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Zinc carbenoid-mediated chain extension of β-keto amides

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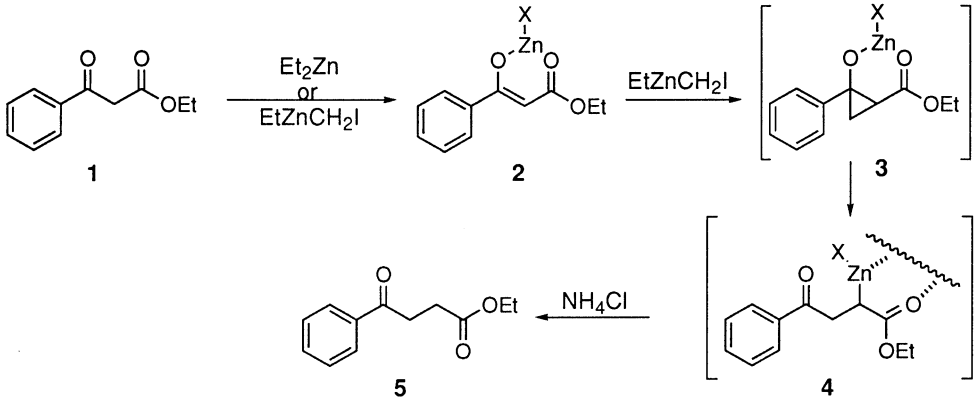
Abstract—The reaction of β-keto amides with ethyl(iodomethyl)zinc provides access to a wide variety of γ-keto amides, including primary, secondary, and tertiary amides. Although the reaction of α-substituted β-keto amides are in many cases unsatisfactory, the method can be applied to a broad spectrum of substrates that possess imide and olefinic functionality.

1. Introduction

The ability to selectively manipulate the length of a carbon chain or enlarge an existing carbon framework provides opportunities for incorporating structural diversity in molecule assembly. One common strategy in chain extension and ring enlargement involves formation of strained ring systems, which fragment upon exposure to suitable reaction conditions to give longer carbon frameworks.[1] The efficient preparation of 1,4-dicarbonyl compounds from shorter carbon chains through formation and fragmentation of a cyclopropyl alkoxide first appeared in the literature twenty-five years ago. In this instance a β-keto ester was converted to an enamine, reacted with the Simmons–Smith reagent, and fragmented under hydrolytic conditions.[2] A number of variations on this 'donor–acceptor cyclopropane' strategy were reported, including the use of a trimethylsilyl enol ether as the nucleophilic partner[3] and a stepwise approach which involves the cyclization and fragmentation of radical intermediates.[4] A complementary approach to the donor–acceptor cyclopropanes was reported in which a ketone-derived enol ether is cyclopropanated through reaction with a rhodium carbenoid.[5]

We reported a new chain extension variant in the form of a one-pot chain extension of β-keto esters through treatment of a zinc enolate with the Furukawa reagent ($EtZnCH_2I$).[6]

A generalized mechanistic description is found in Scheme 1. The key to the efficiency of the reaction appears to be the stable, unreactive nature of a Reformatsky-like intermediate **4**. While providing efficient access to simple γ-keto esters, the methodology was much less efficient in the formation of α-substituted γ-keto esters, likely due to a destabilization of intermediate **4**. The chain extension reaction was unsuccessful in the formation of γ-diketones. We more recently reported the application of this carbenoid strategy to the



Scheme 1.

Keywords: chain extension; zinc; carbenoid; keto amide.
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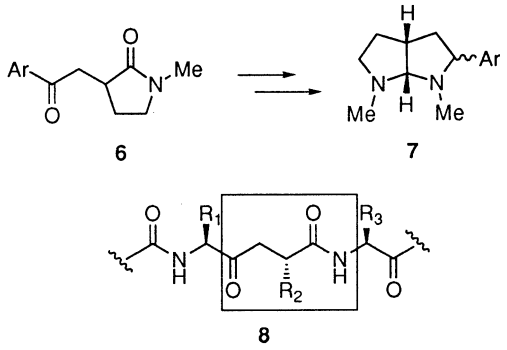


Figure 1.

chain expansion of β-keto phosphonates,[7] although competing cyclopropanation of olefin functionality limits its broad applicability within the phosphonate family (Fig. 1).

Our interest in extending the facile zinc-mediated reaction to the preparation of γ-keto amides is prompted by its utility in a wide variety of biologically relevant systems. Besides appearing as an intermediate (**6**) in the preparation of biologically active compounds like **7**,[8] γ-keto amides are frequently found in ketomethylene isosteric replacements **8** for the peptide bond.[9] The development of an operationally simple approach to the preparation of γ-keto amides would serve to advance both their synthetic accessibility and utility. However, a report[10] that implicated the Furukawa reagent in the N-methylation of amide functionality suggested that N-methylation of β-keto amides might compete with the chain extension. For these reasons we undertook a detailed study of the zinc carbenoid-mediated chain extension of β-keto amides.

2. Results and discussion

A wide variety of methods are available for the preparation of the necessary β-keto amide starting materials, including addition of amines to diketene,[11] acetoacetylation of amines with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one,[12] reaction of amines with β-keto esters or β-keto thioesters,[13] condensation of ketones and isocyanates,[14] and aminolysis of acyl Meldrum's acid.[15] Although the addition of amines to diketene is limited in that it only provides β-keto amides with a methyl group adjacent to the ketone, the simplicity and broad applicability to a variety of amines made it the dominant method chosen for this methodology study.

Table 1.

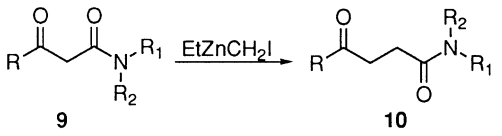
Substrate[a]	R	R_1	R_2	Yield[b] (%)
9a	CH_3	$-(CH_2)_4-$		47
9b	CH_3	*n*-C_4H_9	*n*-C_4H_9	70
9c	CH_3	CH_3	C_6H_5	88
9d	CH_3	CH_3	CH_3	60
9e	C_6H_5	$CH_2C_6H_5$	$CH_2C_6H_5$	42
9f	$C(CH_3)_3$	$CH_2C_6H_5$	$CH_2C_6H_5$	60
9g	C_6H_5	CH_3	CH_3	59
9h	CH_3	*c*-C_6H_{11}	H	81
9i	CH_3	C_6H_5	H	33
9j	CH_3	H	H	10

[a] Specific reaction conditions for each substrate are contained in the Section 4.
[b] Isolated yield of purified material.

A series of α-unsubstituted tertiary β-keto amides **9** were exposed to the Furukawa-modified Simmons–Smith reagent[16] to produce the corresponding γ-keto amides **10**. Initially, reaction conditions identical to those employed with β-keto esters were used. It was later determined that for most substrates 3 equiv. of the zinc carbenoid resulted in clean conversion of all starting material to product, although as many as 6 equiv. could be used without detrimental effects. In some cases the reaction was quenched after 15 min and ^{1}H NMR spectra of the crude reaction mixtures showed complete conversion of starting material to product. When reaction times exceeded 45 min, complex reaction mixtures were observed and yields of the desired products were reduced accordingly.

As indicated in the results tabulated in Table 1, a variety of α-unsubstituted tertiary β-keto amides were chain-extended cleanly in modest to good yields. The efficiency of the reaction was not hampered by the presence of sterically demanding groups or aromatic groups. ^{1}H NMR spectra of the crude reaction mixtures suggested that the desired γ-keto amides, except in one case, were the only products formed. When *N*,*N*-dimethyl 3-oxo-butanamide **9c** was exposed to the zinc carbenoid for greater than 30 min, evidence for competing product formation was observed by chromatographic and spectroscopic techniques. Although the competing products were not identified, mass spectrometry data suggested that condensation reactions took place and led to the formation of high molecular weight compounds. A reduction of the reaction time to 15 min led to an acceptable yield of the desired product. Similar problems were not encountered when *N*,*N*-dimethyl 3-oxo-3-phenyl-propanamide **9g** was chain extended, even when the reaction was allowed to run for 45 min. Yields of water-soluble products were compromised by the necessity to remove the zinc salts through extraction and aqueous work-up.

The tertiary substrates described above did not contain any acidic protons which would likely interfere with the chain extension reaction. The impact of modestly acidic hydrogen atoms on the amide nitrogen was first tested by applying the one-pot zinc carbenoid-mediated chain extension method to two secondary β-keto amides. *N*-Cyclohexyl 3-oxo-butanamide **9h** reacted very cleanly and provided the chain-extended product, *N*-cyclohexyl 4-oxo-pentanamide **10h**, as a pure compound in 81% yield. In contrast, attempted chain extension of **9i** provided material whose ^{1}H NMR spectrum of the crude reaction material was more complex than anticipated. The desired product, *N*-phenyl 4-oxo-pentanamide **10i**, was isolated, although in only 33% yield after recrystallization. No other products were identified, but the 33% yield for the chain-extended product was significantly lower than those obtained for most other substrates. Since efficient chain extension of *N*-phenyl-*N*-methyl 3-oxo-butanamide **10c** had already demonstrated that the toleration of an aromatic group on the amide nitrogen, the reduced yield in the chain extension of **9i** is likely due to the enhanced acidity of the amide hydrogen.



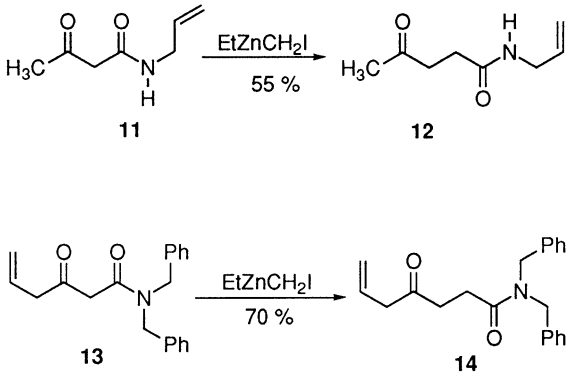
Scheme 2.

However it is important to note that in this substrate, as well as others, no N-methylated products were observed.[10]

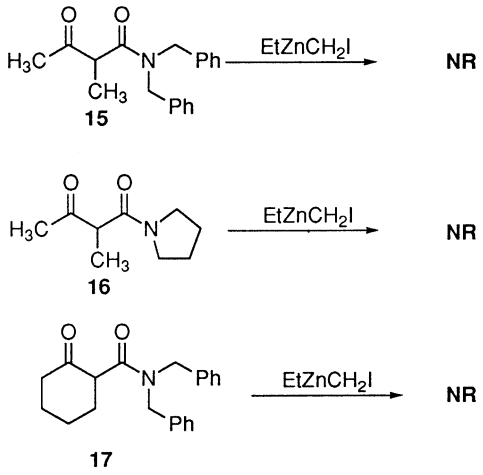
The one-pot chain extension method was also applied to a primary β-keto amide, acetoacetamide **9j**. Once again the ^{1}H NMR spectrum of the crude reaction mixture was more complex than that of the chain extension reactions reported above. The expected product, levulinamide **10j**, was isolated, but the difficulty experienced in extracting the water-soluble product after the aqueous work-up and the generation of numerous unidentified byproducts were responsible for the 10% yield.

Substrates containing olefin functionality were successfully chain-extended when exposed to a zinc carbenoid (Scheme 2). When *N*-(2-propenyl) 3-oxo-butanamide **11** was subjected to zinc-mediated chain extension reaction conditions, the reaction time was limited to 15 min in an effort to prevent cyclopropane formation. The simple chain-extended product **12** was formed in 55% yield. An inseparable byproduct, presumed to be due to concomitant cyclopropane formation, was present in a trace amount (estimated at less than 5% by ^{1}H NMR analysis). Similar results were obtained when *N*,*N*-dibenzyl 3-oxo-6-heptenamide **13** was treated with the Furukawa reagent for 30 min. The simple chain-extended keto amide **14** was again the major product formed; only a trace of cyclopropanated product (estimated at less than 5% by ^{1}H NMR analysis) was evident in the ^{1}H NMR spectrum of the purified product.

We reported in an earlier communication[6] that attempts to prepare γ-keto esters from α-substituted β-keto esters resulted in complex mixtures of products and only modest yields of the desired α-substituted 1,4-dicarbonyl compounds. It was anticipated that similar complications would arise when the one-pot zinc-mediated chain extension reaction was applied to α-substituted β-keto amides. Surprisingly, when *N*,*N*-dibenzyl 2-methyl-3-oxo-butanamide **15** was subjected repeatedly to the zinc carbenoid for 30 min, no reaction was observed (Scheme 3). When the reaction time was extended to several hours, none of the desired chain-extended product was observed. Analysis by ^{1}H- and ^{13}C NMR spectra suggested that substrate decomposition had occurred. No evidence for the formation of chain-extended products were observed with 1-(2-methyl-1,3-dioxobutyl)pyrrolidine **12**, and 2-oxo-cyclohexane-carboxylic acid dibenzyl amide **17**.



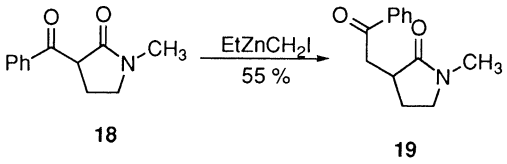
Scheme 3.



Scheme 4.

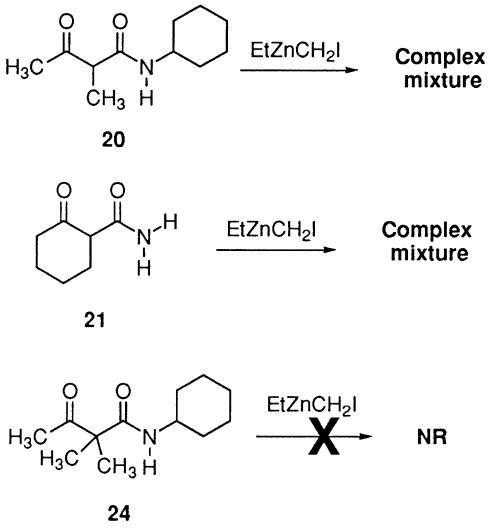
A control reaction was performed to insure that the lack of reactivity of these substrates was not due to inactivation of the zinc carbenoid. A mixture of equal molar amounts of 1-(1,3-dioxobutyl)pyrrolidine **9a** and 1-(2-methyl-1,3-dioxobutyl)pyrrolidine **16** was subjected to chain extension reaction conditions. The ^{1}H NMR spectrum of the crude reaction mixture indicated that compound **9a** was consumed with concomitant formation of the chain-extended product **10a**. Once again no evidence for the formation of the anticipated α-substituted chain-extended product was indicated.

Previous studies on the chain extension reaction[7] had shown that diethyl zinc could be used to form the zinc enolate of a β-keto phosphonate. Addition of the zinc enolate generated in this fashion to a solution of the zinc carbenoid provided the chain-extended product. When this variation was applied to the α-substituted substrate **15**, neither ethane gas evolution nor γ-keto amide products were observed. When 1-(2-methyl-1,3-dioxobutyl)pyrrolidine **16** was treated with one equivalent of neat diethyl zinc and the solvent removed under reduced pressure, a ^{1}H NMR spectrum of the crude residue revealed no evidence of enolate formation. For comparison, the same procedure was applied to the α-unsubstituted β-keto amide **9a**. In this case the ^{1}H NMR spectrum showed clearly that the expected enolate had been formed, although some starting material **9a** was also evident. A lactam, 3-benzoyl-1-methyl-2-pyrrolidone **18**, was subjected to chain extension reaction conditions. A ^{1}H NMR of the crude reaction mixture showed a mixture of starting material and the desired chain-extended product **19**. By extending the reaction time to 2 h, starting material was fully consumed and the pure chain-extended product was obtained in 58% yield (Scheme 4).



18 19

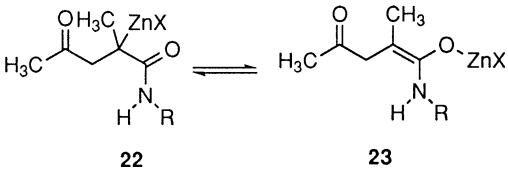
Scheme 5.



Scheme 6.

The inability of the unreactive α-substituted substrates to form enolates is consistent observations of Evans and coworkers.[17] They reported that α-substituted β-keto imides exhibited surprisingly low acidity as evidenced by their resistance to epimerization and H–D exchange in acidic and weakly basic media. The low acidity was attributed to the predisposition of the acyclic methine hydrogen to lie nearly orthogonal to the π-system of the adjacent imide carbonyl function in order to minimize A(1,3) steric interactions (Scheme 5).

The suggestion that enolate formation was involved in chain extension was supported by the NMR investigation of the sole α-substituted-β-keto amide (**18**) that underwent chain extension. Treatment of a $CDCl_3$ solution of α-benzoyl lactam **18** with diethyl zinc resulted in the evolution of a gas and provided a ^1H NMR spectrum that showed a mixture of starting material, enolate, and dissolved ethane gas. While the intermediacy of a zinc enolate appears to be a sufficient for the reaction, an intermediate enol form[18] will experience similar destabilizing interactions to those of the enolate (Scheme 6).

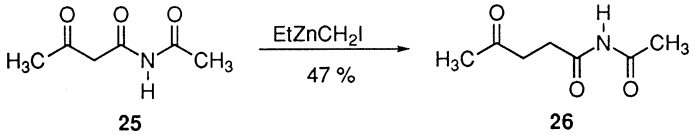


22 23

Scheme 7.

In contrast to the tertiary amides, α-substituted secondary amides were expected to react when subjected to chain extension reaction conditions, since steric interactions between the single substituent on the nitrogen and the α-substituent could be avoided by placement of the amide alkyl substituent *syn* to the amide carbonyl. Indeed, the behavior of *N*-cyclohexyl 2-methyl-3-oxo-butanamide **20** was very different from that of the tertiary substrates. When the reaction of **20** with 5 equiv. of the zinc carbenoid was allowed to proceed for 30 min, an extremely complex reaction mixture was observed. Efforts to obtain cleaner reaction mixtures and to consume starting material through variation of carbenoid equivalents and variation of reaction times from 30 s to 6 h were unsuccessful. Exposure of an α-substituted primary β-keto amide, 2-oxocyclohexanecarboxamide **21**, to chain extension reaction conditions also provided a complex mixture which included significant amounts of starting material. The rapid consumption of the 'excess' zinc carbenoid by the chain extension intermediate appears to be responsible for the complex reaction mixtures, consisting of higher molecular weight materials. One explanation for this behavior is that the presence of the α-substituent promotes isomerization of a relatively unreactive carbon-bound zinc intermediate **22**[19] to a more reactive O-metallated species **23**. This nucleophilic O-metallated species reacts with various electrophilic species to produce a complex array of products, including homologated products. The lack of reactivity of an α-disubstituted secondary β-keto amide **24** with the zinc carbenoid demonstrates that the complex reaction mixtures observed with **20** and **21** were not due to the presence of the secondary amide nitrogen.

A β-keto imide was used to further test the limitations of the chain extension reaction (Scheme 7). *N*-Acetyl acetoacetamide **25** was prepared by reacting diketene with acetamide in the presence of pyridine. Exposure of **25** to the zinc carbenoid for 15 min gave the chain-extended product **26** in 47% yield. Although it had been feared that the enhanced acidity of the imide hydrogen would interfere with the chain extension reaction, the successful preparation of **26** indicated that the presence of acidic protons does not forecast failure. The conclusion that imide functionality, isosteric with the β-dicarbonyl functionality, does not participate in the zinc-mediated reaction was tested by the reaction of two imides, succinimide and diacetamide. Both of these substrates failed to react when exposed to the zinc carbenoid and returned only starting material. The successful chain extension of the β-keto imide **25**, but not of the two imides,



25 26

Scheme 8.

suggest that acidity alone is not a predictor of success (Scheme 8).

3. Conclusion

In conclusion, the reaction of β-keto amides with the Furukawa reagent provides access to a wide variety of γ-keto amides, including primary, secondary, and tertiary amides. Although the reactivity of the α-substituted β-keto amides is in many cases unsatisfactory, the method can be applied to a broad spectrum of substrates that possess imide and olefinic functionality. Efforts are underway to further extend this chain extension reaction to amides systems of biological relevance.

4. Experimental

4.1. General

All reactions were run in oven-dried glassware under nitrogen atmosphere and stirred with teflon-coated magnetic stir-bars. The terms concentrated in vacuo or under reduced pressure refer to the use of a rotary-evaporator. Tetrahydrofuran and diethyl ether were distilled from purple benzophenone ketyl prior to use. Methylene chloride was distilled from phosphorous pentoxide. Ethyl acetate and hexanes were distilled prior to use. Reagents were purchased from commercial suppliers and used without further purification. Diethyl zinc was used as a 1.0 M solution in hexanes. Methylene iodide (CH_2I_2) was purchased from commercial suppliers and non-oxidized copper wire was added as a stabilizer. Column chromatography was performed on EM Science flash silica gel (35–75 μm). Mobile phases were used as noted. Thin Layer Chromatography (TLC) was carried out on EM Science F254 glass plates and visualized by UV and anisaldehyde or phosphomolybdic acid stains. The R_f values were determined with the same solvent used for column chromatography. Melting points were determined using an Electrothermal 9100 digital melting point apparatus and are uncorrected. Low Resolution Mass Spectroscopy were performed by the University of New Hampshire Instrumentation Center on a Perkin–Elmer 2400 Analyzer. High Resolution Mass Spectroscopy was performed at the University of California Riverside Mass Spectrometry Facility.

4.2. Starting material preparation

Starting materials **9a**,[20] **9b**,[20] **9c**,[21] **9d**,[22] **9h**,[20] **9i**,[21] **9j**,[23] **11**,[23] and **25**[24] were prepared by reaction of diketene with the appropriate amine. Starting materials **9e**[25] and **9f**,[25] were prepared by treating a β-keto ester with the corresponding amine. Starting material **18**[26] and **9g**[25] were prepared by a Claisen reaction. Compound **20**[27] was prepared by methylation of the β-keto amide **9h**. Compound **21** was prepared by a literature procedure.[28]

4.2.1. *N,N*-Dibenzyl 3-oxo-6-heptenamide (13). A 25 mL round-bottom flask was equipped with a stir bar, attached to a distillation head, and charged with 468 mg (3.0 mmol) of methyl 3-oxo-6-heptenoate[29] and 591 mg (3.0 mmol) of dibenzylamine. The reaction mixture was heated with stirring in a 160°C oil bath for 3 h and the methanol by-product of the reaction was removed by distillation. The reaction mixture was cooled, diluted with diethyl ether, and neutralized with dilute hydrochloric acid. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica (5:1, hexanes/ethyl acetate; R_f=0.25) to yield 262 mg (27%) of β-keto amide **13** as a clear yellow oil. Ketone and enol tautomers were present in a 90:10 ratio: ^{1}H NMR (360 MHz, $CDCl_3$) δ 14.80 (s, 1H, enol), 7.02–7.50 (m, keto and enol aromatic protons), 5.72–5.84 (m, keto and enol), 5.20 (s, 1H, enol), 4.94–5.04 (m, keto and enol), 4.61–4.62 (m, keto and enol benzylic protons), 4.41 (m, keto and enol benzylic protons), 3.61 (s, 2H, keto), 2.67 (m, keto and enol), 2.26–2.37 (m, keto and enol); ^{13}C NMR (90 MHz, $CDCl_3$) δ 203.7, 178.0, 172.0, 167.5, 136.7, 136.0, 129.1, 128.9, 128.7, 128.4, 128.1, 127.9, 127.5, 126.7, 126.4, 115.6, 50.6, 49.2, 48.4, 42.3, 35.3, 30.5, 27.5 (both keto and enol forms); IR (film) 3100–2900, 1717, 1700, 1653, 1636, 1457; HRMS (EI) M^+ Calcd for $C_{21}H_{23}NO_2$: 321.1727, found: 321.1732.

4.2.2. *N,N*-Dibenzyl 2-methyl-3-oxo-butanamide (15). A 25 mL round-bottom flask was equipped with a stir bar, attached to a distillation head, and charged with 3.6 g (25.0 mmol) of ethyl 2-methyl-acetoacetate and 4.92 g (25.0 mmol) of dibenzylamine. The reaction mixture was heated with stirring in a 160°C oil bath for 3 h and the ethanol by-product of the reaction was removed by distillation. The reaction mixture was cooled, diluted with diethyl ether, and neutralized with dilute hydrochloric acid. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica (3:1, hexanes/ethyl acetate; R_f=0.25) to yield 5.02 g (68%) of β-keto amide **15** as a viscous yellow oil. Only the ketone tautomer was evident by NMR: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.15–7.40 (m, 10H), 4.88 (d, 1H, J=15.7 Hz), 4.59 (d, 1H, J=17.4 Hz), 4.42 (d, 1H, J=15.7 Hz), 4.37 (d, 1H, J=17.4 Hz), 3.66 (q, 1H, J=6.9 Hz), 2.17 (s, 3H), 1.42 (d, 3H, J=6.9 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 205.0, 171.2, 137.0, 136.2, 129.1, 128.7, 128.2, 127.9, 127.6, 126.3, 51.6, 50.1, 48.6, 27.4, 14.1; IR (film) 3100–2850, 1725, 1653, 1600, 1496, 1455, 1420, 1357; HRMS (EI) M^+ Calcd for $C_{19}H_{21}NO_2$: 295.1572, found: 295.1566.

4.2.3. 1-(2-Methyl-1,3-dioxobutyl)pyrrolidine (16). A 100 mL two-necked round-bottom flask was equipped with a stir bar and a reflux condenser and charged with 30 mL of absolute ethanol. Sodium metal (460 mg, 20.0 mmol) was added slowly under nitrogen. When the sodium had reacted completely, 1-(1,3-dioxobutyl)pyrrolidine **9a** (2.95 g, 19.0 mmol) was added to the flask by syringe and the solution was heated to reflux using a heating mantle. Methyl iodide (2.84 g, 20.0 mmol) was added dropwise and refluxing was continued for 12 h. The reaction mixture was cooled and the ethanol was removed under reduced pressure. The residue was diluted with ethyl acetate, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica (ethyl acetate; R_f=0.3) to yield 1.65 g

(51%) of α-methyl β-keto amide **16** as a clear colorless liquid. Only the ketone tautomer was evident by NMR: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.42–3.56 (m, 5H), 2.19 (s, 3H), 1.84–1.92 (m, 2H), 1.95–2.05 (m, 2H), 1.37 (d, 3H, J=7.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 205.4, 168.5, 53.6, 46.9, 46.1, 27.1, 26.1, 24.3, 13.3; IR (film) 3000–2850, 1718, 1635, 1457, 1438; HRMS (EI) M^+ Calcd for $C_9H_{15}NO_2$: 169.1103, found: 169.1106.

4.2.4. 2-Oxo-cyclohexanecarboxylic acid dibenzylamide (17). A 25 mL round-bottom flask was equipped with a stir bar, attached to a distillation head, and charged with 4.25 g (25.0 mmol) of ethyl 2-cyclohexanonecarboxylate and 4.92 g (25.0 mmol) of dibenzylamine. The reaction mixture was heated with stirring in a 160°C oil bath for 3 h and the ethanol by-product of the reaction was removed by distillation. The reaction mixture was cooled, diluted with diethyl ether, and neutralized with dilute hydrochloric acid. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The solid residue was recrystallized from 95% ethanol to yield 2.60 g (32%) of β-keto amide **17** as a white solid (mp=141.5–142.5°C). Only the ketone tautomer was evident by NMR: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.11–7.39 (m, 10H), 5.24 (d, 1H, J=15.1 Hz), 4.44 (d, 1H, J=17.4 Hz), 4.23 (d, 1H, J=17.4 Hz), 4.06 (d, 1H, J=15.1 Hz), 3.59 (dd, 1H, J=10.7, 5.7 Hz), 2.57 (m, 1H), 2.26–2.39 (m, 2H), 2.13 (m, 1H), 2.00–2.03 (m, 2H), 1.84 (m, 1H), 1.63 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.6, 170.5, 136.9, 136.5, 129.0, 128.6, 127.9, 127.7, 127.3, 126.3, 54.6, 49.9, 48.4, 42.0, 30.5, 27.0, 23.7; IR (KBr) 3100–2850, 1710, 1652, 1600, 1495, 1455, 1419; HRMS (EI) M^+ Calcd for $C_{21}H_{23}NO_2$: 321.1727, found: 321.1733.

4.2.5. *N*-Cyclohexyl 2,2-dimethyl-3-oxo-butanamide (24). A 50 mL round-bottom flask was equipped with a stir bar and charged with 15 mL of anhydrous benzene, 7.5 mL of freshly distilled dimethylformamide, and sodium hydride (48 mg of a 60% dispersion in mineral oil, 1.2 mmol). The mixture was cooled to 10°C, then *N*-cyclohexyl-2-methyl-3-oxo-butanamide **20** (197 mg, 1.0 mmol) was dissolved in 1 mL of dimethylformamide and added by syringe. After stirring for 30 min, methyl iodide (284 mg, 2.0 mmol) was added by syringe and the mixture was heated for 15 min in a 40°C oil bath. The mixture was cooled, 10 mL of deionized water was added, and after stirring for 10 min the two phases were separated. The organic phase was washed twice with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica (1:1, hexanes/ethyl acetate; R_f=0.3) to yield 175 mg (80%) of β-keto amide **24** as a yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.69 (s, 1H), 3.74 (m, 1H), 2.23 (s, 3H), 1.83–1.87 (m, 2H), 1.58–1.71 (m, 3H), 1.36 (s, 6H), 1.02–1.34 (m, 5H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 209.4, 171.0, 56.0, 48.5, 32.7, 26.0, 25.4, 24.7, 22.3; IR (film) 3325, 2950–2800, 1750, 1675.

4.3. Chain extension reactions

4.3.1. 1-(1,4-Dioxopentyl)pyrrolidine (10a). A 50 mL round-bottom flask was equipped with a stir bar and charged with 15 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 5.0 mL, 5.0 mmol) under an inert atmosphere. The solution was cooled to 0°C and methylene iodide (0.40 mL, 5.0 mmol) in methylene chloride (2.5 mL) was added dropwise. The resulting white suspension was stirred for 10 min, then 1-(1,3-dioxobutyl)pyrrolidine **9a** (155 mg, 1.0 mmol) was added rapidly by syringe. The mixture was stirred for 30 min at 0°C, quenched with saturated aqueous ammonium chloride, and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica (ethyl acetate; R_f=0.2) to yield 79 mg (47%) of γ-keto amide **10a** as a clear colorless liquid that provided spectra consistent with those reported in the literature.[26] ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.41–3.49 (m, 4H), 2.80 (t, 2H, J=6.5 Hz), 2.53 (t, 2H, J=6.5 Hz), 2.22 (s, 3H), 1.92–2.00 (m, 2H), 1.81–1.89 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 208.1, 170.0, 46.4, 45.7, 37.9, 30.2, 28.4, 26.0, 24.4; IR (film) 2975–2875, 1716, 1627, 1455, 1367, 1167.

4.3.2. *N,N*-Dibutyl 4-oxo-pentanamide (10b). In the same fashion as described above, *N,N*-dibutyl 3-oxo-butanamide **9b** was treated with 5 equiv. of the Furukawa reagent for 45 min at 0°C. After aqueous work-up the crude residue was chromatographed on silica (3.5:1, hexanes/ethyl acetate; R_f=0.2) to yield 70% of γ-keto amide **10b** as a clear colorless liquid.[30] ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.23–3.33 (m, 4H), 2.78 (t, 2H, J=6.4 Hz), 2.59 (t, 2H, J=6.4 Hz), 2.23 (s, 3H), 1.44–1.60 (m, 4H), 1.25–1.37 (m, 4H), 0.89–0.97 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.7, 170.6, 47.3, 45.5, 37.9, 30.6, 29.8, 29.5, 26.7, 19.9, 19.8, 13.53, 13.49; IR (film) 2960, 2932, 1718, 1631, 1457; HRMS (EI) M^+ Calcd for $C_{13}H_{25}NO_2$: 227.1885, found: 227.1881.

4.3.3. *N*-Phenyl-*N*-methyl 4-oxo-pentanamide (10c). In the same fashion as described above *N*-phenyl-*N*-methyl 3-oxo-butanamide **9c** (191 mg, 1.0 mmol) was treated with 5 equiv. of the Furukawa reagent for 30 min at 0°C. Afer aqueous work-up, the crude residue was chromatographed on silica (1:1, hexanes/ethyl acetate; R_f=0.2) to yield 88% of γ-keto amide **10c** as a clear yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.41–7.45 (m, 2H), 7.32–7.36 (m, 1H), 7.24–7.28 (m 2H), 3.26 (s, 3H), 2.71 (t, 2H, J=6.3 Hz), 2.31 (t, 2H, J=6.3 Hz), 2.17 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.7, 171.8, 143.9, 129.8, 127.9, 127.4, 38.4, 37.3, 30.0, 28.3; IR (film) 3100–2900, 1717, 1654, 1596, 1497, 1389; HRMS (EI) MH^+ Calcd for $C_{12}H_{14}NO_2$: 205.1103, found: 205.1105; HRMS (EI) M^+ Calcd for $C_{12}H_{15}NO_2$: 205.1102, found: 205.1102.

4.3.4. *N,N*-Dimethyl 4-oxo-pentanamide (10d). In a similar fashion as described above, *N,N*-dimethyl 3-oxo-butanamide **9d** was treated with 3 equiv. of the Furukawa reagent for 15 min at 0°C. After aqueous work-up, the residue was chromatographed on silica (1.5:1, hexanes/acetone; R_f=0.2) to yield 60% of γ-keto amide **10d** as a clear colorless liquid. ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.03 (s, 3H), 2.93 (s, 3H), 2.77 (t, 2H, J=6.4 Hz), 2.59 (t, 2H, J=6.4 Hz), 2.22 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 208.1, 171.5, 38.1, 37.0, 36.0, 30.2, 27.2; IR (film) 3000–2800, 1725, 1625; HRMS (EI) M^+ Calcd for $C_7H_{13}NO_2$: 143.0946, found: 143.0944.

4.3.5. *N,N*-Dibenzyl 4-oxo-4-phenyl-butanamide (10e). In

the same fashion as described above, *N*,*N*-dibenzyl 3-oxo-3-phenyl-propanamide **9e** was treated with 4 equiv. of the Furukawa reagent for 30 min at 0°C. After aqueous work-up, the solid residue was recrystallized in 95% ethanol to yield 42% of γ-keto amide **10e** as a white crystalline solid (mp=85.0–86.5°C; lit mp=84–85°C).[31] ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.02–8.10 (m, 2H), 7.21–7.61 (m, 13H), 4.62 (s, 2H), 4.57 (s, 2H), 3.43 (t, 2H, *J*=6.4 Hz), 2.90 (t, 2H, *J*=6.4 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 199.1, 172.4, 137.3, 136.8, 136.4, 133.1, 129.0, 128.6, 128.5, 128.2, 128.1, 127.6, 127.4, 126.6, 49.9, 48.4, 33.8, 27.3.

4.3.6. *N*,*N*-Dibenzyl 5,5-dimethyl-4-oxo-hexanamide (10f). In the same fashion as described above, *N*,*N*-dibenzyl 4,4-dimethyl-3-oxo-pentanamide **9f** was treated with 4 equiv. of the Furukawa reagent for 30 min at 0°C. After an aqueous work-up, the residue was chromatographed on silica (10:1, hexanes/ethyl acetate; R_f=0.2) to yield 60% of γ-keto amide **10f** as a white solid (mp=74.5–75.5°C). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.18–7.39 (m, 10H), 4.59 (s, 2H), 4.52 (s, 2H), 2.94 (t, 2H, *J*=6.3 Hz), 2.68 (t, 2H, *J*=6.3 Hz), 1.20 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 214.9, 172.4, 137.2, 136.4, 128.9, 128.5, 128.0, 127.5, 127.2, 126.5, 49.8, 48.2, 43.9, 32.0, 27.0, 26.6; IR (KBr) 3100–2850, 1703, 1647; HRMS (CI/NH_3) MH^+ Calcd for $C_{22}H_{28}NO_2$: 338.2120, found: 338.2127.

4.3.7. *N*,*N*-Dimethyl 4-oxo-4-phenyl-butanamide (10g). In a similar fashion to that described above, *N*,*N*-dimethyl 3-oxo-3-phenyl-propanamide **9g** was treated with 3 equiv. of the Furukawa reagent for 15 min at 0°C. Following an aqueous work-up, the residue was chromatographed on silica (2:1, hexanes/acetone; R_f=0.15) to yield 59% of γ-keto amide **10g** of a clear yellow oil which provided spectra consistent with those reported in the literature.[32] ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.00–8.04 (m, 2H), 7.52–7.58 (m, 1H), 7.43–7.48 (m, 2H), 3.35 (t, 2H, *J*=6.6 Hz), 3.09 (s, 3H), 2.96 (s, 3H), 2.77 (t, 2H, *J*=6.6 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 199.3, 171.7, 136.9, 133.0, 128.5, 128.1, 37.1, 35.5, 33.7, 27.3; IR (film) 3100–2900, 1685, 1647.

4.3.8. *N*-Cyclohexyl 4-oxo-pentanamide (10h). In a similar fashion to that described above, *N*-cyclohexyl 3-oxo-butanamide **9h** was treated with 5 equiv. of the Furukawa reagent for 30 min at 0°C. After an aqueous work-up, the residue was chromatographed on silica (1:1, hexanes/ethyl acetate; R_f=0.2) to yield 81% of γ-keto amide **10h** as a white solid (mp=105.7–106.5°C) that provided spectra consistent with those reported in the literature.[33] ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.57 (s, 1H), 3.67–3.78 (m, 1H), 2.79 (t, 2H, *J*=6.5 Hz), 2.39 (t, 2H, *J*=6.5 Hz), 2.18 (s, 3H), 1.85–1.94 (m, 2H), 1.65–1.74 (m, 2H), 1.56–1.65 (m, 1H), 1.28–1.41 (m, 2H), 1.06–1.22 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.5, 171.0, 48.2, 38.7, 33.1, 30.2, 30.0, 25.5, 24.8; IR (KBr) 3295, 2934, 2854, 1709, 1632, 1558, 1436.

4.3.9. *N*-Phenyl 4-oxo-pentanamide (10i). In a similar fashion to that described above, then *N*-phenyl 3-oxo-butanamide **9i** (531 mg, 3.0 mmol) was treated with 3 equiv. of the Furukawa reagent for 30 min at 0°C. After aqueous work-up, the solid residue was recrystallized in diethyl ether to yield 33% of γ-keto amide **5i** as a white solid (mp=100.5–101.4°C; lit mp=99–100°C) that was consistent with the literature.[34] ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.48–7.50 (m, 2H), 7.26–7.31 (m, 2H), 7.06–7.10 (m 1H), 2.88 (t, 2H, *J*=6.2 Hz), 2.61 (t, 2H, *J*=6.2 Hz), 2.21 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 208.0, 170.3, 137.9, 128.9, 124.1, 119.7, 38.6, 31.1, 30.0; IR (KBr) 3355, 3200–2800, 1725, 1679, 1546.

4.3.10. 4-Oxo-pentanamide (10j). In a similar fashion to that described above, acetoacetamide **9j** was treated with 4 equiv. of the Furukawa reagent for 30 min at 0°C. After an aqueous work-up, the residue was chromatographed on silica (1:1, hexanes/acetone; R_f=0.2) to yield 10% of γ-keto amide **10j** as a clear colorless oil that provided spectra consistent with those reported in the literature.[35] ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.65 (s, 1H), 5.38 (s, 1H), 2.81 (t, 2H, *J*=6.4 Hz), 2.25 (t, 2H, *J*=6.4 Hz), 2.20 (s, 3H).

4.3.11. *N*-(2-Propenyl) 4-oxo-pentanamide (12). In a similar fashion to that described above, *N*-(2-propenyl) 3-oxo-butanamide **11** was treated with 5 equiv. of diethyl zinc and methylene iodide for 15 min at 0°C. After an aqueous work-up, the residue was chromatographed on silica (ethyl acetate; R_f=0.3) to yield 55% of γ-keto amide **12** as a clear colorless liquid. ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.82 (ddt, 1H, *J*=17.2, 10.2, 5.5 Hz), 5.18 (dd, 1H, *J*=17.2, 1.4 Hz), 5.12 (dd, 1H, *J*=10.2, 1.4 Hz), 3.84–3.88 (m, 2H), 2.82 (t, 2H, *J*=6.4 Hz), 2.45 (t, 2H, *J*=6.4 Hz), 2.19 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.9, 171.7, 134.1, 116.3, 42.0, 38.6, 29.94, 29.88; IR (film) 3300, 1717, 1700, 1653, 1559, 1541; HRMS (EI) M^+ Calcd for $C_8H_{13}NO_2$: 155.0496, found: 155.0551.

4.3.12. *N*,*N*-Dibenzyl 4-oxo-7-octenamide (14). In a similar fashion to that described above, *N*,*N*-dibenzyl 3-oxo-6-heptenamide **13** was treated with 5 equiv. of the Furukawa reagent for 30 min at 0°C. After an aqueous work-up, the residue was chromatographed on silica (5:1, hexanes/ethyl acetate; R_f=0.2) to yield 70% of γ-keto amide **14** as a clear yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.18–7.40 (m, 10H), 5.81 (ddt, 1H, *J*=16.9, 10.1, 6.5 Hz), 5.04 (dd, 1H, *J*=16.9, 1.6 Hz), 4.98 (dd, 1H, *J*=10.1, 1.6 Hz), 4.58 (s, 2H), 4.49 (s, 2H), 2.82 (t, 2H, *J*=6.2 Hz), 2.72 (t, 2H, *J*=6.2 Hz), 2.62 (t, 2H, *J*=7.4 Hz), 2.34–2.40 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 209.1, 172.2, 137.2, 136.4, 129.0, 128.6, 128.2, 127.6, 127.4, 126.5, 115.2, 49.9, 48.3, 42.0, 37.4, 27.8, 27.1; IR (film) 3100–2900, 1713, 1650; HRMS (CI/NH_3) MH^+ Calcd for $C_{22}H_{26}NO_2$: 336.1963, found: 336.1971.

4.3.13. 1-Methyl-3-phenacyl-2-pyrrolidone (19). In a similar fashion to that described above, 3-benzoyl-1-methyl-2-pyrrolidone **18** was treated with 4 equiv. of the Furukawa reagent for 2 h at 0°C. After aqueous work-up, the residue was chromatographed on silica (2:1, hexanes/acetone; R_f=0.2) to yield 58% of γ-keto amide **19** as a clear yellow oil which provided spectra consistent with those reported in the literature.[36] ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.97–7.99 (m, 2H), 7.54–7.60 (m, 1H), 7.43–7.49 (m, 2H), 3.71 (m, 1H), 3.30–3.43 (m, 2H), 2.94–3.05 (m, 2H), 2.89 (s, 3H), 2.48 (m, 1H), 1.68 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.3, 175.8, 136.6, 133.2, 128.6, 128.0, 47.7,

40.7, 37.7, 29.9, 25.7; IR (film) 3100–2850, 1685 (broad), 1600, 1500, 1460, 1410, 1275; HRMS (EI) M^+ Calcd for $C_{13}H_{15}NO_2$: 217.1103, found: 217.1107.

4.3.14. *N*-Acetyl 4-oxo-pentanamide (26). In a similar fashion, *N*-acetyl acetoacetamide **25** was treated with 3 equiv. of the Furukawa reagent for 15 min at 0°C. After an aqueous work-up, the residue was chromatographed on silica (1.5:1, hexanes/ethyl acetate; R_f=0.3) to yield 47% of γ-keto imide **26** as a white solid (mp=111.3–112.6°C). ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.86 (s, 1H), 2.80 (s, 4H), 2.33 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.0, 173.0, 172.0, 37.2, 31.1, 29.9, 25.0; IR (film) 3250, 3150, 1735, 1715, 1701; HRMS (CI/CH_4) M^+ Calcd for $C_7H_{11}NO_3$: 219.1259, found: 219.1255.

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