Chemistry—Methods
Research Article
doi.org/10.1002/cmtd.202500067
Chemistry Europe
European Chemical Societies Publishing

www.chemistrymethods.org

Sequential Ester Homologation–Nucleophile-Guided Functionalization: A Chemoselective Access to Thioesters, Amides, and Acids

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The homologation of esters—in the presence of a lithium carbenoid—to thioesters, amides, and carboxylic acid is reported. By controlling the tetrahedral intermediate collapsing and promoting a series of rearrangements ultimately leading to a high electrophilic ketene, the subsequent incorporation of S-, N-, and O-nucleophilic elements furnishes the title compounds. Despite the coexistence of multiple (concomitant) equilibria and short-living entities, the protocol features remarkable chemocontrol and flexibility. Notably, the formal oxidation state of the final compounds is retained.

1. Introduction

The insertion of a constant unit within an existing bond, usually referred as homologation, is a fundamental operation in chemical synthesis enabling to convert the *n*-th member of an organic skeleton into its *(n + 1)*-th analog.[1] The concept, first introduced in 1844 by C. Gerhardt,[2] constitutes nowadays a potent tool for the precise editing of organic molecules, thus finely tuning their key physical–chemical descriptors.[3] Pioneered by Arndt and Eistert employing diazomethane as the prototypal C1-delivery agent,[4] homologation methodologies can currently work under nucleophilic,[5,6] electrophilic,[7,8] or radical[9–13] regimes (**Scheme 1**a). From a mechanistic perspective, depending on the logic underpinning the process, the release of the methylene fragment can be followed either by the retention of the chemical functionality exhibited by the acceptor or, alternatively by its modification. The venerable Matteson homologation of boronic esters[14,15]—more recently adapted to design (stereocontrolled) iterative sequences as showcased by Aggarwal,[16–19] Dong,[20,21] and Blackmore[22,23]—illustrates the crucial role of 1,2-metalate rearrangements in C1-insertion processes (Scheme 1b).[24–27] Thus, the formation of a boron-*ate* complex through the release of a carbenoid—as the competent C1 source—is followed by the carbanion-shift leading to the homologated adduct featuring the initially present boron residue. The outcome of the homologative event is, however, imparted by the chemical nature of the recipient moiety.[5] In fact, when carbon-centered platforms (carbonyl and carboxylic derivatives) are used, the final products (epoxides or substituted ketones)—derived from the evolution of the corresponding intermediates—do not preserve the original functionalities,[28–30] thus making these processes homologations only *lato sensu* (Scheme 1c).[31–33] C. Kowalski and coworkers recognized that in case of forming an incipient α,α-dibromoketone from an ester and $LiCHBr_2$—the appropriate adoption of conditions enabling sequential enolate, β-oxido carbenoid, and ynolate formation (*vide infra*)—results in the formation of a ketene.[34–38] This highly electrophilic species[39] could be then intercepted by an alcohol (in acidic medium), therefore providing the homologated ester. It is significant to underline the conceptual analogy with the Arndt—Eistert homologation of a carboxylic derivative according to its Wolff-type variant,[40] also relying on the generation of a ketene.

Leveraging on our interest on C1-insertions into *sp*-hybridized systems,[41] we reasoned that the reaction of an ester and a carbenoid—in the presence of an *externally* added nucleophilic element—could offer a strategically convenient access to carboxylic congeners (thioesters, amides or esters), thus, introducing a methylene unit, followed by the permutation of the initially present ester group (Scheme 1d).[42] Two aspects of the proposed methodology are worth of highlighting: a) the transformation could be regarded as a homologative nucleophilic functionalization of the carboxylic derivative in which the constitutive sp^2-hybridized carbon undergoes a C1-insertion followed by a formal acyl substitution and, b) the oxidation state of the carboxylic group is not altered at the end of the process. As a consequence, it could be envisaged an homologative conversion of

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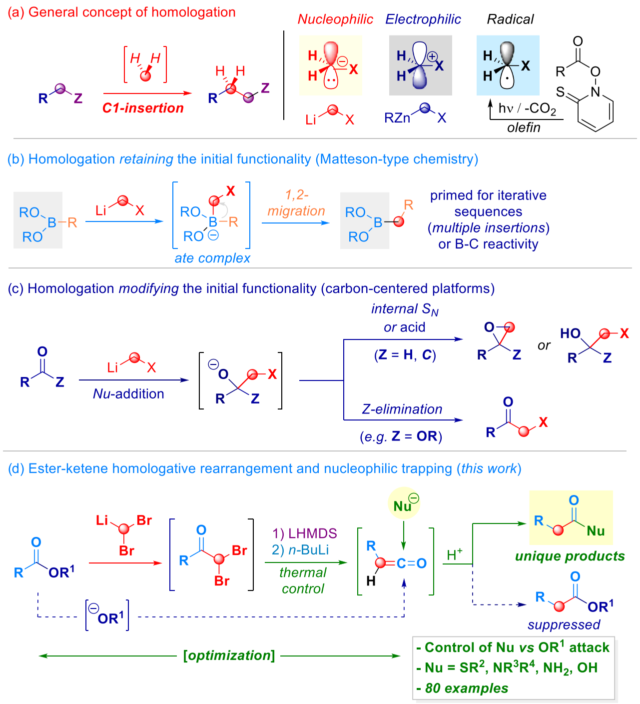
Supporting information for this article is available on the WWW under https://doi.org/10.1002/cmtd.202500067



Scheme 1. General context of the presented work.

starting esters into both more (e.g., *S*-analogs)[43–49] or less reactive (e.g., *N*- and *O*-ones) congeners.[50]

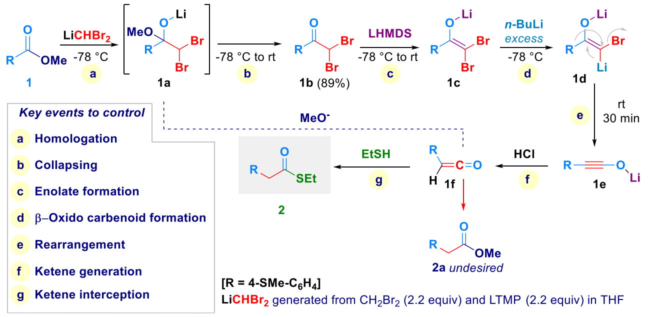
We anticipate the existence—as a consequence of the multiple equilibria and (de)-protonative events simultaneously existing during the rapid interconversion of short-lived and labile intermediates—of a complex scenario, in which the lastly added nucleophilic species should compete with the nucleophiles already present which could react with the ketene. To make productive the hypothesis, it is crucial to control the reactivity of the ketene toward the alkoxide (inherently present after the tetrahedral intermediate collapsing) and the external functionalizing nucleophile. Ideally, the former should be suppressed in favor of the latter. Through the analysis of the critical steps of the transformation, we report herein a divergent homologative protocol of carboxylic esters to thio-, nitrogen-, and oxo-analogs.

2. Results and Discussion

2.1. Reaction Design and Optimization

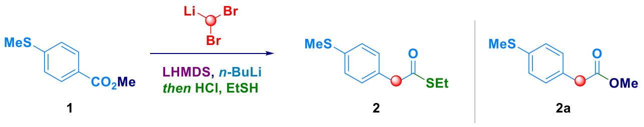
Cognizant of the concomitant intervention of (at least) seven chemical events, we discuss them separately, taking into account that optimizing the access to **1d** would dramatically simplify the protocol. This is due to the demonstrated possibility to reach it via alternative mechanisms[35,51] which are responsible for the presence of reactive species difficulty in the direct obtainment of **1d** (**Scheme 2**).

Methyl 4-(methylthio)benzoate (**1**) was selected as the model substrate for the homologative thioesterification in the presence of ethanethiol (**Table 1**).



Scheme 2. Analysis of the reaction mechanism.

Table 1. Optimization of the reaction stoichiometry.



Entry	*n*-BuLi [equiv]	EtSH [equiv]	HCl [equiv]	Yield of 2a [%][a]	Yield of 2 [%][a]
1	5.5	2	10	14	55
2	6	2	10	11	72
3	6.5	2	10	13	71
4	6	2.8	10	7	76
5	6	3.5	10	–	81
6	6	3.5	5	–	63
7	6	3.5	7	–	79
8	6	3.5	6	–	85

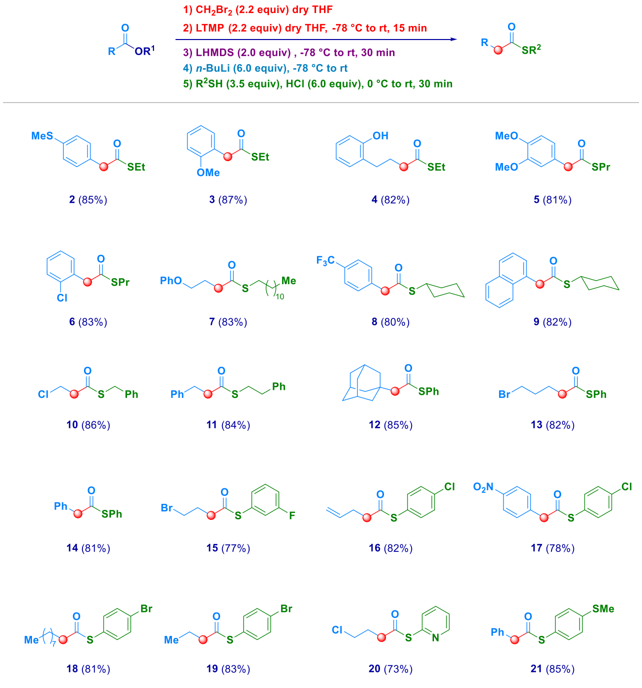
[a] Isolated yield.

i) By generating $LiCHBr_2$ according to our previously reported procedure starting from CH_2Br_2 and LTMP-LiBr (in THF at −78 °C),[52] intermediate **1a** was formed. ii) We considered that forcing its collapsing to dibromoketone **1b** could result in a more convergent access to the key carbenoid **1 d** (via enolate **1c**), being a thermal increase a strategically convenient operation for securing the purpose.[53] Notably, it would mitigate the risk of a steric-dependent collapsing,[54,55] thus establishing conditions of wide applicability. As a matter of fact, upon acidic quenching of the reaction mixture subjected to thermal increase (−78 °C to rt within 15 min) dibromoketone **1b** was obtained as the unique product in excellent yield after acidic quenching. iii) Next, we focused on controlling the enolate formation: after stirring the mixture containing dibromoketone for additional 15 min at rt, the temperature was dropped (again) to −78 °C prior to the addition of the base (lithium bis(trimethylsilyl)amide) to secure the formation of **1c**. iv) Subsequently (after 20 min), *n*-BuLi was employed to induce the key bromine-lithium exchange to give the β-oxido *sp*^{2}-type lithium carbenoid **1d**. Although the original Kowalski's protocol relied on two consecutive additions of *n*-BuLi at −78 °C,[53] separated by a thermal increase to 0 °C, we noticed the correct genesis of **1d** through a simplified technique consisting in realizing a *single* addition of *n*-BuLi (5.5 equiv) at −78 °C. It should be emphasized that the considerable stoichiometric excess of the organolithium is fundamental for enabling the quantitative Br/Li exchange in a chemical environment in which is persistent the presence of acidic protons [TMP-H and H-HMDS previously formed during steps a) and b), respectively] able to neutralize it. v) Finally, the simple stirring of the mixture containing **1d** for 30 min at rt is pivotal for promoting the rearrangement to the ynolate **1e**,[34,35] direct precursor of ketene **1f**.

vi) To take advantage of the electrophilic reactivity of the ketene, a series of different conditions for its interception with EtSH were screened (Table 1). Firstly, the mixture containing **1f** was added dropwise to a cooled (0 °C) THF solution containing 2 equiv of the thiol and 10 equiv of HCl and, after removing the cooling bath and continuing the stirring for 1 h, the desired product **2** was obtained in 55% yield, together with the corresponding ester **2a** (entry 1). Considering critical the stoichiometric loading of *n*-BuLi for the formation of **1 d** (vide supra), the slight increasing to 6 equiv. proved to be adequate (entries 2-3). Because methyl ester **2a** was originated *via* the attack of the methoxide ion to the ketene (released during the tetrahedral intermediate collapsing, **1a** → **1b**), the augmenting of the amount of mercaptan progressively suppressed the side product (**2a**) in favor of the desired thioester (entries 4-5). The existence of (labile) acid-base equilibria among the reactant species taking part to the process was also evident by the stoichiometry of the acid, suggesting 6.0 equiv as the optimal one, guaranteeing to recover **2** in excellent 85% isolated yield (entries 6–8).

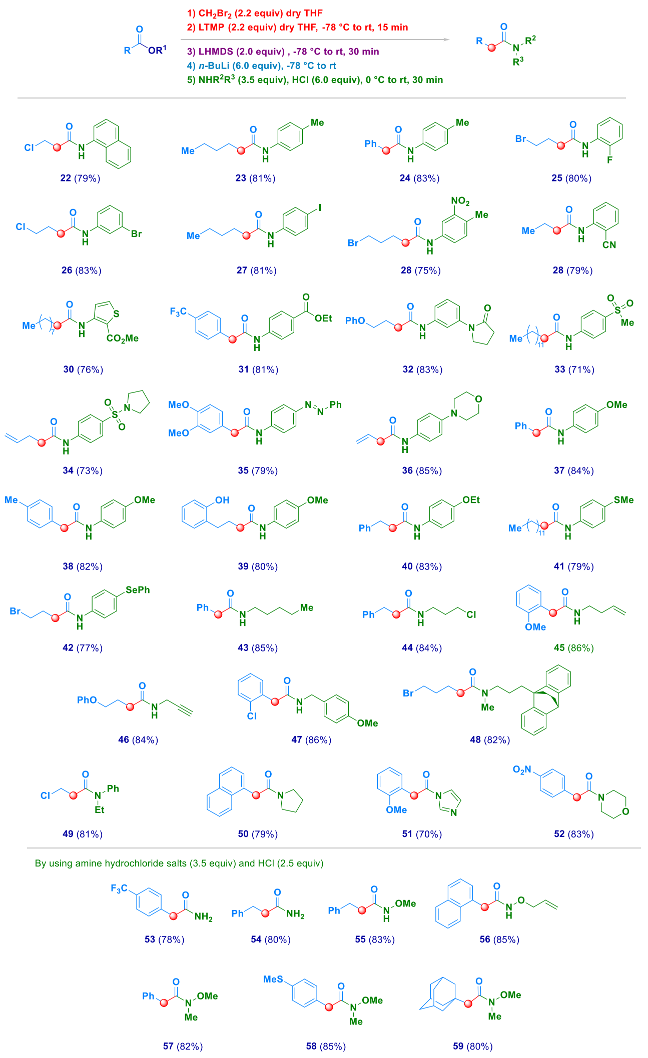
2.2. Reaction Scope

Once the optimal conditions have been established, we next examined the scope of the reaction (**Scheme 3**). The protocol proved to be very flexible, allowing the transformation of different functionalized esters into both the corresponding *S*-alkyl and *S*-aryl thioesters. The use of linear aliphatic thiols (**2**–**11**) was particularly effective and not influenced by the progressive increasing of the steric hindrance of the attacking mercaptan, as evidenced by employing cyclohexyl-analogs (**8**–**9**). Notably, the protocol could be advantageously applied to a lactone (coumarin), thus yielding—through a single operation—compound **4** exhibiting a phenol functionality. The selectivity of the reaction was further highlighted by engaging a α-chloroacetate (**10**) and a α-phenylacetate (**11**) for which the presence of acidic protons did not interfere with the homologating procedure. Less nucleophilic (hetero)aromatic thiols (**12**–**21**) accomplished the attack of the ketene in comparable efficiency regardless the presence of substitution elements [*e.g.*, halogens (**16**–**19**), 2-pyridyl- (**20**) and thioether (**21**)] modulating the relative nucleophilicities. It is worth to note the negligible effect displayed by the constitutive characteristics of the starting esters: the method was validated both in the case of aliphatic and aromatic ones. Some additional consideration is pertinent: a) no significant difference was observed by installing functional groups varying esters electrophilicities; b) the bulky adamantyl analog (**12**) underwent the transformation without affecting the effectiveness; c) an olefin potentially susceptible of Simmons–Smith-type cyclopropanation in the presence of a carbenoid[56] could be retained in the final product (**16**); d) analogously, the conditions employed enabled to preserve the nitro group, potentially susceptible of modification in the presence of carbenoids;[53] e) reactive sp^3-carbon atoms featuring a halogen atom [chlorine (**10**, **20**) and bromine (**13**, **15**)] primed for concomitant lithium exchange or nucleophilic displacement,[57] were perfectly tolerated; and f) although HCl is required (and used in 6:1 ratio with the ester) for the ketene interception, it has not a detrimental effect on acid-labile substituents (methoxy) placed on the aromatic groups (**3**, **5**).[58] This fact might be rationalized with its role in controlling acid-base equilibria rather than promoting ethers cleavage Scheme 3.



Scheme 3. Scope of the homologative thioesterification of esters.

Encouraged by these results, we next focused at extending the method for the preparation of homologated amides[59] *coeteris paribus* in the presence of amines (**Scheme 4**). Although these nucleophiles are protonated in acidic medium and precipitate, the progressive addition of the solution of the ynolate causes the restoring of the reactive lithium amide form, thus allowing a productive ketene attack. Similarly to the preparation of thioesters, uniformly high chemical yields and chemocontrol were evident. Among the small library of amides prepared (**22**–**52**), it is remarkable the level of functionalization of the amines used. Not only they can incorporate halogens (**25**–**27**) but also other groups potentially exchangeable in the presence of organolithiums, such as the selenyl- (**42**) or the propargyl- (**46**) analogs. Moreover, reactive electrophiles including nitrile (**28**), esters [**30** and **31**, the latter directly formed with the anesthetic drug benzocaine), lactam (**32**), among others common moieties (e.g., sulfonyl (**33**), sulfonamide (**34**), diazo (**35**), morpholine (**36**), ethers (**37**–**40**), thioether (**41**)) did not interfere with the success of the method. As anticipated, the switching from (hetero)aromatic to aliphatic amines was possible with both primary and secondary congeners. It should be emphasized the straightforward

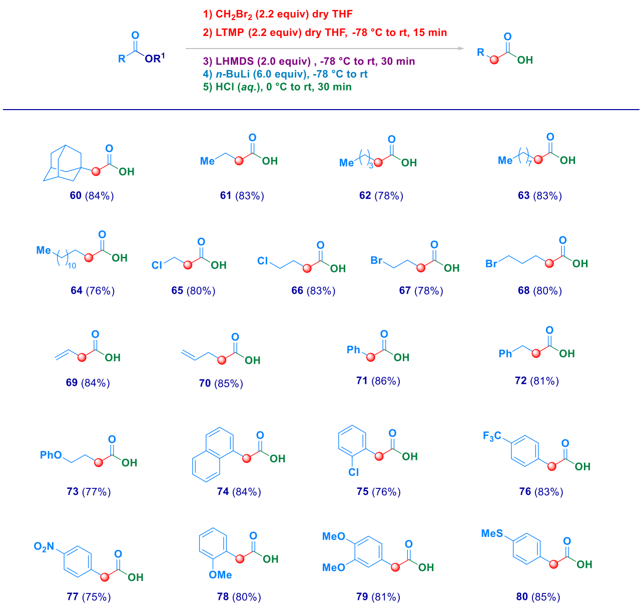


Scheme 4. Scope of the homologative amidation of esters.

use of the antidepressant agent maprotiline *en route* to analog **48** in which the reactive ω-bromo alkyl chain was unaffected under the nucleophilic conditions. Furthermore, also mixed aliphatic-aromatic (**49**), cyclic [pyrrolidinyl- (**50**), imidazole-1-yl- (**51**), and *N*-morpholinyl (**52**)] could be easily accessed with the methodology.

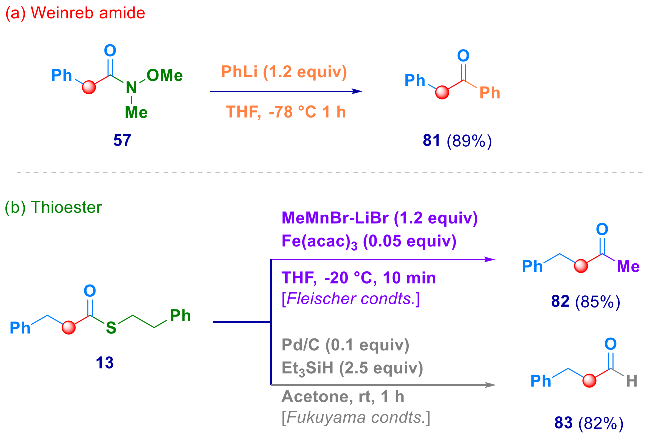
The procedure features significant flexibility for preparing primary (**53-54**), *N*-alkoxy (**53-54**), and *N*-methyl-*N*-methoxy amides (Weinreb-type),[60,61] as well. Because of the commercial availability of the corresponding hydrochlorides of the requested amines, the conclusive ketene trapping can be advantageously performed in the presence of just 2.5 equiv of HCl.

The unique opportunity offered by the genesis of the reactive ketene en route to further diversify the final product was also deduced when a simple acidic quenching was realized (**Scheme 5**). Under these conditions water, acting as a nucleophile, smoothly furnishes the corresponding carboxylic acids (**60–80**) in comparable yields and selectivity. It should be noted that an analogous operation could be accomplished with diazomethane according to an Arndt–Eistert–Wolff synthesis starting from higher reactive acid halides (or anhydrides).[62,63] However, the well-known drawbacks associated to this C1-source are intrinsic limiting factors for its application in both academic and company laboratories,[64,65] thus making the herein described strategy a more convenient approach to homologated acids from widely available esters.



Scheme 5. Scope of the homologative carboxylation of esters.

Finally, we briefly screened the utility of some selected products in standard synthetic protocols (**Scheme 6**). Weinreb amide **57** is conveniently used for preparing ketone **41** through the reaction with an organolithium. It should be observed that by adding this strong nucleophile to the homologated ester (instead of **57**) could result in the production of the corresponding carbinol via an uncontrollable double addition.[50] Thus, the facile homologative functionalization to the Weinreb amide provides a platform directly primed for the chemoselective ketone installation. Moreover, according to the recently reported Fleischer's protocol for iron-catalyzed cross-coupling of thioesters and organomanganese reagents,[66] we were able to forge a C—C bond starting from thioester **13**. Finally, by applying Fukuyama's procedure for the



Scheme 6. Functionalization of selected compounds.

reduction of thioesters to aldehydes with silyl hydrides,[67] the homologated aldehyde **83** was obtained.

3. Conclusion

In summary, we have designed a reliable protocol enabling the homologative conversion of esters into thioesters, amides, and carboxylic acids. Upon forming a tetrahedral intermediate with lithium dibromomethane—acting as a C1-donor agent—a series of deprotonation/lithiation events conducts to a high electrophilic ketene which undergoes a nucleophilic addition in the presence of the externally added sulfur, nitrogen, or oxygen elements. Crucial for the success of the method is suppressing the interception of the ketene by the initially ejected alkoxide anion. This is, because of the sequential processes occurring simultaneously, the individuation of adequate conditions hampering the reactivity of the alkoxide was found to be general and not depending on the nature of the nucleophile used. Notably, the transformation does not require the employment of diazomethane as the homologating agent and preserves the formal oxidation state of the original ester. This aspect, rather unusual when carbonyls and carboxylic derivatives undergo homologation sequences, would introduce—within the organic chemist's toolbox—an effective procedure for contemporaneously elongate and functionalizing common organic arrays.

Acknowledgements

The authors thank the University of Vienna, the University of Turin, the University of Milan, and All-4-Labels Group (Hamburg, Germany) for generous funding. Financial support from PRIN projects n. 20228W9TBL (L. C.), n. 2022JLSZMY (V. P.), and FWF-Austria Project n. P 37068-B (V. P.) is gratefully acknowledged.

Open access funding provided by Universitat Wien/KEMÖ.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: carbenoids · chemoselectivity · esters · homologation · nucleophilic addition

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Manuscript received: May 18, 2025
Revised manuscript received: June 6, 2025
Version of record online: June 27, 2025