A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

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Accepted Article

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Authors: Maximilian Andreas Ganiek, Maria Vladislavovna Ivanova, Benjamin Martin, and Paul Knochel

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201810158
Angew. Chem. 10.1002/ange.201810158

Link to VoR: http://dx.doi.org/10.1002/anie.201810158
http://dx.doi.org/10.1002/ange.201810158

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10.1002/anie.201810158

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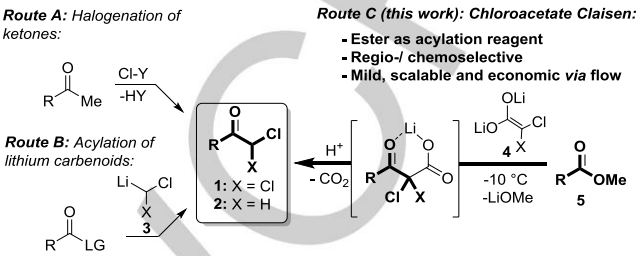
Mild Homologation of Esters *via* Continuous Flow Chloroacetate Claisen Reactions

Maximilian A. Ganiek, Maria V. Ivanova, Benjamin Martin* and Paul Knochel*

Abstract: The selective chloromethylenation of functionalized esters using chloroacetic acid (CA) and LiHMDS (HMDS = hexamethyldisilazide) in a continuous flow setup is reported. This Claisen homologation is for the first time extended to bis-chloromethylenation using dichloro-acetic acid (DCA), thus giving access to under-explored *α*,*α*'-bis-chloroketones. The use of flow conditions enables an efficient generation and reaction of the unstable chloroacetate dianion intermediates, leading to unprecedented mild and scalable reaction conditions at an economic reagent stoichiometry (-10 °C, < 1 min, 1.0–2.4 equiv. dianion). The clean reaction profiles allows the subsequent use of the unpurified crude products, which is demonstrated in the synthesis of various heterocycles of broad interest. Furthermore, we report a novel, catalyst-free substitution of the obtained monochloro ketone products with (hetero)aryl zinc enolates leading to valuable 1,4-diketones.

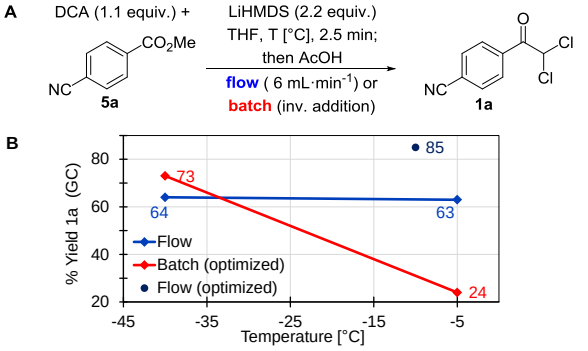
Mono- and bis-*α*-chloro ketones are useful bis-electrophiles (C-Cl and C=O; compare **1**, X = Cl and **2**, X = H, Scheme 1), which accounts for their widespread use, particularly in cyclocondensations leading to heterocycles.[1] Such cyclizations of functionalized precursors are cost-economic, avoid challenging cross-coupling steps and transition metal purging,[2] thus making novel approaches to pre-functionalized *α*-chloro ketones **1** and **2** an attractive goal. The halogenation of ketones[4] requires dealing with challenging waste streams, toxic reagents and corrosivity, especially on scale (**Route A**, Scheme 1).[5] Furthermore, such halogenations are known to suffer from low regioselectivity, multiple halogenation, and incompatibilities with several common functionalities.[4,6] In contrast, the acylation of lithium carbenoids of type **3** allows avoiding the issues of site-selectivity mono- or bis-chlorination *a priori* (**Route B**). Recent research in lithium carbenoid chemistry by *Pace* and others has underlined the possibilities of such an approach.[7] Due to the thermal instability of the involved lithium carbenoid species,[7a] several flow protocols were devised to enhance the practicality of halomethyl lithium chemistry.[8] However, several drawbacks of **Route B** will remain: (i) halomethyl lithium reagents are incompatible with a number of electrophilic functionalities; (ii) the availability of pro-nucleophiles like CH_2ClBr is increasingly restricted due to environmental legislation;[9] (iii) monohalo-homologation leading to chloroketones **1** usually requires the use of special acylating agents to avoid overaddition.[7b,e,g] From a standpoint of maximizing functional group-tolerance, minimizing environmental impact and using broadly available starting materials, a chloroacetate *Claisen* ester homologation (**CAC**, **Route C**) would provide an attractive alternative.[10]



Scheme 1. Different routes towards *α*-chloroketones (**1**, **X** = **H**) and bis-*α*,*α*'-chloroketones (**1**, **X** = **Cl**).

In this *Claisen*-type homologation, chloroacid lithium dianions (**4**) undergo acylation with esters (**5**). The primary addition product liberates CO_2 after the workup and thereby excludes over-addition to, or enolisation of, **1** and **2**.[7b,8b] However an inspection of literature-known applications of dianions **4** suggests their use in stoichiometric excess (up to 4 equiv.) at cryogenic conditions (-78 °C for hours).[11] Furthermore, despite the above mentioned potential, compatibility with sensitive functional groups or extension beyond mono-chloro ketones **1** was not yet demonstrated. Based on our previous experience[12] and inspired by innovative flow chemistry applications,[13] we report that the use of a flow reactor enables highly chemoselective **CAC** reactions under attractive conditions through the improved handling of exothermic reactions.

Preliminary batch experiments showed that 4-cyano methylbenzoate (**5a**) readily undergoes **CAC** homologation with DCA (1.1 equiv) and LiHMDS (2.2 equiv), leading to chloroketone **1a** after quenching with AcOH (Scheme 2A).



Scheme 2. Performance comparision of flow and batch reactors in the dichloromethylenation of 4-cyano methylbenzoate (**5a**).

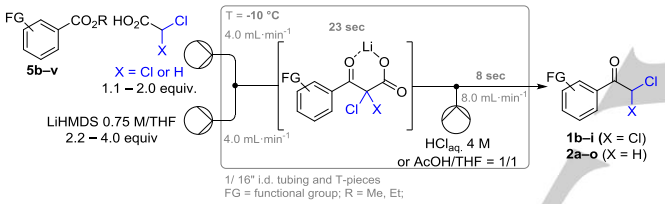
Batch optimization of this model reaction[14] provided **1a** in a maximum GC-yield of 73%, if a mixture of **5a** and DCA (1.1 equiv., 0.6 M) in THF was added dropwise to a LiHMDS solution (2.2 equiv., 0.75 M in THF) in a -40 °C cooling bath over 1.0 min, followed by 1.5 min stirring and addition of an excess of AcOH in one portion (Scheme 2B). Significant yield drops were observed at higher temperatures, which is likely due to the limited heat removal capacity of the batch reactor. In contrast,

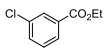
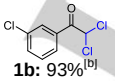
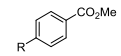
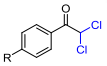
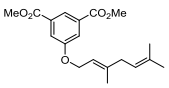
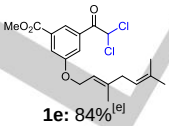
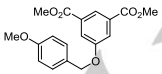
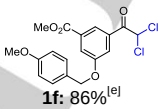
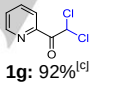
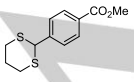
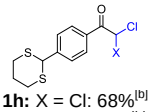
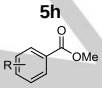
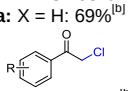
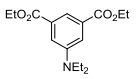
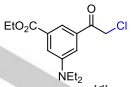
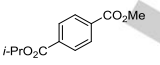
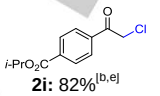
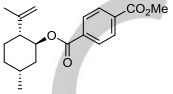
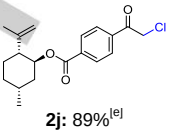
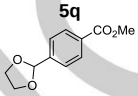
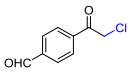
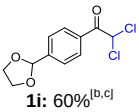
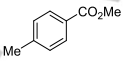
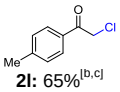
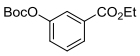
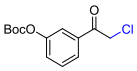
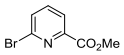
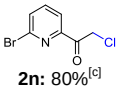
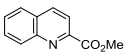
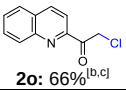
[*] M. A. Ganiek, Dr. Maria V. Ivanova, Prof. Dr. P. Knochel, Ludwig-Maximilians-Universität München, Department Chemie
Butenandtstrasse 5-13, Haus F, 81377 München (Germany)
E-mail: paul.knochel@cup.uni-muenchen.de
Dr. B. Martin
Novartis Pharma AG, Chemical Development, Fabrikstrasse, 4002 Basel, Switzerland
E-mail: benjamin.martin@novartis.com

10.1002/anie.201810158

by transferring the reaction to a flow setup with *in-line* acidic quench the yield of **1a** was unchanged at either -40 °C or -5 °C at a 6 mL·min^{-1} total flowrate and 2.5 min residence time.[15] Shortening of the residence time to 23 sec and increasing the total flow rate to 16 mL·min^{-1} improved the yield of **1a** further to 85% GC-yield (81% isolated).[14] With these optimized conditions established, the chemoselectivity of the **CAC** protocol was tested (Table 1). Ethyl esters such as **5b** can be employed yielding the dichloroketone **1b** in 93% yield (entry 1). Furthermore, sensitive electrophilic functional groups like an additional ester or a nitro group remained untouched and gave the dichloroketones **1c–d** in 76–98% yield (entries 2–3). Pleasingly, functional groups which are reactive under halogenation conditions[6] such as allyl and benzyl ethers (**5e–f**) are tolerated by **CAC** bis-chlorohomologation (81–86%, entries 4–5). Also the (*iso*)-picolinate **5g** posed no challenge for bis-chloromethylenation after switching to an AcOH quench (92%, entry 6). Submitting dithiane[6] benzoic ester **5i** to either bis-chloromethylenation or monochloromethylation gave almost identical yields of the expected chloroketones **1h** and **2a** (68–69%, entries 7–8).

Table 1. Continuous flow chlorohomologation of aromatic esters **5b–w**, leading to bis-*α*-chloroketones **1b–i** or mono-chloroketones **2a–o**.



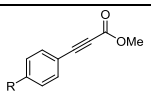
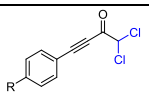
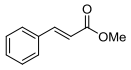
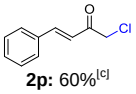
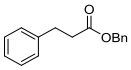
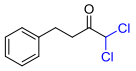
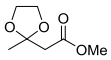
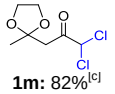
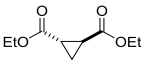
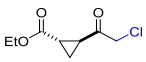
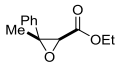
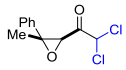
Entry	Ester	Chloroketone **1** or **2** [a]
1	 **5b**	 **1b:** 93%[b]
2	 **5c:** R = CO_2Me	 **1c:** 85%
3	**5d**: R = NO_2	**1d:** 76%
4	 **5e**	 **1e:** 84%[e]
5	 **5f**	 **1f:** 86%[e]
6	 **5g**	 **1g:** 92%[c]
7	 **5h**	 **1h:** X = Cl: 68%[b]
8	**5h**	**2a:** X = H: 69%[b]
9	 **5i:** R = 4-F	 **2b**, R = 4-F :98%[b]
10	**5j:** R = 4-Br	**2c**, R = 4-Br: 81%[b]
11	**5k:** R = 2,4-F	**2d**, R = 2,4-F: 81%[b]
12	**5l:** R = 3-CF_3	**2e**, R = 3-CF_3 : 96%[b]
13	**5m:** R = 4- CH_2Cl	**2f**, R = 4-CH_2Cl 80%[b]
14	**5n:** R =4-SCF_3	**2g**, R =4-SCF_3**:** 98%
15	 **5o**	 **2h:** 85%[d]
16	 **5p**	 **2i:** 82%[b,e]
17	 **5q**	 **2j:** 89%[e]
18	 **5r**	 **2k:** 71%
19	 **5r**	 **1i:** 60%[b,c]
20	 **5s**	 **2l:** 65%[b,c]
21	 **5t**	 **2m:** 76%
22	 **5u**	 **2n:** 80%[c]
23	 **5v**	 **2o:** 66%[b,c]

[a] Isolated yield on a 1.0–2.4 mmol scale. 1.1 equiv. dianion and *aq.* HCl were used. [b] 1.5–2.4 equiv dianion were used. [c] A solution of AcOH/THF = 1/1 v/v was used. [d] 3% of double ester homologation product was formed. [e] No addition to esters with secondary alcohol detected.

Additionally a range of *o-*,*m,*-and *p*-halogenated mono-chloroacetophenones and related CF_3-, SCF_3-, and CH_2Cl-bearing chloroketones **2b–g** were obtained in excellent yields, confirming the tolerance of aryl halogenides and the low acidity of reagent **4** (entries 9–14). Besides symmetrical diesters (**5c, e** and **5o**) also sterically biased (**5p–q**) diesters underwent a single homologation to the expected mono-chloroketones **2h–j** in 82–89% yield and excellent selectivity even in presence of intentionally added excess reagent (entries 15–17). More electron-rich benzoic esters **5r–t** required the use of >1.1 equiv. of dianion **4** to furnish the desired products **1i** and **2k–m** in satisfying yields of 60–76% (entries 18–21). Furthermore, by choosing between the different quench methods, the acetal of ester **5r** could be largely preserved (**1i**, 60%)[16] or removed *in-situ* to give the aldehyde (**2k,** 71%; entries 18–19). Finally, bromopyridine **5u** and quinoline **5v** furnished the heterocyclic chloroketones **2n-o** in 66–80% yield. In order to further broaden the scope of flow **CAC** reactions, various representative non-aromatic esters were subjected to the established reaction conditions (Table 2).

10.1002/anie.201810158

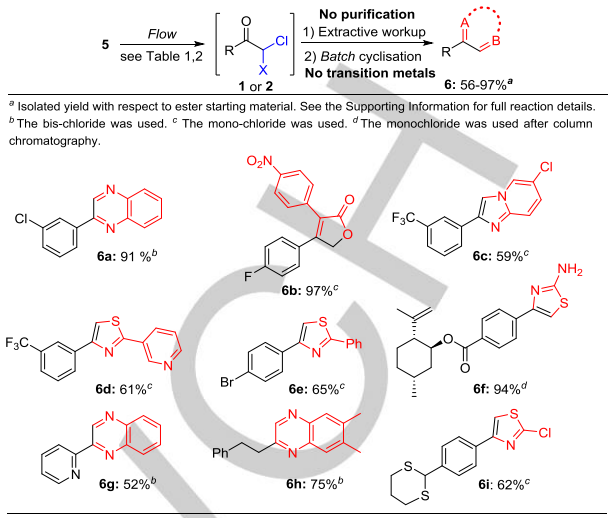
Table 2. Continuous flow **CAC** of non-aromatic esters **5w–ac**, leading to mono- or bis-α-chloroketones **1j–n** and **2p–q.**

Entry	Ester	Chloroketone **1** or **2** [a]
1	 **5w**, R = H	 **1j:** 96%
2	**5x**, R = NO_2	**1k:** 63%[b]
3	 **5y**	 **2p:** 60%[c]
4	 **5z**	 **1l:** 60%
	 **5aa**	 **1m:** 82%[c]
5	 **5ab**, *d.r.* = 99 : 1	 **2q:** 61%, , *d.r.* = 99 : 1[d]
6	 **5ac**, *d.r.* = 1.3 : 1.0	 **1n**: 45%, *d.r.* = 3.0 : 1.0[c]

[a] Isolated yield of analytically pure compound. 2.1–2.4 equiv. dianion and aqueous HCl were used if not stated otherwise. [b] 1.2 equiv dianion were used for homologation. [c] A solution of AcOH/THF = 1/1 v/v was used for quenching. [d] No double ester homologation product was detected.

Thus, propriolates **5w–x** were smoothly bis-chloromethylenated under standard conditions in 63–95% yield (entries 1–2). Likewise, vinylic ester **5v** and aliphatic ester **5z** underwent **CAC** mono- or bischloro homologation in 60% yield in the presence of excess reagent. Notably, the aliphatic homologation product **1m** shows a regioselectivity opposite to that of analogous halogenation reactions.[17] Furthermore, the cyclopropane *trans*-diester[18] **5ab** furnished the stereoisomerically pure cyclopropanoate **2q** in 61% yield. A related reaction with ethyl glycidate **5ac** (*d.r.* = 1.3:1.0) gave diastereochemically enriched *trans*-bis-chloroketone 1n (*d.r.* = 3.0:1.0) in 45% yield.

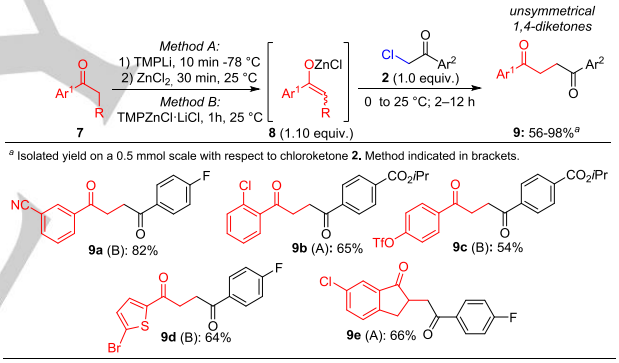
The clean profiles of the **CAC** reaction products allowed us to perform cyclocondensation reactions with the reaction crudes after a simple extractive workup (Scheme 3, yields with respect to the initial ester). Using this telescoped protocol, pharmaceutically relevant[19] heterocyclic compounds which are nitrogen-rich (**6a**; **d**; **g–h**), display advantageous halogenation for further manipulations (**6c**; **e**; **i**) or acidic protons (**6b**; **f**) were obtained in good to excellent yields (56–98%) over two steps. Notably, the cyclization precursors **1l**, **2a**, **2j**, which are challenging to obtain without **CAC** methods, were successfully transformed to **6f** and **6h–i** respectively in 52–98% yields. The use of chloroketones as cross-coupling electrophiles in the presence of common catalytically active metals is a known challenge.[21] Gratifyingly, we found that acetophenone-derived zinc enolates of type **8** underwent a selective substitution reaction with chloroketones **2** even in the absence of catalysts.



[a] Isolated yield with respect to ester starting material. See the Supporting Information for full reaction details. [b] The bis-chloride was used. [c] The mono-chloride was used. [d] The monochloride was used after column chromatography.

Scheme 3. Utilization of functionalized chloroketones **1** or **2** obtained as crude products (except **6f,** purified) in cyclisation reactions leading to heterocycles **6**.[20]

Thus, valuable polyfunctional 1,4-diketones **9a–e** were accessed in 54–82% yield under mild conditions (25 °C, 2–12 h Scheme 4).This method constitutes a straightforward, and to the best of our knowledge, novel synthesis of these important precursors to Paal-Knorr chemistry.



[a] Isolated yield on a 0.5 mmol scale with respect to chloroketone **2.** Method indicated in brackets.

Scheme 4. Utilization of functionalized chloroketones **2** in substitution reactions with zinc enolates **8** leading to functionalized 1,4-diketones **9**.[20]

In summary, the flow chloroacetate *Claisen* homologation method fills a methodological gap by converting highly functionalized esters to useful haloketones with excellent chemoselectivity. We demonstrated that the crude haloketones could then be converted into a variety of follow-up heterocyclic compounds of biological interest. Finally, a transition-metal free synthesis of polyfunctional 1,4-diketones was developed using **CAC** products as electrophiles.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (SFB 749, B2 and C6) for financial and Vapourtec for technical support. M. A. G. thanks the German Academic Scholarship Foundation for a fellowship. Helpful discussions with F. Venturoni, J. Sedelmeier and B. Schenkel (Novartis Pharma) are gratefully acknowledged.

Keywords: flow chemistry• chloroketones• homologation• Claisen reaction•

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[20] Additional examples are attatched to the Supporting Information.

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10.1002/anie.201810158

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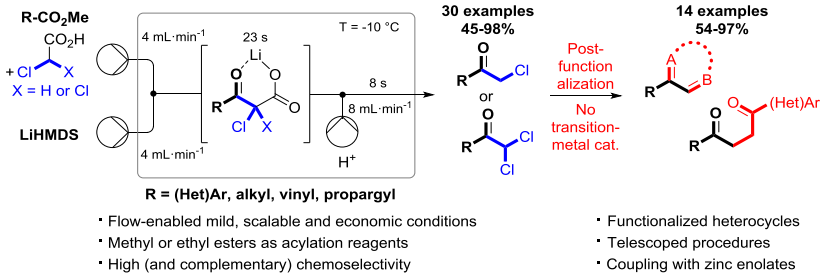

Maximilian A. Ganiek, Maria V. Ivanova, Benjamin Martin, Paul Knochel**
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Mild Homologation of Esters via Continuous Flow Chloroacetate Claisen Reactions

The highly chemoselective chloromethylenation of functionalized esters using (di)chloroacetic acid ((D)CA) and LiHMDS (HMDS = hexamethyldisilazide) in a continuous flow setup is reported. Flow conditions enabled an efficient handling of the reaction, leading to unprecedented scalability under mild reaction conditions and at an economic reagent stoichiometry (-10 °C, < 1 min, 1.0–2.4 equiv. dianion). The clean reaction profile allows the use of the unpurified crude products in various heterocycle syntheses. Additionally, a novel, catalyst-free substitution of monochloro ketones with (hetero)aryl zinc enolates is reported leading to valuable 1,4-diketones.