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Tandem homologation-acylation chemistry: Single and double homologation

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ABSTRACT

Treatment of β-dicarbonyls with the Furakawa-variant of the Simmons-Smith reagent results in homologation and production of an intermediate zinc enolate. Treatment of the enolate with various acylating agents generate products with both γ-dicarbonyl functionality and β−dicarbonyl functionality. In situ exposure of the acylated product to additional zinc carbenoid effects a second regiospecific homologation reaction.

The generation of functionalized furans, pyrroles, and thiophenes has attracted significant interest due to the prevalence of these heterocyclic ring systems in natural products and materials science applications. Although all of these heterocycles can be formed from 1,4-dicarbonyl compounds through application of the Paal-Knorr synthesis [1–3], the challenges associated with preparing highly functionalized 1,4-diketone starting materials have impacted the broad application of this method of heterocycle formation. Creative approaches based on the Stetter reaction [4], conjugate additions [5], and transformation of furan systems [6] have been developed to address this challenge, although there is still a need in the synthetic community for new methods in 1,4-diketone synthesis. Our interest in the development of tandem reaction strategies based on a zinc carbenoid-mediated homologation reaction has led to the identification of a novel, practical approach to functionalized 1,4-dicarbonyl systems.

Homologation of β-keto esters to their γ-keto counterparts through the use of Furukawa-modified zinc carbenoid [7] was first reported in 1997 [8]. Subsequently, the scope of this homologation reaction has been expanded to include the use of other β-keto substrates [9,10] and the ability to functionalize at both the α and β-positions of the γ-keto product. Regioselective functionalization of the β-position has been achieved through the use of substituted zinc carbenoids [11], while regioselective functionalization of the α-position has been achieved by tandem reactions of zinc enolate 2 with a variety of electrophiles including carbenoids [12], halogens [13], activated imines [14], aldehydes [15], and thioesters [16] (Scheme 1).

Compounds obtained from tandem homologation reactions have been shown to be appropriate substrates for a variety of heterocycles through application of Paal-Knorr synthesis [16–18]. Oxidation of the tandem homologation-aldol products with PCC provided the 1,4-dicarbonyls [16,17] used for Paal-Knorr synthesis [18]. The use of thioesters to successfully trap the organometallic intermediate (2) was reported as a direct method for the formation of 1,4-dicarbonyls [16], although other acylating agents, like acid chlorides and benzotriazole-activated acids, were not successful in trapping the intermediate. The use of anhydrides was not discussed in this report.

Recently our group reported the total synthesis of papyracillic acid B and 4-epi-papyracillic acid C using the zinc-mediated homologation methodology [19]. These members of the papyracillic acid family of natural products [20], which contains a spiro-fused cyclic ketal core, were synthesized through the use of a tandem homologation-acylation reaction. This key step constituted the first reported example of an anhydride being used to trap reactive intermediate 2, so our success in trapping the organometallic intermediate with anhydrides suggested an expanded investigation of the process, with a goal of increased efficiency and the minimization of byproduct formation.

An investigation of a general homologation/acylation strategy revealed that optimization of stoichiometry was key to the

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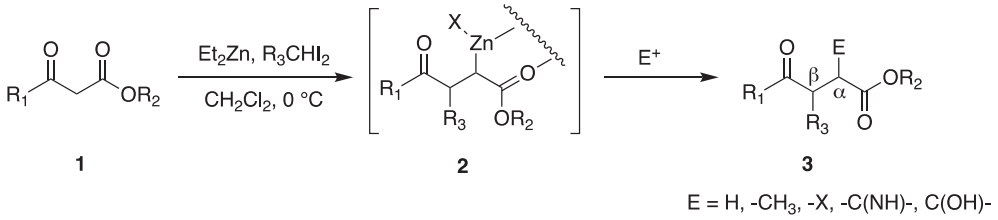
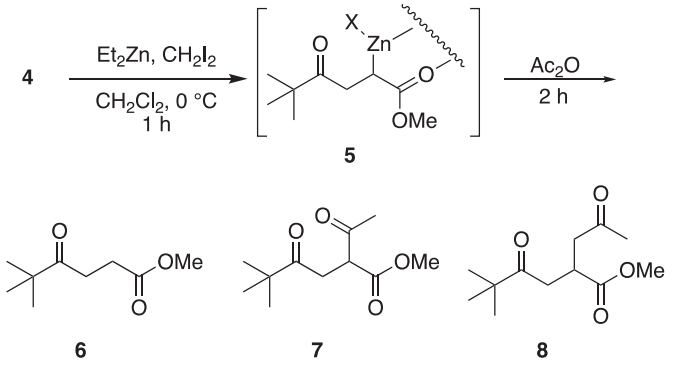


1 2 3

Scheme 1. Tandem Chain Extension Chemistry.

minimization of byproducts formed in the tandem reaction (Table 1). For example, treatment of methyl pivaloylacetate (4) with three equivalents of carbenoid followed by the addition of acetic anhydride led to the formation of three main products: γ-keto ester 6, the desired acylated product (7), as well as a homologue of the acylation product (8). It was hypothesized that this result arises from the formation of a new β-keto ester (7), which introduces an acidic proton capable of quenching unreacted organometallic compound 5, thereby providing the simple homologated product (6). Once compound 7 is deprotonated, the zinc enolate can react with another equivalent of carbenoid to produce compound 8. The yield of the desired product (7) was greatly improved by treatment of methyl pivaloylacetate with three equiv of diethylzinc, followed by one equiv of diiodomethane and finally 1.5 equiv of acetic anhydride (Table 1, entry 2). The first equiv of diethylzinc served to deprotonate methyl pivaloylacetate (4), while a second equivalent reacted with diiodomethane to form the carbenoid required for homologation of the β-keto ester. Since only one equivalent of carbenoid was generated, the further homologation of compound 7 to provide 8 was avoided. The third equivalent of diethylzinc was necessary to remove the acidic proton on acylated compound 7, preventing the organometallic intermediate 5 from being quenched before acylation took place. Conversely, treatment of methyl pivaloylacetate with four equiv of carbenoid followed by the addition of acetic anhydride (Table 1, entry 3) demonstrated that it is possible to bias the reaction towards the formation of compound 8.

Table 1
Optimization of tandem chain extension-acylation reaction using methyl pivaloylacetate.



5 6 7 8

Entry	Et_2Zn (equiv)	CH_2I_2 (equiv)	Ac_2O (equiv)	6(%)[a]	7(%)[a]	8(%)[a]
1	3	3	1	30	24	46
2	3	1	1.5	17	83 (63)[b]	0
3[c]	4	4	1	28	11	61

[a] Relative abundance using relative integrations from ^1H NMR analysis of the crude reaction mixture.
[b] Isolated yield of purified material.
[c] Diethylzinc and methyl pivaloylacetate were stirred for 10 min prior to adding diiodomethane.

The order of addition involving acetic anhydride was crucial to efficient homologation-acylation. When acetic anhydride was added to three equivalents of ethyl(iodomethyl)zinc before the addition of methyl benzoylacetate (9), a second regioisomer 11 was formed in addition to the desired product 12 (Scheme 2). The formation of the isomer 1 may be due to formation of small quantities of tricarbonyl 10 before homologation of 9 has had a chance to occur. Compound 17 contains two ketones that provide competing sites for methylene insertion in the homologation reaction.

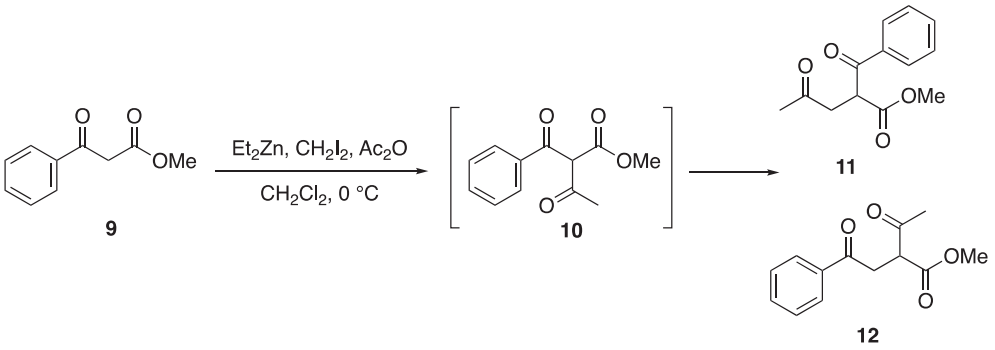
Upon optimization of the tandem homologation-acylation conditions, a range of β-keto carbonyl substrates and acylating agents were examined with respect to the efficiency of the reaction (Table 2). Benzoic anhydride and isobutyric anhydride (Table 2, entries 2 and 3) typically provided higher yields than acetic anhydride, suggesting that bulkier acylating agents were more efficient.

The range of β-keto esters demonstrates that bulky or aromatic substituents on the ketone or ester do not compromise the efficiency of the tandem reaction sequence. When allyl acetoacetate or *t*-butyl acetoacetate (Table 2, entries 4–7) were used as starting materials, lower yields of products were obtained. These reduced yields may be due to Lewis acid-catalyzed decomposition of the esters or due to the susceptibility of the olefin to cyclopropanation when in the presence of zinc-carbenoid. Use of a β-keto tertiary amide (15) and β-keto imide (16) (Table 2, entries 10 and 11) in the tandem reaction also proved to be suitable for the production of acylated γ-keto compounds.

In addition to the use of anhydrides, alternate acylating agents were investigated. Use of phenyl formate as the electrophile resulted in a complex reaction mixture with no evidence of the desired product. Treatment of methyl benzoylacetate with the zinc carbenoid followed by addition of acetyl chloride resulted in formation of the unsubstituted γ-keto ester 26 [21] through protic quenching of the organometallic intermediate (Scheme 3). The source of the proton may have been residual HCl generated from acetyl chloride or from the acetyl chloride's acidic α-proton. Efforts to purify acetyl chloride were not successful in prohibiting protic quenching. Additional reactions with acid chlorides provided similar results.

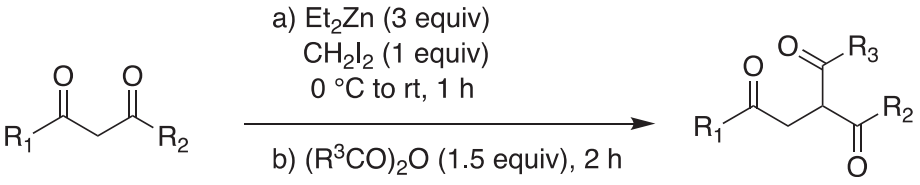
Benzotriazole-activated acetic acid (27) [22] could be used as an acylating agent with moderate success (Scheme 4), a result that stands in contrast to an earlier report [16]. In addition, Boc-protected lactam 28 [23] was reacted with compound 4 using the optimized homologation-acylation conditions (Scheme 4). This successfully provided compound 36 as a mixture of constitutional and configurational isomers.

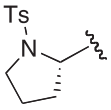
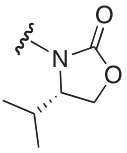
Utility of the tandem homologation acylation reaction in



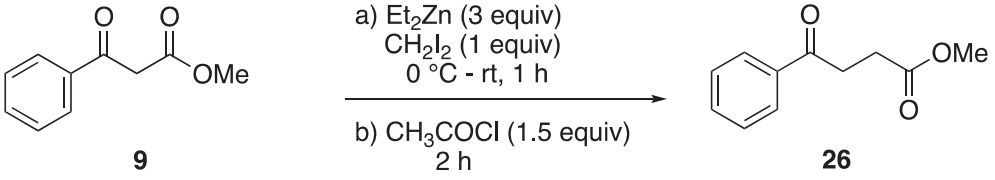
Scheme 2. Formation of regioisomers in the homologation-acylation reaction.

Table 2
Tandem chain-extension acylation of (β)-keto carbonyls.

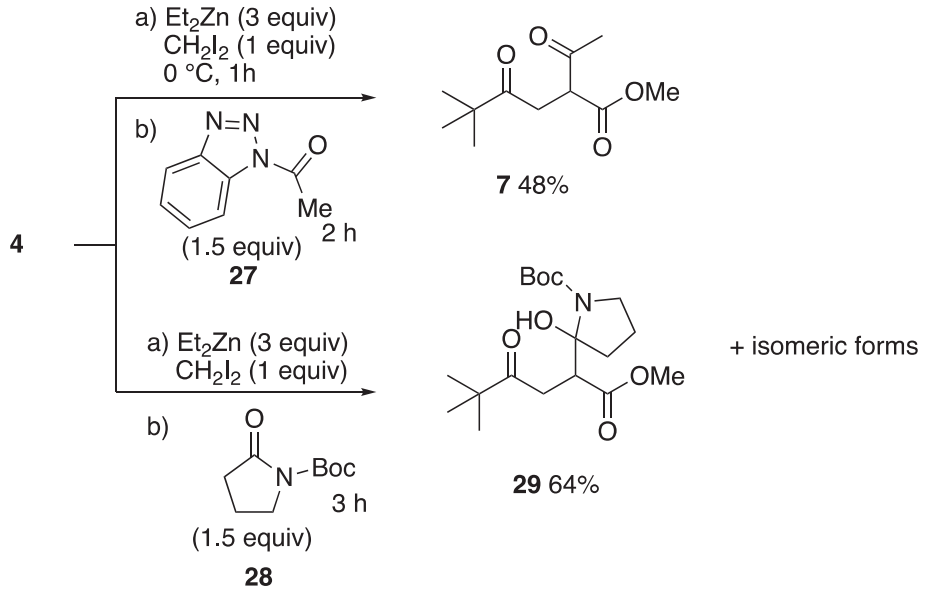


Entry	SM	R^1	R^2	R^3	Product	Yield (%)
1	4	*t*-Bu	-OMe	Me	7	63
2	4	*t*-Bu	-OMe	i-Pr	17	80
3	4	*t*-Bu	-OMe	Ph	18	95
4	13	Me	-Ot-Bu	Me	19	50
5	13	Me	-Ot-Bu	Ph	20	46
6	14	Me	$-OCH_2CH{=}CH_2$	Me	21	44
7	14	Me	$-OCH_2CH{=}CH_2$	Ph	22	55
8	9	Ph	-OMe	Me	12	50
9	9	Ph	-OMe	Ph	23	65
10	15	Me	$-NMe_2$	Ph	24	81
11	16			Ph	25	53

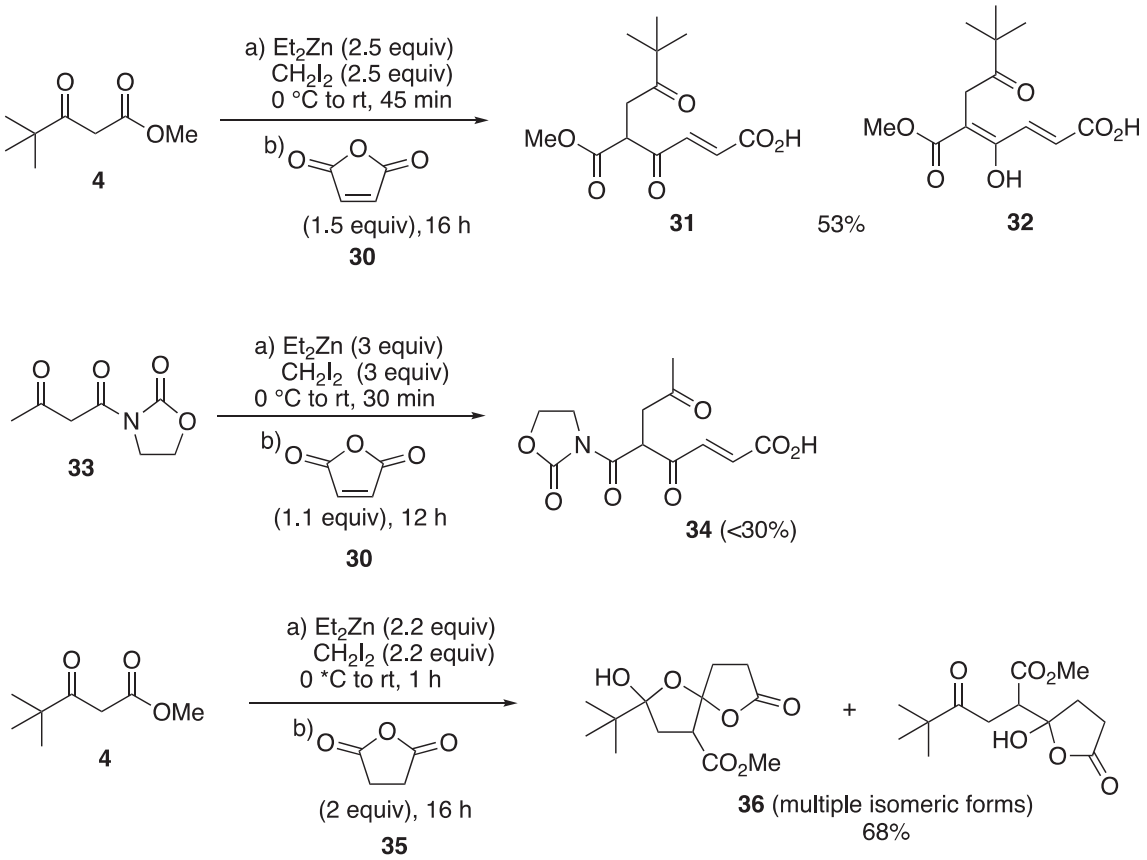
application to the synthesis of the papyracillic acid [20] family of natural products required the use of a cyclic anhydride to trap the organometallic intermediate (2). A broader investigation of tandem reactions that utilized cyclic anhydrides with various starting β-dicarbonyls was undertaken. Treatment of methyl pivaloylacetate (4) with ethyl(iodomethyl)zinc followed by addition of maleic anhydride gave rise to a mixture of products (Scheme 5). Close examination of the crude reaction mixture by NMR spectroscopy revealed that maleic anhydride did indeed trap the homologated intermediate through an acylation reaction. A similar result, which includes isomerization of the alkene, was observed when β-keto imide (33) [14] was subjected to the same homologation reaction



Scheme 3. Attempted acylation with acetyl chloride.



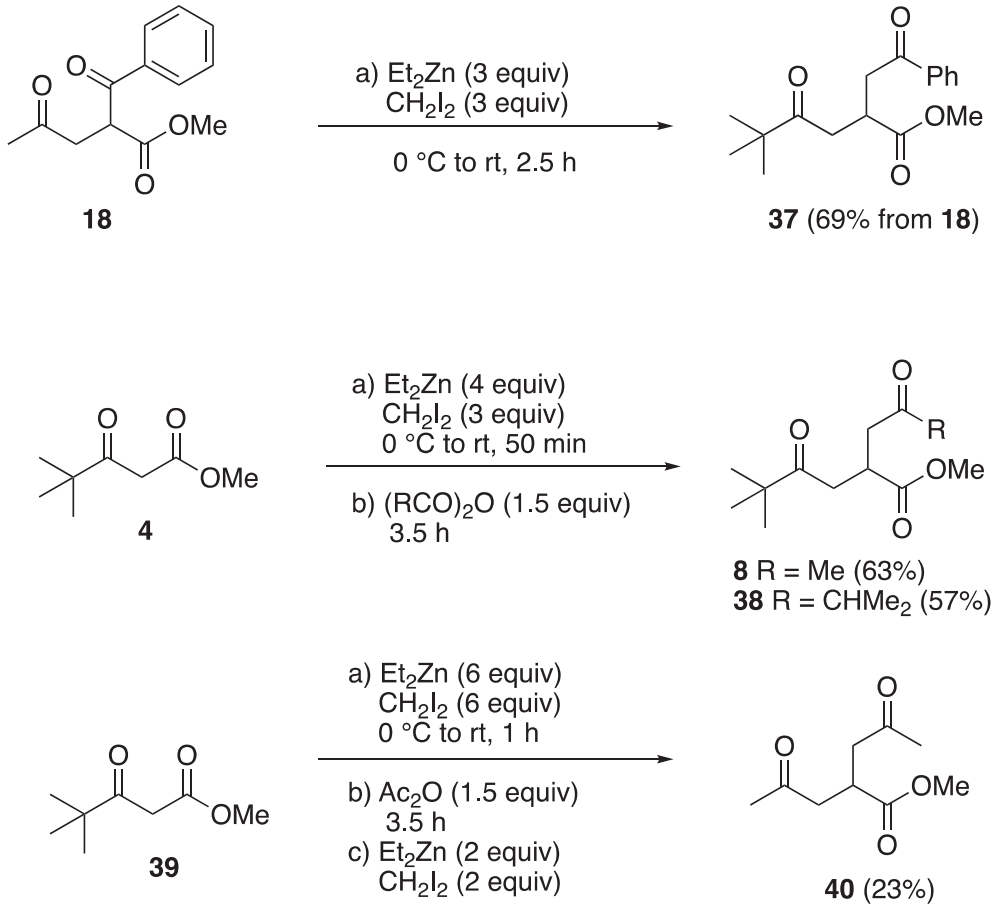
Scheme 4. Acylation with alternative electrophiles.



Scheme 5. Tandem chain-extension acylation with cyclic anhydrides.

conditions. Succinic anhydride (35) was also explored as an acylating agent. Exposure of methyl pivaloylacetate (4) to carbenoid followed by addition of succinic anhydride produced a mixture of at least three isomeric compounds. Analysis of the NMR spectra revealed the presence of ketal resonances, which affirmed that the spiroketal core could be formed directly through a tandem homologation-acylation reaction. These results were consistent with the observations made when using methoxymaleic anhydride in our synthetic route to the papyracillic acid family of natural products [19].

As suggested by the inadvertent formation of 15 during optimization studies, zinc carbenoid-mediated homologation of the



Scheme 6. Sequential homologation reactions.

acylated product should be possible. The potential for additional homologation was confirmed (Scheme 6) by the successful formation of 37 in 69% by treatment of compound 18 with three equiv of ethyl(iodomethyl)zinc.A one-pot tandem reaction featuring homologation-acylation-homologation was developed by treating β-keto ester starting materials with a greater excess of carbenoid and the use of longer reaction times. For example, treatment of compound 4 with excess carbenoid for 3.5 h in the presence of an anhydride provided compounds 8 and 38 in 63% and 57%, respectively. One-pot double homologation of methyl acetoacetate (39) to form 40 was also successfully accomplished, albeit in a modest 23%. Efforts to perform double homologation reactions that involved acylation with benzoic anhydride were unsuccessful. For example, exposure of 9 to carbenoid and benzoic anhydride provided 23, the result of single homologation, regardless of the number of equivalents of carbenoid and reaction time. This result is consistent with the inability to perform further homologation of purified 23.

In summary, a tandem chain extension-acylation reaction has been developed to produce α-acylated γ-keto carbonyls. Cyclic and acyclic anhydrides, benzotriazole-activated carboxylic acids, and cyclic imides were shown to be effective acylating agents. The tandem homologation acylation reaction proceeds in modest to good yields when starting from a diverse array of β-keto carbonyl compounds. Rapid assembly of differentially functionalized 1,4-diketones products is available from this method.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132223.

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