acrylonitriles of type 10.

| # | substrate | electrophile | product[a] |
|---|-----------|--------------|------------|
| 1 | 8a, E/Z = 50/50 | 3p | 10ap: 75%, Z/E = 68/32 |
| 2 | 8a, E/Z = 50/50 | 3l | 10al: 60%, Z/E = 64/36 |
| 3 | 8a, E/Z = 50/50 | 3q | 10aq: 98%, Z/E = 53/47 |
| 4 | 8b, E/Z = 65/35 | 3r | 10br: 85%, Z/E = 55/45 |
| 5 | 8c, E/Z > 99/1 | 3q | 10cq: 67%, Z/E = 58/42 |
| 6 | 8d, E/Z = 80/20 | 3k | 10dk: 58%, Z/E > 99/1 |
| 7 | 8e, E/Z = 69/31 | 3e[1] | 10ee: 74%, E/Z = 77/23 |
| 8 | 8e, E/Z = 69/31 | 3k | 10ek: 82%, Z/E = 76/24 |

[a] Yield of analytically pure product. [b] 10 mol% CuCN·2LiCl.

in n-hexane. The resulting sodiated acrylonitriles and alkenyl sulfides were subsequently trapped in batch with various electrophiles such as aldehydes, ketones, disulfides and allylic bromides affording functionalized acrylonitriles and alkenyl sulfides. This flow-procedure was successfully extended to other acrylates by using Barbier-type conditions.

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### Conflict of interest

The authors declare no conflict of interest.

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