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Synthesis and characterization of chiral di(N-protected-α-amino)diazo-β-diketones from α-diazoketones and imidazolides derived from amino acids

Ibrahim A.M. Saraireh

Department of Chemistry, Al-Hussein Bin Talal University, Ma'an, Jordan

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ABSTRACT

Di(N-protected-α-amino)diazo-β-diketones were prepared by the reaction of activated N-protected-α-amino acids (imidazolides) with α-diazoketones, derived from natural amino acids, in the presence of lithium diisopropylamide in tetrahydrofuran as the solvent at −78 °C.

The pollution of the environment by metal ions and their ability to contaminate living species is a significant problem. Removal of these metal ions from human systems by ligands which can easily bind these metal ions through the formation of stable complexes is important. Also, the deficiency of some metal ions in humans can cause several diseases. Since L-amino acids are naturally occurring amino acids, L-amino acid diazo-β-diketone ligands may be effective in binding metal ions for the removal of hazardous metal ions or for the introduction of important metal ions.

Numerous papers have been published on the synthesis of N-protected α-amino acids and α-diazoketones derived from natural amino acids.[1] N-protected α-aminodiazoketones have been prepared from L-amino acids and dipeptides and used as precursors for the synthesis of N-protected α-amino β-diketones.[2] The synthesis of α-amino protected acyldiazomethanes involves the activation of the carboxyl group of N-protected α-amino acids followed by acylation with diazomethane. The acid chloride,[3] active ester,[4] and mixed anhydride methods[5] have also been employed for this type of activation. The acid chloride method is not applicable for some protecting groups because of their lability toward acid or oxazolone formation.

α-Diazocarbonyl compounds ($RCOCHN_2$) have an acidic hydrogen on the methine group, which can readily be removed by a strong base to furnish a nucleophilic anion capable of condensation[6] with activated N-protected amino acids[7] to furnish high yields of diazo-β-diketones. Lithium diisopropylamide (LDA) is the base of choice leading to high yields for the condensation of α-diazocarbonyls with activated N-protected amino acids. Carbonyldiimidazole (CDI) is a suitable activating reagent for N-protected amino acids and leads to the formation of imidazolides.[8–11] These imidazolides can be treated directly with diazolithioketones to give high yields of the corresponding diazo-β-diketones.

N-protected amino acids were converted into α-diazoketones via the acid chloride or mixed anhydride by treatment with ethereal diazomethane (Scheme 1) in good yields following purification by chromatography. In addition, N-protected amino acids were converted into imidazolides by treatment with 1,1′-carbonyldiimidazole in tetrahydrofuran (Scheme 2).

The N-protected amino acid derived diazoketones **4–6** could be easily metallated by addition to a solution of LDA in THF at −78 °C. The resulting solution was treated with the imidazolides **7–9** to form the diazo-β-diketones **10–15** (Scheme 3). After aqueous work-up, purification of the residue by chromatography gave good yields of pure products.

In conclusion, N-protected amino acids were converted into α-diazoketones via the acid chloride or mixed anhydride intermediates by treatment with ethereal diazomethane. Subsequent reaction with an imidazolide, prepared by the treatment of an N-protected amino acid with CDI, gave the title products in good yields.

α-Diazoketones via mixed anhydrides: General procedure

The N-protected amino acid (27.0 mmol) in dry Et_2O (60 ml) and THF (60 ml) was stirred at −20 °C under a nitrogen atmosphere. To this solution, Et_3N (3.8 ml, 1 equiv) followed by isobutyl chloroformate (3.7 ml, 1 equiv) were added. The solution was

E-mail address: ibrahim9997@yahoo.com

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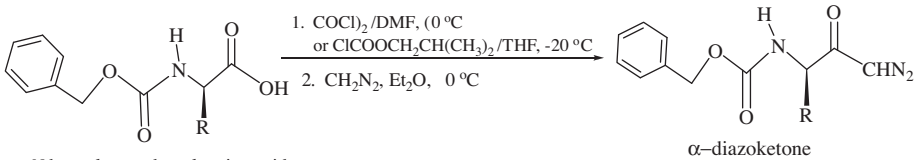
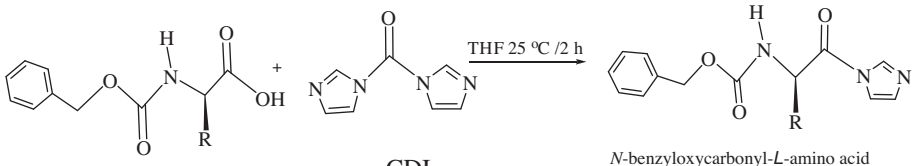


N-benzyloxycarbonyl amino acid

1 R = -CH_3
2 R = -$CH(CH_3)_2$
3 R = -CH_2Ph

4 R = -CH_3 (84%)
5 R = -$CHCH_3)_2$ (75%)
6 R = -CH_2Ph (88%)

Scheme 1. This reaction shows converted N-protected amino acids into α-diazoketones via the acid chloride or mixed anhydride by treatment with ethereal diazomethane at 0 °C.



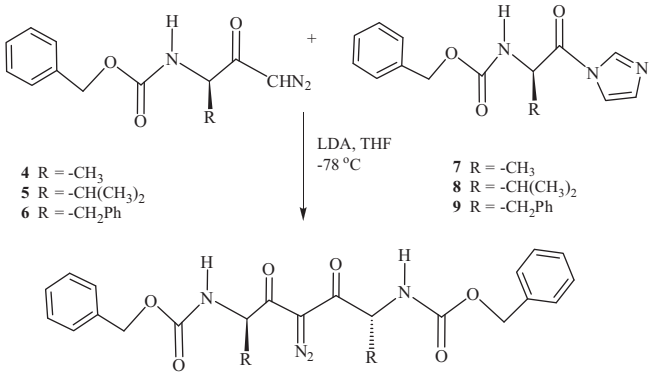
N-benzyloxycarbonyl-*L*-amino acid

1 R = -CH_3
2 R = -$CH(CH_3)_2$
3 R = -CH_2Ph

N-benzyloxycarbonyl-*L*-amino acid imidalzolide

7 R = -CH_3
8 R = -$CH(CH_3)_2$
9 R = -CH_2Ph

Scheme 2. This reaction shows converted of N-protected amino acids into imidazolides by treatment with 1,1'-carbonyldiimidazole (CDI) in tetrahydrofuran.



4 R = -CH_3
5 R = -$CH(CH_3)_2$
6 R = -CH_2Ph

7 R = -CH_3
8 R = -$CH(CH_3)_2$
9 R = -CH_2Ph

10 R = -CH_3 (77%)
11 R = -$CH(CH_3)_2$ (72%)
12 R = -CH_2Ph (80%)
13 R = -CH_3, -CH_2Ph (74%)
14 R = -CH_2Ph, -$CH(CH_3)_2$ (71%)
15 R = -$CH(CH_3)_2$, -CH_3 (76%)

Scheme 3. This reaction shows formation of diazo-peta-diketones from reaction of metallated of α-diazoketone by (LDA) with imidazolide.

stirred for 30 min and then allowed to warm to −10 °C. At this temperature ethereal CH_2N_2 (2 equiv), was added via a pressure equalizing dropping funnel over 30 min. The solution was stirred for a further 3 h while warming to room temperature. The mixture was evaporated to a third of its original volume using a rotary evaporator with an AcOH trap to destroy residual CH_2N_2. The solution was diluted with Et_2O (50 ml) and washed with H_2O (50 ml), saturated aqueous $NaHCO_3$ (50 ml), and brine (50 ml). The organic fraction was dried and evaporated to give the crude α-diazoketone which was purified by silica gel chromatography (EtOAc–hexane 2:8–3:7). **CAUTION!** Diazomethane is toxic and explosive. Extreme care should be taken in handling and using this compound. See also the Supplementary data.

Benzyl [(2*R*)-4-diazo-3-oxobutan-2-yl]carbamate (4)

Following the general procedure *N*-benzyloxycarbonyl-L-alanine **1** (27 mmol, 6 g) was converted into title compound **4**. Purification using EtOAc–hexane as eluent furnished the diazoketone **4** (5.7 g, 84%) as a pale-yellow solid. Mp 90–91 °C, $[\alpha]_D^{20}$ −59.08 (*c* 1, MeOH). Found: C, 58.2; H, 5.22; N, 16.98. $C_{12}H_{13}N_3O_3$ requires C, 58.3; H, 5.3; N, 17.0. ν_{max}(KBr) 3315 (NH), 2105 (CHN_2), 1722 ($NHCO_2Bn$), 1645 cm^{-1} ($COCHN_2$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (3H, d, *J* = 7.1 Hz, CH_3CH), 4.30 (1H, m, CH(N)CO), 5.20 (2H, s, OCH_2Ph), 5.54 (1H, br s, CHN_2), 5.76 (1H, br s, NH), 7.26–7.35 (5H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 53.7, 54.5, 67.1, 128.2, 128.3, 128.6, 136.4, 155.9, 194.1.

Synthesis of N-Protected-α-amino acid imidazolides

Benzyl [(2*R*)-1-(1*H*-imidazol-1-yl)-1-oxopropan-2-yl]carbamate (7)

To a stirred solution of 1 (3.80 g, 17.2 mmol) in dry THF (50 ml), carbonyldiimidazole (CDI) (3.07 g, 18.9 mmol) was added under nitrogen at 25 °C. After stirring for 2 h at 25 °C the in situ prepared alaninylimidazolide was used directly in the next step without isolation.

Synthesis of 2-diazo-1,3-diketones 10–15

Dibenzyl [(2*R*, 6*R*)-4-diazo-3,5-dioxoheptane-2,6-diyl]carbamate (10)

A cold (−78 °C) solution of LDA (10.8 ml of a 1.6 M solution in cyclohexane, 17.2 mmol) was added over 15 min under nitrogen via a syringe to a stirred solution of carbamate **4**, (2.13 g, 8.60 mmol) in dry THF (30 ml) at −78 °C. A solution of imidazolide **7** (prepared as described above) was added dropwise over 15 min under nitrogen via a cannula at such a rate so as to keep the temperature below −78 °C, and stirring was continued for an

additional 2 h. AcOH (12 μL, 17.2 mmol) in dry THF (5 ml) was added. The mixture was allowed to warm to room temperature and H_2O (20 ml) was added. The product was extracted with Et_2O (3 × 50 ml) and the combined organic extracts washed with saturated aqueous $NaHCO_3$ (50 ml) and brine (50 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a brown oil. Purification by column chromatography using EtOAc/*n*-hexane (3:7) as eluent furnished the title compound **10** (2.996 g, 77%) as a yellow oil. Anal. Calcd $C_{23}H_{24}N_4O_6$ C 61.06, H 5.35, N 12.38. Found: C, 60.99; H, 5.21; N, 12.24. ν_{max}(KBr) 3315 (NH); 2099 (CN_2); 1705 (CO_2CH_2); 1631 ($COCN_2$); 1520 cm^{-1} (Ph). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (6H, d, J = 7 Hz, CH_3CH), 4.48 (2H, m, 2 N–CH–CO), 5.11 (4H, s, 2 OCH_2Ph), 5.41 (2H, br s, 2NH), 7.2–7.40 (10 H, m, 2 Ph), ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 51.7, 55.1, 67.1, 128.2, 128.3, 128.6, 136.4, 155.9, 194.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.093.

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