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α-Amino diazoketones derived from *L*-serine and *L*-threonine: Synthesis, insertion reactions and ylide formations[†]

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Abstract

The synthesis of enantiopure α-amino diazoketones derived from *L*-serine and *L*-threonine is described. Their catalyzed X–H insertion reactions and ylide formations with allyl sulfides with concomitant 2,3-sigmatropic rearrangements are also reported.

Keywords: *L*-Serine, *L*-threonine, α-amino diazoketone, insertion reactions, sulfonium ylide.

1. Introduction

Amino acid-derived enantiopure α-amino diazoketones have recently emerged as a new class of chiral-group transfer agents.[1] These diazoketones undergo a number of useful reactions, e. g. inter- and intramolecular insertion reactions, oxidations, addition reactions to aldehydes and ketones, etc. to produce a variety of α-amino ketones under mild and recemization-free conditions. The derived α-amino ketones have been further transformed to several bioactive heterocycles and 1,2-amino alcohols. α-Amino diazoketones derived from various amino acids have been studied towards these ends. However, there are no reports on serine or threonine-derived α-diazoketones, except for a solitary example of a Boc-serine derived α-amino diazoketone and its intramolecular N–H insertion reaction.[2] In continuation of our studies on the use of enantiopure α-diazoketones in asymmetric synthesis,[3] we became interested in α-amino diazoketones derived from *L*-serine and *L*-threonine and describe herein their synthesis, catalyzed S–H and O–H insertion reactions and ylide formations with allyl sulfides.

2. Results and discussion

L-Serine (**1a**) and *L*-threonine (**1b**) were first N,O-diprotected with formaldehyde[4] and further N-protected with ethyl chloroformate to give the novel oxazolidine carboxylic acids (**2a, b**) in 88% and 96% yields, respectively (Scheme 1, Table I). The latter were then converted to the desired α-amino diazoketones (**3a, b**) in good yields via the mixed anhydride method. Once in hand, their catalyzed S–H insertion reactions to PhSH were first investigated. Best results were

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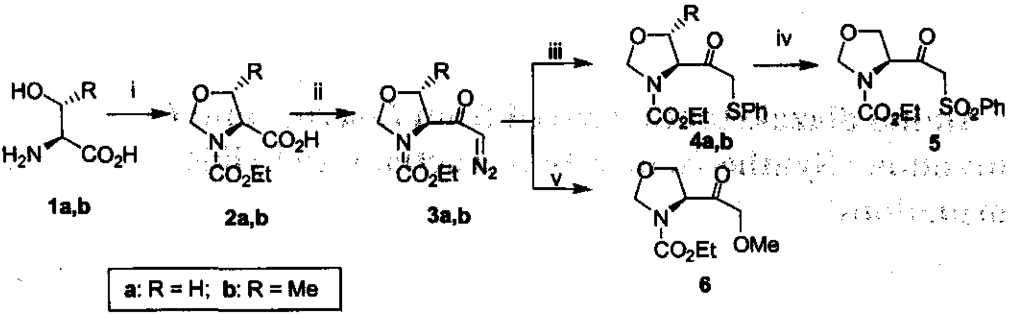


Scheme 1. (i) 40% Formalin, 2N NaOH, overnight then acetone, $ClCO_2Et$, $NaHCO_3$, 0°C; (ii) Et_3N, $ClCO_2Et$, THF, 0°C, then excess CH_2N_2, ether, 0°C; (iii) $InCl_3$ (5–6 mol%), PhSH, CH_2Cl_2, rt; (iv) $NaIO_4$, water, rt; (v) $RuCl_2(PPh_3)_3$ (4–5 mol%), MeOH, benzene, refulx.

obtained with $InCl_3$ as the catalyst[5] (superior to $Rh_2(OAc)_4$, $Cu(OAc)_2$ or $BF_3.Et_2O$) which led to the formation of the oxazolidinyl thiophenyl ketones (**4a, b**) in high yields within 1 h at room temperature. Synthetic utility of these thiophenyl adducts was shown via $NaIO_4$ oxidation of **4a** to the β-ketosulfone (**5**) (60%) which, in analogy to other γ-amino β-ketosulfones,[6] promises to be an useful chiron for the synthesis of functionalized serinyl ketones. Intermolecular O–H insertion reactions of these diazoketones, however, turned out to be problematic. Thus, $Rh_2(OAc)_2$ or $BF_3.Et_2O$ failed to catalyze the insertion reaction of **3a** to MeOH. Complex product mixtures were obtained in these reactions. We have previously shown that $InCl_3$ is not a suitable catalyst for O–H insertion reactions[5] and hence it was not tried in this case. Ultimately, $RuCl_2(PPh_3)_3$[3b,f] turned out to be the catalyst of choice which led to the formation of the methoxy ketone (**6**) in 56% yield (Scheme 1).

Catalyzed reactions of α-diazoketones leading to ylide formation and their subsequent rearrangements have been widely used in organic synthesis.[1a,7] However, apart from a few reports on ylide-forming reactions of diazopenicillanates with allyl chalcogenides,[8] enantiopure α-diazoketones have not been used in such sequences. Towards this end, we have studied the Cu-catalyzed reactions of **3a, b** with allyl phenyl sulfide (**7**) which led to rapid formation of the α-amino-α′-thiophenyl homoallyl ketones (**9a, b**) via *in situ* generation of the allyl sulfonium ylides (**8**) and their facile 2,3-sigmatropic rearrangements (Scheme 2). The yields of these reactions were only moderate (30–35%), as often is observed in intermolecular reactions of allyl sulfides with other α-diazoketones, and were found to be highly dependent on the reaction conditions. Best results were obtained with $Cu(acac)_2$ as the catalyst (superior to $Rh_2(OAc)_4$) in benzene at 80°C using short contact times (5 min). Reactions carried out in THF or CH_2Cl_2 gave incomplete conversions. Even when carried out in benzene, prolonged heating of the reaction mixture or slow additions of **3a, b** to a mixture of **7** and the catalyst did not improve the yields and, in fact, lowered them considerably, perhaps due to dimerization and/or secondary reactions of the α-diazoketones with the product α-thiophenyl ketones.[9] The products (**9a, b**) were both formed as diastereomeric mixtures which, without separation, were desulfurized with Zn/NH_4Cl[10] to produce the α-amino homoallyl ketones (**10a, b**) in good yields (Scheme 2, Table I). Allyl selenides also reacted with **3a, b** in an analogous fashion,[11] but catalyzed reactions of **3a, b** with benzyl sulfides and selenides led to complex product mixtures. Although enantiopure α-amino ketones are usually prepared by the nucleophilic α-amino acylations

Table I
Physical data for the compounds prepared (Schemes 1 and 2)

Compound no.	Yield (%)	m. p. (°C)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Molecular formula[a]	IR ($CHCl_3$) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)
2a	88	Oil	−67.87 (6.2)	$C_7H_{11}NO_5$ (189.02)	3400–3010 (br), 2970, 2880, 1710, 1695, 1420	1.30 (t, 3H, *J* = 7.1), 3.80–4.20 (m, 3H), 4.60–4.82 (m, 2H), 4.96–5.10 (m, 2H), 8.06 (s, 1H)
2b	96	Oil	−91.17 (2.0)	$C_8H_{13}NO_5$ (203.03)	3680–2500 (br), 1700, 1420	1.26 (brs, 3H), 1.47 (d, 3H, J 6.0), 4.00 (s, 1H), 4.19 (q, 2H, *J* = 6.9), 4.28 (qn, 1H, *J* 6.1), 4.83 (d, 1H, *J* = 3.0), 5.17 (s, 1H), 7.30 (s, 1H)
3a	55	92–93[b]	−128.98 (6.1)	$C_8H_{11}N_3O_4$ (213.04)	3045, 2950, 2120, 1710, 1635, 1420	1.30 (t, 3H, *J* = 7.0), 4.00–4.44 (m, 5H), 4.86 (dd, 2H, *J* = 4.0, 12.0), 5.56 (s, 1H)
3b	54	Oil	−153.57 (2.0)	$C_9H_{13}N_3O_4$ (227.05)	3000, 2100, 1920, 1630, 1460, 1410	1.27 (t, 3H, *J* = 7.1), 1.44 (d, 3H, *J* = 6.0), 3.90 (d, 1H, *J* = 4.2), 4.18 (q, 3H, *J* = 7.0), 4.77 (d, 1H, *J* = 4.5), 5.22 (s, 1H), 5.60 (s, 1H)
4a	87	Oil	−22.97 (3.7)	$C_{14}H_{17}NO_4S$ (299.16)	3020, 2900, 1710, 1480, 1450	1.29 (t, 3H, *J* = 7.0), 3.85–3.94 (m, 3H), 4.09–4.19 (m, 3H), 4.65 (brs, 1H), 4.90–5.02 (brd, 2H), 7.19–7.30 (m, 5H)
4b	92	Oil	−58.66 (2.7)	$C_{15}H_{19}NO_4S$ (309.17)	3060, 2980, 2930, 1710, 1580, 1420	1.25 (brs, 3H), 1.37 (d, 3H, *J* = 6.0), 3.90 (s, 2H), 4.12–4.19 (m, 4H), 4.86 (d, 1H, *J* = 3.0), 5.16 (m, 1H), 7.21–7.35 (m, 5H)
5	60	Oil	−41.80 (0.6)	$C_{14}H_{17}NO_6S$ (331.14)	3000, 2980, 2950, 1710, 1595, 1440	1.28 (t, 3H, *J* = 7.0), 4.12–4.26 (m, 4H), 4.33–4.38 (m, 2H), 4.63 (t, 1H, *J* = 5.8), 4.94–5.01 (m, 2H), 7.58–7.95 (m, 5H)
6	54	Oil	−46.20 (1.8)	$C_9H_{15}NO_5$ (217.14)	3020, 2980, 2840, 1730, 1690, 1450	1.27 (t, 3H, *J* = 7.2), 3.43 (s, 3H), 4.88 (dd, 1H, *J* = 4.2, 9.0), 4.15–4.24 (m, 5H), 4.64 (br s, 1H), 4.92–4.99 (m, 2H)
10a	68	Oil	−12.61 (2.0)	$C_{11}H_{17}NO_4$ (227.11)	3020, 2980, 2960, 1710, 1560, 1440	1.25 (m, 3H), 2.34 (q, 2H, *J* = 7.0), 2.63 (br s, 2H), 4.40 (dd, 1H, *J* = 3.9, 8.0), 4.19 (q, 2H, *J* = 7.0), 4.42 (brm, 1H), 4.97–5.06 (m, 3H), 5.73–5.86 (m, 1H)
10b	66	Oil	−85.62 (1.6)	$C_{12}H_{19}NO_4$ (241.08)	2980, 2910, 2875, 1700, 1410	1.25 (brs, 3H), 1.42 (d, 3H, *J* = 6.0), 2.34 (q, 2H, *J* = 7.2), 2.63 (m, 2H), 3.91–3.99 (m, 1H), 4.06 (qn, 1H, *J* = 6.0), 4.17 (q, 2H, *J* = 6.7), 4.84 (brs, 1H), 4.97–5.07 (m, 2H), 5.17–5.25 (m, 1H), 5.73–5.86 (m, 1H).

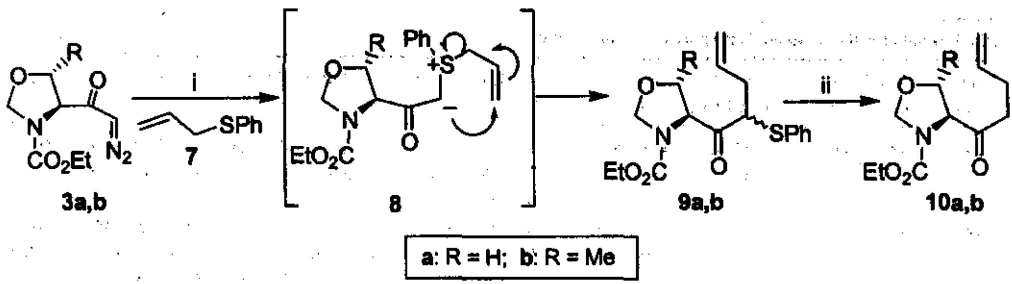
[a]Satisfactory microanalyses obtained : C±0.14, H±0.13, N±0.09.
[b]Recrystallization from EtOAc/petroleum ether.

of RLi/RMgX reagents,[12] the organometallic-free approach shown here for **10a, b**, despite its moderate yield, is an attractive alternative.

Recently, functionalized serinyl ketones have found considerable use in the synthesis of γ-hydroxy-β-amino acids, amino sugars and sphingosine analogs.[13] We are currently investigating the use of β-ketosulfone (**5**) and the homoallyl ketones (**10**) in this direction.

3. Experimental

All the m. p.s are uncorrected. Elemental analyses were carried out at the Indian Association for the Cultivation of Science. IR spectra were taken on a Perkin–Elmer R-297 spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 300 (300 MHz) instrument and are reported in ppm downfield from tetramethylsilane as internal standard. Optical rotations were measured on a Jasco DIP-360 polarimeter. Column chromatography was performed on



Scheme 2. (i) $Cu(acac)_2$ (10 mol%), benzene, 80°C, 5 min; (ii) Zn, NH_4Cl, THF, rt, 30 h.

silica gel (60–120). Petroleum ether refers to the fraction boiling at 60–80°C. $RuCl_2(PPh_3)_3$ was prepared following a literature procedure.[14]

3.1. *General procedure for the synthesis of 1,3-oxazolidine carboxylic acid (**2a, b**)*

To a solution of *L*-serine or *L*-threonine (9.5 mmol) in 2N NaOH (5 ml) at 0°C, 40% formalin (1 ml) was added and the mixture allowed to stand overnight at 0°C. Acetone (5 ml) and $NaHCO_3$ (0.85 g, 10.1 mmol) were added to this solution followed by dropwise addition of ethyl chloroformate (1.36 g, 1.2 ml, 12.5 mmol) under vigorous stirring. The reaction mixture was allowed to warm to ambient temperature over 2 h after which it was diluted with water (2 ml), extracted with ether (5 ml) and the ether layer discarded. The aqueous layer was acidified with 3N HCl, extracted with CH_2Cl_2 (3 × 10 ml) and the organic layer was dried (Na_2SO_4). Evaporation of solvent gave **2a, b** as colourless oils (Table I).

3.2. *General procedure for the preparation of 1,3-oxazolidinyl α-diazoketones (**3a, b**)*

To a solution of Et_3N (1.2 ml, 8.5 mmol) and the oxazolidine carboxylic acid (**2a** or **b**) (8.2 mmol) in THF (10 ml), ethyl chloroformate (0.9 ml, 9.1 mmol) was added dropwise at 0°C. A white precipitate appeared after a few minutes and the stirring was continued for another 30 min at 0°C. The mixture was filtered and the filtrate added to an ice-cold ethereal solution (40 ml) of diazomethane [CAUTION: highly toxic, prepared from nitrosomethyl urea (4.5 g, 43.6 mmol) and KOH (3.0 g, 53.5 mmol) in water (6 ml)].[15] The reaction mixture was allowed to reach ambient temperature, then aq. $NaHCO_3$ (10%, 20 ml) was added and the ether layer was separated. The aqueous layer was extracted with ether (2 × 10 ml) and the combined organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The diazoketones were then purified by column chromatography over silica gel (20% EtOAc in petroleum ether) (Table I).

3.3. *General procedure for S-H insertion reactions of the 1,3-oxazolidinyl α-diazoketones **3a, b**: Preparation of (**4a, b**)*

To a stirred solution of thiophenol (0.5 ml) and $InCl_3$ (0.005 g, 5-6 mol%) in CH_2Cl_2 (2 ml) a solution of the α-diazoketone **3** (0.65 mol) was added dropwise in CH_2Cl_2 (2 ml) over a period of 30 min. After the addition was complete, it was stirred at room temperature for 1 h. The reaction mixture was then washed with aq. NaOH solution (10%, 5 ml). Then the aqueous layer was extracted with CH_2Cl_2 (5 ml) and the combined organic layer was dried (Na_2SO_4). Removal of solvent under reduced pressure followed by column chromatography over silica gel (5–10% EtOAc in petroleum ether) gave the inserted products (**4a, b**) (Table I).

3.4. *(4′S)-1-(3′-Ethoxycarbonyl-1′,3′-oxazolidine-4′-yl)-2-phenylsulfonylethanone (5)*

A mixture of the α-thiophenyl ketone (**4a**) (0.3 g, 1.01 mmol) and $NaIO_4$ (0.65 g, 3.01 mmol) in water (5 ml) was stirred at room temperature until the α-thiophenyl ketone spot vanished on TLC. The reaction mixture was extracted with CH_2Cl_2 (2 × 20 ml), the organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel (30–40% EtOAc in petroleum ether) to give **5** as an oil (Table I).

3.5. *(4′S)-1-(3′-Ethoxycarbonyl-1′,3′-oxazolidine-4′-yl)-2-methoxyethanone (6)*

A solution of **3a** (0.2 g, 0.95 mmol) in benzene (2 ml) was added dropwise to a refluxing mixture of MeOH (2 ml), $RuCl_2(PPh_3)_3$ (0.005 g) in benzene (2 ml) over a period of 30 min. Heating was continued until the spot of the α-diazoketone vanished on TLC. The solvent was then evaporated, CH_2Cl_2 (10 ml) added and washed with water (10 ml). The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and purified by preparative TLC over silica gel (25% EtOAc in petroleum ether) to give the inserted product (**6**) (Table I).

3.6. *General procedure for the preparation of **10a, b***

A solution of **3a** or **b** (0.6 mmol), allyl phenyl sulfide (**7**) (0.18 g, 1.2 mmol) and $Cu(acac)_2$ (10 mol%) in benzene (1.2 ml) was immersed in an oil bath preheated to 80°C. After 5 min at 80°C, the solvent was removed under reduced pressure and CH_2Cl_2 (5 ml) was added. It was then washed with water, dried and evaporated to give **9a** or **b** (diastereomeric mixtures) which was purified by preparative TLC over silica gel (30% EtOAc in petroleum ether). Activated zinc (0.4 g, 6.1 mmol) and saturated aq. NH_4Cl solution (2.5 ml) were added to a solution of **9a** or **b** (0.2 mmol) in THF (3 ml) and the mixture stirred at room temperature for 30 h. It was then filtered and extracted with CH_2Cl_2 (3 × 5 ml). Removal of the solvent followed by preparative TLC over silica gel (15% EtOAc in petroleum ether) gave **10a, b** as colourless oils (Table I).

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