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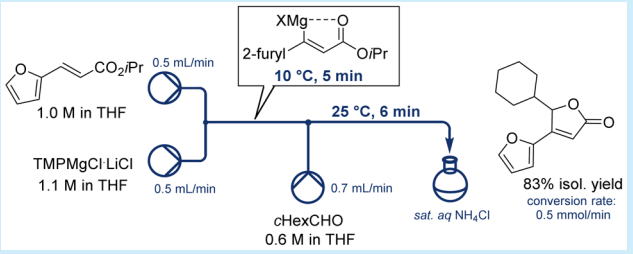
Continuous Flow Magnesiation or Zincation of Acrylonitriles, Acrylates, and Nitroolefins. Application to the Synthesis of Butenolides

Maximilian A. Ganiek, Matthias R. Becker, Marthe Ketels, and Paul Knochel*

Department of Chemistry, Ludwig-Maximilians-Universität, Butenandtstr. 5-13, 81377 Munich, Germany

Supporting Information

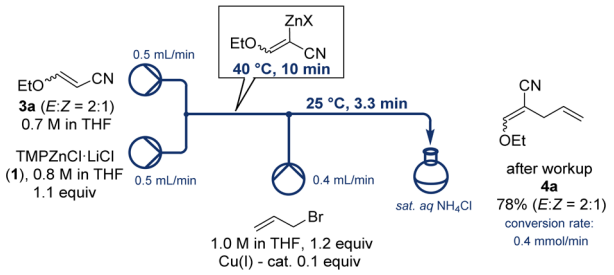
ABSTRACT: Scalable continuous flow procedures are reported for the metalation and downstream functionalization of β-substituted acrylates. The flow conditions allow the metalation of acrylonitriles, acrylates, and nitroolefins at 0.25−2.50 mmol/min conversion rates. Magnesiations can be performed with short residence times (1−20 min) and near-ambient temperature using TMPMgCl·LiCl. Further, high temperature zincation (≤90 °C) using TMPZnCl·LiCl is possible. This method allows a simple entry to 2(5*H*)-furanones by flow generation of magnesiated acrylates and a subsequent reaction with aldehydes.



The directed metalation of α,β-unsaturated carbonyl derivatives is an important reaction since, after quenching with various electrophiles, highly functionalized unsaturated products are obtained.[1] These compounds are useful building blocks for the synthesis of natural products and heterocycles,[2] many of which are biologically relevant, such as *tetronic acids*.[3] The lithiation of acrylate derivatives and nitroolefins is often complicated by polymerization and side reactions.[4] Hence, such lithiations are usually carried out at low reaction temperatures (−78 or −110 °C).[1a,4] The use of kinetically highly active bases such as TMPZnCl·LiCl[5] (**1**, TMPH = 2,2,6,6-tetramethylpiperidine), $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$,[6] or zincate bases[7] improves the stability of the organometallic intermediates but still requires low metalation temperatures.[8] The conduction of reactions under flow conditions often improves yields and selectivities.[9] Previously we have shown that continuous flow technology also dramatically improves metalation reactions.[10] Herein, we wish to report the use of TMPZnCl·LiCl[5] (**1**) and TMPMgCl·LiCl (**2**)[11] for the flow metalation and functionalization of various acrylates, acrylonitriles, and nitroolefins leading to, after quenching with various electrophiles, polyfunctional unsaturated products.

Our initial studies focused on the flow metalation of acrylonitriles and nitroolefins, which are notoriously known to polymerize under basic conditions. For instance, we found that 3-ethoxy-acrylonitrile (**3a**, *E*:*Z* = 2:1) was smoothly zincated at the α-position with TMPZnCl·LiCl (**1**) at 40 °C within 10 min in a flow apparatus[12] (Scheme 1). After an *in-line* quench with allyl bromide in the presence of a copper catalyst (10% CuCN·2LiCl),[13] the expected product **4a** (*E*:*Z* = 2:1) is obtained in 78% isolated yield. In contrast, a reported batch synthesis of **4a** using LDA for the metalation requires a −110 °C temperature for the lithiation and −110 to −50 °C for the subsequent allylation.[14]

Scheme 1. Zincation and Allylation of 3-Ethoxy-acrylonitrile (3a) in Continuous Flow



This zincation procedure has a broad scope (Table 1). Thus, allylation of zincated **3a** with 3-bromo-1-cyclohexene or Pd(0)-catalyzed Negishi cross-coupling[15−17] with 4-iodoanisole gave the expected products (**4b−c**) in 92−96% yield (entries 1−2). Furthermore, *E*-cinnamonitrile (**3b**) reacts smoothly with TMPZnCl·LiCl (**1**) at 90 °C[18] within 10 min, and after allylation the cinnamonitrile **4d** is obtained in 75% yield (entry 3). Repeating the allylation reaction on a 10 mmol scale does not require any reaction condition changes[19] and furnishes **4d** in an improved yield of 83% after a ca. 35 min reaction time and purification. Negishi cross-coupling[15,17] of α-zincated **3b** with 4-iodoanisole proceeds in flow within 25 min at 60 °C leading to the cinnamonitrile **4e** (99%, *E*:*Z* = 8:1, entry 4). Furthermore, quenching of zincated **3b** with benzaldehyde (10 min, 70 °C) produces the allylic alcohol in 63% as the single *E*-

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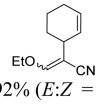
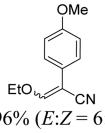
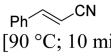
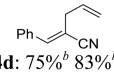
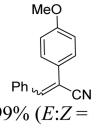
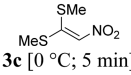
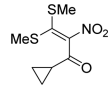
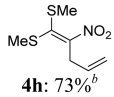
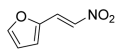
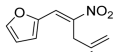
Table 1. Flow Zincation of Acrylonitriles and Nitroolefins (3) with TMPZnCl·LiCl (1) and *in-Line* Quenching with Electrophiles Leading to α-Functionalized Products (4)

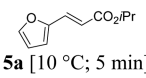
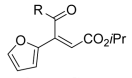
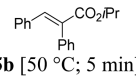
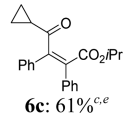
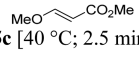
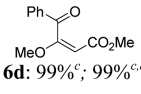
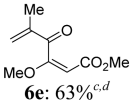
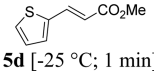
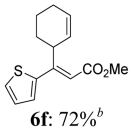
entry	substrate [metalation conditions]	electrophile	product[a]
1	**3a** [40 °C; 10 min]		 **4b**: 92% (*E*:*Z* = 2:1)[b,g]
2	**3a**		 **4c**: 96% (*E*:*Z* = 6:1)[c,g]
3	 **3b** [90 °C; 10 min]		 **4d**: 75%[b] 83%[b,f]
4	**3b**		 **4e**: 99% (*E*:*Z* = 8:1)[c,g]
5	**3b**	PhCHO	 **4f**: 63%[d]
6	 **3c** [0 °C; 5 min]		 **4g**: 64%[e]
7	**3c**		 **4h**: 73%[b]
8	 **3d** [25 °C; 3.3 min]		 **4i**: 78%[b]

[a]Yield of isolated product after column chromatographical purification. [b]Obtained by a Cu-catalyzed allylation.[13] [c]Obtained using 2 mol % $[Pd(dba)_2]$ and 4 mol % P(2-furyl)$_3$.[15] [d]Obtained by adding 10 mol % TMSCl to PhCHO. [e]Obtained by a Cu-catalyzed acylation.[13] [f]Yield on a 10 mmol scale. [g]Yield based on the amount of electrophile used.

stereoisomer (entry 5). The α-zincation of nitroolefins typically required temperatures from −50 to 0 °C under batch conditions.[8] We found that the zincation of nitroolefins **3c−d** proceeds under continuous flow conditions at 0−25 °C and leads to new α-functionalized nitroolefins (**4g−i**) after *in-line* allylation or acylation (entries 6−8).

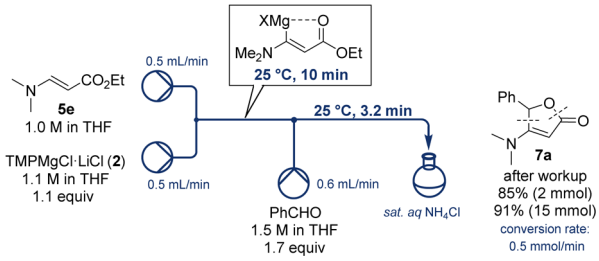
Acrylic esters require stronger bases such as TMPMgCl·LiCl (**2**) in order to undergo efficient metalation.[8] Thus, β-magnesiation occurs readily without notable isomerization, polymerization, or attack of the ester if short flow residence times and temperatures between 10 and 50 °C (Table 2, entries 1−5) were used. For instance, β-(2-furyl) acrylate (**5a**) is cleanly β-magnesiated at 10 °C within 5 min despite the presence of several acidic protons (on the furan ring[11a]). The thiophene analog (**5d**) in contrast required lower temperatures (≤20 °C) to suppress metalation of the heteroaromatic moiety. The resulting low conversion of **5d** at such low temperatures could not be increased with longer residence times (5 or 15 min). However, increased flow rates[20] (5 mL/min during mixing and metalation) triggered high conversion of **5d** and the desired allylated product **6f** was obtained in 72% yield in the presence of 5% CuCN·2LiCl[13] (entry 6).

Table 2. Flow Magnesiation of Acrylate Substrates (5) with TMPMgCl·LiCl (2) Followed by *in-Line* Allylation and Acylation Leading to β-Functionalized Products (6)

entry	substrate [metalation conditions]	electrophile	product[a]
1	 **5a** [10 °C; 5 min]	cC_3H_5COCl	 **6a**: *c*-C_3H_5: 69%[c,e]
2	**5a**	*t*BuCOCl	**6b**: *t*-Bu: 68%[c,e]
3	 **5b** [50 °C; 5 min]	cC_3H_5COCl	 **6c**: 61%[c,e]
4	 **5c** [40 °C; 2.5 min]	PhCOCl	 **6d**: 99%[c]; 99%[c,d]
5	**5c**		 **6e**: 63%[c,d]
6	 **5d** [-25 °C; 1 min]		 **6f**: 72%[b]

[a]Yield of isolated product after column chromatographical purification. [b]Obtained by a Cu-catalyzed allylation.[13] [c]Obtained by a Cu-catalyzed or Cu-mediated acylation.[13] [d]15 mmol scale. [e]Yield based on the amount of electrophile used.

Scheme 2. Flow Synthesis of Furan-5*H*-one (7a) from Acrylate (5e)



To broaden the scope of the flow metalation/quenching sequence, we have investigated acylations of magnesiated acrylates with acid chlorides (entries 1−5). Remarkably, after optimization of the flow reaction conditions (temperature, flow rate, residence time, and catalyst loading) the preparation of highly electrophilic Michael acceptors such as **6a−e** was performed without substantial polymerization. Thus, the flow rates chosen for the benzoylation of **5c** allow the production of ca. 1 mmol of product (**6d**) per min (entry 4). Running the benzoylation of **5c** for 15 min gives 15 mmol of enone ester **6d** in 99% yield after isolation, confirming the good scalability[19] of this method. Interestingly, the acylation of magnesiated **5c** with methacrylol chloride allows the synthesis of the methyl ester of

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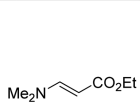
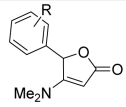
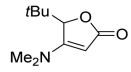
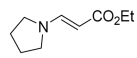
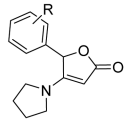
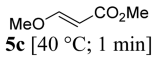
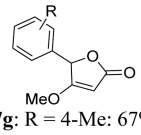
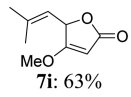
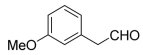
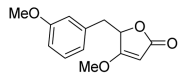
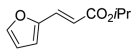
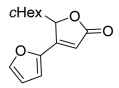
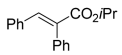
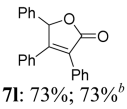
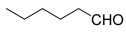
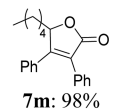
Table 3. Synthesis of Butenolides (7) by Magnesiation of Acrylates (5) and Quenching with Aldehydes in Flow

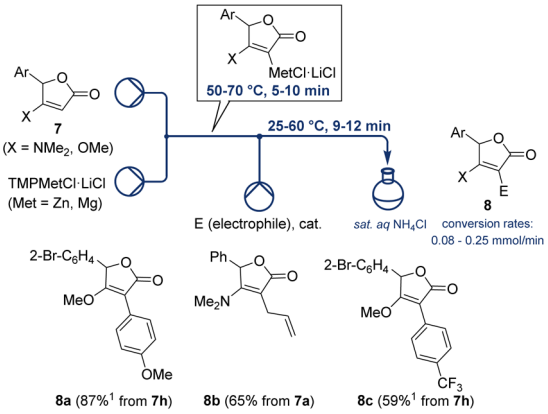
entry	substrate [metalation conditions]	electrophile	product[a]
1	 **5e** [25 °C; 10 min]	 R = 4-Cl	 **7b**: R = 4-Cl: 64%
2	**5e**	R = 3-OMe	**7c**: R = 3-OMe: 79%
3	**5e**	*t*BuCHO	 **7d**: 81%
4	 **5f** [25 °C; 10 min]	 R = 2-Br	 **7e**: R = 2-Br 70%
5	**5f**	R = 4-SMe	**7f** : R = 4-SMe: 67%
6	 **5c** [40 °C; 1 min]	 R = 4-Me	 **7g**: R = 4-Me: 67%
7	**5c**	R = 2-Br	**7h**: R = 2-Br: 61%; 67%[b]
8	**5c**		 **7i**: 63%
9	**5c**		 **7j**: 65%
10	 **5a** [10 °C; 5 min]	*c*HexCHO	 **7k**: 83%[c]
11	 **5b** [50 °C; 5 min]	PhCHO	 **7l**: 73%; 73%[b]
12	**5b**		 **7m**: 98%

[a]Yield of isolated product after column chromatographical purification. Quenching with the electrophile was performed at 25 °C. [b]Yield on a 10 mmol scale. [c]Yield based on the amount of electrophile used.

penicillic acid[21] in 63% yield (entry 5). Applying fast flow rates (5 mL/min) during the acylation suppressed in this case side reactions to an acceptable extent.[20]

Many butenolides are biologically active,[3] and their synthesis by the addition of β-metalated acrylates to aldehydes is well-known.[1a,2a,4b−d] Whereas β-lithiated acrylates often give low yields upon addition to an aldehyde,[4b,c] their β-magnesiated counterparts react smoothly to the desired products.[8] For example, *E*-ethyl 2-dimethylamino acrylate (**5e**) is quantitatively magnesiated with TMPMgCl·LiCl (**2**) at room temperature within 10 min in continuous flow (Scheme 2).

Scheme 3. Synthesis of 3,4,5-substituted Butenolides (8) by Continuous Flow Metalation of the 3-Position



[1]Yield based on the amount of electrophile used.

In-line quenching with benzaldehyde leads to butenolide **7a** (85−91%) after lactonization (Scheme 2). This butenolide synthesis has a broad scope, and a range of furan-2(5*H*)-ones (**7b−m**) have been prepared in an analogous manner in 61−98% yield (Table 3). Electron-poor and -rich aromatic aldehydes (entries 1−2; 4−5), as well as α,β-unsaturated (entry 8), benzylic (entry 9), or aliphatic aldehydes (entries 3, 10, 12) were used as electrophiles. Scaling up of the reactions leading to **7h** and **7l** to 10 mmol (entries 7 and 11) proceeded without loss of yield after reaction times of 4 min (**7h**) and 40 min (**7l**). Since furan-2(5*H*)-ones with substituents in the 3-position are occurring in bioactive molecules,[3] we have further developed flow metalations of butenolides **7** (Scheme 3) in this position. Thus, the high temperature zincation (70 °C, 5 min) of butenolide **7h** using TMPZnCl·LiCl (**1**) leads to bisarylic tetronates **8a** and **8c** in 59−87% yield after cross-coupling[15,16] with the corresponding aryl iodides (Scheme 3). Furthermore, magnesiation (50 °C, 10 min) of **7a** was achieved with TMPMgCl·LiCl (**2**), leading to the corresponding 3,4,5-substituted butenolide (**8b**) after Cu(I)-catalyzed allylation[13] in 65% yield. This method offers novel substitution patterns under mild and practical conditions and employs easily accessible starting materials.

In summary, we have demonstrated a practical flow magnesiation and zincation of acrylate derivatives allowing the synthesis of highly substituted unsaturated molecules and butenolides of potential biological relevance. Despite the sensitive nature of some intermediates, flow technology enables the use of high temperatures without the production of extensive amounts of side products. The scale-up of these reactions is achieved without any further optimization by running the flow reactions for longer time periods. In some cases, a beneficial effect of working at high flow rates (≥5 mL/min)[20] was noted. Further extensions to the flow metalation of sensitive substrates are currently being investigated in our laboratories.

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■ ASSOCIATED CONTENT

Supporting Information

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Detailed experimental procedures and characterization data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: paul.knochel@cup.uni-muenchen.de.

Notes

The authors declare no competing financial interest.

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