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The Invention of Radical Reactions. Part XXXIV.[1] Homologation of Carboxylic Acids to α-Keto Carboxylic Acids by Barton-ester Based Radical Chain Chemistry

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Abstract: Carboxylic acids can be transformed into the homologous α-keto acids by Barton-ester based radical chemistry. This method was especially successful when ethyl α-trifluoroacetoxy acrylate was used as a radical trap.

INTRODUCTION

Since Berzelius first described[2] the properties of pyruvic acid in 1835, considerable interest has developed in α–keto acids. It has long been known that α-oxo carboxylic acids play an important role in various biochemical and metabolic pathways.[3-10]

Knowledge of α–keto acids and a general pathway for their synthesis is desirable especially for a better understanding of amino acid metabolism.

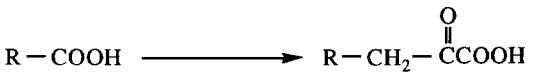
The synthetic significance of α–keto acids and their usefulness has been described by Bergmann and Grafe[5] and extended by Shemin and Herbst[6] for the synthesis of peptides. α–Keto acids are also of major importance not only as useful intermediates in the biosynthesis of fats, carbohydrates, proteins, porphyrins and nucleic acids,[7] but also in the therapy of certain medical conditions, e.g. uremia and nitrogen accumulation disorders.[8] Recently, Giese[9] also used α–keto acids to synthesize 3-deoxy-D-manno-2-octulosonic acid (KDO) which has important biological functions at the cell surfaces of Gram negative bacteria.[10]

Due to the important biological role of this functional group, a number of different methods for the preparation of α-keto acids have been developed.[11-35] We report here a new radical synthesis for the transformation of carboxylic acids into their α-oxo acid homologs.[36]

This paper is dedicated to Professor L Ghosez on the occasion of his 60th birthday.

Objective and Proposed Method

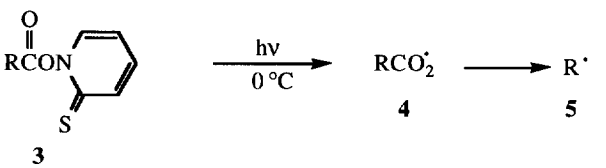
The goal of the following work is to describe a new and more convenient method for the transformation shown in **eq.1**; i.e. the conversion of acids **1** into homologous α-keto acids **2**.[37]



1 **2**

Equation 1

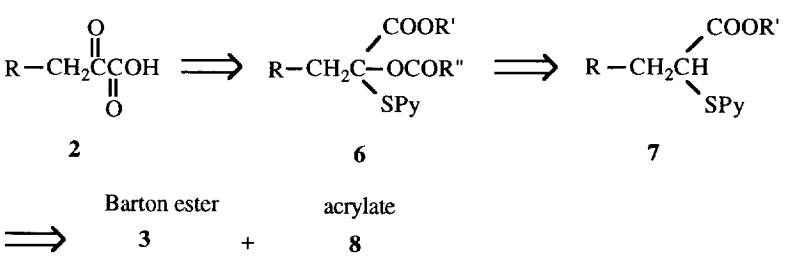
Here we demonstrate the transformation of C_n carboxylic acids **1** into C_{n+2} α-keto acids **2**.[36] This strategy[1a, 38-40] is again based on the chemistry of the disciplined carbon radicals **5** generated from *O*-acyl-*N*-hydroxy-2-thiopyridone derivatives **3** *via* the corresponding acyloxy radicals **4** (**eq. 2**).[41-44]



3 **4** **5**

Equation 2

It has been shown previously, that phenyl vinyl sulfone is a suitable radical trap[45] which allows us to develop an alternative[38] to the Arndt-Eistert reaction.[46] The use of this trap allows the homologation of carboxylic acids. In order to form a terminal α-keto acid group, an extra carbonyl group is needed in the the α-position. The ideal olefin would theoretically be an alkyl acrylate.[47] Thus, we believed it would be possible to use such olefins as synthons for the synthesis of α-keto acids (**Scheme 1**).



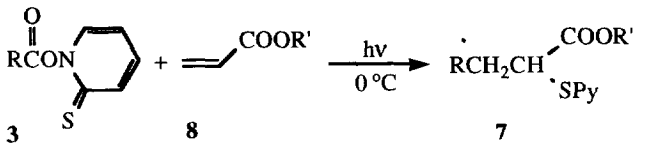
2 **6** **7**

3 **8**

Scheme 1

Synthesis of α-Keto Acids using Alkyl Acrylates

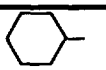
Methyl acrylate **8a** and ethyl acrylate **8b** were chosen as radical traps since they are readily available. The addition reactions of primary, secondary, and tertiary acid derived radicals were each examined (**eq. 3, Table 1**).



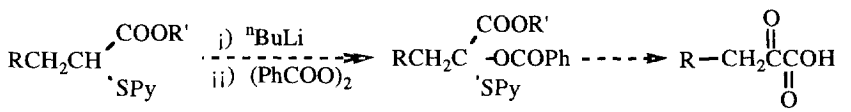
3 8 7

Equation 3

Table 1 Yields of the addition of radicals to olefins **8a** and **8b**.

R =		R' =		yield (%)	
3a	$PhCH_2CH_2$–	**8a**	Me	**7a**	98
		8b	Et	**7b**	96
3b		**8a**	Me	**7c**	95
		8b	Et	**7d**	93
3c		**8a**	Me	**7e**	94
		8b	Et	**7f**	91

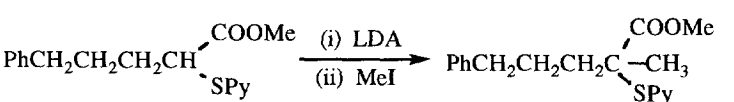
The elaboration of the addition product **7a** to the desired keto acid **2** was studied using a variety of methods. Benzoylation of the radical addition product **7a** was attempted using benzoyl peroxide together with several bases (NaH, ^{n}BuLi, LDA), over the temperature range -78 °C to 0 °C (**Scheme 2**).



7 6 2

Scheme 2

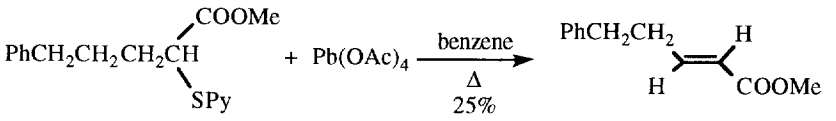
However, in each case studied no reaction was observed and the starting material was recovered unchanged. A blank experiment proved that LDA was indeed forming the anion (using the same compound, **7a** and LDA, followed by CH_3I to quench the anion afforded 90% of compound **9** (**eq. 4**)). However, the use of LDA followed by dry benzoyl peroxide still gave back the starting material.



7a 90% **9**

Equation 4

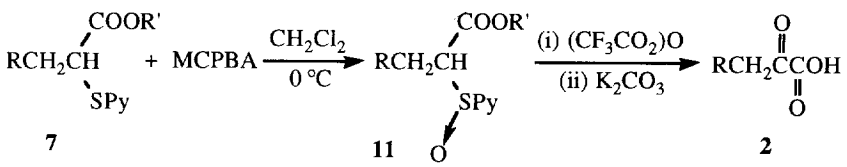
When lead tetraacetate (LTA)[48] was used instead of benzoyl peroxide, the starting material was again recovered unchanged. Following the procedure of Cox and Mosher,[49] using only LTA and refluxing in benzene, a 25% yield of the elimination product **10** and a 75% yield of the starting material **7a** (**eq. 5**) were isolated. The reaction of **7a** at room temperature with LTA and pyridine, again gave back starting material. Replacing lead tetraacetate by iodosobenzene diacetate[50] as the oxidant also led to the complete recovery of starting material.



7a **10**

Equation 5

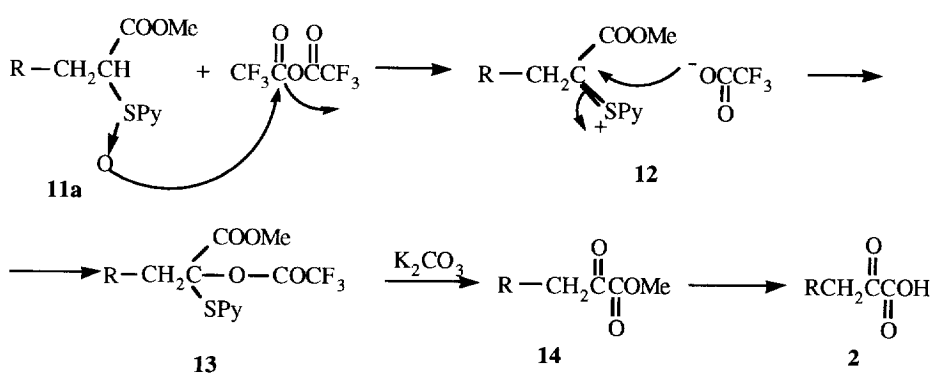
Following the Pummerer rearrangement-based procedure developed earlier,[1a, 36] the addition product **7** was oxidized to the corresponding sulfoxide **11a** using MCPBA. Reaction with trifluoroacetic anhydride[51b,c] then gave the Pummerer-type[51a] intermediate which was hydrolyzed with K_2CO_3/MeOH (**Scheme 3, Table 2**).



7 **11** **2**

Scheme 3

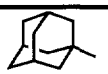
The formation of the keto ester is facilitated by elimination of the thiopyridyl unit as shown in **Scheme 4**.



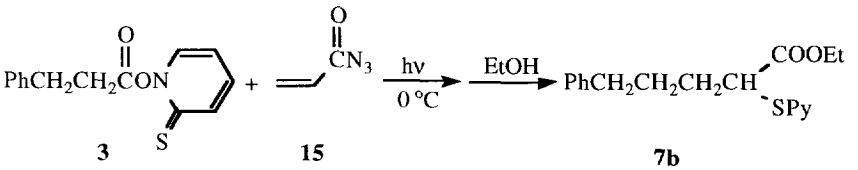
11a **12** **13** **14** **2**

Scheme 4

Table 2 Radical homologation of carboxylic acids to α-keto acids using the Pummerer rearrangement.

R =	R' =	yield (%)	
		7 → 11	**7 → 2**
a: $PhCH_2CH_2$–	Me	95	85
	Et	95	85
b: 	Me	92	82
	Et	92	82
c: 	Me	89	81
	Et	89	81

We were also interested in examining various olefins as radical traps in an attempt to improve this process. Acryloyl azide **15** was prepared from acryloyl chloride by treatment with sodium azide in a 64% yield.[52] Irradiation of Barton ester **3a** in the presence of acryloyl azide **15**, afforded addition product **7b** in 89% yield after workup with ethanol (**Scheme 5**).



Scheme 5

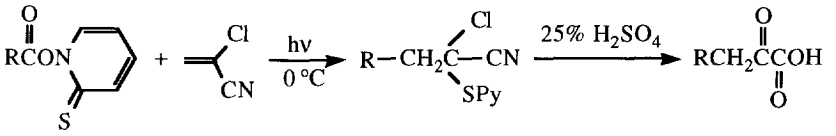
The yield of the addition product is related to the competition between the radicophilic thiocarbonyl group of *N*-hydroxy thiopyridone derivatives and the electrophilic olefin trap. The alkyl acrylates gave better addition yields (95%) than the acryloyl azide (89%).

Study of 1,1-Disubstituted Olefins for the Synthesis of α-Keto Acids

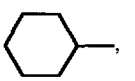
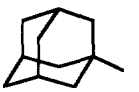
Although the method developed above is useful for transforming acids to homologous α-keto acids, it still has the same limitations associated with the oxidation step. In the case of certain substrates it would be ideal if the oxidation step could be eliminated. Thus, to improve this method the application of disubstituted olefins was studied.

First we chose a readily available olefin, 2-chloroacrylonitrile **16**. This olefin reacted smoothly with radicals. The yield of addition product **17** was determined by ^1H NMR. Hydrolysis of the crude adducts with

25% sulfuric acid (**Scheme 6**) led to an overall conversion from the Barton ester **3** to the α-keto acid **2** in low to moderate yield (**Table 3**).

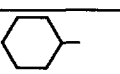
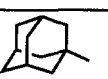


3 **16** **17** **2**

R = **a**: $PhCH_2CH_2$–, **b**:  , **c**: 

Scheme 6

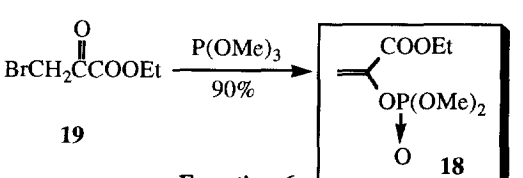
Table 3 Radical homologation of carboxylic acids to α-keto acids with olefin **16**.

	yield (%)		
	a: $PhCH_2CH_2$–	**b**: 	**c**: 
3 → **17**	90[x]	74[x]	56[x]
17 → **2**	45[y]	42[y]	45[y]
3 → **2**	40	31	25

[x]Determined by NMR. [y]Isolated yield.

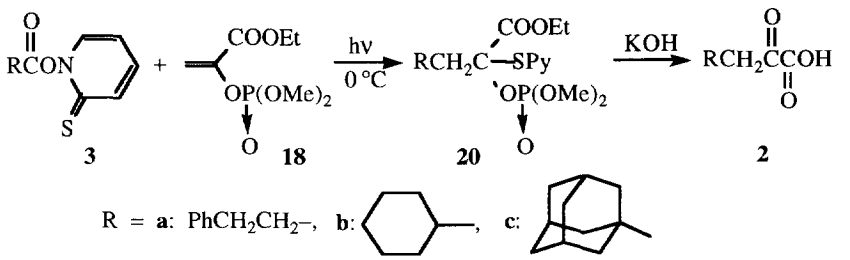
As shown in **Table 3**, the addition yield of tertiary radicals was also low. We tried to increase the yield of the addition product by the addition of more equivalents of olefin **16** without success.

Since 1-cyanovinyl phosphate is a good radical trap, we became interested in the preparation of acrylate **18**.[53] Acrylate **18** was obtained in 90% yield by treating ethyl bromopyruvate **19** with trimethyl phosphite (**eq. 6**). As previously described, we first irradiated the *N*-hydroxy thiopyridone derivatives **3a-c** in the presence of **18** followed by hydrolysis with 1M potassium hydroxide to obtain the desired homologous α-keto acids **2** (**Scheme 7, Table 4**).[54]



19 **18**

Equation 6



Scheme 7

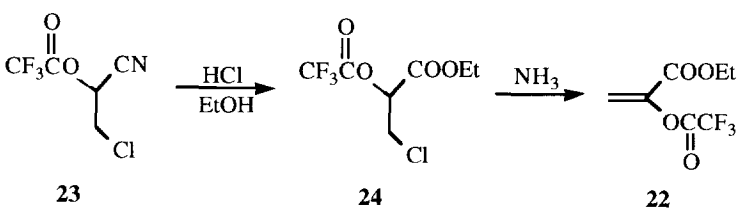
Table 4 Radical homologation of carboxylic acids to α-keto acids with olefin **18**.

R =	**3** → **20** yield[x] (%)		**20** → **2** yield[y] (%)	**3** → **2** Total yield (%)	
	2 equiv. of **18**	5 equiv. of **18**		2 equiv. of **18**	5 equiv. of **18**
$PhCH_2CH_2$–	85	92	89	76	82
	76	83	85	65	71
	54	69	87	47	60

[x]Determined by NMR. [y]Isolated yield.

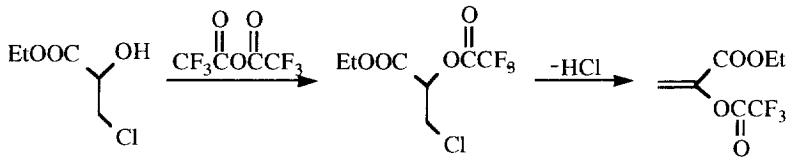
As shown in **Table 4** the yields of **2** obtained using 1-cyanovinyl phosphate (60-82%) are substantial improvement compared to the yields obtained with 2-chloroacrylonitrile (25-40%) (**Table 3**).

For acid homologation the best olefin was 1-trifluoroacetoxy acrylonitrile **30**. Thus, it was assumed that 1-trifluoroacetoxy acrylate **22** would also serve as a good radical trap. 1-Trifluoroacetoxy acrylate **22** has been obtained by treating 1-trifluoroacetoxy-2-chloropropionitrile **23** with dry HCl/EtOH to solvolyze the nitrile to the corresponding ester **24**. Addition of NH_3 promoted elimination to give the desired product **22** (**Scheme 8**).[55]



Scheme 8

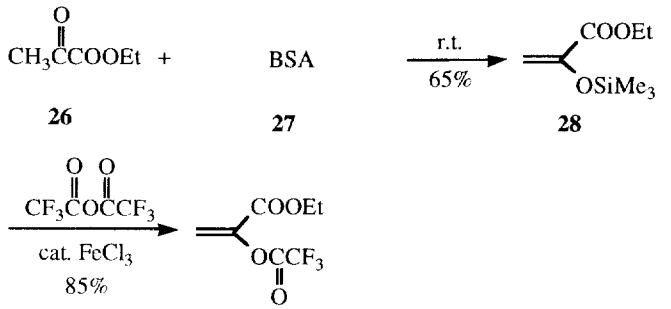
A similar method started with 2-hydroxy-3-chloropropionate **25**. This alcohol reacts first with trifluoroacetic anhydride and then NH_3, to afford the desired olefin **22** (**Scheme 9**).



25 **23** **22**

Scheme 9

The problem with these two methods is that the starting materials **23** and **25** are not readily available. Thus, we tried using the method for preparing 1-trifluoroacetoxy acrylonitrile **21** to prepare the olefin **22**. Ethyl pyruvate **26** reacts with *N,O*-bis(trimethylsilyl)acetamide (BSA) **27** to afford olefin **28**. Olefin **28** was then treated with trifluoroacetic anhydride in the presence of a catalytic amount of ferric chloride to yield the desired olefin **22** (**Scheme 10**).[56] Although this is a good method, we aimed at preparing **22** in fewer steps and in high yield.

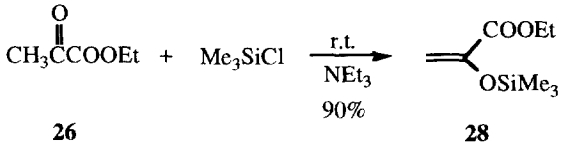


26 **27** **28** **22**

Scheme 10

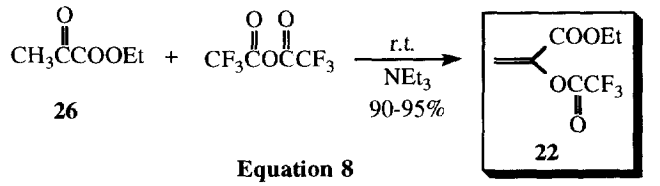
Creary and co-workers[57] prepared benzoyl trimethylsiloxy ethylene, which is similar to **28** using 1-phenylpropane-1,2-dione and chlorotrimethylsilane followed by treatment with triethylamine. We used this method by mixing ethyl pyruvate **26** and chlorotrimethylsilane followed by the dropwise addition of triethylamine at room temperature to afford **28** in 90% yield (**eq. 6**). We then extended this method by using trifluoroacetic anhydride instead of Me_3SiCl. When we repeated the reaction with trifluoroacetic anhydride 1-trifluoroacetoxy acrylate **22** was isolated in 90-95% yield (**eq. 8**).

The use of olefin **22** for the synthesis of α-ketoacids was then examined with primary, secondary, and tertiary radicals at 0 °C. Hydrolysis of the trapping product with aqueous potassium carbonate furnished the corresponding homologous α-keto acids **2** (**Scheme 11, Table 5**).



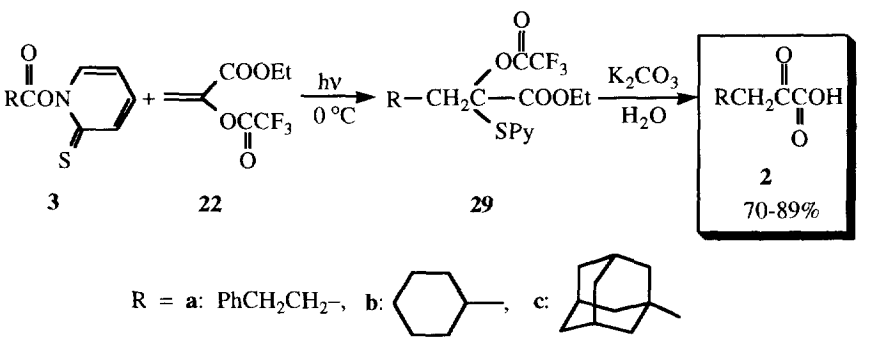
26 **28**

Equation 7



26 **22**

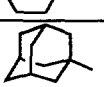
Equation 8



3 **22** **29**

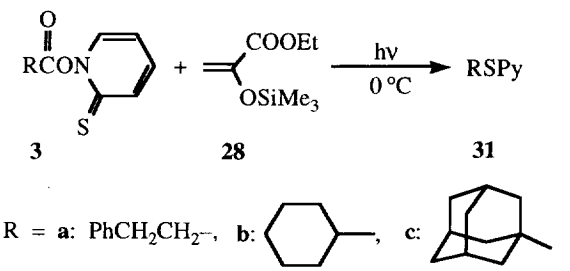
Scheme 11

Table 5 Radical homologation of carboxylic acids to α-keto acids with olefin **22**.

R =	yield (%)		
	3 → 29	**29 → 2**	**3 → 2**
a: $PhCH_2CH_2$–	97	92	89
b: 	90	90	81
c: 	75	93	70

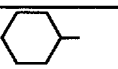
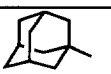
So far, 2-trifluoroacetoxy acrylate **22** has shown the best addition yield (75-97%) and the best hydrolysis yield (90-93%).

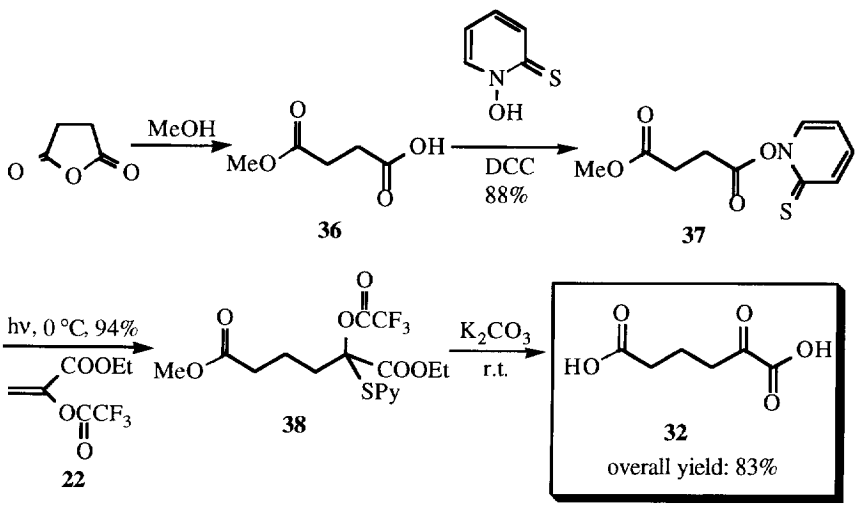
We have found earlier,[1a] that we did not have good addition yields with the capto-dative olefin trimethylsilylvinyl nitrile **30**. Boger and Mathvink[58] used olefin **28** as a radical trap in their phenyl selenoester/^{n}BuSnH system to afford the addition product in 54% yield. However in our system, after irradiation, we only isolated 90% of the rearranged product **31** and olefin **28** remained unreacted (**eq. 9**).



Equation 9

Table 6 Yields of the rearranged product in the attempted reaction of radicals with olefin **28**.

R =	a: $PhCH_2CH_2$–	b: 	c: 
3 → **31** Yield (%)	95	91	91



Scheme 12

From these studies we concluded that the 2-(trifluoroacetoxy)acrylate **22** was the olefin of choice for the Barton ester based radical synthesis of α-keto acids.

Based on our strategy that includes the use of **22** as a radical trap, we have synthesized the expensive 2-oxoadipic acid **32** in 83% overall yield. The monomethyl ester of succinic acid **36** was synthesized by the procedure of Cason.[59]

Coupling of **36** with *N*-hydroxy-2-thiopyridone cleanly afforded the corresponding Barton ester **37** in 88% yield, which was then irradiated in the presence of olefin **22** to afford addition product **38** in 94% yield. Hydrolysis with the aqueous potassium carbonate gave compound **32** in 99% yield (for the hydrolysis step) (**Scheme 12**). This method leads to a higher overall yield (83 %) than the method previously reported.[60] It can be used generally for primary, secondary, and tertiary radicals.

The olefin **22** as well as its congener 2-trifluoroacetoxy acrylonitrile **30**, studied in Part XXXIII[1a] should be excellent electrophilic partners in Diels-Alder chemistry. Some preliminary experiments were promising.

Conclusion

Among the different olefins prepared and studied, α-trifluoroacetoxy acrylate gave the best results for the synthesis of α-keto acids. The synthetic potential of this methodology was demonstrated with a Barton ester-based radical synthesis of the expensive 2-oxoadipic acid in 83% overall yield.[62]

Experimental

General Procedures and Starting Materials.

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Proton NMR (^{1}H NMR) spectra were recorded at 200 MHz with either a Varian XL-200E or a Varian Gemini-200 instrument. Carbon NMR (^{13}C NMR) spectra were recorded at 50 MHz with either a Varian XL-200E or a Varian Gemini-200 instrument. Proton and carbon chemical shifts are reported on the delta scale as parts per million (ppm) downfield from tetramethylsilane (TMS) as internal reference. Mass spectra (MS) were obtained by Dr. T. Sharp on a VG analytical Model 70-S Spectrometer. Infrared (IR) spectra were recorded on a Perkin-Elmer 881 Spectrometer. GC-MS analyses were performed on a Hewlett-Packard 5790A GC interfaced with a 5970A mass selective detector and a Hewlett-Packard model 9133 computer. Analytical gas chromatographic separations were performed on either a Chrompack Model 439 gas chromatograph or a Chrompack Model 437S gas chromatograph. Each GC was equipped with a J&W scientific (0.52 mm x 15m) DB-1 column and a flame ionization detector.

All water and air sensitive reactions were performed under an argon atmosphere in oven-dried glassware. All syringe transfers were performed according to standard techniques.

Tetrahydrofuran (THF, Fisher Scientific) and diethyl ether (Fisher Scientific) were distilled from sodium benzophenone ketyl under nitrogen immediately before use. Methylene chloride (CH_2Cl_2 , J. T. Baker or Mallinckrodt) was distilled from CaH_2 under nitrogen immediately before use. Absolute ethanol (Aaper Alcohol and Chemical Co., 200 proof) was degassed with argon and sealed with a septum prior to use. Triethylamine (Aldrich) and pyridine (Fisher Scientific) were distilled from KOH prior to use, and stored over 4A molecular sieves.

Thin layer chromatography (TLC) was performed using pre-coated aluminum plates which had an 0.2 mm layer of Silica Gel 60 F-254 (Merck - EM Science). Preparative TLC was carried out using pre-coated 20 x 20 cm glass plates having a 2 mm layer of Silica Gel GF (Analtech). Radial chromatography was performed on a Chromatotron with a glass rotor, coated with a 2 mm layer of Silica Gel 60 PF-254 (EM Scientific). Column chromatography was performed using Aldrich Silica Gel (130-270 mesh). Chromatographic solvent systems are indicated in the text. Celite used for filtration was either Celite 521 (Aldrich) or neutral alumina from Fisher (80-200 mesh).

Reagents were generally obtained from commercial sources and were used without further purification except as noted in the text.

General procedure A for the synthesis of *N*-hydroxy-pyridine-2-thione esters.

1,3-Dicyclohexylcarbodiimide (DCC, 1 equiv) and *N*-hydroxypyridine-2-thione (1 equiv) were dissolved in dry CH_2Cl_2 under an argon atmosphere. The solution was protected from light and kept at or below 0 ^{0}C. The appropriate carboxylic acid (1 equiv) in dry CH_2Cl_2 was added dropwise to the solution, and the reaction mixture was then allowed to warm up to room temperature. The yellow solution was quickly filtered through a bed of silica gel (again protected from light) and the silica gel was washed with some more CH_2Cl_2. The organic layers were then combined and concentrated to give a yellow crystalline product. The product can be further purified by recrystallization from CH_2Cl_2/hexanes and stored in a cool dark place until further use.

General procedure B for the synthesis of *N*-hydroxy-pyridine-2-thione esters.

N-hydroxy-pyridine-2-thione (1 equiv.) was dissolved in dry methylene chloride. The flask containing the solution was wrapped with aluminum foil to shield it from light, and cooled to 0 °C in an ice bath under an argon atmosphere. Dry pyridine (1 equiv.) was added dropwise to the solution. One equivalent of the appropriate acid chloride in dry methylene chloride was added dropwise. The solution was allowed to warm to room temperature with stirring. After two hours at room temperature, the yellow solution was quickly filtered through a silica gel column covered with aluminum foil. The column was then eluted with additional CH_2Cl_2. The organic solutions were combined and concentrated. The yellow solid was recrystallized from CH_2Cl_2/hexanes.

***N*-(Methyl succinoyloxy)-pyridine-2-thione (37)** was prepared from succinic acid monomethyl ester by following general procedure A. The compound was a yellow solid (90% yield): mp 95 °C; IR (CH_2Cl_2) 1813, 1732, 1524, 1442, 1412, 1207, 1072 cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 2.85 (m, 2H), 3.03 (m, 2H), 3.73 (s, 3H), 6.65 (m, 1H), 7.3 (m, 1H), 7.65 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.0, 28.4, 52.1, 112.6, 133.7, 137.21, 137.7, 168.1, 172.1, 175.7 ppm; Anal. Calcd for $C_{10}H_{11}NO_4S$: C, 49.79; H, 4.56; N, 5.81. Found: C, 49.69; H, 4.66; N, 5.89%.

General method for the photolysis of *N*-hydroxy-pyridine-2-thione esters.

The appropriate *N*-hydroxy-pyridine-2-thione derivative (1 equiv.) was dissolved in dry CH_2Cl_2 under argon (0.3M). The solution was irradiated at 0 °C with a 150W tungsten lamp (25 cm from reaction flask) until the reaction was complete by TLC. The products were quantified by isolation on silica gel (30% ethyl acetate/hexane).

General procedure for the photolysis of pyridine-2-thione derivatives with olefins.

The appropriate pyridine-2-thione derivative (1 equiv.) was dissolved in dry CH_2Cl_2 under argon (0.3M). The olefin (2 equiv.) was added and the reaction mixture was irradiated at 0-5 °C with a 150W tungsten lamp (25 cm from the reaction flask) until the reaction was complete by TLC. The products were quantified by either isolation on silica gel (30% ethyl acetate-hexane) or by ^{1}H NMR (with dioxane as internal standard). However, the crude product may be hydrolyzed without purification.

1-Phenylethyl-2'-thiopyridine (31a)[43e] was prepared by following the general procedure. The compound is a yellow liquid (95% yield): IR (CH_2Cl_2) 3011, 2904, 1605, 1512, 1423, 1314, 1205, 1115 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 3.0 (t, 2H, J = 7.14 Hz), 3.45 (t, 2H, J = 7.14 Hz), 7.0 (m, 1H), 7.1-7.4 (m, 6H), 7.5 (m, 1H), 8.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 31.5, 35.9, 119.4, 122.4, 126.4, 128.3, 128.5, 128.6, 135.9, 149.5. MS, m/e (relative intensity), 215 (M^+, 1.5), 111 (100), 91 (45), 65 (32).

1-Cyclohexyl-2'-thiopyridine (31b)[43e] was prepared by following the general procedure . The compound is a yellow liquid (94% yield): IR (CH_2Cl_2) 2911, 1432, 1311, 1262, 1115 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.2-1.8 (m, 8H), 2.0-2.2 (m, 2H), 3.7-3.9 (m, 1H), 6.9 (m, 1H), 7.1 (m, 1H), 7.4 (m, 1H), 8.4 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.6, 25.7, 33.0, 42.6, 119.0, 122.6, 135.7, 149.2 ppm; MS, m/e (relative intensity): 193 (M^+, 2.1), 111 (100).

1-Adamantyl-2'-thiopyridine (31c)[43e] was prepared by following the general procedure . The compound is a yellow liquid (91% yield): IR (CH_2Cl_2) 2875, 2840, 1570, 1565, 1412, 1310, 1208 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.75 (m, 6H), 2.12 (m, 9H), 7.05 (m, 1H), 7.40 (m, 1H), 7.55 (m, 1H), 8.5 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 29.8, 36.2, 43.3, 49.9, 119.7, 121.5, 136.3, 149.4 ppm; MS, m/e (relative intensity), 245 (M^+, 2.2), 135 (100) 111 (90).

1-Propanyl-2'-thiopyridine (31d) was prepared by following the general procedure. The compound was a yellow liquid (91% yield): IR (CH_2Cl_2) 1416, 1402, 1308, 1255 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.0-1.1 (t, 3H, J = 7.44 Hz), 1.6-1.8 (m, 3H), 3.15 (t, 2H, J = 7.4 Hz), 7.0 (m, 1H), 7.2 (m, 1H), 7.45 (m, 1H), 8.4 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3, 22.6, 31.69, 119.0, 121.9, 135.7, 149.2 ppm; MS, m/e (relative intensity): 153 (M^+, 2.2), 111 (100), 43 (57).

Methyl 3-(2'-thiopyridyl) propanoate (37) was prepared by following the general procedure . The compound was a yellow liquid (91% yield): IR (CH_2Cl_2) 2923, 1735, 1472, 1442, 1328, 1256, 1131, 1105, 1030 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 2.8 (t, 2H, J = 7.1 Hz), 3.45 (t, 2H, J = 7.1 Hz), 3.7 (a, 3H), 6.95 (m, 1H), 7.15 (m, 1H), 7.4-7.5 (m, 1H), 8.4 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.8, 43.3, 51.7, 119.4, 122.3, 135.8, 149.4, 158.1, 172.5 ppm.

Methyl 5-phenyl-2-(2'-thiopyridyl)pentanoate (7a) was prepared by following the general procedure with methyl acrylate (98% yield); IR (CH_2Cl_2) 3033, 2935, 2852, 1723, 1563, 1433, 1254, 1205, 1153, 1132, 1038 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.7-2.1 (m, 4H), 2.65 (t, 2H, J = 7.26 Hz), 3.69 (s, 3H), 4.65 (t, 1H, J = 7.22 Hz), 6.95 (m, 1H), 7.1-7.3 (m, 6H), 7.45 (m, 1H), 8.4 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.7, 31.3, 35.2, 45.9, 52.3, 119.8, 122.1, 125.7, 128.2, 128.2, 136.0, 141.6, 149.2, 157.0, 172.9 ppm; MS, m/e (relative intensity), 301 (M^+, 4.2), 241 (29.6), 196 (51.6), 182 (59.0), 164 (51.6), 111 (100), 91 (99.7), 78 (54.5), 67 (42.0); Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.74; H, 6.35; N, 4.65. Found: C, 67.90; H, 6.43; N, 4.48%.

Ethyl 5-phenyl-2-(2'-thiopyridyl)pentanoate (7b) was prepared by following the general procedure with ethyl acrylate (96% yield); IR (CH_2Cl_2) 3061, 3028, 2984, 2861, 1718, 1576, 1491, 1414, 1370, 1263, 1158, 1123, 1089, 1025 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.2 (t, 3H, J = 7.16 Hz), 2.1-1.6 (m, 4H), 2.65 (t, 2H, J = 7.4 Hz), 4.1-4.25 (q, 2H, J = 7.16 Hz), 4.6 (t, 1H, J = 7.26 Hz), 6.95 (m, 1H), 7.1-7.3 (m, 6H), 7.43 (m, 1H), 8.35 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 28.7, 31.3, 35.2, 46.2, 61.0, 119.7, 122.1, 125.6, 128.1, 128.2, 135.9, 141.5, 149.1, 157.2, 172.3 ppm; MS, m/e (relative intensity), 315 (M^+, 19.4), 270 (9.5), 241 (15.6), 196 (22.1), 164 (50.9), 111 (100), 91 (66.3), 78 (28.5), 67 (19.3); Anal. Calcd for $C_{18}H_{21}NO_2S$: C, 68.6; H, 6.72; N, 4.44; S, 10.16. Found: C, 68.5; H, 6.94; N, 4.26; S, 9.70%.

Methyl 3-cyclohexyl-2-(2'-thiopyridyl)propanoate (7c) was prepared by following the general procedure with methyl acrylate (95% yield); IR (CH_2Cl_2) 2934, 2850, 1723, 1542, 1432, 1249, 1205, 1153, 1132, 1034 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 2.1-1.1 (m, 13H), 3.55 (s, 3H), 4.7 (t, 1H, J = 7.9 Hz), 7.0 (m, 1H), 7.2 (m, 1H), 7.5 (m, 1H), 8.4 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.1, 25.9, 26.2, 32.7, 35.3, 39.0, 44.3, 60.8, 119.5, 121.6, 135.8, 149.1, 157.4, 172.8 ppm; MS, m/e (relative intensity), 301 (M^+, 42), 241 (29.6), 196 (51.6), 182 (59.0), 164 (51.6), 111 (100), 91 (99.7), 78 (54.5), 67 (42.0); HRMS Calcd for $C_{15}H_{21}NO_2S$: 279.12943. Found: 279.12939.

Ethyl 3-cyclohexyl-2-(2'-thiopyridyl)propanoate (7d) was prepared by following the general procedure with ethyl acrylate (93% yield); IR (CH_2Cl_2) 2983, 2927, 2852, 1721, 1576, 1448, 1415, 1358, 1263, 1157, 1123, 1092, 1033 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 2.0-1.8 (m, 16H), 4.1-4.25 (q, 2H, J = 7.22 Hz), 4.6 (t, 1H, J = 7.76 Hz), 7.0 (m, 1H), 7.2 (m, 1H), 7.45 (m, 1H), 8.4 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 25.9, 26.2, 32.7, 35.3, 39.0, 44.3, 60.8, 119.5, 121.6, 135.8, 149.1, 157.4, 172.8 ppm; MS, m/e (relative intensity), 293 (M^+, 8.4), 248 (5.9), 210 (94.7), 164 (50.3), 151 (30.2), 111 (100), 78 (29.0), 67 (24.4), 55 (34.1), 41 (35.6); HRMS Calcd for $C_{16}H_{23}NO_2S$: 293.14509. Found: 293.14511.

Methyl 3-(adamant-1-yl)-2-(2'-thiopyridyl)propanoate (7e)[43e] was prepared by following the general procedure with methyl acrylate (94% yield); IR (CH_2Cl_2) 3033, 2918, 2845, 1722, 1513, 1423, 1254, 1205, 1143, 1132, 1038 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 2.0-1.5 (m, 17H), 3.7 (s, 3H), 4.65 (m, 1H), 7.0 (m, 1H), 7.2 (m, 1H), 7.5 (m, 1H), 8.4 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.5, 33.2, 36.8, 41.2, 42.0, 46.6, 52.3, 119.8, 122.2, 136.0, 157.2, 173.9 ppm; MS, m/e (relative intensity), 331 (M^+, 9.4), 196 (100), 164 (24.5), 135 (34.6), 111 (75.3) 79 (29.3); HRMS Calcd for $C_{19}H_{25}NO_2S$: 331.16075. Found: 331.16085.

Ethyl 3-(adamant-1-yl)-2-(2'-thiopyridyl)propanoate (7f)[43e] was prepared by following the general procedure with ethyl acrylate (91% yield); IR (CH_2Cl_2) 2908, 2849, 1723, 1576, 1448, 1414, 1157, 1022 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 2.0-1.2 (m, 17H), 4.1-4.3 (q, 2H, J = 7.08 Hz), 4.6 (dd, 1H, J = 8.77 Hz, 8.77 Hz), 7.0 (m, 1H), 7.2 (m, 1H), 7.5 (m, 1H), 8.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 28.5, 33.2, 36.8, 41.6, 42.1, 46.4, 61.1, 119.8, 122.2, 136.0, 149.3, 157.4, 173.4 ppm; MS, m/e (relative intensity), 345 (M^+, 11.0), 300 (6.2), 272 (4.8), 178 (13.2), 164 (41.4), 135 (54.8), 111 (100), 79 (41.1), 67 (22.2); HRMS Calcd for $C_{20}H_{27}NO_2S$: 345.17641. Found: 345.17694.

2-Chloro-2-(2'-thiopyridyl)-butanitrile (17a) was prepared by following the general procedure with **16** (90% yield); IR (CH_2Cl_2) 3017, 2930, 1562, 1484, 1441, 1411, 1277, 1145, 1117, 1040, 1026 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 2.1-2.2 (m, 1H), 2.4-2.7 (m, 1H), 2.73 (t, 2H, J = 6.4 Hz), 7.2-7.4 (m, 6H), 7.5 (m, 1H), 7.68 (m, 1H), 8.6 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.8, 34.5, 42.6, 63.1, 116.5, 123.1, 126.1, 126.9, 128.2, 128.4, 137.1, 140.4, 150.2, 152.6 ppm; MS, m/e (relative intensity), 302 (M^+, 4.7), 267 (73.1), 112 (61.6), 111 (100), 91 (87.8), 78 (40.9); HRMS Calcd for $C_{16}H_{15}ClN_2S$ 302.06464. Found: 302.06445.

2-Chloro-3-cyclohexyl-2-(2'-thiopyridyl)-propanitrile (17b) was prepared by following the general procedure with **16** (74% yield); IR (CH_2Cl_2) 2930, 1482, 1449, 1421, 1259, 1150, 1109, 1026 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 0.9-2.1 (m, 11H), 2.4 (t, 2H, J = 6.4 Hz), 7.3 (m, 1H), 7.6 (m, 1H), 7.75 (m, 1H), 8.65 (m, 1H).

3-Adamant-1-yl-2-chloro-2-(2'-thiopyridyl)-propanitrile (17c) was prepared by following the general procedure with **16** (56% yield); IR (CH_2Cl_2) 2930, 1472, 1445, 1429, 1249, 1105, 1026 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.5-2.1 (m, 15H), 2.4 (s, 2H), 7.3 (m, 1H), 7.5 (m, 1H), 7.75 (m, 1H), 8.75 (m, 1H).

Ethyl 5-phenyl-2-(2'-thiopyridyl)-2-trifluoroacetoxy pentanoate (29a) was prepared by following the general procedure with **22** in a NMR tube without isolation (97%): ^1H NMR ($CDCl_3$) δ 1.2 (t, 3H, J = 7.2 Hz), 1.85 (m, 2H), 2.4 (t, 2H, J = 7.14 Hz), 2.65 (t, 2H, J = 7.16 Hz), 4.2 (q, 2H, J = 7.2 Hz), 7.15 (m, 1H), 7.2-7.3 (m, 5H), 7.45 (m, 1H), 7.65 (m, 1H), 8.6 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 25.2, 34.9, 35.4, 62.9, 93.3, 123.7, 122.9, 126.0, 128.3, 128.4, 130.22, 137.3, 140.9, 149.9, 151.6, 165.9 ppm.

Ethyl 3-cyclohexyl–2-(2'-thiopyridyl)-2-trifluoroacetoxy propanoate (29b) was prepared by following the general procedure with **22** in a NMR tube without isolation (90%): ^1H NMR ($CDCl_3$) δ 0.9-2.0 (m, 13H), 2.4 (m, 2H), 4.15 (m, 2H), 7.35 (m, 1H), 7.65 (m, 1H), 7.75 (m, 1H), 8.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.5, 25.2, 26.0, 28.0, 33.7, 42.5, 62.9, 93.5, 124.1, 131.0, 137.9, 149.4, 151.3, 165.9 ppm.

Ethyl 3-adamant-1-yl–2-(2'-thiopyridyl)-2-trifluoroacetoxy propanoate (29c) was prepared by following the general procedure with **22** in a NMR tube without isolation (75%): ^1H NMR ($CDCl_3$) δ 1.2 (t, 3H, J = 7.2 Hz), 1.6-2.0 (m,

15H), 2.3-2.65 (m, 2H), 4.15 (m, 2H), 7.4 (m, 1H), 7.6 (m, 1H), 7.8 (m, 1H), 8.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4, 28.5, 36.5, 42.5, 48.7, 62.9, 92.9, 124.4, 131.2, 138.41, 149.0, 151.2, 165.9 ppm.

Ethyl 5-(methoxycarbonyl)-2-(2'-thiopyridyl)-2-trifluoroacetoxy-pentanoate (38) was prepared by following the general procedure with **22** in a NMR tube without isolation (94%): ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.2 Hz), 1.9 (m, 2H), 2.4 (m, 4H), 3.7 (s, 3H), 4.25 (q, 2H, J = 7.2 Hz), 7.31 (m, 1H), 7.56 (m, 1H), 7.7 (m, 1H), 8.6 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 19.1, 33.0, 35.4, 51.5, 63.0, 92.9, 123.6, 130.2, 137.2, 150.0, 151.6, 165.8, 172.8 ppm.

General method for the oxidation of pyridylthio groups thiopyridine (-SPy) to the mixture of the corresponding R and S sulfoxides (-SOPy).

A solution of MCPBA (1 equiv.) in dry CH_2Cl_2 was added dropwise to the appropriate thiopyridine (-SPy) derivative (1 equiv.) in dry CH_2Cl_2 at 0-5 °C under argon. On completion of the reaction (TLC), the mixture was diluted with CH_2Cl_2, washed with sodium thiosulfate, sodium bicarbonate, water, and brine, and then dried over $MgSO_4$. The organic layer was concentrated under reduced presure and the product quantified by ^{1}H NMR (with dioxane as internal standard).

Methyl 5-phenyl-2-(pyridine-2'-sulfinyl)pentanoate (11a) was prepared by following the general procedure (95% yield); IR (CH_2Cl_2) 3058, 3029, 2951, 2861, 1721, 1600, 1573, 1491, 1423, 1270, 1152, 1037, 989 cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 1.7-1.9 (m, 1.8H), 2.0-2.2(m, 1.2H), 2.5 (t, 0.8H, J = 7.12 Hz), 2.65 (t, 1.2H, J = 7.12 Hz), 3.5 (s, 1.8H), 3.7 (s, 1.2H), 3.8-4.0 (m, 1H), 7.05 (m, 1H), 7.1-7.3 (m, 5H), 7.35 (m, 1H), 7.9 (m, 1H), 8.6 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.0, 28.6, 35.0, 51.6, 66.5, 119.8, 124.6, 125.6, 127.9, 128.0, 137.4, 140.9, 149.1, 162.4, 166.1, and 23.7, 28.2, 34.8, 52.3, 67.5, 120.2, 124.8, 125.5, 127.9, 127.8, 137.6, 140.8, 149.2, 162.5, 168.4 ppm; MS, m/e (relative intensity), 317 (M^+, 4.2), 286 (0.8), 269 (9.6), 259 (1.5), 156 (64.1), 127 (47.0), 105 (97.8), 91 (100), 78 (93), 65 (45.4); HRMS Calcd for $C_{17}H_{19}NO_3S$: 317.10867. Found: 317.10871.

Ethyl 5-phenyl-2-(pyridine-2'-sulfinyl)pentanoate (11b) was prepared by following the general procedure (95% yield); IR (CH_2Cl_2) 3060, 3029, 2986, 2937, 2863, 1733, 1601, 1574, 1491, 1446, 1421, 1367, 1331, 1248, 1084, 1054 cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 1.0 (t, 1.5H, J = 7.12 Hz), 1.25 (t, 1.5H, J = 7.12 Hz), 1.8 (m, 1.8H), 2.1-2.2(m, 1H), 2.5 (t, 1H, J = 7.12 Hz), 2.65 (t, 1H, J = 7.12 Hz), 3.8-3.9 (m, 1H), 3.7 (s, 1.2H), 3.9-4.0 (q, 1H, J = 7.12 Hz), 4.1-4.2 (q, 1H, J = 7.12 Hz), 7.05 (m, 1H), 7.1-7.3 (m, 5H), 7.35 (m, 1H), 7.9 (m, 1H), 8.6 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.5, 25.3, 28.6, 35.0, 60.7, 66.3, 119.9, 124.5, 125.5, 127.9, 127.9, 137.3, 140.9, 149.0, 162.5, 165.6, and 13.7, 23.7, 28.2, 34.8, 61.4, 67.5, 120.3, 124.7, 125.4, 128.0, 127.8, 137.5, 140.8, 149.2, 162.6, 167.9 ppm; MS, m/e (relative intensity), 331 (M^+, 0.3), 269 (0.2), 256 (0.5), 156 (7.3), 111 (14.1), 104 (12.1), 91 (100), 78 (22.1), 67 (16.5), 28 (38.1).

Methyl 3-cyclohexyl-2-(pyridine-2'-sulfinyl)propanoate (11c) was prepared by following the general procedure (92% yield); IR (CH_2Cl_2) 2931, 2853, 1734, 1574, 1560, 1422, 1329,1262, 1165, 1085, 1038 cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 0.8-2.0 (m, 13H), 3.5 (m, 1.8H), 3.8 (s, 1.2H), 3.8-4.0 (m, 1H), 7.45 (m, 1H), 8.0-7.9 (m, 2H), 8.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.6, 25.8, 32.2, 32.8, 35.2, 51.7, 64.4, 119.8, 124.7, 137.4, 149.2, 162.6, 166.5, and 25.4, 25.7, 31.7, 32.6, 34.9, 52.4, 65.8, 120.3, 124.8, 137.6, 149.3, 162.7, 168.9 ppm; MS, m/e (relative intensity), 295 (M^+, 0.7), 187 (26.9), 156 (28.3), 156 (28.3), 111 (34.9), 78 (100), 67 (57.9), 55 (90.0), 41 (86.6); HRMS Calcd for $C_{15}H_{21}NO_3S$: 295.40268. Found: 295.40169.

Ethyl 3-cyclohexyl-2-(pyridine-2'-sulfinyl)propanoate (11d) was prepared by following the general procedure (92% yield); IR (CH_2Cl_2) 2985, 2928, 2853, 1725, 1574, 1446, 1256, 1217, 1158, 1086, 1052 cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 1.0-1.9 (m, 14H), 1.9-2.1 (m, 2H), 3.85-4.0 (m, 2H), 4.2-4.3 (m, 1H), 7.4-7.5 (m, 1H), 7.9-8.0 (m, 2H), 8.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 25.7, 26.0, 31.7, 32.9, 35.2, 60.8, 64.2, 120.1, 124.6, 137.4, 149.1, 162.8, 166.0, and 13.8, 25.5, 25.9, 31.1, 32.4, 35.1,

61.5, 65.9, 120.5, 124.8, 137.6, 149.3, 162.9, 168.5 ppm; MS, m/e (relative intensity), 308 (M^+-1, 0.5), 236 (1.5), 183 (9.4), 127 (27.4), 111 (26.0), 78 (100), 67 (31.4), 51 (59.2), 39 (57.6).

Methyl 3-adamant-1-yl-2-(pyridine-2'-sulfinyl)propanoate (11e) was prepared by following the general procedure (89% yield); IR (CH_2Cl_2) 2918, 2851, 1727, 1575, 1560, 1446, 1423, 1353, 1326, 1298, 1264, 1176, 1160, 1086, 1050 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.3-2.0 (m, 17H), 3.49 (s, 1.86H), 3.76 (s, 1.14H), 3.84 (dd, 0.38H, J = 3.06 Hz, 12.9 Hz), 3.95 (dd, 0.62H, J = 3.06 Hz, 12.9 Hz), 7.45 (m, 1H), 8.0-7.85 (m, 2H), 8.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.0, 32.2, 36.2, 41.2, 41.5, 51.6, 61.8, 119.7, 124.7, 149.0, 162.4, 167.0, and 27.9, 31.8, 36.1, 38.8, 41.1, 52.3, 63.5, 120.3, 124.8, 137.5, 149.2, 162.4, 169.4 ppm; MS, m/e (relative intensity), 347 (M^+, 1.8), 228 (25.2), 213 (16.7), 164 (13.9), 135 (100), 93 (36.4), 79 (51.7), 41 (29.4), 28 (85.7); HRMS Calcd for $C_{19}H_{25}NO_3S$: 347.47844. Found: 347.47931.

Ethyl 3-adamant-1-yl-2-(pyridine-2'-sulfinyl)-propanoate (11f) was prepared by following the general procedure (89% yield); IR (CH_2Cl_2) 2985, 2907, 2849, 1725, 1575, 1445, 1424, 1368, 1323, 1297, 1258, 1220, 1161, 1105, 1053 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.1-2.0 (m, 20H), 3.8-4.3 (m, 3H), 7.45 (m, 1H), 8.0-7.85 (m, 2H), 8.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.5, 28.0, 32.5, 36.3, 39.4, 41.7, 61.8, 62.3, 120.0, 124.8, 137.4, 149.1, 162.7, 166.6, and 13.8, 28.1, 32.1, 36.4, 38.3, 41.4, 60.9, 63.8, 120.6, 124.9, 137.8, 149.3, 162.9, 166.0 ppm; MS, m/e (relative intensity), 360 (M^+-1, 1.0), 332 (3.9), 284 (5.7), 235 (10.0), 213 (51.1), 178 (22.3), 135 (100), 79 (49.1), 67 (19.5).

General method for the hydrolysis of a sulfoxide (-SOPy) to an acid (homoacid, keto acid, malonic acid).

Trifluoroacetic anhydride (5 equiv.) was added to a solution of appropriate sulfoxide (1 equiv.) in CH_2Cl_2 under argon at room temperature. After 2 h the reaction mixture was concentrated under reduced pressure and K_2CO_3 (10 equiv.)/H_2O (10 ml)/acetone (5 mL) was added. The solution was stirred overnight at room temperature. The acetone was removed under reduced pressure and the aqueous layer was washed with CH_2Cl_2 (20 mL), acidified with 1M HCl to pH=1 and extracted with ethyl acetate (10 mL X 3). The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by crystallization from ethyl acetate/hexane.

2-Oxo-5-phenylpentanoic acid (2a) was prepared by following the general procedure (85% yield): mp 65 °C (lit. mp 65 °C); IR (CH_2Cl_2) 3029, 1778, 1719, 1606, 1547, 1447, 1321, 1220, 1109 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 2.0 (m, 2H), 2.65 (t, 2H, J = 7.8 Hz), 2.9 (t, 2H, J = 7.26 Hz), 7.1-7.3 (m, 5H), 11.2 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 24.5, 34.7, 37.2, 126.1, 128.4, 128.5, 140.9, 160.6, 195.7 ppm; MS, m/e (relative intensity), 192 (M^+, 4.4), 165 (11.2), 117 (35.1), 104 (100), 91 (81.2), 28 (65.8).

2-Oxo-3-cyclohexylpropanoic acid (2b)[61] was prepared by following the general procedure (82% yield): IR (CH_2Cl_2) 3416, 2929, 2854, 1781, 1722, 1448, 1375, 1231, 1169, 1094, 1040 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 0.9-2.0 (m, 11H), 2.77 (d, 2H, J = 6.72 Hz), 11.2 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 25.8, 25.9, 32.9, 33.4, 45.2, 161.4, 195.1 ppm; MS, m/e (relative intensity), 170 (M^+, 0.6), 125 (40.9), 97 (61.6), 55 (100), 41 (44.0), 28 (21.4).

2-Oxo-3-adamany-1-ylpropanoic acid (2c) was prepared by following the general procedure (81% yield): mp 90-92 °C; IR (CH_2Cl_2) 3429, 2908, 1789, 1724, 1446, 1376, 1196, 1041 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.6-1.8 (m, 12H), 2.0 (m, 3H), 2.69 (s, 2H), 11.2 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 28.4, 34.5, 36.3, 42.1, 49.9, 162.0, 195.7 ppm; MS, m/e (relative intensity), 222 (M^+, 0.6), 206 (0.5), 177 (93.8), 149 (25.9), 135 (100), 93 (47.3), 79 (56.3), 69 (60.3), 45 (78.1); HRMS Calcd for $C_{13}H_{18}O_3$: 222.12964. Found: 222.13002.

2-Oxo-hexanedioic acid (32) was prepared by following the general procedure (83% yield): mp 118-119 °C (lit.[60] 123-125 °C, hydrate); IR (KBr) 3429, 2908, 1778, 1720, 1446, 1376, 1196, 1041 cm^{-1} ; ^1H NMR (aceton) δ 1.8 (m, 2H), 2.4 (t, 2H, J = 7.24 Hz), 2.9 (t, 2H, J = 7.14 Hz), 11.2 (bs, 1H); ^{13}C NMR (aceton) δ 18.8, 32.9, 38.1, 162.3, 175.7, 195.4 ppm.

Methyl 1-methyl-5-phenyl-1-(pyridine-2'-thiyl)pentanate (9).

A 1.6 M hexane solution of ^{n}BuLi (6.4 mL) was added dropwise to a solution of compound **7a** (10 mmole) in dry THF (15 ml) at -78 °C under argon for 5 min. After stirring for 20 min, methyl iodide (10.5 mmole) was added and the reaction mixture was allowed to warm to room temperature for 1h. The reaction was then quenched with saturated aqueous NH_4Cl solution (20 mL), and extracted with CH_2Cl_2 (4 x 20 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The product was isolated on silica gel (30% ethyl acetate/hexane) (90% yield): IR (CH_2Cl_2) 2957, 1727, 1576, 1419, 1268, 1125 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.65 (s, 3H), 1.7-2.1 (m, 2H), 2.65 (t, 2H, J = 7.26 Hz), 3.11 (t, 2H, J = 7.22 Hz), 3.7 (s, 3H), 7.0 (m, 1H), 7.1-7.3 (m, 6H), 7.5 (m, 1H), 8.4 (m, 1H); MS, m/e (relative intensity), 315 (M^+, 15.7), 196 (27.3), 111 (100), 104 (32.8), 91 (36.3); HRMS Calcd for $C_{18}H_{21}NO_2S$: 315.12930. Found: 315.12909.

Acryloyl azide (15).[52]

Sodium azide (5g, 77mmole) was dissolved in distilled water (12 mL) in a 50 ml 2 neck flask equipped with a reflux condenser and a dropping funnel, and cooled to 0 °C in an ice bath. Acryloyl chloride (5g, 55 mmole, 4.49 mL) was dissolved in dry toluene (14 mL), and added dropwise into the magnetically stirred cold sodium azide solution. The reaction mixture was stirred for 3 h at 0 °C, the organic layer was seperated and washed with cold saturated Na_2CO_3 solution and brine and dried over $CaCl_2$. The solvent was evaporated under reduced pressure (64% yield): IR (toluene) 2153 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 5.9-6.0 (m, 1H), 6.0-6.2 (m, 1H), 6.4-6.5 (m, 1H).

Dimethyl (1-ethoxycarbonyl)vinyl phosphate (18).[53]

Trimethyl phosphite (0.1 mole) was added dropwise to ethyl bromopyruvate (0.1 mole) at 0 °C under argon. The reaction mixture was stirred at room temperature for 1 h, then at 50 °C for 1 h. The product was isolated by distillation at 104-108 °C, 1 mmHg (92% yield): IR (CH_2Cl_2) 2963, 1740, 1634, 1450, 1375, 1281, 1192, 1057 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.34 (t, 3H, J = 7.1 Hz), 3.88 (d, 6H, J = 11.3 Hz), 4.29 (q, 2H, J = 7 Hz), 5.62 (t, 1H, J = 2.5 Hz), 5.98 (t, 1H, J = 2.36 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 55.9, 55.1, 61.8, 110.8, 110.9, 143.7, 143.6, 161.5 ppm; MS, m/e (relative intensity), 224 (M^+, 8.2), 179 (12.3), 151 (8.3), 127 (100), 109 (68.5); HRMS Calcd for $C_7H_{13}O_6P$: 224.24502. Found: 224.24582.

Ethyl 1-(trifluoroacetoxy)acrylate (22).[55]

Triethylamine (0.15 mole) and trifluoroacetic anhydride (0.2 mole) were added dropwise to a solution of ethyl pyruvate (0.1 mole) in dry CH_2Cl_2 (20 mL) at 0 °C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was evaporated under reduced pressure. The product was isolated by distillation at 46-48 °C, 8-9 mmHg (95% yield): IR (CH_2Cl_2) 2990, 1806, 1738, 1652, 1353, 1310, 1226, 1172, 1130, 1014, 936 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.34 (t, 3H, J = 7.12 Hz), 4.30 (q, 2H, J = 7.12 Hz), 5.72 (d, 1H, J = 2.6 Hz), 6.25 (d, 1H, J = 2.58 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 62.4, 105.7, 111.4, 117.2, 122.7, 115.6, 143.5, 153.9, 154.8, 155.7, 156.6, 159.5 ppm.

Ethyl 1-trimethylsilyloxyacrylate (28).[58]

Triethylamine (11 mmole) and trimethylsilyl chloride (11 mmole) were added to a solution of ethyl pyruvate (10 mmole) in dry CH_2Cl_2 (10 mL) at 0 °C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solvent was evaporated under reduced pressure and the product was then isolated by distillation at 80-85 °C, 760 mmHg (90% yield): IR (CH_2Cl_2) 1738, 1639, 1415, 1321, 1281, 1182, 1055 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 3.025 (s, 9H), 1.33 (t, 3H, J = 7.16 Hz), 4.23 (q, 2H, J = 7.16 Hz), 4.88 (d, 1H, J = 1.1 Hz), 5.61 (d, 1H, J = 1.1 Hz); ^{13}C NMR ($CDCl_3$) δ -0.1, 14.1, 61.1, 103.9, 147.1, 164.4 ppm.

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