Tetrahedron Letters 49 (2008) 5751–5754

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Direct introduction of glycine/mercaptoacetic acid units into electron-poor alkenes: a novel route to functionally rich α-amino/α-mercapto acids

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ARTICLE INFO

Article history:
Received 10 June 2008
Revised 14 July 2008
Accepted 18 July 2008
Available online 24 July 2008

Keywords:
α-Amino acids
α-Mercapto acids
Michael addition
Lewis acid
Stereoselective synthesis
Activated alkenes

ABSTRACT

The first example of an operationally simple direct introduction of glycine/mercaptoacetic acid units into electron-poor alkenes is reported. In this protocol, Lewis acid-catalyzed Michael addition of activated glycine or mercaptoacetic acid, that is 2-phenyl-1,3-oxazol-5-one or 2-methyl-2-phenyl-1,3-oxathiolan-5-one, to various electron-poor alkenes in water/1,4-dioxane (1:2, v/v) solvent system diastereoselectively affords the corresponding functionally rich α-amino acids or α-mercapto acids, respectively, in high yields at ambient temperature.

The Michael addition of various nucleophiles to highly electron deficient olefins has proven to be an atom-economical and versatile transformation.[1] Although there are numerous reports on the Michael addition of various aldehydes and ketones to activated alkenes, there is no report on the addition of glycine/mercaptoacetic acid to activated alkenes, which is the target reaction of the present investigation.[2] The products of this reaction are multifunctionalized α-amino/α-mercapto acids, which are of significant chemical and pharmacological interest.[3] For example, β-substituted α-amino acids are present in several peptidic natural products, and γ-nitro-α-amino acids act as open chain precursors for a convenient synthesis of γ-lactam analogues of β-lactam antibiotics.[4,5] Furthermore, these amino acids themselves are a useful source of chiral substrates, auxiliaries and catalysts in various fields of organic chemistry.[6] As a consequence, a great deal of effort has been dedicated to the development of efficient and practical synthetic methods for both natural and non-natural α-amino acids, which are of considerable importance in a variety of fields including chemistry and biology.[7]

Mercaptoacetic acid derivatives have been found to be oxytocin inhibitors in the avian vasodepressor (AVD) assay.[8] From a chemical viewpoint, α-mercapto acids have been utilized as substrates for the synthesis of bioactive molecules and medicines, and are also used as reagents for the identification of carbonyl compounds.[9]

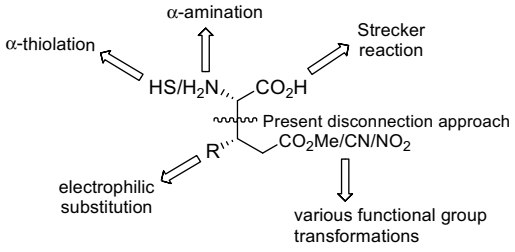

Figure 1. Various functionalities installed in the target molecule.

Table 1
Optimization of the Lewis acid catalyst

Entry	Catalyst (mol %)	Time (h)	Yield[a] (%)	*Syn*/*anti*[b]
1	$CuCl_2{\cdot}2H_2O$ (20)	15	30	66:34
2	$FeCl_3{\cdot}7H_2O$ (20)	14	42	71:29
3	$Ce_2(SO_4)_3$ (20)	12	51	73:27
4	$Ce_2(SO_4)_3$/NaI (1:1) (20)	12	66	78:22
5	$CeCl_3{\cdot}7H_2O$ (20)	10	60	76:24
6	$CeCl_3{\cdot}7H_2O$/NaI (1:1) (10)	8	67	80:20
7	$CeCl_3{\cdot}7H_2O$/NaI (1:1) (20)	8	85	94:6
8	$CeCl_3{\cdot}7H_2O$/NaI (1:1) (25)	8	85	94:6

[a] Yield of isolated and purified products.
[b] As determined by ^1H NMR of the crude products.

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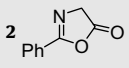
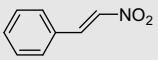
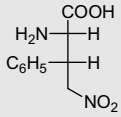
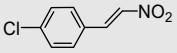
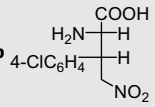
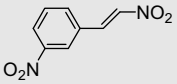
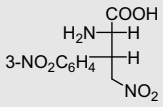
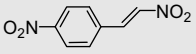
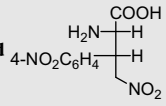
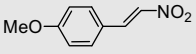
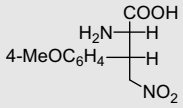
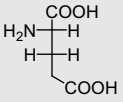
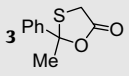
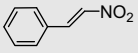
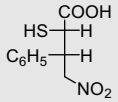
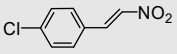
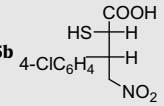
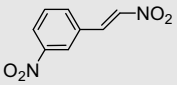
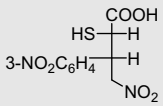
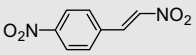
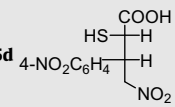
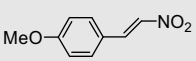
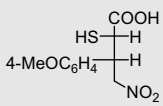
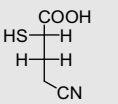
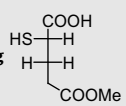
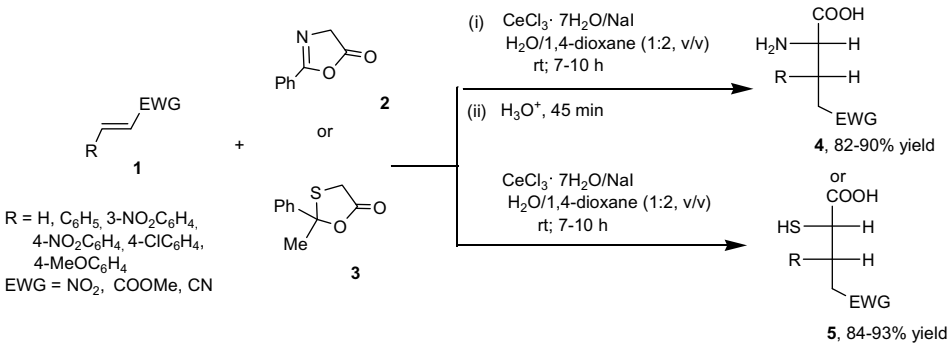
doi:10.1016/j.tetlet.2008.07.103

Table 2
Diastereoselective synthesis of α-amino acids **4** and α-mercapto acids **5** from electron-poor alkenes **1**

Entry	Lactone **2** or **3**	Alkene **1**	Product **4** or **5**	Yield (%)[a,b] (Time, h)[c]	*Syn*/*anti*[d]
1	**2** 		**4a** 	83 (10)	93:7
2	**2**		**4b** 	87 (9)	94:6
3	**2**		**4c** 	86 (10)	95:5
4	**2**		**4d** 	90 (8)	94:6
5	**2**		**4e** 	82 (10)	93:7
6	**2**		**4f** 	83 (9)	–
7	**3** 		**5a** 	85 (8)	94:6
8	**3**		**5b** 	89 (7)	95:5
9	**3**		**5c** 	92 (9)	96:4
10	**3**		**5d** 	93 (7)	95:5
11	**3**		**5e** 	84 (9)	94:6
12	**3**		**5f** 	88 (8)	–
13	**3**		**5g** 	85 (8)	–

[a] Yield of isolated and purified products.
[b] All compounds gave C, H and N analyses within ±0.38% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.
[c] Stirring time at rt (excluding the time required for debenzoylation of **7** to give **4**, Scheme 2).
[d] As determined by ^{1}H NMR of the crude products.



Scheme 1. Synthesis of α-amino acids **4** and α-mercapto acids **5** from electron-poor alkenes **1**.

Therefore, the medicinal and synthetic utility of α-amino and α-mercapto acids is the major driving force for attracting organic and medicinal chemists to devise their diverse syntheses.

In this Letter, we report a convenient installation of versatile functional groups such as amino, mercapto, carboxylic acid, nitro, ester, cyano and aryl on the activated olefinic double bond of methyl acrylate, acrylonitrile and nitrostyrenes (Fig. 1) via a C–C bond forming Michael reaction.

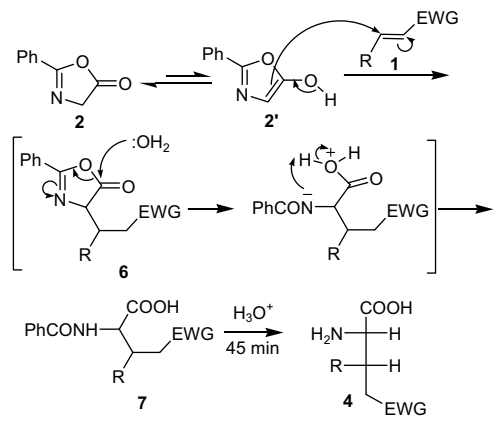
The present synthesis of the target functionalized α-amino/α-mercapto carboxylic acids is an outcome of our continuous interest in Michael type reactions for developing new routes to chemically and pharmacologically relevant compounds.[10]

Initially, we investigated the Michael addition of glycine/mercaptoacetic acid to electron-poor alkenes but did not obtain the desired products **4** or **5**, probably due to the presence of free –COOH and $–NH_2$ or –SH groups. Instead, we turned our attention to activate the glycine and mercaptoacetic acid units by converting them into 2-phenyl-1,3-oxazol-5-one **2** and 2-methyl-2-phenyl-1,3-oxathiolan-5-one **3**, respectively.[11,12] This worked well as the –COOH and $–NH_2$ or –SH groups of glycine/mercaptoacetic acid were blocked, and their methylene group was activated to act as the Michael donor.[15]

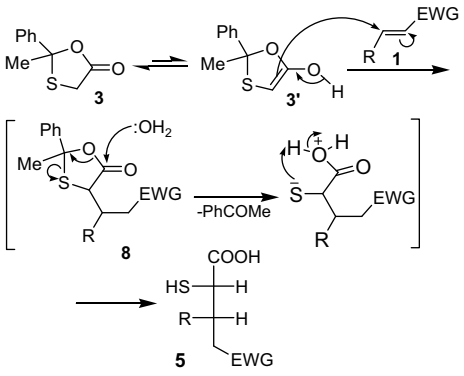
As regards the choice of catalyst, we tested several Lewis acids for the synthesis of the representative compound **5** (R = Ph; EWG = NO_2) using a water/1,4-dioxane (1:2, v/v) solvent system. The best result was obtained in the case of the $CeCl_3{\cdot}7H_2O$/NaI (1:1) catalyst system (Table 1, entry 7). This is in conformity with the earlier observation that the catalytic activity of $CeCl_3{\cdot}7H_2O$ increases dramatically in the presence of an iodide source, such as NaI, owing to the formation of a complex, which exhibits stronger Lewis acid character than $CeCl_3{\cdot}7H_2O$.[13] The optimum catalyst loading for the $CeCl_3{\cdot}7H_2O$/NaI (1:1) system was found to be 20 mol %. A decrease in the amount of catalyst decreased both the yield and diastereoselectivity considerably (Table 1, entry 6). However, a higher catalyst loading did not appreciably increase the yield and diastereoselectivity (Table 1, entry 8). Next, optimization of the solvent for the synthesis of representative compound **5** (R = Ph; EWG = NO_2) was undertaken. It was found that amongst H_2O, MeOH, EtOH, 1,4-dioxane, MeOH/H_2O (2:1), EtOH/H_2O (2:1) and 1,4-dioxane/H_2O (2:1), the best solvent system in terms of the yield and diastereoselectivity was 1,4-dioxane/H_2O (2:1). In order to investigate the substrate scope of the reaction, various electron–poor alkenes such as [*E*]-β-nitrostyrenes, methyl acrylate and acrylonitrile were reacted under the optimized reaction conditions. The yields and diastereoselectivities were consistently good (Table 2), the highest yield being 93% (Table 2, entry 10) and the best *syn* stereoselectivity being 96% (Table 2, entry 9). The strategy followed for the envisaged diastereoselective synthesis of α-amino acids **4** and α-mercapto acids **5** was successfully realized by stirring a mixture of 2-phenyl-1,3-oxazol-5-one **2** or 2-methyl-2-phenyl-1,3-oxathiolan-5-one **3** and activated alkene **1** with the Lewis acid catalyst $CeCl_3{\cdot}7H_2O$/NaI in water/1,4-dioxane at rt for 7–10 h (Scheme 1). Isolation and purification by recrystallization from EtOAc–hexane (1:20) afforded compounds **4** and **5** in 82–93% yields (Table 2). The formation of **4** and **5** was highly diastereoselective in favour of the *syn* isomer.

The diastereomeric ratios in the crude isolates were determined by ^{1}H NMR spectroscopy to note any alteration of these ratios during subsequent purification. The crude isolates of **4** and **5** were found to be diastereomeric mixtures containing 93–96% of the *syn* isomer. On the basis of ^{1}H NMR spectroscopy and literature precedent,[14] the *syn* configuration was conclusively assigned to **4**, **5** and **7**, as their coupling constant ($J_{2H,3H}$ = 3.9–4.1 Hz) was smaller than that for the minor *anti* isomer ($J_{2H,3H}$ = 8.3–9.4 Hz). The coupling constant for vicinal protons of the analogous *syn* isomer is reported to be $J_{2H,3H}$ = 4.8 Hz and that of the *anti* isomer $J_{2H,3H}$ = 9.6 Hz.[14a] Similarly, the coupling constants reported by Kamimura et al.[14b] for the *syn* ($J_{2H,3H}$ = 4.3 Hz) and *anti* ($J_{2H,3H}$ = 7.9 Hz) isomers are comparable to that of compounds **4**, **5** and **7**. Furthermore, 3-H signals for *syn* isomers of compounds **4**, **5** and **7** always appeared in the lower field (δ = 3.18–3.50) than the corresponding signals for *anti* isomers (δ = 2.85–3.08), which is in conformity with the earlier observation.[14b]

The formation of compounds **4** and **5** may be explained by intermolecular nucleophilic attack of C-4 of 2-phenyl-1,3-oxazol-5-one **2** or 2-methyl-2-phenyl-1,3-oxathiolan-5-one **3** at the double bond of alkene **1** (e.g., at the α-carbon of β-nitrostyrene) to afford the Michael adducts **6** and **8** (Schemes 2 and 3). The adduct **6** upon hydrolysis gave **7**,[15] which on debenzoylation afforded the target α-amino acid **4**[16] as depicted in Scheme 2. Similarly, the adduct **8** afforded α-mercaptoacetic acid **5**[17] following removal of



Scheme 2. A plausible mechanism for the formation of α-amino acids **4**.



Scheme 3. A plausible mechanism for the formation of α-mercapto acids **5**.

acetophenone during the course of reaction, without requiring any additional deprotection step (Scheme 3).

In conclusion, we have developed a novel method for direct introduction of glycine/mercaptoacetic acid units into electron-poor alkenes via Lewis acid-catalyzed Michael reaction to afford functionally rich α-amino acids and α-mercapto acids. The present synthetic protocol involves simple operations at ambient-temperature to give high yields and diastereoselectivities of the products in a one-pot procedure and which may find application in organic synthesis.

Acknowledgement

We sincerely thank SAIF, CDRI, Lucknow, for providing microanalyses and spectra.

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15. *General procedure for the synthesis of N-benzoyl-α-amino acids* **7**: A mixture of activated alkene **1** (1 mmol), 2-phenyl-1,3-oxazol-5-one **2** (1 mmol), $CeCl_3{\cdot}7H_2O$ (0.2 mmol) and NaI (0.2 mmol) in 15 mL of water/1,4-dioxane (1:2 v/v) was stirred at room temperature for 7–10 h (Table 2). After completion of the reaction (monitored by TLC), water (10 mL) was added and the product was extracted with CH_2Cl_2 (3 × 15 mL). The combined extract was dried over Na_2SO_4, filtered, concentrated under reduced pressure and the crude product thus obtained was recrystallized from ethyl acetate to afford an analytically pure **7**. Physical data of representative compound **7a** (R = Ph, EWG = NO_2: yellowish solid, yield 91%, mp 205–207 °C. IR (KBr) ν_{max} 3310, 3000, 2985, 2845, 1725, 1657, 1602, 1588, 1451, 753, 705 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6 + D_2O/TMS) δ: 3.50 (ddd, 1H, J = 8.1, 4.1, 5.2 Hz, 3-H), 3.86 (d, 1H, J = 4.1 Hz, 2-H), 4.60 (dd, 1H, J = 12.9, 5.2 Hz, 4-H_a), 4.79 (dd, 1H, J = 12.9, 8.1 Hz, 4-H_b), 7.15–7.95 (m, 10H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6/TMS) δ: 31.9, 58.8, 76.2, 125.4, 126.3, 127.6, 128.5, 129.7, 132.4, 133.9, 148.8, 167.3, 174.2. EIMS (*m/z*) 328 (M^+). Anal. calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.44; H, 4.58; N, 8.29.
16. *General procedure for the synthesis of α-amino acids* **4**: Compound **7** (1 mmol) was refluxed in H_2SO_4/H_2O (8 mL, 4:3, v/v) for 45 min in an oil-bath. The reaction mixture was cooled, precipitated benzoic acid was filtered off and the filtrate was neutralized by adding concentrated NH_4OH (specific gravity 0.88) under ice cooling. The crude product thus precipitated was recrystallized from aqueous methanol to afford an analytically pure sample of **4**. Physical data of representative compound **4a**: yellowish solid, yield 83%, mp 180–183 °C. IR (KBr) ν_{max} 3340, 3005, 2988, 2852, 1720, 1600, 1585, 1450, 748, 708 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6 + D_2O/TMS) δ: 3.21 (ddd, 1H, J = 7.9, 4.0, 4.8 Hz, 3-H), 3.86 (d, 1H, J = 4.0 Hz, 2-H), 4.57 (dd, 1H, J = 12.5, 4.8 Hz, 4-H_a), 4.81 (dd, 1H, J = 12.5, 7.9 Hz, 4-H_a), 7.10–7.19 (m, 5H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6/TMS)) δ: 35.3, 62.1, 76.9, 125.0, 126.4, 128.7, 148.2, 173.9. EIMS (*m/z*) 224 (M^+). Anal. calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.91; H, 5.68; N, 12.11.
17. *General procedure for the synthesis of α-mercapto acids* **5**: The procedure followed was the same as described for the synthesis of **7** (Ref. 15) except that 1,3-oxathiolan-5-one **2** (1 mmol) was used instead of 1,3-oxazol-5-one **1** (1 mmol). The crude product was recrystallized from aqueous methanol to afford an analytically pure sample of **5**. Physical data of representative compound **5a**: yellowish solid, yield 85%, mp 110–112 °C. IR (KBr) ν_{max} 3008, 2982, 2845, 2580, 1718, 1598, 1583, 1445, 745, 704 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6 + D_2O/TMS) δ: 3.18 (ddd, 1H, J = 7.7, 3.9, 4.8 Hz, 3-H), 3.89 (d, 1H, J = 3.9 Hz, 2-H), 4.64 (dd, 1H, J = 12.7, 4.8 Hz, 4-H_a), 4.79 (dd, 1H, J = 12.7, 7.7 Hz, 4-H_b), 7.12–7.21 (m, 5$H_{arom.}$), ^{13}C NMR (100 MHz, DMSO-d_6/TMS)): δ 36.2, 46.5, 78.5, 125.2, 126.4, 128.7, 148.2, 173.9. EIMS (*m/z*) 241 (M^+). Anal. calcd for $C_{10}H_{11}NO_4S$: C, 49.78; H, 4.60; N, 5.81. Found: C, 49.47; H, 4.93; N, 6.04.