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Catalytic syntheses of γ-functionalized α-keto esters from thioacetals and *N*,*O*-acetals

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Dedicated to Professor Dr. Dieter Enders on the occasion of his 65th birthday

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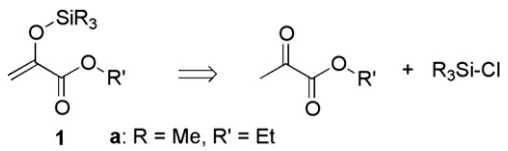
ABSTRACT

Ethyl 2-(trimethylsilyloxy)acrylic ester (**1a**) reacts with thioacetals providing the corresponding α-keto-γ-thio esters in good to satisfactory yields. Whereas aminals do not react, *N*,*O*-acetals lead to γ-amino-α-keto esters in good to excellent yields. All reactions proceed under mild reaction conditions, and no additional work up is required. Subsequent transformations of the obtained products to the corresponding α-oximes have been demonstrated.

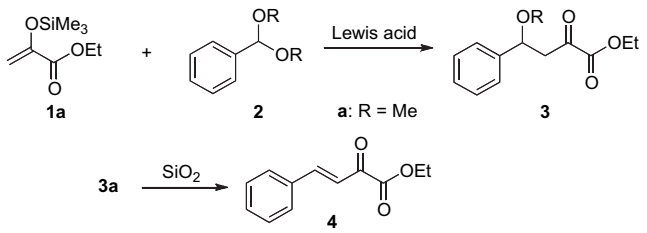
1. Introduction

Synthesizing densely functionalized molecules by easy means will always be a major challenge in organic chemistry. Key to success is the choice of appropriate starting materials. (Trialkylsilyloxy)acrylic esters **1** possess unique properties due to the captodative 1,1-substitution of the double bond bearing an electron-donating trialkylsilyloxy and an electron-withdrawing carbonyl group. Generally, syntheses of such unsaturated esters are straightforward and involve reactions between the corresponding pyruvates and trialkylsilyl chloride (Scheme 1).[1]



Scheme 1. (Trialkylsilyloxy)acrylic esters and their access from pyruvates and trialkylsilyl chloride.

Despite the interesting structural features of (trialkylsilyloxy) acrylic esters, only a rather limited number of reports dealing with synthetic applications of such compounds can be found in the literature. Those include the use of **1** in radical polymerization reactions[2] and applications as dienophiles in Diels–Alder reactions.[3] Baltas reacted **1** with epoxyaldehydes in Mukaiyama-aldol type reactions furnishing ulosonic and heptulosonic esters and analogues thereof.[4] Photocycloaddition reactions with **1** were studied by Bach, who prepared tetrahydrocyclobuta[*c*]-quinolin-3(4*H*)-ones as part of his (+)-meloscine synthesis.[5] Finally, the majority of applications stem from Sugimura, who reported reactions, such as the one between ethyl 2-(trimethylsilyloxy)acrylate (**1a**) and (dimethoxymethyl)benzene (**2a**), which provided γ-alkoxy-α-keto ester **3a** in good yield when performed in the presence of an excess of borontrifluoride etherate.[6] The product could then be reduced to β,γ-unsaturated α-keto ester **4**,[7] which itself proved valuable for synthetic organic chemistry (Scheme 2).[8]



Scheme 2. Synthesis of β,γ-unsaturated α-keto ester **4**.

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Recently, we improved Sugimura's protocol by developing a catalytic version of this synthetically useful C–C-bond forming process.[9] With $Cu(OTf)_2$ as Lewis acid, side reactions resulting from the acid sensitivity of the starting materials and products were avoided, and a simple room temperature work up afforded γ-alkoxy-α-keto esters **3** in yields up to 99%. Various functional groups were tolerated under these mild reaction conditions allowing a broadening of the reaction scope.

With the goal to extend the product portfolio, we turned our attention to reactions between ethyl 2-(trimethylsilyloxy)acrylate (**1a**) and other electrophiles. Starting from thioacetals and aminal-type compounds we envisaged the preparation of α-keto esters with thio or amino substituents at the γ-position. Here, we present the results of this study.

2. Results and discussion

Taking into account the importance of sulfur-containing compounds in organic synthesis,[10] conversions of thioacetals **5** were first investigated. For the preparation of suitable starting materials aldehydes were treated with thiols in the presence of CuBr as catalyst following a method described by Adapa.[11] A Lewis acid screening (Table 1) in reactions between ethyl 2-(trimethylsilyloxy) acrylate (**1a**) and thioacetal **5a** obtained from benzaldehyde and ethanethiol revealed that scandium(III)triflate was the optimal catalyst. Use of 10 mol % of this Lewis acid, which is known to act as catalyst in a variety of organic reactions,[12] provided α-keto-γ-thio ester **6a** in 62% yield (entry 1). An attempt to improve this result by addition of trifluoroethanol to the reaction mixture remained unsuccessful affording **6a** in only 19% yield (entry 2).[13] To our surprise, the yield of **6a** was also low (20%, entry 3) with copper(II)triflate, which had been the best metal catalyst in the acetal transformations. Applying 10 mol % of borontrifluoride etherate led to the same result (entry 4). Zinc triflate proved inactive (entry 5).

Next, the reaction scope was studied. All catalyses were performed with 10 mol % of $Sc(OTf)_3$ in dichloromethane at 0 °C. The results are summarized in Table 2.

Table 1
Screening of Lewis acids in reactions between **1a** and Thioacetal **5a**[a]

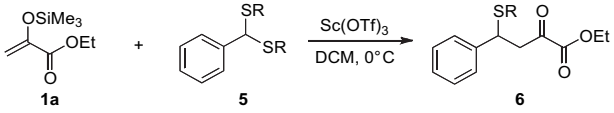
Entry	Lewis acid	% Yield[b]
1	$Sc(OTf)_3$	62
2	$Sc(OTf)_3$[c]	19
3	$Cu(OTf)_2$	20
4	$BF_3 \cdot OEt_2$	20
5	$Zn(OTf)_2$	—

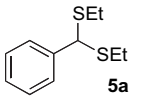
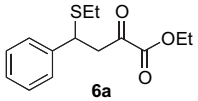
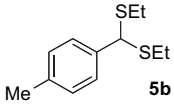
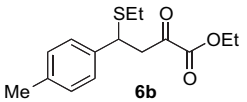
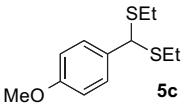
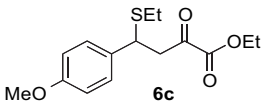
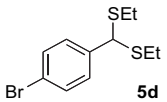
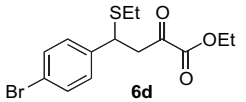
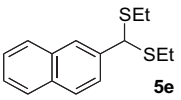
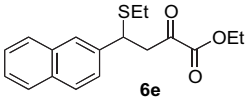
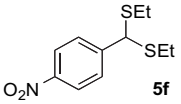
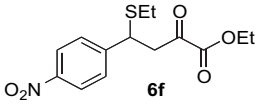
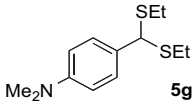
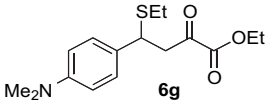
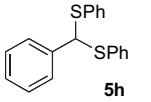
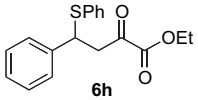
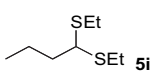
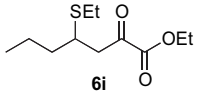
[a] Reaction conditions: the Lewis acid (10 mol %) was dissolved in DCM, and the resulting solution was cooled to 0 °C before **1a** and **5a** were added.
[b] After column chromatography.
[c] Trifluoroethanol (1.1 equiv) was added.

The reactions between ethyl 2-(trimethylsilyloxy)acrylate (**1a**) and thioacetals **5** to give the corresponding α-keto-γ-thio esters **6** proved to be more challenging than the previously studied analogous transformations starting from **1a** and acetals.[9] In particular, the product isolation was difficult due to the formation of several side products, which could not be identified. The best result was obtained in the reaction between **1a** and 1-[bis(ethylthio)methyl] benzene (**5a**). After a careful optimization of the reaction time and temperature the yield of α-keto-γ-thio ester **6a** reached 62% (Table 2, entry 1). Using thioacetals with substituted arenes led to lower yields. For example, *p*-methyl and *p*-methoxy-substituted arylthioacetals **5b** and **5c** gave the corresponding products in only 49% and 53% yield, respectively (entries 2 and 3). Also the thioacetals derived from *p*-bromobenzaldehyde and 2-naphthylcarbaldehyde (**5d** and **5e**, respectively) reacted with **1a**, but the yields of the resulting α-keto-γ-thio esters **6d** and **6e** were low (14% and 35%, entries 4 and 5). To our disappointment, several compounds did not react at all. For example, no product was found in attempts to use *p*-nitro- and *p*-dimethylamino-substituted thioacetals **5f** and **5g**, respectively, as electrophiles (entries 6 and 7). The same was true for thioacetal **5h** (entry 8), which was easily prepared from benzaldehyde and thiophenol, and aliphatic thioacetal **5i** (entry 9).

Possible functionalizations of the resulting products were demonstrated by the conversion of **6a** into oxime **7**. Following a method described by Skarzewski,[14] α-oxime-γ-thio ester **7** was

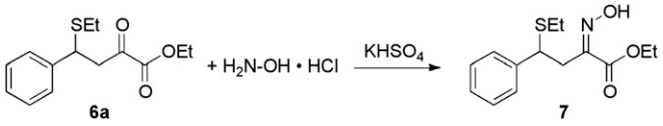
Table 2
Substrate scope in reactions between **1a** and Thioacetals **5**



Entry	Substrate **5**	Product **6**	% Yield[a]
1	 **5a**	 **6a**	62
2	 **5b**	 **6b**	49
3	 **5c**	 **6c**	53
4	 **5d**	 **6d**	14
5	 **5e**	 **6e**	35
6	 **5f**	 **6f**	—
7	 **5g**	 **6g**	—
8	 **5h**	 **6h**	—
9	 **5i**	 **6i**	—

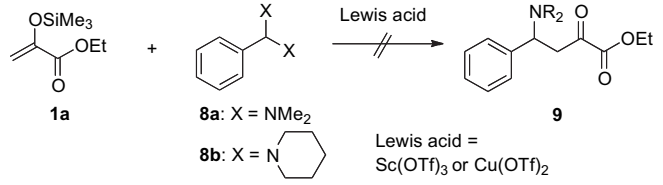
[a] After column chromatography.

obtained in 74% yield upon treatment of **6a** with the HCl salt of hydroxylamine in the presence of $KHSO_4$ (Scheme 3). Eventually, compound **7** could provide access to carboxy-substituted isoxazoles by intramolecular ring-closure in analogy to the work by Skarzewski[14] or γ-thio-substituted amino acids (by C=N reduction followed by N–O cleavage).



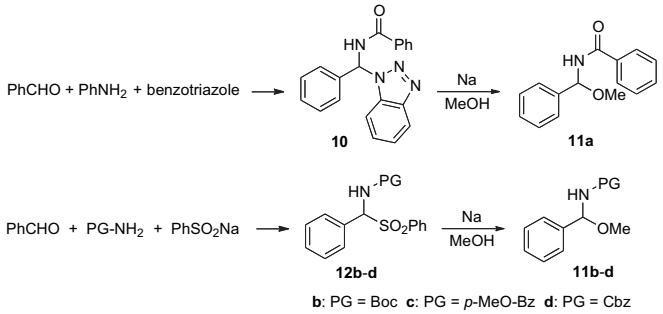
Scheme 3. Reaction between α-keto-γ-thio ester **6a** and hydroxylamine.

With the vision to prepare analogous γ-amino α-keto esters **9**, we focused our attention on reactions between **1a** and aminals **8** (Scheme 4). However, neither bis(dimethylamino)-substituted **8a**[15a] nor bis(pyrrolidinyl)benzaminal (**8b**)[15b] could sufficiently be activated by $Cu(OTf)_2$ or $Sc(OTf)_3$. No reactions occurred in solvents, such as dichloromethane or diethyl ether.



Scheme 4. Attempted reactions between **1a** and aminals **8** leading to γ-amino-α-keto esters **9**.

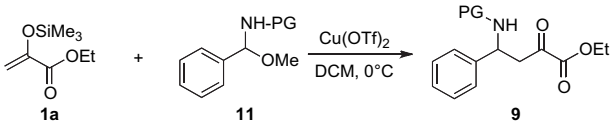
Hypothesizing that aminals were too stable under the applied reaction conditions protected *N*,*O*-acetals **11** were tested as electrophiles next. Benzoyl-protected **11a** was selected as model substrate. Its synthesis started from benzaldehyde, aniline, and benzotriazole and proceeded via intermediate **10** (Scheme 5, top).[16] For the preparations of *N*,*O*-acetals **11b–d** bearing other *N*-protecting groups a protocol developed by Dujardin was subsequently used (Scheme 5, bottom).[17]

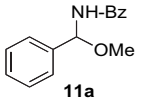
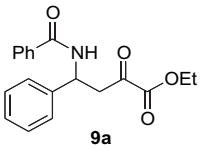
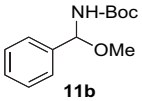
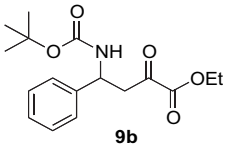
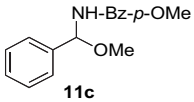
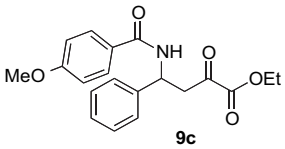
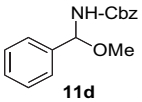
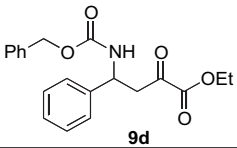


Scheme 5. Syntheses of protected *N*,*O*-acetals **11**.

To our delight, $Cu(OTf)_2$ smoothly catalyzed the reaction between **1a** and *N*,*O*-acetal **11a**, and in the presence of 10 mol % of this metal salt product **9a** was obtained in 72% yield (Table 3, entry 1). In contrast, $Sc(OTf)_3$ was inactive. Optimization studies revealed 0 °C to be the reaction temperature of choice, and DCM to be the most suitable solvent. More strongly coordinating media hampered the catalysis, and no product was observed. From *N*,*O*-acetals **11b–d** with Boc, *p*-methoxybenzoyl, and Cbz groups at the nitrogens the corresponding γ-amino-α-keto esters (**9b–d**) were obtained in yields of 51%, 53%, and 98%, respectively (Table 3, entries 2–4).

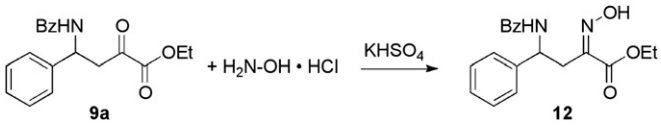
Table 3
Synthesis of γ-amino-α-keto esters **9**[a]



Entry	Substrate	Product	% Yield[b]
1			72
2			51
3			53
4			98

[a] Reaction conditions: $Cu(OTf)_2$ (0.1 equiv) was dissolved in DCM, and the resulting solution was cooled to 0 °C before the acetal (1 equiv) and the acrylic ester (1.5 equiv) were added.
[b] After column chromatography.

Finally, possible functionalizations of products **9** were shown by the reaction of γ-amino-α-keto ester **9a** with the HCl salt of hydroxylamine in the presence of $KHSO_4$, which gave oxime **12** in 97% yield (Scheme 6).



Scheme 6. Reaction between α-keto-γ-thio ester **9a** and hydroxylamine.

3. Conclusion

A simple method for the preparation of γ-substituted α-keto esters has been developed. Starting from ethyl (trimethylsilyloxy) acrylic ester (**1a**) and differently substituted acetals the corresponding products with γ-thio or γ-amino groups have been obtained in good yields. Either scandium(III)triflate or copper(II) triflate served as catalysts. No tedious work up was required, and for product isolation the reaction mixture could be directly submitted to column chromatography. Subsequent reactions with hydroxylamine afforded the corresponding α-oximes revealing the possibility to further functionalize the initial products. In future studies we plan to utilize the products as key building blocks for potentially bioactive heterocycles. Attempts to render the reaction sequence asymmetric are currently being pursued in our laboratory.

4. Experimental section

4.1. General information

All solvents were dried before use. Dichloromethane was distilled over CaH_2. Analytical TLC was performed with aluminum sheets silica gel 60 F_{254}, and the products were visualized by UV detection or by $KMnO_4$-stain. Flash chromatography was carried out with silica gel 60 (63–100 mesh) as the stationary phase. NMR spectra were recorded at 300 or 400 MHz (^{1}H NMR) and 75 or 100 MHz (^{13}C NMR). Chemical shifts (δ) are given in parts per million relative to TMS (δ=0 ppm) or the solvent residual peak ($CDCl_3$: δ=7.26 ppm) as internal standard. Coupling constants J are reported in Hertz and coupling patterns are described as br=broad, s=singlet, d=doublet, dd=doublet of doublet, t=triplet, q=quartet, m=multiplet. IR were recorded on a FT system and wave numbers are given in cm^{-1}.

If not otherwise mentioned all reagents were purchased from commercial suppliers and used without further purification. All reactions were carried out under argon atmosphere using standard Schlenck-technique. Ethyl 2-(trimethylsilyloxy)acrylic ester (**1a**),[1] compounds **8a**[15a] and **8b**[15b] as well as **11a**[16a] were synthesized according to literature procedures. Thioacetals and *N*,*O*-acetals were prepared according to the slightly modified literature procedures described below.

4.2. General procedure for the synthesis of thioacetals[11]

The aldehyde (5 mmol) and the thiol (11 mmol) were dissolved in acetonitrile (10 mL) and CuBr (0.25 mmol) was added. The reaction mixture was then stirred overnight at room temperature. After the addition of 4 N NaOH (10 mL), the mixture was extracted with DCM and the combined organic layers were washed with water. After drying over $MgSO_4$ the solvents were evaporated. The product was purified by column chromatography, using a mixture of pentane and ether (10:1) as eluent.

*4.2.1. 1-[Bis(ethylthio)methyl]benzene (**5a**).*[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J=7.4 Hz, 6H), 2.39–2.59 (m, 4H), 4.85 (s, 1H), 7.16–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 26.2, 52.4, 127.7, 128.5, 140.5.

*4.2.2. 1-[Bis(ethylthio)methyl]-4-methylbenzene (**5b**).*[19] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15–1.17 (m, 6H), 2.26 (s, 3H), 2.38–2.59 (m, 4H), 4.83 (s, 1H), 7.06 (d, J=8.4 Hz, 2H), 7.26 (d, J=7.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 21.1, 26.2, 52.2, 127.6, 129.2, 137.4, 137.5.

*4.2.3. 1-[Bis(ethylthio)methyl]-4-methoxybenzene (**5c**).*[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J=7.8 Hz, 6H), 2.45–2.56 (m, 4H), 3.79 (s, 3H), 4.89 (s, 1H), 6.82–6.85 (m, 2H), 7.34–7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 26.3, 51.9, 55.4, 128.9, 132.4, 158.9.

*4.2.4. 1-[Bis(ethylthio)methyl]-4-bromobenzene (**5d**).*[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J=7.4 Hz, 6H), 2.39–2.57 (m, 4H), 4.80 (s, 1H), 7.25–7.28 (m, 2H), 7.37–7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 26.4, 51.8, 121.5, 129.4, 131.6, 139.6.

*4.2.5. 1-[Bis(ethylthio)methyl]-4-nitrobenzene (**5e**).*[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J=7.4 Hz, 6H), 2.48–2.56 (m, 4H), 4.94 (s, 1H), 7.59–7.62 (m, 2H), 8.16–8.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 26.4, 51.8, 123.8, 128.6, 147.2, 148.1.

*4.2.6. 2-[Bis(ethylthio)methyl]naphthalene (**5f**).*[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.4 Hz, 6H), 2.49–2.65 (m, 4H), 5.09 (s, 1H), 7.44–7.50 (m, 2H), 7.62–7.64 (m, 1H), 7.80–7.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 26.4, 52.6, 65.9, 125.8, 126.1, 126.2, 126.3, 127.6, 127.8, 128.6, 132.9, 133.0, 137.6.

*4.2.7. 1-[Bis(ethylthio)methyl]-4-dimethylaminobenzene (**5g**).*[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.17 (m, 6H), 2.40–2.56 (m, 4H), 2.88 (s, 6H), 4.83 (s, 1H), 6.58–6.62 (m, 2H), 7.22–7.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 26.3, 40.6, 52.0, 112.2, 128.5, 149.9.

*4.2.8. 1-[Phenyl(phenylthio)methyl]benzene (**5h**).*[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (s, 1H), 7.20–7.37 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.4, 127.8, 127.9, 128.0, 128.4, 128.8, 132.5, 134.5, 139.7.

*4.2.9. 1-Bis(ethylthio)butane (**5i**).*[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J=7.3 Hz, 3H), 1.23 (t, J=7.4 Hz, 6H), 1.48–1.56 (m, 2H), 1.73–1.78 (m, 2H), 2.52–2.70 (m, 4H), 3.77 (t, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 14.7, 20.8, 24.2, 38.3, 51.2.

4.3. General procedure for the synthesis of the α-keto-γ-thio esters 6

$Sc(OTf)_3$ (0.04 mmol) was dissolved in DCM (2 mL) and cooled to 0 °C. Then, the thioacetal (0.4 mmol) and acrylic ester **1a** (0.6 mmol) were added. The reaction was monitored by TLC and after consumption of the starting materials the reaction mixture was submitted to column chromatography. The product was isolated by using pentane/diethyl ether 20:1 as eluent.

*4.3.1. Ethyl 4-(ethylthio)-2-oxo-4-phenyl-butanoate (**6a**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, J=7.4 Hz, 3H), 1.27 (t, J=7.2 Hz, 3H), 2.24–2.32 (m, 2H), 3.33 (d, J=7.4 Hz, 2H), 4.21 (q, J=7.2 Hz, 2H), 4.30–4.37 (m, 1H), 7.14–7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.2, 25.3, 43.4, 45.7, 62.6, 127.5, 127.7, 128.6, 129.0, 141.2, 160.4, 191.1; MS (EI, 70 eV) m/z (%) 266.1 ([M]$^+$, 10), 249.1 (10), 248.0 (60), 205.1 (11), 175.0 (9), 151.1 (53), 135.1 (13), 131.1 (100), 121.1 (9), 105.1 (36), 104.1 (23), 103.1 (26), 91.1 (14), 77.2 (16), 45.3 (12); IR (capillary) 3451, 2978, 2923, 1729, 1602, 1451, 1264, 1080, 749, 700, 571 cm^{-1}; HRMS ($C_{14}H_{18}O_3{}^{32}S$) calcd: 266.0971, found: 266.0971.

*4.3.2. Ethyl 4-(ethylthio)-4-(4-methylphenyl)-2-oxo-butanoate (**6b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, J=7.4 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H), 2.25 (s, 3H), 2.26–2.28 (m, 2H), 3.31 (d, J=7.4 Hz, 2H), 4.21 (q, J=7.1 Hz, 2H), 4.28–4.33 (m, 1H), 7.03–7.05 (m, 2H), 7.16–7.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.4, 25.4, 43.2, 45.9, 62.6, 127.5, 129.1, 129.2, 129.8, 137.1, 138.1, 161.0, 191.3; MS (EI, 70 eV) m/z (%) 280.1 ([M]$^+$, 7), 262.1 (33), 219.1 (16), 165.1 (21), 146.1 (12), 145.1 (100), 119.1 (18), 118.1 (12), 117.1 (21), 115.1 (14), 91.2 (12); IR (capillary) 3415, 2979, 2921, 1905, 1729, 1598, 1448, 1262, 1080, 818, 518 cm^{-1}; HRMS ($C_{15}H_{20}O_3{}^{32}S$) calcd: 280.1128, found: 280.1130.

*4.3.3. Ethyl 4-(ethylthio)-4-(4-methoxyphenyl)-2-oxo-butanoate (**6c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14–1.17 (m, 3H), 1.32–1.36 (m, 3H), 2.31–2.35 (m, 2H), 3.36–3.39 (m, 2H), 3.79 (s, 3H), 4.25–4.31 (m, 2H), 4.35–4.40 (m, 1H), 6.83–6.86 (m, 2H), 7.27–7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.4, 25.4, 42.9, 46.0, 55.3, 62.7, 113.9, 128.8, 131.0, 133.0, 148.3, 160.4, 191.3; MS (EI, 70 eV) m/z (%) 296.1 ([M]$^+$, 17), 235.1 (49), 181.1 (11), 162.2 (13), 161.1 (100), 134.1 (16); IR (capillary) 3447, 2921, 1729, 1592, 1512, 1253, 1077, 1032, 836, 545 cm^{-1}; HRMS (ESI, MeOH) calcd ($C_{15}H_{20}O_4SNa$): 319.0974, found: 319.0972.

*4.3.4. Ethyl 4-(4-bromophenyl)-4-(ethylthio)-2-oxo-butanoate (**6d**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, J=7.4 Hz, 3H), 1.27 (t, J=6.9 Hz, 3H), 2.28 (q, J=7.4 Hz, 2H), 3.29 (d, J=7.4 Hz, 2H), 4.15–4.37 (m, 3H), 7.17–7.49 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.2, 25.3, 42.8,

45.6, 62.7, 121.2, 129.5, 130.2, 131.7, 132.4, 140.4, 160.4, 190.0; MS (EI, 70 eV) *m*/*z* (%) 346.0 ([M+H]$^+$, 3), 328.0 (21), 326.0 (21), 285.0 (8), 283.0 (9), 231.0 (15), 229.0 (16), 211.0 (88), 210.1 (12), 209.0 (100), 184.0 (14), 183.0 (19), 182.0 (12), 132.2 (14), 130.1 (11), 104.2 (20), 103.2 (31), 102.2 (75), 101.2 (12), 89.2 (20), 77.3 (20), 76.3 (15), 75.2 (14), 51.4 (11); IR (capillary) 3452, 2977, 2922, 1731, 1606, 1484, 1262, 1073, 1012, 826 cm^{-1}; HRMS (ESI, MeOH) calcd ($C_{14}H_{17}O_3BrSNa$): 366.9970, found: 366.9976.

*4.3.5. Ethyl 4-(ethylthio)-4-(naphthalene-2-yl)-2-oxo-butanoate (**6f**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, *J*=7.4 Hz, 3H), 1.28 (t, *J*=7.1 Hz, 3H), 2.27–2.37 (m, 2H), 3.45–3.48 (m, 2H), 4.21–4.27 (m, 2H), 4.56 (t, *J*=7.4 Hz, 1H), 7.42–7.55 (m, 3H), 7.72–7.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.4, 25.4, 43.7, 45.6, 62.7, 124.9, 125.5, 125.8, 126.1, 127.1, 128.2, 132.5, 137.8, 160.0, 190.6; MS (EI, 70 eV) *m*/*z* (%) 316.1 ([M]$^+$, 21), 298.1 (20), 255.1 (11), 237.1 (32), 201.1 (17), 182.1 (15), 181.1 (100), 155.1 (24), 154.1 (30), 153.1 (32), 152.1 (27); IR (film) 2977, 1725, 1596, 1233, 1079, 1018, 928, 817, 748, 698 cm^{-1}; HRMS ($C_{18}H_{20}O_3{}^{32}S$) calcd: 316.1128, found: 316.1129.

*4.3.6. 4-Ethylthio-4-phenyl-2-hydroxyimino-butyrate (**7**).* α-Keto-γ-thio ester **6a** was dissolved in ethanol and hydroxylamine hydrochloride (1 equiv) and $KHSO_4$ (0.2 equiv) were added. The reaction mixture was stirred overnight and then, the solvent was evaporated before the residue was submitted to column chromatography. The product was isolated by using a mixture of pentane and diethyl ether (8:2) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, *J*=7.4 Hz, 3H), 1.19 (t, *J*=7.2 Hz, 3H), 2.27 (q, *J*=7.4 Hz, 2H), 3.04–3.24 (m, 2H), 4.12 (q, *J*=7.2 Hz, 2H), 4.24–4.32 (m, 1H), 7.12–7.30 (m, 5H), 9.65 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.3, 25.2, 31.5, 45.5, 61.8, 127.4, 127.6, 127.7, 128.4, 141.5, 150.3, 163.1; MS (EI, 70 eV) *m*/*z* (%) 281.2 ([M]$^+$, 1), 266.3 (5), 265.2 (16), 264.2 (100), 152.2 (9), 151.2 (96), 130.1 (30), 129.2 (14), 128.1 (35), 123.2 (14), 121.1 (15), 115.1 (15), 107.1 (17), 104.2 (16), 103.2 (39), 102.2 (10), 91.2 (15), 79.2 (19), 78.2 (13), 77.2 (31), 45.4 (20); IR ($CHCl_3$) 3278, 2921, 1723, 1447, 1300, 1189, 1022, 861, 757, 700, 522 cm^{-1}; HRMS ($C_{14}H_{19}O_3N^{32}S$) calcd: 281.1080, found: 281.1087.

*4.3.7. N-(Methoxy(phenyl)methyl)benzamide (**11a**).*[16a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 3H), 6.37 (d, *J*=9.3 Hz, 1H), 6.64 (d, *J*=9.1 Hz, 1H), 7.32–7.54 (m, 8H), 7.79–7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.3, 81.8, 125.9, 127.1, 128.5, 128.6, 131.9, 133.7, 139.3, 167.2.

4.4. General procedure for the synthesis of *N,O*-acetals 11b–d

Benzaldehyde (20 mmol), the amine (10 mmol), the sodium salt of benzenesulfinic acid (25 mmol), and formic acid (20 mmol) were dissolved in a mixture of water (20 mL) and methanol (10 mL). After stirring overnight the reaction mixture was cooled to 0 °C. The resulting participate was filtered off and then dissolved in DCM. After drying of the organic phase over $MgSO_4$ the solvent was evaporated. Then, the product was added to sodium methanolate prepared from sodium (3 equiv) and methanol (3 equiv per 1 equiv Na). After stirring overnight water was added. The resulting participate was filtered off, dissolved in DCM, and the organic phase was dried over $MgSO_4$. The solvent was evaporated to yield the clean product.

*4.4.1. tert-Butyl N-[methoxy(phenyl)methyl]carbamate (**11b**).*[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 3.39 (s, 3H), 5.06 (br d, *J*=8.5 Hz, 1H), 5.76 (d, *J*=9.4 Hz, 1H), 7.19–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 55.7, 83.4, 125.8, 128.4, 128.5, 128.9, 129.7, 139.4.

*4.4.2. 4-Methoxy N-[methoxy(phenyl)methyl]benzamide (**11c**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.54 (s, 3H), 3.85 (s, 3H), 6.63 (d, *J*=9.4 Hz, 1H), 6.48 (d, *J*=9.2 Hz, 1H), 6.91–7.83 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.4, 56.2, 81.8, 113.9, 125.9, 128.5, 128.6, 128.9, 139.5, 162.0; MS (EI, 70 eV) *m*/*z* (%) 256.1 ([M−CH_3]$^+$, 3), 135.1 (100), 121.2 (20), 107.1 (11), 105.2 (10), 104.1 (10), 92.2 (21), 78.3 (65), 64.3 (12), 51.4 (13); IR (KBr) 3270, 2943, 1633, 1497, 1252, 1184, 1073, 1029, 845, 741, 683 cm^{-1}; HRMS (ESI, MeOH) ($C_{16}H_{17}O_3N$) calcd ([M+K]$^+$): 310.0840, found: 310.0842.

*4.4.3. Benzyl N-[methoxy(phenyl)methyl]carbamate (**11d**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46 (s, 3H), 5.16 (s, 2H), 5.35 (br m, 1H), 5.89 (d, *J*=9.9 Hz, 1H), 7.29–7.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.7, 67.1, 84.0, 125.8, 128.1, 128.3, 128.5, 128.6, 136.1, 139.1, 155.9; MS (ESI, MeOH) *m*/*z* (%) 294.3 ([M+Na]$^+$); IR (KBr) 3292, 1693, 1533, 1246, 1083, 971, 690 cm^{-1}; HRMS (ESI, MeOH) ($C_{16}H_{17}O_3N$) calcd ([M+Na]$^+$): 294.1101, found: 294.1104.

4.5. General procedure for the synthesis of γ-amino-α-keto esters 9

$Cu(OTf)_2$ (0.04 mmol) was dissolved in DCM (2 mL) and cooled to 0 °C. The *N,O*-acetal (0.4 mmol) and acrylate **1a** (0.6 mmol) were added, and the reaction monitored by TLC. After complete consumption of the acrylic ester the reaction mixture was submitted to column chromatography. The product was isolated using a mixture of pentane and ethyl acetate (8:2) as eluent.

*4.5.1. Ethyl 4-benzamido-2-oxo-4-phenylbutanoate (**9a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J*=7.1 Hz, 3H), 3.29 (dd, *J*=10.9, 5.5 Hz, 1H), 3.48 (dd, *J*=9.9, 6.6 Hz, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 5.54 (m, 1H), 6.78 (d, *J*=7.4 Hz, 1H), 7.27–7.72 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 44.9, 50.3, 62.8, 126.5, 126.9, 127.9, 128.6, 128.9, 131.7, 133.8, 140.0, 160.4, 166.8, 191.9; MS (EI, 70 eV) *m*/*z* (%) 326.3 ([M+H]$^+$, 1), 252.3 (19), 220.3 (41), 210.2 (21.8), 146.2 (13), 131.2 (25), 105.2 (100), 104.3 (13), 77.3 (43), 51.4 (13); IR (KBr) 3335, 1723, 1632, 1526, 1281, 1044, 696 cm^{-1}; HRMS (ESI, MeOH) ($C_{19}H_{19}O_4N$) calcd ([M+H]$^+$): 326.1367, found: 326.1383.

*4.5.2. Ethyl 4-[(tert-butoxycarbonyl)amino]-2-oxo-4-phenylbutanoate (**9b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, *J*=7.2 Hz, 3H), 1.41 (s, 9H), 3.35–3.37 (m, 2H), 4.28 (q, *J*=7.2 Hz, 2H), 5.14–5.92 (m, 2H), 7.21–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 28.3, 45.9, 51.2, 126.3, 127.8, 128.6, 128.8, 140.7, 155.0, 160.4, 191.6; MS (EI, 70 eV) *m*/*z* (%) 321.1 ([M]$^+$, 3), 320.2 (11), 266.1 (11), 264.1 (16), 248.2 (12), 221.2 (32), 220.2 (8), 206.2 (34), 205.1 (20), 193.1 (13), 192.1 (68); IR (film) 3389, 2979, 1724, 1499, 1367, 1251, 1169, 1069, 701, 603 cm^{-1}; HRMS (ESI, MeOH) ($C_{17}H_{23}O_5N$) calcd ([M+Na]$^+$): 344.1468, found: 344.1468.

*4.5.3. Ethyl 4-(4-methoxybenzoylamido)-2-oxo-4-phenylbutanoate (**9c**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, *J*=7.0 Hz, 3H), 3.41 (dd, *J*=11.1, 5.4 Hz, 1H), 3.57 (dd, *J*=9.6, 6.9 Hz, 1H), 3.81 (s, 3H), 4.27 (q, *J*=7.0 Hz, 2H), 5.64 (dd, *J*=7.2, 5.9 Hz, 1H), 6.85–6.89 (m, 2H), 6.98 (d, *J*=7.9 Hz, 1H), 7.26–7.40 (m, 5H), 7.69–7.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 44.9, 50.1, 55.3, 62.7, 113.7, 126.2, 127.9, 128.9, 140.4, 160.5, 162.3, 166.4, 192.0; MS (EI, 70 eV) *m*/*z* (%) 355.2 ([M]$^+$, 1), 220.1 (12), 136.1 (8), 135.1 (100), 131.1 (10), 107.1 (7), 104.2 (7), 92.1 (8), 77.2 (13); IR (film) 3445, 3278, 2937, 1725, 1620, 1543, 1504, 1367, 1252, 1035, 847, 698 cm^{-1}; HRMS ($C_{20}H_{21}O_5N$) calcd: 355.1414, found: 355.1414.

*4.5.4. Ethyl 4-{[(benzyloxy)carbonyl]amino}-2-oxo-4-phenylbutanoate (**9d**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, *J*=7.1 Hz, 3H), 3.32–3.42 (m, 2H), 4.25 (q, *J*=7.1 Hz, 2H), 5.05 (d, *J*=4.4 Hz, 2H), 5.24 (br m, 1H), 5.54 (br d, *J*=8.0 Hz, 1H), 7.28–7.33 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 45.5, 51.5, 62.8, 67.0, 126.3, 127.8, 128.1, 128.5, 128.8, 136.2, 140.4, 155.5, 160.3, 191.4; MS (EI, 70 eV) *m*/*z* (%)

282.1 ([M−CO_2Et]$^+$, 4), 146.1 (10), 104.1 (10), 91.2 (100), 65.2 (6); IR (KBr) 3338, 1720, 1683, 1531, 1265, 1046, 735, 697 cm^{-1}; HRMS (ESI, MeOH) ($C_{20}H_{22}O_5N$) calcd: 356.1492, found: 356.1492.

*4.5.5. Ethyl 4-benzamido-2-hydroxyimino-4-phenylbutanoate (**12**).* γ-Amino-α-keto ester **9a** (0.2 mmol) was dissolved in ethanol (2 mL). Hydroxylamine hydrochloride (0.2 mmol) and $KHSO_4$ (0.005 mmol) were added, and the reaction mixture was then stirred overnight. After washing with water (5 mL) the mixture was extracted with diethyl ether (3×5 mL). The combined organic phases were dried over $MgSO_4$, and the solvent evaporated to yield the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J=7.1 Hz, 3H), 3.18 (d, J=8.24 Hz, 2H), 4.28 (q, J=7.1 Hz, 2H), 5.54 (m, 1H), 7.32–7.48 (m, 9H), 7.78–7.80 (m, 2H), 10.57 (br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 32.0, 52.1, 62.4, 125.9, 127.0, 127.5, 128.5, 128.7, 131.6, 133.7, 141.7, 150.0, 164.6, 166.8; MS (ESI, MeOH) m/z (%) 341.1 ([M+H]$^+$); IR (KBr) 3320, 1721, 1640, 1530, 1426, 1318, 1196, 1014, 697 cm^{-1}; HRMS (ESI, MeOH) ($C_{19}H_{20}N_2O_4$) calcd: 341.1482, found: 341.1495.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra of all unknown compounds. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.013.

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