New convenient access to thioesters of α-amino acids from *N*,*N*-disubstituted 2-aminoalk-2-enals

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N,*N*-Disubstituted 2-aminoalk-2-enals **1** react with alkyl- or arylthiols to give unexpected thioesters of α-amino acid **3** in good yields. The same type of product is formed when substrate **1b** is treated with ethane-1,2-dithiol. The reaction proceeds *via* an intermediate 1,2-adduct which is transformed, after a 1,3-shift, into the final thioester **3**.

Introduction

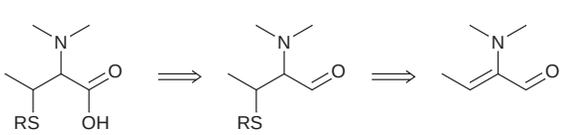
N,*N*-Disubstituted 2-aminoalk-2-enals are compounds of particular interest as versatile building blocks in modern organic synthesis. They contain formyl and protected amino groups which are attached to the same sp^2 carbon atom. In view of this multifunctional reactivity, the compounds could readily provide essential access to various biologically important products and natural analogues.

The β-thio-α-amino acids and their derivatives occupy a significant place among the bioactive compounds because of their considerable use for the treatment of various diseases.[1] One of the simple routes to this type of compound could be the Michael addition of thiols to the α,β-unsaturated carbonyl system. This process has been shown to be an important reaction in synthetic organic chemistry as well as an important process.[2]

In general, the reaction of thiols with α,β-unsaturated aldehydes, ketones and esters is a typical 1,4-addition which proceeds under mild conditions giving the Michael adducts in good yield.[2,3] In some cases the use of base as a catalyst or heating to reflux is required.[4] Similar transformations have been observed in the series of 2-functionally substituted alk-2-enals and esters. Thus, only conjugate addition of thiols onto 2-alkoxy- or 2-alkylthioalk-2-enals occurs under basic conditions.[5] However, in the latter case the Michael adducts may react further with excess thiol on the carbonyl group in the presence of acid (HCl, $BF_3{\cdot}Et_2O$) leading to the thioacetals of β-alkylthio substituted aldehydes.[6]

The same addition direction is observed when 2-haloalk-2-enals are treated with thiols in the presence of K_2CO_3 at 80 °C[7] or $BF_3{\cdot}Et_2O$ at −78 °C.[6a] At the same time, some examples have been reported in which the reaction of 2-haloalk-2-enals with S-nucleophiles follow the classical Ad-S_N-E sequence leading to the 2-alkyl(aryl)thioalk-2-enals in good yields.[8] In the reaction of α-halo-α,β-unsaturated esters or ketones with thiols, the Michael adducts formed initially[9] are converted into the final products of *ipso*-substitution of the halogen atom.[10] Finally, the treatment of *N*,*N*-disubstituted α-amino-α,β-unsaturated esters with thiols affords the corresponding Michael adduct as the only product.[11]

So our strategy based on the *N*,*N*-disubstituted 2-aminoalk-2-enals **1**, was to add the thiols onto the substrates **1** followed by the oxidation of the formyl group (Scheme 1).

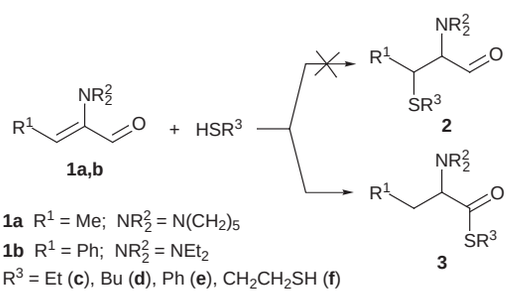


Scheme 1

In this paper we describe full synthetic and mechanistic details of the reaction of *N*,*N*-disubstituted 2-aminoalk-2-enals **1** with thiols.[12]

Results and discussions

To our surprise, the treatment of *N*,*N*-disubstituted 2-aminoalk-2-enals **1a**,**b** with alkyl- or arylthiols does not lead to the expected 1,4-adducts. In all cases only the thioesters of α-amino acid **3** were isolated in good yields. No Michael adduct of type **2** was detected in the reaction mixture (Scheme 2).



Scheme 2

In order to determine the scope and utility of this reaction, the 2-aminoalk-2-enals, 2-piperidinobut-2-enal **1a** and 2-diethylamino-3-phenylpropenal **1b**, were treated with various thiols (ethane-, butane- and benzenethiol as well as ethane-1,2-dithiol) under different reaction conditions. The results obtained are presented in Table 1.

We have found that the electronic and steric considerations of the initial substrates **1a**,**b** have no significant influence on the reaction course: the thioesters **3** were obtained in good yields as the sole product in both the crotonic and cinnamic series.

A change in the substrate **1** : thiol ratio does not influence the reaction course. In fact, when 2-diethylamino-3-phenylpropenal **1b** is treated with one or two equivalents of butanethiol in benzene, after 4 h the thioester **3bd** was isolated exclusively (Table 1, entries 6 and 8). The product obtained does not depend on the nature of solvent used in the reaction: the same thioester **3bd** is formed as a sole product in the reaction of the alkenal **1b** with butanethiol in both benzene and THF (Table 1, entries 6 and 9). However, according to ^1H NMR spectroscopy data, when THF is employed as a solvent the reaction mixture contains approximately 20% of the starting materials after 4 h at reflux. The low rate of transformation of **1b** into **3bd** in this case seems to be due to the lower boiling of the solvent. Finally, the

Table 1 Reaction of *N*,*N*-disubstituted 2-aminoalk-2-enals **1** with thiols

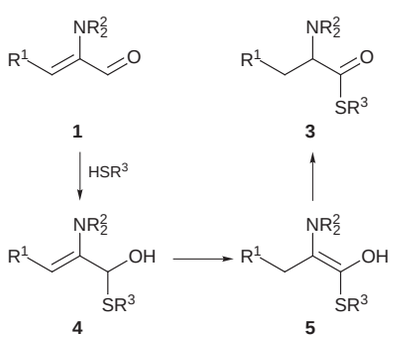
Entry	Initial reagents: **1**	Initial reagents: R^3	Ratio **1** : thiol	Conditions	Product	Yield (%)[a]
1	**1a**	Et	1 : 1	PhH, reflux, 7 h	**3ac**	40
2	**1a**	Bu	1 : 2	THF, 0 °C, 1 month	**3ad**	80[b]
3	**1a**	Bu	1 : 2	PhH, reflux, 6 h	**3ad**	87
4	**1a**	Ph	1 : 2	PhH, 0 °C, 14 days	**3ae**	60
5	**1b**	Et	1 : 1	PhH, reflux, 7 h	**3bc**	70
6	**1b**	Bu	1 : 1	PhH, reflux, 4 h	**3bd**	75 (~100[b])
7	**1b**	Bu	1 : 1	PhH, rt, 7 days	**3bd**	73
8	**1b**	Bu	1 : 2	PhH, reflux, 4 h	**3bd**	70
9	**1b**	Bu	1 : 1	THF, reflux, 4 h	**3bd**	79[b]
10	**1b**	$HS(CH_2)_2$	1 : 1	PhH, reflux, 4 h	**3bf**	~100[b]
11	**1b**	$HS(CH_2)_2$	1 : 1	PhH, rt, 7 days	**3bf**	~100[b]

[a] Yield of the isolated product. [b] Yield according to ^{1}H NMR after evaporation of the reaction mixture.

results were unaffected by changes in temperature: the same reaction course takes place when **1b** is treated with butanethiol both at room temperature and under reflux (Table 1, entries 6 and 9).

The above results lead to the conclusion that unlike other 2-substituted or unsubstituted alk-2-enals, *N*,*N*-disubstituted 2-aminoalk-2-enals **1** react with thiols in a different way. The reason for this behaviour is believed to be due to the electron-rich amino group NR^2_2 which could cause strengthening of the p,π-interaction between the nitrogen lone pair and the double bond. As a result, an increase in the negative charge at the β-carbon atom occurs and the conjugation characteristics of the α,β-unsaturated aldehyde are destroyed completely.[13]

As the formation of the thioesters **3** *via* the Michael adduct defies explanation, another mechanistic pathway must be operating. On the basis of the obtained results and the electronic structure of the initial substrates it may be suggested that the process starts with the 1,2-addition of the S-nucleophile and results in the formation of the hemithioacetal **4** (Scheme 3). The



Scheme 3

latter compound undergoes a 1,3-shift by Zaitsev's rule to give the enol **5** which is immediately transformed into the final thioester **3**.

In an effort to confirm experimentally this multistep sequence of transformations, the reaction of the 2-diethylamino-3-phenylpropenal **1b** with ethane-1,2-dithiol has been studied. As is well known, this bidentate nucleophile is a useful reagent for the protection of the carbonyl group under mild conditions.[14] However, in the absence of catalyst, the intermediate **4** (Scheme 3) undergoes a double bond shift rather than an intramolecular condensation to yield exclusively ester **3bf**.

By analogy with trimethylamino-[15] or trimethylcyanosilanes,[16] the formation of the corresponding silyl ethers could be expected when the initial substrate **1** is treated with trimethylsilyl derivatives of thiols. Actually, only the signals of the starting materials were registered in the NMR spectrum of the reaction mixture after prolonged warming of the substrate **1b** with an equimolar quantity of butylthiotrimethylsilane in benzene. Indeed, only starting materials were recovered after 17 h of reflux. Unfortunately, the results concerning the use of a catalyst in the reaction are not clear: the treatment of **1b** with butylthiotrimethylsilane in the presence of ~5×10^{-4} equivalent of the solid potassium cyanide-18-crown-6 complex[17] gave a mixture of non-identified products.

Conclusion

The results presented here indicate that the course of the reaction between thiols and *N*,*N*-disubstituted 2-aminoalk-2-enals **1** is completely opposite to that observed earlier for other 2-substituted alk-2-enals. While the latter react with thiols to provide, as a rule, the Michael adducts, the thioesters **3** are formed in high yields from the nitrogen-bearing analogues **1**. This remarkable and unexpected one-pot reaction of **1** with S-nucleophiles can be regarded as a new convenient approach to the synthesis of α-amino acid derivatives and deserves further investigation.

Experimental

^{1}H and ^{13}C NMR spectra were recorded in deuteriochloroform on Bruker DPX-250 and JEOL FX-90Q spectrometers with HMDS as an internal standard; coupling constants (*J*) are given in Hz. MS analysis (EI, 60 eV) was performed on an LKB-2091 instrument. IR spectra were recorded on a Specord 75-IR spectrometer. All solvents were distilled prior to use.

The 2-piperidinobut-2-enal **1a** and 2-diethylamino-3-phenylpropenal **1b** were prepared from the corresponding 2-haloalk-2-enals by the halogen substitution reaction with the secondary amines as previously reported.[18] Butylthiotrimethylsilane has been prepared by silylation of butanethiol utilizing a routine literature procedure.[19]

Reactions of 2-aminoalk-2-enals 1 with thiols (general procedure)

A solution of the 2-aminoalk-2-enal **1** (5–15 mmol) and thiol (10–30 mmol) in benzene or THF (10–15 ml) was stirred under reflux or kept at room temperature for a convenient time (Table 1). The solvent was evaporated; the vacuum distillation of the residue afforded compound **3**.

***S*-Ethyl 2-piperidinobutanethioate 3ac.** Bp 78 °C (1 mmHg) (Found: C, 61.35; H, 9.83; N, 6.50; S, 14.89. $C_{11}H_{21}NOS$ requires C, 61.39; H, 10.34; N, 6.53; S, 14.98%); ν_{max} (film)/cm^{-1} 1670 (C=O); δ_H (250 MHz) 0.93 (3H, t, *J* 7.6), 1.22 (3H, t, *J* 7.6), 1.4–1.8 (8H, m), 2.5–2.6 (4H, m), 2.80 (2H, q, *J* 7.6), 3.05 (1H, t, *J* 7.1); δ_C (62.9 MHz) 11.2 (CH_3CH_2CH), 14.6 (CH_3-CH_2S), 21.6 (CH_2) 22.8 (CH_2S), 24.4, 26.3 (CH_2 *piperidine*),

50.9 ($N(CH_2)_2$), 76.5 (CH), 201.9 (C=O). *m*/*z* (EI, 60 eV) 126 (100).

***S*-Butyl 2-piperidinobutanethioate 3ad.** Bp 105 °C (2 mmHg) (Found: C, 64.08; H, 10.82; N, 6.04; S, 13.52. $C_{13}H_{25}NOS$ requires C, 64.15; H, 10.35; N, 5.75; S, 13.17%); ν_{max} (film)/cm^{-1} 1665 (C=O); δ_H (250 MHz) 0.86 (3H, t, *J* 7.0), 0.90 (3H, t, *J* 7.0), 1.3–1.4 (4H, m), 1.45–1.75 (8H, m), 2.45–2.60 (4H, m), 2.77 (2H, t, *J* 7.0), 3.03 (1H, dd, *J* 7.9 and 6.2); δ_C (62.9 MHz) 11.4 (CH_3 *ethyl*), 13.6 (CH_3 *butyl*), 21.9 (CH_2CH), 22.1 (CH_2S), 24.6, 26.5 (CH_2 *piperidine*), 28.3, 31.7 (CH_2CH_2), 51.1 ($N(CH_2)_2$), 76.8 (CH), 202.2 (C=O). *m*/*z* (EI, 60 eV) 126 (100).

***S*-Phenyl 2-piperidinobutanethioate 3ae.** Bp 125 °C (1 mmHg) (Found: C, 68.19; H, 8.05; N, 5.05; S, 11.92. $C_{15}H_{21}NOS$ requires C, 68.40; H, 8.04; N, 5.32; S, 12.17%); ν_{max} (film)/cm^{-1} 1695 (C=O); δ_H (250 MHz) 0.99 (3H, t, *J* 7.5), 1.40–1.80 (8H, m), 2.65 (4H, t, *J* 5.3), 3.19 (1H, dd, *J* 7.3 and 6.7), 7.36 (5H, m); δ_C (62.9 MHz) 11.8 (CH_3), 21.4 (CH_2), 24.5, 26.4 (CH_2 *piperidine*), 51.2 ($N(CH_2)_2$), 76.5 (CH), 127.4, 128.8, 128, 134.4 (arom), 201.0 (C=O). *m*/*z* (EI, 60 eV) 126 (100).

***S*-Ethyl 2-diethylamino-3-phenylpropanethioate 3bc.** Bp 120–121 °C (1 mmHg) (Found: C, 67.94; H, 8.89; N, 4.88; S, 12.39. $C_{15}H_{23}NOS$ requires C, 67.88; H, 8.73; N, 5.28; S, 12.08%); ν_{max} (film)/cm^{-1} 1670 (C=O); δ_H (90 MHz) 1.02 (6H, t, *J* 7.0), 1.17 (3H, t, *J* 7.0), 2.60 (4H, q, *J* 7.0), 2.76 (2H, q, *J* 7.0), 2.83, 3.12 (2H, AB-syst., *J* 13.7 and 6.8), 3.68 (1H, t, *J* 6.8), 7.21 (5H, m); δ_C (22.49 MHz) 13.6 (CH_3CH_2N), 14.4 (CH_3CH_2S), 22.9 (CH_2S), 33.5 (CH_2), 44.2 (NCH_2), 71.6 (CH), 125.7, 128.0, 129.0, 139.3 (arom), 202.5 (C=O). *m*/*z* (EI, 60 eV) 177 (14), 176 (100), 91 (10).

***S*-Butyl 2-diethylamino-3-phenylpropanethioate 3bd.** Bp 149–150 °C (1 mmHg) (Found: C, 70.11; H, 9.54; N, 5.08; S, 11.34. $C_{17}H_{27}NOS$ requires C, 69.58; H, 9.27; N, 4.77; S, 10.92%); ν_{max} (film)/cm^{-1} 1665 (C=O); δ_H (90 MHz) 0.95 (3H, t, *J* 7), 1.02 (6H, t, *J* 7.0), 1.35–1.45 (4H, m), 2.61 (4H, q, *J* 7.0), 2.76 (2H, t, *J* 7.0), 2.80, 3.11 (2H, AB-syst., *J* 14.3 and 7.1), 3.69 (1H, t, *J* 7.1), 7.21 (5H, m); δ_C (22.49 MHz) 13.6 (CH_3CH_2N), 13.8 (CH_3 *butyl*), 22.0 (CH_2S), 28.5, 31.6 (CH_2CH_2), 34.0 (CH_2CH), 44.5 (NCH_2), 71.9 (CH), 126.0, 128.2, 129.3, 139.5 (arom), 202.7 (C=O). *m*/*z* (EI, 60 eV) 176 (14), 175 (100), 91 (11).

Reaction of 2-diethylamino-3-phenylpropenal 1b with ethane-1,2-dithiol

A solution of **1b** (2.0 g, 10 mmol) and ethane-1,2-dithiol (0.9 g, 10 mmol) in benzene (10 ml) was refluxed for 4 h. Evaporation of the solvent under reduced pressure provided 2.8 g (~100%) of pure *S*-(2-mercaptoethyl) 2-diethylamino-3-phenylpropanethioate **3bf** as an oil: ν_{max} (film)/cm^{-1} 1670 (C=O), 2550 (S-H); δ_H (250 MHz) 1.03 (6H, t, *J* 7), 2.56 (4H, q, *J* 7), 2.77–3.13 (6H, m), 3.68 (1H, dd, *J* 7.3 and 6.7), 7.20 (5H, m); δ_C (62.9 MHz) 13.6 (CH_3), 24.3 (CH_2S), 32.7 (CH_2SH), 33.3 (CH_2), 44.3 (NCH_2), 71.7 (CH), 126.0, 128.1, 129.1, 139.2 (arom), 202.7 (C=O). *m*/*z* (EI, 60 eV) 176 (100), 161 (59), 86 (23). This compound is unstable and decomposed upon attempts to distil the product.

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