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# Tandem Chain Extension-Homoenolate Formation: The Formation of α-Methylated-γ-Keto Esters

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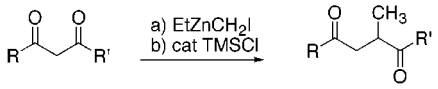
## ABSTRACT




**A tandem chain extension–homoenolate formation reaction is described. The treatment of β-keto esters with the Furukawa reagent followed by exposure to a catalytic amount of trimethylsilyl chloride provides access to an ester homoenolate.**

The formation of carbon skeletons continues to demand significant expenditures of energy and time in organic synthesis. The selective chain extension of easily accessed carbon frameworks is one possible solution to the formation of challenging structures. One strategy for chain extension or ring expansion has been to generate strained ring systems that upon fragmentation generate extended carbon chains.[1]

We have recently reported an operationally simple approach to the chain extension of β-keto esters,[2] β-keto amides,[3] and β-keto phosphonates[4] that utilizes the Furukawa reagent,[5] ethyl(iodomethyl)zinc. We have proposed (Scheme 1) that the reaction proceeds through cyclopropanation of the enolate to provide a donor−acceptor cyclopropane, which fragments to give an intermediate ester enolate equivalent and is quenched to provide the γ-keto ester. Practical application of this methodology appeared limited to the use of α-unsubstituted-β-keto esters, since the placement of substituents at the α-position resulted in complex reaction mixtures due to formation of over-alkylated products. We now report a variation on the chain extension reaction that provides a partial solution to this problem.

Investigation of the chain extension reaction stoichiometry revealed that formation of the enolate consumes the first equivalent of either the Furukawa reagent or diethyl zinc.[6] In an effort to minimize the amount of diethyl zinc utilized in the reaction, we undertook an investigation of alternative bases for the formation of the enolate **2**. Formation of the potassium enolate through addition of a 1.0 M solution of KHMDS in toluene to β-keto ester **1**, followed by transfer to the preformed Furukawa reagent, resulted in the unexpected formation of a mixture of products (Scheme 2), dominated by the appearance of the α-methylated γ-keto ester **6**. This mixture of products was in sharp contrast to the clean reactions observed when either diethyl zinc or the Furukawa reagent was used to initiate the reaction through enolate formation. An intriguing observation was that even substoichiometric amounts (0.5 equiv) of KHMDS provided enhanced α-methylation, as high as a 9:1 ratio of **6**:**5** as determined by NMR analysis of the crude reaction mixture.

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(6) Identical results are obtained if 1 equiv of diethylzinc is used instead of the first equivalent of ethyl(iodomethyl)zinc. In both instances enolate formation is observed through NMR analysis with concomitant generation of ethane gas.

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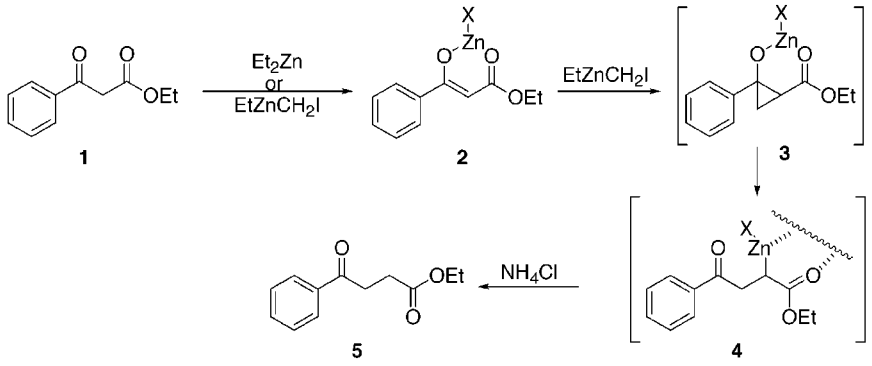
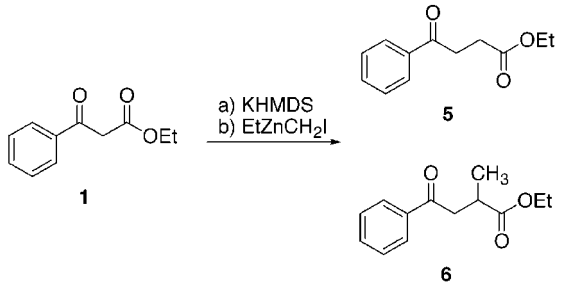
**Scheme 1**




Although the 52% isolated yield of α-methylated material in the KHMDS reaction was not entirely satisfactory, the unusual nature of the product warranted continued study.

**Scheme 2**



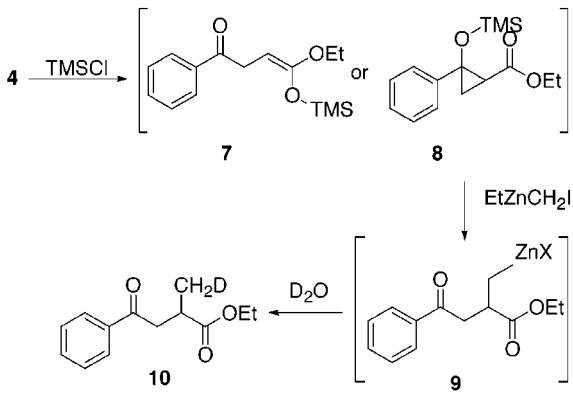

Since treatment of a β-keto ester with KHMDS results in the formation of the potassium enolate and generation of the conjugate acid, HMDS, we intended to explore the influence of both the counterion and the conjugate acid. Treatment of the β-keto ester **1** with the Furukawa reagent in the presence of substoichiometric potassium iodide (0.5 equiv) revealed an increase in α-methylation, although the ratio of α-methylated product **6** to simple chain extension product **5** was only 3:2. Because potassium iodide is not soluble in methylene chloride, the experiment was repeated with a soluble metal salt, sodium tetraphenylborate. Once again, the α-methyl chain-extended product was formed, but the simple chain extension product was the major product; the ratio of the two products was again approximately 3:2. These results indicate that change in the counterion influences the α-methylation reaction, although no counterions were identified that provided the product selectivity provided by KHMDS.

The influence of the conjugate acid of KHMDS was probed by treatment of the β-keto ester **1** with the Furukawa reagent followed by addition of 0.2 equiv of HMDS. This revealed that α-methylation was the dominant reaction pathway (9:1 ratio of **6**:**5**) in the absence of a potassium or sodium cation and that appearance of the α-methylation product cannot be attributed to a simple counterion effect. To test the influence of the amine functionality, β-keto ester **1** was treated with diisopropylamine or triethylamine in the same fashion as described above for HMDS. Although the $^1$H NMR spectra of crude reaction mixtures showed traces of the α-methylated product **6**, the simple chain-extended material **5** was the major product formed. From this result it was clear that HMDS was exerting influence over product distribution in a fashion unrelated to its nature as a basic amine.

We concluded that KHMDS and HMDS were promoting α-methylation through the influence of the trimethylsilyl (TMS) group. To test this hypothesis, 0.2 equiv of trimethylsilyl chloride (TMSCl) were added to the reaction mixture immediately after the ester substrate was combined with the zinc carbenoid. Once again, the $^1$H NMR spectrum of the crude reaction mixture showed a ratio of the α-methylated chain-extended product **6** to the simple chain-extended **5** product of approximately 9:1.

A mechanistic description of the reaction is illustrated in Scheme 3. After cyclopropanation and ring opening to a dimeric zinc species **4**,[7] the trimethylsilyl group appears to promote fragmentation of the dimeric species and generation of an activated nucleophile. This nucleophile could be either TMS-ketene acetal **7** or the donor−acceptor cyclopropane **8**, although the absence of any apparent Ireland−Claisen rearrangement pathway with an allyl ester discourages

**Scheme 3**

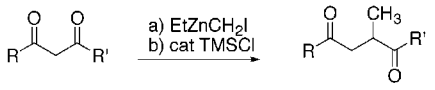


consideration of the ketene acetal intermediate.[8] It is important to note that trimethylsilyloxycyclopropanes, like **8**, have been implicated in reactions with exceptional carbon electrophiles,[9] including zinc-carbenoids.[10] Either potential nucleophilic intermediate would be expected to attack the electrophilic carbenoid and provide the zinc homoenolate **9**.[11] Anionic character at the newly incorporated methyl group was demonstrated by quenching the reaction mixture with $D_2O$ to provide **10**.

A number of variables were modified to test their impact on the efficiency of the reaction. The number of equivalents of the zinc carbenoid were varied from four to six with no apparent impact. The amount of TMSCl was varied from 10 mol % to 80 mol %, again with no apparent influence. The timing of addition of TMSCl to the reaction mixture was varied from 30 s to 10 min after addition of the substrate to the carbenoid, and the duration of the reaction after addition of TMSCl was varied from 10 to 45 min. In only one case was there a clear reduction in the ratio of the α-methyl chain-extended product to the simple chain-extended product, determined by analysis of the $^1$H NMR spectra of the crude reaction mixtures. When TMSCl was added 10 min after adding the ester substrate **1** to the carbenoid and the reaction was quenched after another 10 min, the ratio of the α-methyl product **6** to the simple chain-extended product **5** was 3:1 rather than approximately 9:1 as usually observed. The 10-min reaction time was evidently insufficient to achieve the higher ratio. When the same substrate was allowed to react for 30 min after addition of TMSCl, the α-methylated product was favored by a >9:1 ratio and isolated in 70% yield.

Several α-methyl $\gamma$-keto esters and amides (**12**, **14**, **16**, **18**) were prepared from $\beta$-keto esters and amides using the tandem chain extension−homoenolate formation procedure (Scheme 4). Yields of the major product after purification

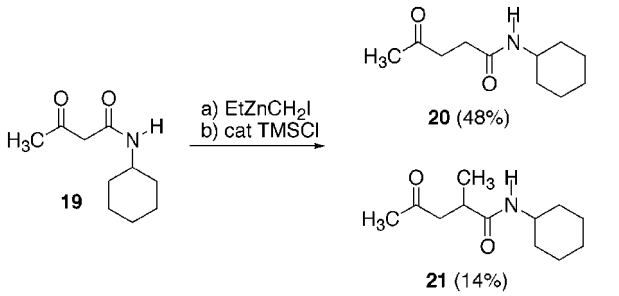
**Scheme 4**




**11** R = $CH_3$, R' = $OCH_3$ **12** R = $CH_3$, R' = $OCH_3$ (63%)
**13** R = $CH_3$, R' = OtBu **14** R = $CH_3$, R' = OtBu (73%)
**15** R = $CH_3$, R' = $OCH_2Ph$ **16** R = $CH_3$, R' = $OCH_2Ph$ (57%)
**17** R = $C_6H_5$, R' = $N(CH_3)_2$ **18** R = $C_6H_5$, R' = $N(CH_3)_2$ (53%)

by column chromatography varied from 57% to 73%. As these results demonstrate, the efficiency of the tandem reaction was not hindered by the presence of a bulky substituent or aromatic group on the ester oxygen or by the presence of amide functionality. In every case, a small amount of the simple chain-extended product was observed in the $^1$H NMR spectra of the crude reaction mixtures. The reaction was attempted with a secondary $\beta$-keto amide, *N*-cyclohexyl 3-oxo-butanamide **19**,[12] with very different results. The substrate was added to 5 equiv of the zinc carbenoid, 40 mol % of TMS-Cl was added after 30 s, and the reaction was quenched after 30 min. The $^1$H NMR spectrum of the crude reaction mixture showed that the α-unsubstituted chain-extended product **20**[13] was the major product rather than the expected α-methyl chain-extended product **21**; the ratio of the two products was approximately 3:1. Efforts were made to increase the yield of the α-methyl chain-extended product by modifying the amount of TMSCl and timing of the addition; however, ratio of the α-unsubstituted product to the α-substituted product could not be improved.

**Scheme 5**




A likely explanation for these results is that the carbon-bound zinc intermediate **4** is partially quenched by the secondary $\beta$-keto amide hydrogen before TMSCl transforms it to a reactive TMS-containing species **7** or **8**, thus interfering with the α-alkylation reaction. When secondary $\beta$-keto amides are chain-extended without the use of TMS−Cl,[3] this partial quenching of intermediate **4** would result in formation of the same product as is generated with an ammonium chloride quench. Quenching of intermediate **7** or **8** with the acidic amide proton prior to reaction with the zinc carbenoid is an alternative and synthetically equivalent explanation. Regardless of the mechanism, it is clear that the presence of an acidic proton inhibits the α-methylation reaction.

To test the amide-quenching hypothesis, a chain extension reaction (no addition of TMSCl) of secondary $\beta$-keto amide substrate **19** was quenched after 30 min with excess $D_2O$

(7) The dimeric nature of the intermediate has not been unequivocally established in the present situation; however, the intermediate bears remarkable spectroscopic and reactivity similarity to a Reformatsky reagent. Reformatsky reagents have been shown to be dimeric in the crystalline state, as well as through molecular weight determinations in solution. (a) Orsini, F.; Pelizzoni, F.; Ricci, G. *Tetrahedron* **1984**, *40*, 2781. (b) Orsini, F.; Pelizzoni, F.; Ricci, G. *Tetrahedron Lett*. **1982**, *25*, 3945.

(8) A Reformatsky−Claisen reaction of a zinc-ketene acetal would require elevated temperatures (refluxing benzene). Baldwin, J. E.; Walker, J. A. *J. Chem. Soc., Chem. Commun*. **1973**, 117.

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(13) Saito, K.; Sato, T. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 3601−3605.

and the reaction mixture was purified by column chromatography. The $^{1}H$ and $^{13}C$ NMR spectra show clearly that deuterium has been only partially incorporated on the α-carbon with the estimated ratio of deuterated to non-deuterated products being approximately 3:2. This result supports the contention that the amide hydrogen can quench intermediate **4** and interfere with the α-alkylation reaction, thereby accounting at least in part for the low yield of the α-methyl chain-extended product **21**. Some reduction in yield may also be attributable to a protic quench of the TMS-containing intermediate **7** or **8** with the acidic hydrogen, but no evidence for that phenomenon has been obtained.

The tandem chain-extension/α-methylation reaction of esters and amides provides access to α-methylated $\gamma$-keto esters and amides, compounds that were not accessible through chain extension of α-methylated $\beta$-keto esters. Activation of a Reformatsky-like intermediate **4** with TMSCl appears to promote methylation through formation of a trimethylsilyloxycyclopropane **8**. Less efficient formation of α-methylated products was observed with alkili metal counterions. An attractive explanation is that counterions other than zinc affect the equilibrium between the cyclopropyl alkoxide (**3**) and the open ketene acetal intermediates (**4**).[11b]

Manipulation of the reaction to incorporate groups other than methyl at the α-position would provide a general solution to the inefficient reactivity of α-substituted $\beta$-keto esters.[2] Successful trapping of the intermediate zinc-enolate equivalent **4** (Reformatsky-like) through the introduction of aldehydes has been accomplished in our laboratories,[14] yet the α-methylation reaction provides a potential general solution to the problem. Since a proposed intermediate **9** in the α-methylation reaction is a zinc ester homoenolate, it should be possible to trap the homoenolate through addition of a suitable electrophile[15] or by metal-mediated coupling.[16] Efforts are presently underway in our laboratory to utilize the homoenolate intermediate in a reaction that will involve three sequential carbon−carbon bond-forming reactions.

**Acknowledgment.** This research was funded by a grant from the National Institutes of Health (GM60967-01).

**Supporting Information Available:** Detailed experimental procedures, including spectroscopic data, are available for compounds **6**, **10**, **12**, **14**, **16**, **18**, and **20**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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