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On the Acylation Reactions of Aza-allyl Carbanions Derived from N-[Bis(methylthio)methylene]glycine Ethyl Ester and N-[Bis(methylthio)methylene]benzylamine

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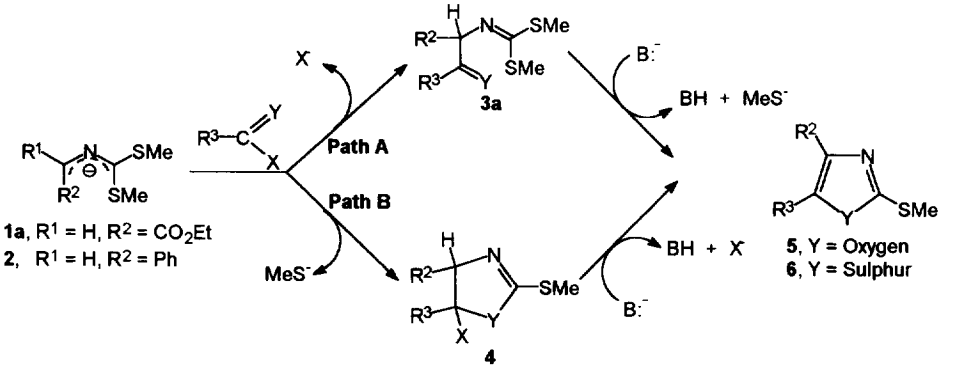
Abstract: New aspects of the acylation reaction of the aza-allyl anions derived from **1** and **2** have been studied. Under suitable reaction conditions, oxazoles **5**, α,α–disubstituted α-acyl-α-amino acid derivatives **3**, and α,β-didehydroamino acid derivatives **7** can be prepared. A new 1,3-diamino-2-propanol derivative **8** was isolated by reaction of the *C*-acyl intermediate derived from *N*-[bis(methylthio)methylene]- benzylamine **2** and the anion **2**⁻ through an *in situ* addition-cyclocondensation tandem reaction.

INTRODUCTION

Whereas the reaction of simple organometallics with acylating reagents has found wide application in organic synthesis,[1] limited use of enolate anions has been made in this context due to the ambident chemical behaviour of these species. Attack on oxygen dominates for most enolates.[2] However, treatment of the anion derived from **1a**[3] with a variety of acylating or thioacylating reagents in the presence of two equivalents of a

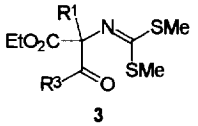


Scheme 1

base gives rise to oxazoles[4] **5** or thiazoles[5] **6** following either a C-acylation/cyclocondensation or a *C*-addition/cyclocondensation/1,2-elimination pathway (Scheme 1, path A and path B respectively).

In a similar fashion, treatment of the aza-allyl anion derived from **2** with methyl dithiobenzoate[6] gave rise to the corresponding thiazole **6a**. In this case, the dihydrothiazole **4a** ($R^2 = R^3 = Ph$, X = SPh, Y = S) was isolated from the reaction mixture as a single diastereomer. This observation suggests the possibility of a *C*-addition/cyclocondensation/1,2-elimination route for the formation of thiazoles **6** (Scheme 1, path B). These findings prompted us to investigate the formation of the corresponding *C*-acylated derivatives of iminodithiocarbonates **1** and **2**.

Described herein is the study of the acylation reactions of the aza-allyl anions derived from **1** and **2**, which under different experimental conditions lead to a variety of products: i) the α-acyl-α-amino acid derivatives **3**, which have been used as starting materials for the diastereoselective synthesis of non-proteinogenic α-amino acids;[7] ii) the α,β-didehydroamino acid derivatives **7**, which are interesting in connection with the synthesis of enzyme inhibitors or as starting materials for the preparation of uncommon amino acids;[8,9] iii) the 2-hydroxy-1,3-propylenediamine derivative **8** (Figure 1).



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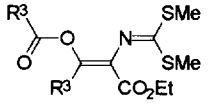

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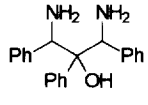


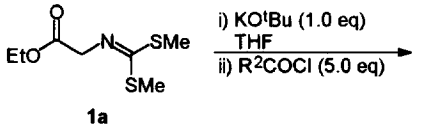
8

Figure 1

RESULTS

The results of the reaction of the anions derived from the iminodithiocarbonates **1** with acylating reagents are gathered in Table 1.

Treatment of the anion derived from **1a** (2.0 equiv. KO^{t}Bu, THF, -78°) with acid chlorides or monothioesters (1.0 equiv.) gave rise to oxazole **5** formation.[4] However, reaction with ethyl chloroformate (1.0



1a **7a-d**

7a, $R^3 = CH_3$ **7b**, $R^3 = Ph$

7c, R^3 = 2-Furyl **7d**, R^3 = 2-Thienyl

Scheme 2

equiv.) in the presence of one equivalent of the base (KO^{t}Bu, THF, -78°) afforded the 2-aminomalonate derivative **3a** (entry 1). On the other hand, the reaction with an excess of an acid chloride (5.0 equiv.) led to the β-hydroxy-α,β-didehydro-α-amino acid derivatives[9] **7** (entries 8 - 11) (Scheme 2).

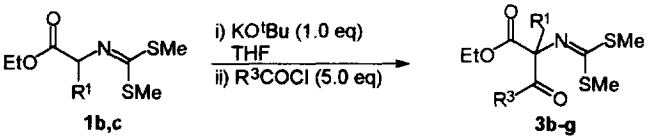
Table 1. Reaction of the Anions of **1** with Acylating Reagents R^3COCl

Entry	1	R^1	R^3	Product	Yield (%)[a]
1	**1a**	H	EtO	**3a**	82[b,c]
2	**1b**	CH_3	CH_3	**3b**	55
3	**1b**	CH_3	Ph	**3c**	50
4	**1b**	CH_3	^{i}Pr	**3d**	55
5	**1b**	CH_3	2-Furyl	**3e**	45
6	**1c**	$PhCH_2$	CH_3	**3f**	45
7	**1c**	$PhCH_2$	Ph	**3g**	55
8	**1a**	H	CH_3	**7a**	95[b]
9	**1a**	H	Ph	**7b**	95[b]
10	**1a**	H	2-Furyl	**7c**	90[b]
11	**1a**	H	2-Thienyl	**7d**	90[b]

a) Pure, isolated yield. b) Based on recovered **1a**. c) Oxazole derivative was not detected in the reaction crude.

Compounds **7** were formed as single geometric isomers with Z geometry, as deduced from their ^{1}H-NMR ($CDCl_3$, 300 MHz) spectra and NOE data on **7a**. Thus, a 3% enhancement of the CH_3S signal (δ = 2.52 ppm, s) was observed upon irradiation of the CH_3-CO signal (δ = 1.89 ppm, s).

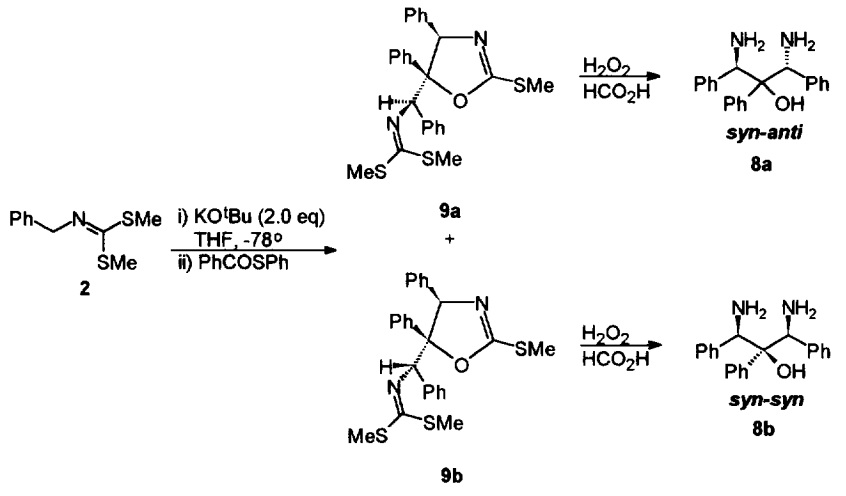
Reaction of the anions derived from **1b,c** (1.0 equiv. KO^{t}Bu, THF, -78°) with a variety of acid chlorides (5.0 equiv.) gave rise to the corresponding acylated products **3b-g** (table 1, entries 2 - 7). These were the sole reaction products (Scheme 3).



1b,c **3b-g**

3b, $R^1 = CH_3$, $R^3 = CH_3$ **3e**, $R^1 = CH_3$, R^3 = 2-Furyl
3c, $R^1 = CH_3$, $R^3 = Ph$ **3f**, $R^1 = PhCH_2$, $R^3 = CH_3$
3d, $R^1 = CH_3$, $R^3 = {}^i$Pr **3g**, $R^1 = PhCH_2$, $R^3 = Ph$

Scheme 3



Scheme 4

Last, when the iminodithiocarbonate **2** was deprotonated (2.0 equiv. KO^{t}Bu, THF, -78°) and treated with S-phenyl monothiobenzoate (1.0 equiv.), oxazole **5a** was obtained only in minor amounts, compounds **9** being the major reaction products (Scheme 4). These compounds were obtained as a mixture of the two diastereomers **9a** and **9b** (1 : 2.5). Separation of both diastereomers by silica-gel chromatography followed by oxidative hydrolysis[3] of each one under non-epimerizing conditions afforded the 1,3-diamino-2-hydroxypropanol derivatives **8.**[10]

The assignment of the relative configurations of compounds **9** has been carried out with the aid of their NMR data as well as those of **8**, together with molecular mechanics calculations[11] on **9**. Thus, the assignment of protons H6 (**9a**, δ = 4.81 ppm, s; **9b**, δ = 5.11 ppm, s) and H4 (**9a** = **9b**, δ = 5.41 ppm, s) was deduced from the H,C-COSY spectra of **9a** and **9b**. The observation of an identical chemical shift for H4 in both isomers indicates that **9a** and **9b** are epimers on the exocyclic carbon C6. The assignment of the relative configurations of C4 and C5 in **9a** and **9b** has been deduced by comparison of the $^3J_{C,H}$ values observed in their non-decoupled ^{13}C-NMR spectra with the theoretical values estimated for the four possible racemates of **9** by molecular mechanics[11] and a semiquantitative Karplus calculation.[12] The results are given in Table 2.

The inspection of these data suggests that for isomers 4R*5S*6S* and 4R*5S*6R* the value of $^3J_{C2,H4}$ is higher than that of $^3J_{C\text{-}ipso,H4}$, whereas the opposite applies for isomers 4S*5S*6R* and 4S*5S*6S*. Comparison with the values experimentally observed for **9a** ($^3J_{C2,H4}$ = 7.2 Hz, $^3J_{C\text{-}ipso,H4}$ = 4.3 Hz) and **9b** ($^3J_{C2,H4}$ = 7.7 Hz, $^3J_{C\text{-}ipso,H4}$ = 4.0 Hz) allows for the stablishment of a *cis* relative disposition of the phenyl groups on C4 and C5 for both **9a** and **9b**.

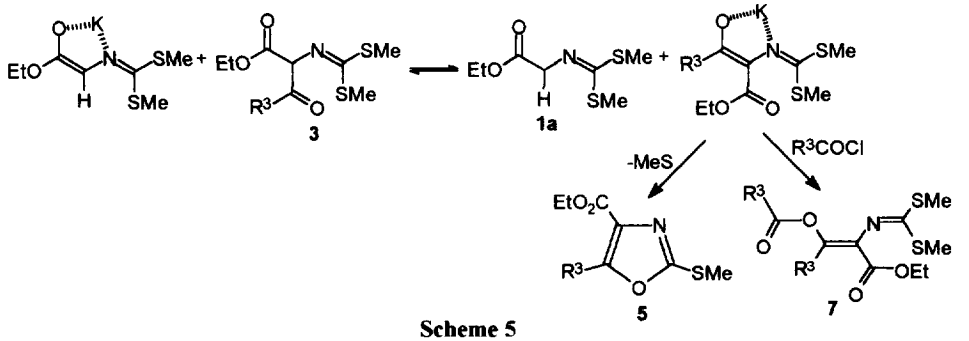
Table 2. Dihedral Angles and Coupling Constants Calculated for **9**.

	4R*5S*6S*		4R*5S*6R*		4S*5S*6R*		4S*5S*6S*	
	Angle (Deg)	$^3J_{C,H}$ (Hz)	Angle (Deg)	$^3J_{C,H}$ (Hz)	Angle (Deg)	$^3J_{C,H}$ (Hz)	Angle (Deg)	$^3J_{C,H}$ (Hz)
C2-N-C4-H4	-135	4.9	-131	4.4	123	3.3	131	4.4
C_{ipso}-C5-C4-H4	-100	1.1	-107	1.6	-8	6.7	-20	6.0

The assignment of the relative configuration of C6 in **9a** and **9b** was made on the basis of the chemical shifts of C1 and C3 in compounds **8a** (C1, δ =58.1 ppm; C3, δ = 66.05) and **8b** (C1, δ = 63.0 ppm; C3, δ = 63.1 ppm), taking into account that a *meso* form should give a nearly identical value of these parameters. Therefore, a relative configuration 1R*,3R* was assigned to **8a** (C_2 symmetry) and 1R*, 3S* to **8b** (*meso* form). Hence, the stereochemistry 4R*,5S*,6R* was assigned to **9a** and 4R*,5S*,6S* to **9b**.

DISCUSSION

The reaction of **1a** with one equivalent of an acid chloride or monothioester in the presence of two equivalents of a strong base (KO^{t}Bu / THF) gave rise to oxazole **5** formation[3] *via* irreversible enolization of the acylated intermediate **3**. When only one equivalent of the base is used, a transenolization equilibrium between the anion of **1a** and the acylated derivative **3** operates for oxazole formation (Scheme 5).[13] This behaviour has also been reported for the acylation of α-metalated isonitriles.[14]



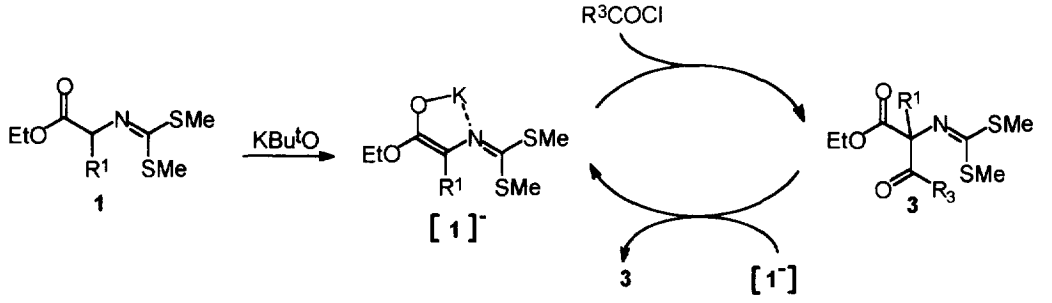
Scheme 5

Enolization of **1a** with one equivalent of KO^{t}Bu followed by reaction with ethyl chloroformate allowed for the isolation of **3a**. Oxazole formation is avoided in this case due to the lower acidity of the α-hydrogen in **3a** and the lower nucleophilicity of the enolized ester group as compared with the rest of acylated derivatives **3**

(R^3 = CH_3, Ph, 2-Furyl, 2-Thienyl). As a matter of fact, compound **3a** was only enolized in a 10% extension, as inferred from the inspection of the ^{1}H-NMR ($CDCl_3$, 300 MHz) spectrum of **3a**.

C-acyl derivatives of **1b,c** are interesting building blocks for the preparation of serine analogues, bis-glycinyl carbinols and other non-proteinogenic α-amino acids.[7] In the presence of an excess of acid chloride (5.0 equiv.), *O*-acylation of the enolized acylated intermediate competes with cyclization with the iminodithiocarbonate moiety, thus superceeding oxazole formation. The selective formation of the α,β-didehydro-α-amino acid derivatives **7** as a single *Z* isomer can be accounted for by chelation of the metal with the enolic oxygen and the nitrogen of the iminodithiocarbonate group in the corresponding enolate (Scheme 5).[15]

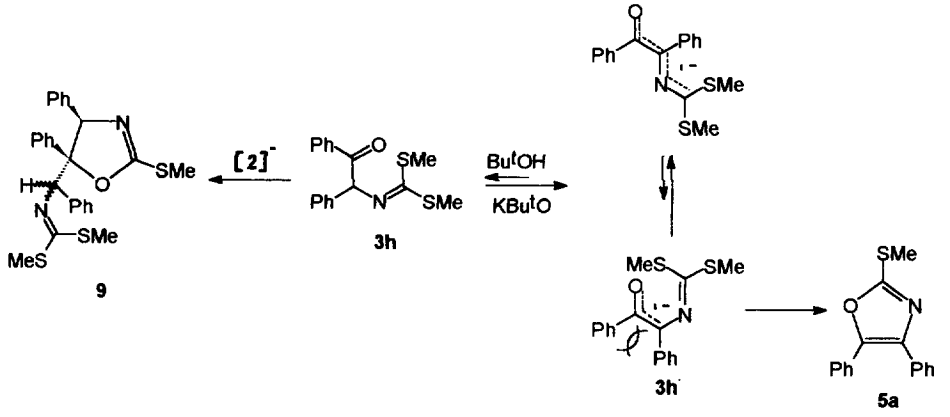
Product enolization is not a problem in the acylation reactions of **1b** (R^1 = CH_3) or **1c** (R^1 = $PhCH_2$). However, compounds **3b-g** were obtained only in moderate yields, even in the presence of an excess of acid chloride (5.0 equiv.). This can be attributed[16] either to the lower nucleophilicity of the aza-allyl anions derived from **1b,c** as compared with **1a** or to the competition of a retro-Claisen between **3** and the anion of **1a** (Scheme 6).



Scheme 6

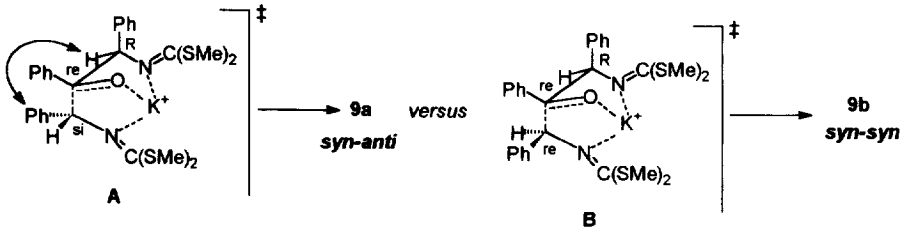
On the other hand, treatment of the anion of **2** with S-phenyl monothiobenzoate (2.0 equiv.) furnished the oxazole **5a** as a minor product (13%), whereas the oxazoline **9** became the major compound of the reaction mixture (44%). An explanation of this behaviour could be adscribed to the steric hindrance for the *s*-cis/*s*-trans interconversion of the anion **[3h$^-$]**, as this could prevent the formation of the oxazole. Thus, the oxazoline **9** could be originated by a competitive reaction between the anion [**2**$^-$] and **3h** allowing for the *in situ* cyclization of the adduct (Scheme 7).

This result shows that the *C*-acylated compounds **3** are intermediates of oxazole formation *via* enolization and cyclocondensation. This behaviour is different from that previously reported for the thioacylation processes[5,6] and it could be explained by the difference in nucleophilicity between oxygen and sulphur.



Scheme 7

Compound **9** was obtained as a mixture of two diastereomers (**9a** : **9b** = 1 : 2.5) which were epimeric on C6 (cf. Scheme 4). Interconversion was unobserved upon submission of either diastereomer to the basic conditions of the original experiment (2.0 equiv. KO^{t}Bu, THF, -78°C, 30 min). This result supports the hypothesis of a kinetic control for the reaction. The stereochemical outcome can be interpreted on the basis of a Felkin-Ahn[17a] transition state model (Scheme 8), which provides the same *syn*-facial diastereoselectivity[18] that the Cram's cyclic model *via* a chelation control.[17b] In fact, chelation of the metal with the lone pairs on the carbonyl oxygen and the nitrogen of the iminodithiocarbonate in **3h** would favour the attack of the nucleophile from the diastereotopic face opposite to the phenyl group. Attack in a *lk* fashion (**B**) would give **9b**, while an *ul* approach (**A**) would give rise to **9a**, the latter being disfavoured due to the 1,3-diaxial Ph-H interaction in **A**, which is not present in **B**.[19] Note that both situations benefit by the chelation of the metal to the carbonyl oxygen and to the iminodithiocarbonate groups of both **3h** and the incoming nucleophile.



Scheme 8

CONCLUSIONS

The acylation of **1a** gave rise to the formation of the *C*-acyl derivatives **3**, which were transformed into oxazoles in the presence of an additional equivalent of base. The reaction of **1a** with ethyl chloroformate (1 equiv. of base) allowed for the obtention of the malonate derivative **3a**. In this way, the use of an excess of acid chloride (5 : 1) prevented oxazole formation by *O*-acylation of the enolates derived from the corresponding α-acyl-α-amino acids **3**, giving rise to the acyl vinylethers **7** as pure *Z*- isomers. The α,α-disubstituted α-acyl-α-amino acids **3b-g** have been prepared by *C*-acylation of **1b** and **1c**. On the other hand, the acylation of the anion derived from **2** showed an unusual outcome leading to the formation of the 1,3-diamino-2-propanol derivative **8** with three stereogenic centres in a diastereoselective fashion. These results widen the scope and limitations of the acylation reaction.

EXPERIMENTAL SECTION

All starting materials were commercially available research-grade chemicals and used without purification. Iminodithiocarbonates **1** and **2** have been prepared according to the previously described procedures.[5] Silica gel 60 F_{254} was used for TLC and the spots were detected with UV. Flash column chromatographies were carried out on silica gel 60. Melting points are uncorrected. IR spectra have been recorded as $CHCl_3$ solutions or KBr pellets. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75.5 MHz, respectively, in $CDCl_3$ solutions with TMS as internal reference. Full assignment of ^{13}C NMR signals has been carried out with the aid of 2D heteronuclear ^1H-^{13}C correlations and some coupled ^{13}C NMR spectra.

Diethyl 2-*N*-[bis(methylthio)methylene]aminomalonate 3a. To a solution of KBu^{t}O (0.198 g, 1.77 mmol) in dry THF (12 mL) at -78°C, a solution of ester **1a** (0.350 g, 1.69 mmol) in THF (1 mL) was added dropwise and the solution was stirred for 30 min at -78°C. After addition of a solution of ethyl chloroformate (0.192 g, 1.77 mL) in THF (1 mL), stirring was maintained at -78°C for 30 min and the mixture was then allowed to reach rt. Evaporation of the solvent under reduced pressure led to a pale yellow oil which was treated with H_2O (5 mL) and Et_2O (10 mL). The organic layer was decanted and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine until neutral pH, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure led to a pale yellow oil which was purified by flash chromatography (hexane/ethyl acetate: 85/15) to give a colourless oil (41%): IR (neat) ν 1740, 1565 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) (keto form) δ 1.28 (6H, t, ^3J=7.2 Hz), 2.48 (3H, s), 2.60 (3H, s), 4.26 (2H, q, ^3J=7.2 Hz), 4.27 (2H, q, ^3J=7.2 Hz), 5.11 (1H, s); (enol form) δ 1.27 (6H, t, ^3J=7.2 Hz), 2.44 (3H, s), 2.57 (3H, s), 4.23 (2H, q, ^3J=7.2 Hz), 4.30 (2H, q, ^3J=7.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) (keto form) δ

13.8, 14.7, 15.1, 61.9, 68.3, 97.5, 166.8, 167.4. Anal. Calcd. for $C_{10}H_{17}NO_4S_2$: C, 43.01; H, 6.09; N, 5.02; S, 22.94. Found: C, 42.97; H, 6.15; N, 5.38; S, 22.56.

Acylation of Ethyl *N*-[bis(methylthio)methylene]alaninate 1b and *N*-[bis(methylthio)methylene]-phenylglycinate 1c. General Procedure. To a solution of KBu^{t}O (1.01 g, 9.04 mmol) in dry THF (20 mL) at -78°C, a solution of ester **1b** (2.0 g, 9.04 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred for 30 min at -78°C. After addition of the corresponding acyl chloride (45.20 mmol), stirring was maintained at -78°C for 30 min and the mixture was then allowed to slowly reach rt. The stirring was maintained for 20 h at rt. Evaporation of the solvent under reduced pressure led to pale yellow oil which was treated with H_2O (15 mL) and Et_2O (20 mL). The organic layer was decanted and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic layers were successively washed with a solution of $NaHCO_3$ (5%, until basic pH) and brine (3 x 50 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure led to a crude product which was purified by a flash chromatography (hexane/ethyl acetate: 90/10).

Ethyl 2-acetyl-*N*-[bis(methylthio)methylene]alaninate 3b. Colourless oil (55%). IR (KBr) ν 1740, 1710, 1580 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, t, ^{3}J=7.2 Hz), 1.60 (3H, s), 2.41 (3H, s), 2.44 (3H, s), 2.57 (3H, s), 4.19 (1H, qd, ^{3}J = 7.2 Hz, ^{2}J = 10.8 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 15.2, 16.1, 18.7, 26.1, 61.6, 76.8, 161.6, 170.1, 207.0. Anal. Calcd. for $C_{10}H_{20}NO_3S_2$: C, 45.62; H, 7.60; N, 5.32; S, 24.33. Found: C, 45.81; H, 7.32; N, 5.02; S, 24.62).

Ethyl 2-benzoyl-*N*-[bis(methylthio)methylene]alaninate 3c. White solid (50%). Mp = 60 - 61°C (hexane-ethyl acetate). IR (KBr) ν 1750, 1695, 1570 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, t, ^{3}J=7.5 Hz), 1.85 (3H, s), 2.29 (3H, s), 2.48 (3H, s), 4.16 (1H, qd, ^{2}J=10.8 Hz, ^{3}J=7.5 Hz), 4.20 (1H, qd, ^{2}J=10.8 Hz, ^{3}J=7.2 Hz), 7.35-7.41 (2H, m), 7.47-7.52 (1H, m), 7.92-7.95 (2H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 15.0,16.0, 20.0, 61.6, 75.3, 127.9, 129.5, 132.9, 134.4, 160.9, 171.8, 195.7. Anal. Calcd. for $C_{15}H_{19}NO_3S_2$: C, 55.31; H, 5.84; N, 4.30; S, 19.66. Found: C, 54.96; H, 6.03; N, 4.25; S, 19.80.

Ethyl 2-^{t}Butyryl-*N*-[bis(methylthio)methylene]alaninate 3d (55%). IR (neat) ν 1745, 1610, 1580 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (6H, dd, ^{3}J = 7 Hz, ^{3}J = 7 Hz), 1.23 (3H, t, ^{3}J = 7 Hz), 1.56 (3H, s), 2.42 (3H, s), 2.54 (3H, s), 3.54 (1H, septuplet, ^{3}J = 7 Hz), 4.17 (2H, q, ^{3}J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 15.3, 16.3, 19.4, 19.7, 19.8, 35.9, 61.7, 76.7, 161.5, 170.4, 213.2 Anal. Calcd. for $C_{12}H_{21}NO_3S_2$: C, 49.46; H, 7.26; N, 4.81. Found: C, 49.34; H, 7.27; N, 4.85.

Ethyl 2-(2-Furoyl)-N-[bis(methylthio)methylene]alaninate 3e (45%). Mp = 79 - 80°C (hexane-ethyl acetate). IR (KBr pellet) ν 1730, 1610, 1560 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, t, ^{3}J=7.2 Hz), 1.82 (3H, s), 2.44 (3H, s), 2.47 (3H, s), 4.17 (1H, qd, ^{2}J=10.8 Hz, ^{3}J=7.2 Hz), 4.22 (1H, qd, ^{2}J=10.8 Hz, ^{3}J=7.2 Hz), 6.49 (1H, dd, ^{3}J=3.6, 1.8 Hz), 7.18 (1H, d, ^{3}J=3.6 Hz), 7.60 (1H, d, ^{3}J=1.8 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$)

δ 13.8, 15.0, 16.1, 19.2, 61.7, 75.0, 111.7, 119,9, 146.5, 149.9, 161.7, 170.9, 184.4. Anal. Calcd. for $C_{17}H_{17}NO_4S_2$: C, 49.40; H, 5.38; N, 4.43; S, 20.26. Found: C, 49.82; H, 5.56; N, 4.02; S, 19.97.

Ethyl 2-acetyl-*N*-[bis(methylthio)methylene]phenylalaninate 3f. White solid (45%). Mp = 46 - 47 °C (hexane - ethyl acetate). IR (KBr) ν 1745, 1715, 1580 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, t, ^3J = 7 Hz), 2.07 (3H, s), 2.23 (3H, s), 2.62(3H, s), 3.53, 3.60 (2H, dd, J_{AB} = 14 Hz), 4.18 (2H, m), 7.02 - 7.23 (5H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 15.5, 16.3, 29.3, 39.0, 61.9., 80.3, 126.7, 127.9, 130.4, 135.9, 161.1, 169.7, 209.5. Anal. Calcd. for $C_{16}H_{21}NO_3S_2$: C, 56.63; H, 6.17; N, 7.29. Found: C, 56.75; H, 6.47; N, 7.50.

Ethyl 2-benzoyl-*N*-[bis(methylthio)methylene]phenylalaninate 3g. White solid (50%). Mp = 71 - 72°C (hexane-ethyl acetate). IR (KBr) ν 1750, 1690, 1580 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03(3H, t, ^3J = 7 Hz), 3.22 (6H, s), 3.72, 3.84 (2H, dd, J_{AB} = 14 Hz), 4.10 (2H, m), 7.08 - 8.0 (10H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 15.3, 16.2, 39.1, 61.8, 79.5, 126.8, 127.9, 128.2, 129.7, 130.4, 132.9, 130.4, 170.4, 195.9. Anal. Calcd. for $C_{21}H_{23}NO_3S_2$: C, 62.82; H, 5.77; N, 3.39. Found: C, 62.83; H, 5.75; N, 3.38.

Reaction of N-[Bis(methylthio)methylene]glycinate 1a with Acid Chlorides. Synthesis of 7a-d. General Procedure. To a solution of KBu^{t}O (1.01 g, 9.04 mmol) in dry THF (20 mL) at -78°C, a solution of ester **1a** (1.87 g, 9.04 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred for 30 min at -78°C. After addition of the corresponding acyl chloride (45.20 mmol) the mixture was stirred for 20 h at rt. Evaporation of the solvent under reduced pressure led to pale yellow oil which was treated with H_2O (15 mL) and Et_2O (20 mL). The organic layer was decanted and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic layers were successively washed with a solution of $NaHCO_3$ (5%, until basic pH) and brine (3 x 50 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure led to a crude product which was purified by a flash chromatography (hexane/ethyl acetate: 90/10). **1a** was recovered in 50% yield.

(Z)-Ethyl 3-acetoxy-2-[bis(methylthio)methyleneamino]-2-butenoate 7a. White solid (95%). Mp = 69 - 70 °C (hexane - ethyl acetate). IR (KBr) ν 1770, 1720, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, t, ^3J = 7 Hz), 1.89 (3H, s), 2.21 (3H, s), 2.52 (6H, bs), 4.18 (2H, q, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 15.1, 17.5, 20.9, 60.7, 128.9, 144.5, 161.9, 168.5, 169.1. MS: 291 (M, 3%), 248 (19.6%), 201 (80%), 156 (100%). Anal. Calcd. for $C_{11}H_{17}NO_4S_2$: C, 45.34; H, 5.88; N, 4.81. Found: C, 45.44; H, 5.72; N, 4.92.

(Z)-Ethyl 3-benzoyloxy-2-[bis(methylthio)methyleneamino]cinamate 7b. White solid (95%). Mp = 119 - 120 °C (hexane - ethyl acetate). IR (KBr) ν 1770, 1720, 1670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, t, ^3J = 7 Hz), 2.50 (6H, bs), 4.13 (2H, q, ^3J = 7 Hz), 7.31 - 7.62 (8H, m), 8.21 (2H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 15.1, 60.9, 127.3, 127.8, 128.3, 128.9, 129.2, 129.9, 130.0, 133.28, 133.6, 141.33, 162.8, 164.7, 169.1. MS: 415 (M, 25%), 310 (100%), 263 (84%). Anal. Calcd. for $C_{21}H_{21}NO_4S_2$: C, 60.70; H, 5.09; N, 3.37. Found: C, 60.81; H, 5.18; N, 3.45.

(Z)-Ethyl 2-[bis(methylthio)methyleneamino]-3-(2-furoyl)oxy-3-(2-furyl)acrylate 7c. White solid (95%). Mp = 127 - 129 °C (hexane - ethyl acetate). IR (KBr) ν 1760, 1710, 1680 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, t, ^3J = 7 Hz), 2.58 (6H, s), 4.16 (2H, q, ^3J = 7 Hz), 6.46 (1H, dd, ^3J = 4 Hz, ^4J = 2 Hz), 6.59 (2H, m), 7.41 (1H, d, ^3J = 4 Hz), 7.45 (1H, d, ^3J = 2 Hz), 7.67 (1H, dd, ^3J = 2 Hz, ^4J = 2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 15.5, 61.4, 112.3, 112.5, 112.8, 113.7, 119.8, 121.9, 143.9, 146.8, 147.2, 148.7, 156.3, 161.9, 170.7. Anal. Calcd. for $C_{17}H_{17}NO_6S_2$: C, 51.63; H, 4.33; N, 3.54. Found: C, 51.82; H, 4.44; N, 3.62.

(Z)-Ethyl 2-[bis(methylthio)methyleneamino]-3-(2-Thienoyl)oxy-3-(2-thienyl)acrylate 7d. White solid (95%). Mp = 123 - 125 °C (hexane - ethyl acetate). IR (KBr) ν 1770, 1710, 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (3H, t, ^3J = 7 Hz), 2.63 (6H, s), 4.15 (2H, q, ^3J = 7 Hz), 7.03 (1H, dd, ^3J = 5 Hz, ^4J = 4 Hz), 7.21 (1H, dd, ^3J = 5 Hz, ^4J = 4 Hz), 7.32 (1H, dd, ^3J = 4 Hz, ^4J = 1 Hz), 7.44 (1H, dd, ^3J = 12 Hz, ^4J = 5 Hz), 7.67 (1H, dd, ^3J = 5 Hz, ^4J = 1 Hz), 8.03 (1H, dd, ^3J = 4 Hz, ^4J = 1 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 15.5, 61.6, 126.9, 127.1, 127.5, 128.2, 130.9, 132.6, 133.7, 135.0, 135.5, 137.8, 160.2, 161.9, 172.7. Anal. Calcd. for $C_{17}H_{17}NO_4S_4$: C, 47.76; H, 4.01; N, 3.28. Found: C, 47.85; H, 4.14; N, 3.16.

Reaction of dimethyl *N*-benzyliminodithiocarbonate 2 with S-Phenyl monothiobenzoate. To a solution of KBu'O (4.78 g, 43 mmol) in dry THF (70 mL) at -78°C, a solution of **1c** (3.97 g, 20 mmol) in THF (15 mL) was added dropwise and the reaction mixture was stirred for 30 min at -78°C. After addition of *S*-phenyl monothiobenzoate (4.82 g, 22 mmol) in THF (15 mL), stirring was maintained at -78°C for 30 min and the temperature was then allowed to slowly rise to rt. After 2 h at rt., H_2O (50 mL) was then added. The reaction mixture was extracted with Et_2O (3 x 50 mL) and the combined organic layers were washed with brine (3 x 50 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure led to a crude (6.8 g) which was purified by two successive flash chromatographies (hexane/ethyl acetate: 90/10 and CH_2Cl_2, respectively). **9** was obtained as a mixture of two isomers: **9a** (0.48 g, 5%) and **9b** (3.73 g, 39%) which were separated and purified by recrystallization from hexane/ethyl acetate.

(4R*,5S*,6R*)-5-*N*-[bis(methylthio)methylene]aminobenzyl-4,5-diphenyl-2-methylthio-4,5-dihydro oxazole 9a. White solid (5%). Mp = 200 - 202°C. IR (KBr) ν 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (3H, s), 2.45 (3H, s), 2.50 (3H, s), 4.81 (1H, s), 5.41 (1H, s), 6.41-7.30 (15H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (q, ^1J=142.4 Hz), 14.8 (q, ^1J=141.4 Hz), 14.9 (q, ^1J=141.4 Hz), 68.7 (dtd, ^1J=136.2 Hz, ^3J=4.0, 4.0 Hz), 79.9 (ddt, ^1J=146.2 Hz, ^3J=3.3, 3.3 Hz), 94.4 (m), 126.6, 126.9, 127.1, 127.3, 127.4, 127.5, 127.7, 128.5, 128.8 (m), 137.3 (dt, ^2J=5.0 Hz, ^3J=7.5 Hz), 138.4 (dt, ^2J=5.0 Hz, ^3J=7.5 Hz), 140.9 (tdd, ^3J=7.7, 4.3, 4.3 Hz), 161.9 (m), 165.9 (qd, ^3J=2.3 Hz), MS (m/z): 478 (1.0%, $M^{+\cdot}$).

(4R*,5S*,6S*)-5-*N*-[bis(methylthio)methylene]aminobenzyl-4,5-diphenyl-2-methylthio-4,5-dihydro-oxazole 9b. Colourless oil (39%). IR (neat) ν 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (3H, s), 2.31 (3H, s), 2.38 (3H, s), 5.11 (1H, s), 5.41 (1H, s), 6.44-7.44 (15H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8 (q,

^{1}J=141.4 Hz), 14.6 (q, ^{1}J=131.2 Hz), 14.7 (q, ^{1}J=131.2 Hz), 72.4 (dtd, ^{1}J=135.5 Hz, ^{3}J=4.0, 8.2 Hz), 76.6 (ddt, ^{1}J=143.2 Hz, ^{3}J=2.0, 4.0 Hz), 96.6 (m), 125.5, , 125.8, 126.6, 126.7, 127.0, 127.2, 127.3, 128.1, 128.7 (m), 136.2 (td, ^{3}J = 7.0 Hz, ^{2}J = 5.0 Hz), 137.1 (td, ^{3}J = 7.5, 4.0 Hz), 162.1 (m), 164.8 (m). MS 478 (1%, M^+).

Oxidative Hydrolysis of 9a,b. Synthesis of 8a,b. To a solution of **9a** or **9b** (51 mg, 0.11 mmol) in formic acid (1.22 g, 26 mmol) at 0°C, a solution of *p*-toluensulfonic acid (95 mg, 0.55 mmol) in H_2O_2 (30%, 110 vol, 0.72 mmol) was added dropwise and the reaction mixture was stirred for 4 h at 0°C. The temperature was then allowed to slowly rise to rt. and the stirring was maintained for 20 h at rt. Evaporation of the solvent under reduced pressure allowed the isolation of a pale yellow oil which was dissolved in Et_2O (5 mL). This ethereal solution was cooled at 0°C and a solution of NaOH 2N (0.2 mL) was then added. The mixture was vigorously stirred until an homogeneous solution was obtained, and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure.

(4R*,5S*,6R*)-1,3-Diamino-1,2,3-triphenyl-2-propanol 8a. (14%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (1H, s), 5.17 (1H, s), 5.44 (1H, bs), 6.66 (2H, d, ^{3}J=6.9 Hz), 6.67 (2H, d, ^{3}J=6.9 Hz), 7.00-7.60 (15H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 58.1, 66.0, 90.0, 137.6, 138.8, 139.7, 126.6, 127.0, 127.4, 127.6, 127.7, 128.1, 128.20, 128.22, 128.3, 128.5, 129.0. Anal. Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.33; H, 7.08; N, 9.01.

(4R*,5S*,6S*)-1,3-Diamino-1,2,3-triphenyl-2-propanol 8b. (66%). 1H NMR (300 MHz, $CDCl_3$) δ 4.39 (1H, s), 4.94 (1H, s), 5.68 (1H, bs), 6.88 (2H, d, ^{3}J=7.0 Hz), 6.89 (2H, d, ^{3}J=7.0 Hz), 7.00-7.60 (15H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 63.0, 63.2, 91.6, 126.3, 126.8, 16.91, 126.93, 127.2, 127.4, 127.5, 127.63, 127.67, 127.7, 127.9, 127.94, 128.1, 128.15, 128.3, 128.5, 128.7, 128.71, 129.3, 136.5, 137.3, 139.2, 139.4, 140.1 ppm. Anal. Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.40; H, 6.74; N, 8.65.

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