1,3-OXAZOLIDIN-5-ONES DERIVED FROM PROLINE AS CHIRAL COMPONENTS IN THE SYNTHESIS OF PREDICTIVE ENANTIOSELECTIVE COUPLING REAGENTS

KATARZYNA KASPEROWICZ-FRANKOWSKA, BEATA KOLESIŃSKA, ANNA GZIK,
KONRAD JASTRZĄBEK and ZBIGNIEW J. KAMIŃSKI*

Institute of Organic Chemistry, Lodz University of Technology, Żeromskiego 116,
90-924 Łódź, Poland

Abstract: 1,3-Oxazolidin-5-ones derived from both enantiomers of proline and trichloroacetaldehyde were prepared and applied as an amine component in the synthesis of chiral predictive triazine-based coupling reagents. The reagents were found to be useful in condensations yielding enantiomerically enriched products from racemic substrates.

Keywords: enantioselective condensation, triazine coupling reagent, peptide synthesis, chirality transfer to nitrogen, chiral nitrogen atom

Limited access to stereochemically homogeneous compounds is a crucial factor inhibiting the search for new pharmaceutically active compounds. Predictive chiral coupling reagents are a novel synthetic tool, enabling enantioselective acylation using racemic carboxylic components (1-3). The most important advantage of predictive enantioselective coupling reagents, particularly for the synthesis of complex molecules, is that configuration, enantiomeric enrichment and the efficiency of the coupling procedure are knowable on the basis of a single model experiment. This is possible due to the modular structure of enantiodifferentiating reagents. The reagents are composed of two fragments: achiral, substituted 1,3,5-triazine derivatives and chiral tertiary amine, which is prone to quaternization and the formation of *N*-triazinylammonium salts when treated with chloro-1,3,5-triazine. The chiral fragment is active throughout the activation step, determining enantioselectivity, but then departs once it has fulfilled its stereoselective function. Thus, all further reaction steps proceed in the presence of the achiral module only, which is the same as one in all well-known achiral triazine reagents (4).

It has been confirmed that the application of a predictive enantiodifferentiating coupling reagent for coupling racemic carboxylic components leads very efficiently to enantiomerically enriched acylated products. The most efficient stereodiscrimination

has been observed for reagents prepared from alkaloids such as strychnine and brucine, bearing a stereogenic center on the nitrogen atom in the bridgehead position of the bicyclic system (1-3). In most cases, incorporation of the single enantiomer of the racemic amino acid substrate affords high yields of peptide chains (in the range of 85-95%), with enantiomeric enrichment reaching up to 98-99%. Unfortunately, chiral reagents obtained from alkaloids occur in only one enantiomeric form and are toxic, which limits the scope of their synthetic applications. In order to overcome these limitations, in this study we attempted to use as a chiral component amino acid derivatives available in both enantiomeric forms. We attempted to obtain 1,3-oxazolidin-5-ones derived from L- and D-proline with a variety of aldehydes. These were then used for the synthesis of new chiral coupling reagents. The advantage of bicyclic 1,3-oxazolidin-5-ones prepared from proline is its configurational stability; an effect of the processes of chirality transfer and chirality self-regeneration postulated by Seebach (5).

MATERIALS AND METHODS

Synthesis of benzaldehyde dimethyl acetal (3a). Typical procedure (6)

To a mixture of benzaldehyde (20 mL, 0.2 mol) and 2,2-dimethoxypropane (49 mL, 0.4 mol), a

* Corresponding author: e-mail: zbigniew.kaminski@p.lodz.pl

catalytic amount of 4-toluenesulfonic acid (50 mg) was added. Acetone was distilled off using a short Vigreux column. After collecting a stoichiometric amount of the acetone, the remaining clear liquid was diluted with dichloromethane (50 mL), cooled to 0°C and washed with a saturated aqueous solution of sodium bicarbonate. The organic phase was collected, dried with anhydrous potassium carbonate and distilled under reduced pressure. Fraction bp = 79°C, p = 11 mm Hg, was collected, yielding benzaldehyde dimethyl acetal (**3a**) (20.44 g, 67%) lit. (7) bp = 79°C, p = 11 mm Hg as colorless liquid.

¹H-NMR (pyridine D₅): δ = 3.59 (s, 6H, OCH₃); 5.79 (s, 1H, -CH-); 7.45-7.72 (m, 5H, C₆H₅) [ppm].

Synthesis of 2,3-dimethoxybenzaldehyde dimethyl acetal (**3b**)

Synthesis was performed according to the typical procedure using 2,3-dimethoxybenzaldehyde (1.66 g, 10 mmol) and 2,2-dimethoxypropane (2.45 mL, 20 mmol), yielding after fractional distillation 2,3-dimethoxybenzaldehyde dimethylacetal (**3b**) (0.44 g, 21%), bp = 149°C p = 19 mm Hg, as colorless liquid.

¹H-NMR (toluene D₈): δ = 3.21 (s, 6H, CH₃O); 3.42 (s, 3H, CH₃O); 3.80 (s, 3H, CH₃O); 5.79 (s, 1H, -CH-); 6.60 (d, 1H, J = 8.2 Hz C₆H₃); 6.92 (t, 1H, J = 7.9 Hz C₆H₃); 7.31 (d, 1H, J = 7.8 Hz C₆H₃) [ppm].

Synthesis of 3,4-dimethoxybenzaldehyde dimethyl acetal (**3c**)

Synthesis was performed according to the typical procedure using 3,4-dimethoxybenzaldehyde (1.66 g, 10 mmol) and 2,2-dimethoxypropane (2.45 mL, 20 mmol), yielding after fractional distillation 3,4-dimethoxybenzaldehyde dimethylacetal (**3c**) (1.17 g, 55%), bp = 124-128°C, p = 0.3 mm Hg, lit. (8) bp = 115-125°C, p = 0.1 mm Hg as a colorless oil.

¹H-NMR (toluene D₈): δ = 3.77 (s, 6H, CH₃O); 4.19 (s, 6H, CH₃O); 5.93 (s, 1H, -CH-); 7.4 (d, 1H, J = 7.5 Hz C₆H₃); 7.66 (m, 3H, C₆H₃) [ppm].

Synthesis of 2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**5a**). Typical procedure

A suspension of L-proline (0.23 g, 2 mmol) in benzaldehyde dimethyl acetal (**3a**) (2 mL) with a catalytic amount of *N*-methylmorpholine 4-toluenesulphonate was heated under nitrogen to a gentle boil and methanol was distilled off using a Vigreux column. The solvent was removed under reduced pressure and the residue was analyzed using a GCMS Perkin Elmer Clarus 580, mass detector Clarus SQ 8

S Column: ELITE 5MS 30 m/0.25 mm/0.5 μm film, temp. program 50°C for 3 min, 5°C/min to 200°C, 20°C/min to 320°C, 320°C for 3 min; m/z from 33 to 350.

Synthesis of (5S)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**L-5d**) from L-proline. Typical procedure

A suspension of L-proline (5.76 g, 50 mmol) and trichloroacetaldehyde hydrate (12.49 g, 75 mmol) in CHCl₃ (60 mL) was heated to a gentle boil for 6 h and the water was removed by azeotropic distillation. The residue was cooled to room temperature and then washed with distilled water (2 × 30 mL). The combined aqueous phases were extracted with chloroform (3 × 10 mL) and the organic extracts were then combined and dried with anhydrous MgSO₄. The solvent was removed under a vacuum and the solid residue was recrystallised from ethanol affording (5S)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**L-5d**) (7.97 g, yield 66%), mp = 102-108°C, lit (9) mp = 108-109°C.

IR (film): ν = 3112 (CH), 2978 (CH), 2899 (CH), 1782 (C=O), 1322 (C-N), 1044 (C-O) [cm⁻¹].

¹H NMR (250 MHz, CDCl₃): δ = 1.71 – 2.44 (m, 4H, -CH₂-CH₂-CH-); 3.13-3.39 (m, 1H, CH₂-N); 3.40-3.68 (m, 1H, CH₂-N-); 4.11-4.36 (m, 1H, -CHC(O)-); 5.22 (s, 1H, -CH-CCl₃) [ppm].

Synthesis of (5R)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**D-5d**) from D-proline

Synthesis was performed using D-proline (11.5 g, 100 mmol) and trichloroacetaldehyde hydrate (24.81 g, 150 mmol) in CHCl₃ (80 mL). (R)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**D-5e**) (6.39 g, yield 55%), mp = 105-107°C, lit. (for L-enantiomer) (9) mp = 108-109°C was obtained. Spectroscopic data were gathered identical to those collected for S enantiomer.

Condensation of 4-methoxybenzoic acid with 4-toluidine mediated by CDMT and (5S)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**L-5d**)

(5S)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**L-5d**) (0.061 g, 0.5 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.044 g, 0.5 mmol) were dissolved in acetonitrile (2 mL) and stirred at room temperature for 24 h. 4-Methoxybenzoic acid (0.038 g, 0.25 mmol) was added and stirring was continued for 3 days until all the CDMT was consumed. 4-toluidine (0.027 g, 0.25 mmol)

was added and the clear solution was left at room temperature for an additional 12 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (10 mL). It was then washed thoroughly with water (5 mL), 1 M aq. HCl (5 mL), water (5 mL), 1 M aq. NaHCO₃ (5 mL) and again with water (5 mL). The solvent was evaporated, affording 4-methoxy-4'-methylbenzanilide (0.024 g, yield 40%) as white solid, mp = 140°C, lit. mp = 150°C (10).

IR (film): ν = 3339, 3080, 3006, 2962, 2917, 2840, 1901, 1746, 1707, 1650, 1595, 1578, 1514, 1499, 1464, 1444; 1402, 1378, 1321, 1307, 1295, 1237, 1178, 1122, 1101, 1030, 967, 936, 898, 837, 811, 792, 760, 653, 639, 626, 610, 541, 504, 430, 399 [cm⁻¹].

¹H-NMR (250 MHz, CDCl₃): δ = 2.34 (s, 3H, CH₃-); 3.87 (s, 3H, -OCH₃); 7.1 (dd, 4H, -C₆H₄, J_1 = 8.23 Hz, J_2 = 48.96 Hz); 7.65 (dd, 4H, -C₆H₄, J_1 = 8.93 Hz, J_2 = 48.96 Hz) [ppm].

Condensation of 4-methoxybenzoic acid with 4-toluidine mediated by CDMT and (5R)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (D-5d)

Condensation was performed as described above, using (5S)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (D-5d) (0.122 g, 0.5 mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.088 g, 0.5 mmol), acetonitril (3 mL), 4-methoxybenzoic acid (0.076 g, 0.5 mmol), 90 μ L (0.5 mmol) DIPEA and 4-toluidine (0.053 g, 0.5 mmol). After evaporation of the solvent, crude 4-methoxy-4'-methylbenzanilide (0.037 g, yield 31%) was obtained as a white solid mp = 140°C, lit. (10) mp = 150°C.

IR(film): ν = 3339, 3080, 3006, 2962, 2917, 2840, 1901, 1746, 1707, 1650, 1595, 1578, 1514, 1499, 1464, 1444, 1402, 1378, 1321, 1307, 1295, 1237, 1178, 1122, 1101, 1030, 967, 936, 898, 837, 811, 792, 760, 653, 639, 626, 610, 541, 504, 430, 399 [cm⁻¹].

¹H-NMR (250 MHz, CDCl₃): δ = 2.34 (s, 3H, CH₃-); 3.87 (s, 3H, -OCH₃); 7.10 (dd, 4H, -C₆H₄, J_1 = 8.23 Hz, J_2 = 48.96 Hz); 7.65 (dd, 4H, -C₆H₄, J_1 = 8.93 Hz, J_2 = 48.96 Hz) [ppm].

Synthesis of Z-Ala-Gly-OMe using (5S)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (L-5d) and CDMT

A solution of (5S)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (L-5d) (0.244 g, 1 mmol) and CDMT (0.175 g, 1 mmol) was stirred at 10°C for 24 h. *rac*-Z-AlaOH (0.446 g, 2 mmol and DIPEA (180 μ L, 1 mmol) were added and stirring

was continued at 10°C for 48 h. H-GlyOMe*HCl (0.126 g, 1 mmol) and DIPEA (180 μ L, 1 mmol) were added and the mixture was stirred for an additional 24 h at room temperature. The solvent was evaporated and the solid residue was dissolved in dichloromethane (25 mL). It was then washed successively with water (25 mL), 1 M aq. NaHSO₄ (25 mL), water (25 mL), 1 M aq. NaHCO₃ (25 mL) and again with water (25 mL). The organic phase was dried with MgSO₄ and filtered. The filtrate was evaporated to dryness, affording crude Z-Ala-Gly-OMe (0.255 g, 87% yield). The solid residue was purified using column chromatography on silica gel. The product was eluted with hexane/ethyl acetate, affording Z-AlaGly-OMe (0.056 g, yield 19%), mp = 93-95°C, $[\alpha]_D^{20}$ = -12.3 (c = 1 g/100 mL), lit. (11) (for Z-L-Ala-Gly-OMe) mp = 96 - 96.5°C, $[\alpha]_D^{25}$ = -27 (c = 1.0, MeOH).

IR (film/NaCl): ν = 3321, 3017, 2966, 2937, 2903, 2274, 2143, 1984, 1815, 1759, 1695, 1666, 1586, 1536, 1480, 1448, 1410, 1374, 1362, 1320, 1247, 1191, 1168, 1127, 1072, 1054, 1017 [cm⁻¹].

¹H-NMR (250 MHz, CDCl₃): δ = 1.41 (d, 3H, J = 6.5 Hz, CH₃-CH-); 3.78 (s, 3H, CH₃O-); 4.11 (q, 2H, J = 7 Hz, CH₃-CH₂-O-); 4.39 (m, 1H, CH₃-CH-); 5.10 (s, 2H, -CH₂O-); 6.61 (broad s, 1H, NH); 7.40 (s, 5H, arom.) [ppm].

Synthesis of Z-AlaGlyOMe using (5R)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (D-5d) and CDMT

Synthesis was performed as described above, using (5R)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (D-5e) (0.244 g, 1 mmol), CDMT (0.175 g, 1 mmol), *rac*-Z-AlaOH (0.446 g, 2 mmol), DIPEA (180 μ L, 1 mmol) H-GlyOMe*HCl (0.126 g, 1 mmol) and DIPEA (180 μ L, 1 mmol). Crude Z-AlaGlyOMe (0.223 g, 76% yield) was afforded as a pale yellow oil. After column chromatography, Z-Ala-Gly-OMe was isolated (0.039 g; yield 13.25%), mp = 89-92°C; lit. (12) (for Z-D-Ala-Gly-OMe), $[\alpha]$ = +16 (c = 0.35 g/100 mL) mp = 94-95°C, lit. (13) (for Z-D-Ala-Gly-OMe) $[\alpha]_D^{20}$ = +26 (c = 1 g/100 mL MeOH). Spectroscopic data were gathered identical to those collected for the product described in 4.2.

RESULTS AND DISCUSSION

The characteristic feature of all the alkaloids which were found to be especially efficient as chiral components in predictive enantioselective coupling reagents was the presence of aromatic rings in proximity to the bridgehead chiral nitrogen atom.

Therefore, in preliminary experiments it was attempted to transform proline into the bicyclic system, through treatment with benzaldehyde or benzaldehyde acetal. Intensive diastereoselection was expected to occur during the process of chirality transfer.

Unexpectedly, contrary to successful experiments with trimethylacetaldehyde described by Seebach (5) or with trichloroacetaldehyde reported by Germanas (14), we were unable to isolate the expected product **5a** with a phenyl group in position 2 of the 1,3-oxazolidinone ring.

GCMS analysis of the reaction mixture showed the presence of the main product at $R_t = 38.85$ sec (see Figure 1), for which the fragmentation pattern is presented in Figure 2.

The fragmentation pattern and molecular ion $[M+1] = 247.1798$ depicted in Figure 2 strongly

suggest that the main product of the reaction is the expected 1,3-oxazolidinone **5a**.

Identification of oxazolidinone as the main reaction product supported the conclusion that **5a** is extremely unstable and readily decomposed during the isolation procedure. To increase the stability of 1,3-oxazolidinone, dimethyl acetals **5b-c** substituted with electron-donating groups G were prepared and used for cyclization with proline. Unfortunately, all attempts to improve the stability of **5a-c** by modulating the electron density in the aromatic ring were unsuccessful. GCMS analysis for all **5b-c** confirmed the presence of the molecular ion and showed the expected fragmentation pattern, analogous to that presented in Figure 2 for **5a**. Therefore, attention was focused on 1,3-oxazolidinone **5d** formed from trichloroacetaldehyde hydrate and proline, as described by Germanas (14).

Scheme 1. Synthesis of oxazolidinone **5a-c** from proline and benzaldehyde dimethyl acetal

Figure 1. GC analysis of a reacting mixture of **4** and **3a**. Column: ELITE 5MS 30 m/ 0.25mm/0.5 μ m film, helium as carrier gas 30 mL/s; temp. program 50°C for 3 min, 5°C/min to 200°C, 20°C/min to 320°C, 320°C for 3 min

Figure 2. Fragmentation pattern for the main product formed in the reaction of proline (**4**) with benzaldehyde dimethyl acetal **3a** (signal at $R_t = 38.85$ min on chromatogram presented in Fig. 1)

Scheme 2. Synthesis of N-triazinylammonium salt **L-7d** via (5S)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**L-5d**) and 2-chloro-4,6-dimethoxy-1,3,5-triazine

Scheme 3. Enantioselective activation of *rac*-Z-Ala-OH using coupling reagent **L-7d** or **D-7d** generated *in situ*

Cyclization via azeotropic dehydration (15) of the mixture of proline and trichloroacetaldehyde hydrate gave the expected product **L-5d** with a 66% yield. The enantiomer **D-5d** was prepared under the same conditions, from D proline, with a 55% yield. In both preparations, the presence of a sharp singlet of C2 proton at 5.20 ppm in the NMR spectrum confirmed the configurational stability of **5d**.

Preliminary studies on the application of **5d** in condensations mediated by triazine-coupling reagents were performed. The model reaction was coupling of 4-methoxybenzoic acid with 4-toluidine. Formation of *N*-triazinylammonium salts **L-7d** and **D-7d** in reactions of **L-5d** or **D-5d** with CDMT was found to proceed slowly. Nevertheless, both enantiomers of **5d** activated 4-methoxybenzoic acid within 3 days and gave the expected substituted benzamide after 24 h of acylation of *p*-toluidine. Thus, even if the prolonged preactivation of CDMT and the formation of **7** in the presence of relatively nucleophilic chloride anion is tiresome, it is not thought to deteriorate the coupling procedure, since the quaternary ammonium group in the bridgehead position is substantially less prone to dealkylation (16). The crucial conditions for successful enantioselective coupling with **5d** were the efficient transfer of chirality onto the nitrogen atom and the suppression of anhydride formation (17).

Enantioselective coupling with a preactivation stage leading to **7d**, followed by 48 h activation of *rac*-Z-Ala-OH, gave crude enantiomerically enriched L-Z-Ala-Gly-OMe using (5S)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**L-5d**) with 87% yield. The opposite enantiomere, D-Z-Ala-Gly-OMe, was isolated with a 76% yield as the crude product of condensation involving (5R)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**D-5d**). In order to remove contamination caused by chiral side-products, both peptides were thoroughly purified on a silica gel column before their enantiomeric composition was determined via photopolarimetric measurements. Measurements showed a preference for the activation of the L enantiomeric form of Z-Ala-OH (L/D ratio = 76/24) when (5S)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**L-5d**) was used as the chiral component in the predictive coupling reagent **L-7d**. In condensation involving (5R)-2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**D-5d**) as the chiral component of **D-7d**, activation of the D enantiomeric form of Z-Ala-OH was preferred (L/D ratio = 76/24).

CONCLUSION

The synthetic versatility of 1,3-oxazolidinone described by Seebach (5) and Germanas (14) was further confirmed by application of 2-(trichloromethyl)-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**5d**), which is accessible in both enantiomeric forms, as the chiral module in predictable enantioselective coupling reagents. As expected, giving access to both enantiomeric forms of the reagent formed *in situ* made it possible to incorporate the expected enantiomeric amino acid residue into the peptide chain from a racemic mixture of substrates. Given that only two equivalents of racemic substrates were used for one equivalent of the chiral coupling reagent, enantiomeric enrichment in this process of kinetic resolution can be considered highly efficient. Unfortunately, our attempts to prepare the more reactive and less sterically hindered 1,3-oxazolidinone have, as yet, been unsuccessful.

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