Synthesis of a Multifunctional Oxazolo[5,4-e][1,4]diazepine Skeleton

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1,4-Benzodiazepines have been the object of intense investigation due to their potential for use in various therapeutic utilities, such as anxiolytic and anticonvulsant activities¹ as well as various biological functions as a privileged skeleton. This skeleton has been applied in the development of cholecystokinin (CCK) receptor A and B antagonists,² opioid receptor ligands,³ platelet-activating factor antagonists,⁴ human immuno-deficiency virus trans-activator Tat antagonists,⁵ reverse transcriptase inhibitors,⁶ and ras farnesyltransferase inhibitors.⁷ During the past decade attention has also been diverted to the synthesis of 1,4-diazepinones with a fused heterocyclic system in place of the benzene ring⁸,⁹ to explore the heterocycle for various biological applications. In particular, triazolo-,¹⁰ thieno-,¹¹ pyrrollo-¹² indole-¹³ and pyrido-diazepines¹⁴ have exhibited new pharmacological activities. Here, we report on the synthesis of a new heterocycle-fused diazepine derivative, oxazolo[5,4-e][1,4]diazepine-5,8-dione (Figure 1). As part of one of our drug discovery programs, we have developed synthetic strategies suitable for the introduction of multiple substituents on the oxazolodiazepine scaffold. The derivative of these strategies could be a useful intermediate in the synthesis of biologically active compounds.

Initial efforts regarding the synthesis of oxazolodiazepine skeleton using the conventional approach is shown in Scheme 1. Coupling reaction of Fmoc-glycine with ethyl 2-amino-2-cyano-acetate generated compound 1 and followed by the treatment of hydrogen chloride gas in anhydrous acetone produced oxazole ring 2. Various coupling agents such as EDC, PyBOP, and HATU were tried to condense the primary amine of oxazole ring 2 with several Fmoc-amino acids to produce compound 3. Amino acid was converted to even acid chloride for carbonyl carbon being more prone to nucleophilic attack. However, due to low nucleophilicity of 5-aminooxazole amine, amide bond formation was not successful. It was determined that even simple acylation with acetyl chloride result in only an 8% yield.

It has been reported that the primary amine on the oxazole ring has low reactivity. Coupling 5-aminooxazole with various acid chloride resulted to form amide bond in poor yields.¹⁵ Generally free 5-aminooxazoles are prone to ring-opening in solution.¹⁶ Stable 5-aminooxazole are essentially limited to those bearing an electron-withdrawing group at the 4-position.¹⁷ In the case of compound 4, Ethyl ester group at 4-position withdraws the resonant electrons including lone pair electrons of 5-aminooxazole. Amino group is also involved in the formation of intramolecular hydrogen bonding to the oxygen atom of the carbonyl group,¹⁸ which may cause redistribution of the electron density in the oxazole ring.

Thus, a new synthetic route of oxazolodiazepine skeleton was designed, as depicted in Scheme 2, having rhodium catalyzed amide incorporation as the key reaction step for functionalization sites. Functionalization sites

Figure 1. Structure of oxazolo[5,4-e][1,4]diazepine skeleton and sites for functionalization.

Scheme 1. Reagents and conditions: (a) Fmoc-GlyOH, EDC, HOBt, NMP, 2 h, 64%; (b) HCl (gas), anhydrous acetone, 3 h, 95%; (c) Fmoc-amino acids (acyl chloride) with various coupling reagents (EDC, PyBOP, HATU).
the introduction of various groups at the oxazole ring system built by the cyclization of diamide compound 11.

The synthesis was initiated with the preparation of an unusual amino acid 6, by the Hoffmann rearrangement of Cbz protected asparagine (5, DL-N-CbzAsnOH) using iodo-benzene diacetate, which in turn was esterified to afford the amino acid ester 7. The Michael addition of acrylonitrile with 7 yielded compound 8, and the subsequent coupling reaction of the secondary amine of 8 with methylmalonyl-chloride resulted in good yields in compound 9. Here, the nitrogen required for oxazole construction was attained by the following two step reaction. After the reaction of compound 9 with 4-acetamidobenzene sulfonyl azide to obtain the diazoderivative 10, the subsequent rhodium(II)-octanoate catalyzed reaction of 10 with 4-methoxybenzamide in toluene resulted in compound 11.19 The incorporated amide and the carboxyester group of compound 11 was then cyclodehydrated using POCl₃ with oxazole derivative 12 in a moderate yield. After the deprotection of the Cbz group of compound 12 under hydrolysis condition yielded compound 13, the final cyclization between the carboxymethyl ester on the oxazole ring and primary amine of compound 13 with trimethyl aluminum delivered the target compound 14. Note that the low yield of the cyclization reaction may be due to another carboxymethyl ester of 13, which could participate in the amide formation in an intermolecular manner, perhaps resulting in a polymerized product.

The conjugation of 13 (Figure 2) might make the ester less reactive, which might facilitate the other competing reactions include inter and intra molecular amidation (The –NH₂ group has 3-different ester groups to react). Also 13 is satirically crowded leading to improper orientation of the groups, which might keep the groups (ester and amine) away from each other hence the less yield of required amide 14. As the mixture is racemate, it may be only one of the enantiomers was involved in the reaction. Another reason of low yield we discussed was the reagent AlMe₃. There is a report which i-Bu₃Al reduced the nitrile to amine.20 It may be a similar type of reaction occurred with –CN group of 13.

To avoid these possibilities which result low yield of forming oxazolodiazepine, we decided to use simpler precursor for cyclization. Compound 1821 and 19 were designed and synthesized through the several steps as shown in scheme 3. However, all trials failed to obtain 20 by using the coupling reagents and AlMe₃. From these results, we assumed the weak reactivity of oxazole ring is a main problem to create the amide bond.

In summary, we achieved the multistep synthesis of a novel heterocyclodiazepine system, an oxazolodiazepine skeleton having potential for use in the construction of derivatives with diverse functional groups around the scaffold.

**Experimental Section**

**General Procedure.** Starting materials, reagents, and
solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and TCI (Tokyo) and used as supplied without further purification. Thin-layer chromatography (TLC) was conducted on precoated silica gel plates (Merck silica gel 60; F254, –0.25 mm) and visualized with either short-wave UV light. Proton nuclear magnetic resonance spectroscopy and spectra were taken in CDCl3 as a colorless semisolid

**Scheme 3.** Synthesis of simple oxazole ring for cyclization. Reagents and conditions: (a) Et3N, CH2Cl2, 84%; (b) 4-aminobenzenesulfonyl azide, Et3N, toluene, 71%; (c) benzamide, Rb2(OEt)4, toluene, 80 °C, 61%; (d) (i) TFAA, ACN, MW, 130 °C, 5 min, (ii) TMSOTf, CH2Cl2, 75%; (e) 5% NaOH (aq), 80% MeOH, 30 min, 88%; (f) EDC, HOBt, DIPEA, DMF or PyBOP, DIPEA, DMF; (g) AlMe3, toluene.


Methyl 3-amino-2-(benzyloxycarbonylamino)propanoate (7). To a solution of amino acid (5.2 g, 31.6 mmol) in MeOH (200 mL), thionyl chloride (2.9 mL, 41.0 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and for 8 h at room temperature. After the solvent was removed, the crude residue was treated with diluted aqueous NaHCO3, extracted with EtOAc, washed with water, and dried over anhydrous Na2SO4. After the solvent was removed, the residue was purified by column chromatography (CH2Cl2:MeOH = 10:1) to obtain 7 as a colorless solid (6.12 g, 77%). 1H NMR (300 MHz, CDCl3) δ 7.30-7.37 (m, 5H), 5.67 (d, J = 5.4 Hz, 1H, NH), 5.12 (s, 2H), 4.46 (m, 1H, NH), 3.77 (s, 3H), 3.08 (t, J = 6.3 Hz, 2H), 2.95 (t, J = 6.4 Hz, 2H), 2.44 (t, J = 6.9 Hz, 2H); MS (ESI) m/z 360.9 ([M+H]+).

Methyl-(benzyloxy carbonylamino)-3-(N-(2-cyanoethyl)-3-methoxy-3-oxopropanamido)propanoate (9). N-Methylmorpholine (3.8 mL, 34.7 mmol) and methylmalonyl chloride (2.0 mL, 19.0 mmol) were added in sequence to the solution of compound 7 (5.4 g, 17.4 mmol) in CH2Cl2 (100 mL) at −15 °C. The resulting mixture was stirred at the same temperature for 2 h and for 12 h at room temperature. The crude residue was washed with EtOAc, washed with 10% aq. KH2PO4 followed by 10% aq. NaHCO3. The organic layer was dried over Na2SO4 and concentrated. The crude residue was purified by flash chromatography (EtOAc) to afford amalonamide 9 (4.9 g, 69%). 1H NMR (300 MHz, CDCl3) δ 7.31-7.39 (m, 5H), 5.71 (d, J = 4.5 Hz, 1H, NH), 5.11 (s, 2H), 4.53 (m, 1H, NH), 4.55 (s, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 3.51 (t, J = 6.6 Hz, 2H), 3.43 (d, J = 2.4 Hz, 2H), 2.66 (t, J = 6.6 Hz, 2H); MS (MALDITOF) m/z 405.5 (M+).
11-trioxo-1-phenyl-2-oxa-4,7,10-triazadecane-5,9-dicarboxylate (11). A solution of diazomalonamide 10 (2.9 g, 6.7 mmol) in toluene (40 mL) was added the solution of 4-methoxybenzamide (1.01 g, 6.7 mmol) and rhodium(II)-octanoate (60 mg, 0.017 mmol) in toluene (40 mL) at 80 °C for a period of 5 min. After the mixture was heated at the same temperature for 4 h, the solvent was evaporated to dryness and the residue was purified by column chromatography (hexane:EtOAc = 1:2) to afford 11 as a diastereomeric mixture (1:1) (960 mg, 26%).

\[ \text{Methyl 4-((2-benzyloxycarbonylamino)-3-methoxy-3-oxopropyl)(2-cyanoethyl)amino)-2-(4-methoxyphenyl)oxazole-4-carboxylate (11).} \]

To a solution of 11 (880 mg, 1.58 mmol) in DMF (3 mL), POCl \(_3\) was added at room temperature. After the reaction mixture was stirred at 60 °C for 3 h, the solvent was evaporated. The crude residue was treated with saturated aqueous NaHCO \(_3\) solution and it was extracted with EtOAc. The organic layer was dried over anhydrous Na\(_2\)SO\(_4\) and evaporated. The residue was purified by column chromatography (CHCl\(_3\):MeOH = 10:1) to obtain a pale yellow solid 12 (340 mg, 40%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.04 (d, \(J = 9.0\) Hz, 2H), 7.25–7.35 (m, 5H), 6.96 (d, \(J = 9.0\) Hz, 2H), 5.64 (t, \(J = 8.7\) Hz, 1H, NH), 5.12 (s, 2H), 4.59 (dd, \(J = 6.6, 13.5\) Hz, 1H), 3.88 (s, 3H), 3.84 (d, \(J = 7.2\) Hz, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.62 (t, \(J = 6.6\) Hz, 2H), 2.65 (t, \(J = 6.6\) Hz, 2H), MS (ESI) m/z 537.1 ([M+H]+).

Methyl 5-((2-amino-3-methoxy-3-oxopropyl)(2-cyano-ethyl)amino)-2-(4-methoxyphenyl)oxazole-4-carboxylate (13). The solution of oxazole 12 (270 mg, 0.50 mmol) in MeOH (10 mL) was treated with 10% Pd on carbon under hydrogen at 1 atm. and stirred at room temperature for 3 h. The reaction mixture was filtered through silica and the filtrate was concentrated. The residue was purified by column chromatography (hexane:EtOAc = 1:3) to obtain 9 (180 mg, 89%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.90 (d, \(J = 9.0\) Hz, 2H), 6.93 (d, \(J = 9.0\) Hz, 2H), 4.18 (m, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.77–3.81 (m, 4H), 3.70 (s, 3H), 2.76 (dt, \(J = 1.5, 6.6\) Hz, 2H); MS (ESI) m/z 403.4 ([M+H]+).

Methyl 4-(2-cyanoethyl)-2-(4-methoxyphenyl)-8-oxo-5,6,7,8-tetrahydro-4H-oxazolo[5,4-e][1]diazepine-6-carboxylate (14). To a solution of 13 (160 mg, 0.39 mmol) in toluene (2 mL), 2.0 M solution of trimethylsilylethyl (0.19 mL, 0.39 mmol) was added at –10 °C and the reaction mixture was allowed to stand for 2 h at room temperature. The solvent was removed under the reduced pressure and the product 14 was separated from the by-products by column chromatography (EtOAc) (11 mg, 8%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.86 (d, \(J = 9.2\) Hz, 2H), 7.50 (m, 3H), 4.89 (br s, 1H), 3.32 (t, \(J = 9.2\) Hz, 2H), 3.12 (s, 3H), 2.81 (t, \(J = 10.8\) Hz, 2H); MS (ESI) m/z 262.2 ([M+H]+).

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References
21. Compound 18: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.26 (d, \(J = 9.2\) Hz, 2H), 7.50 (m, 3H), 4.89 (br s, 1H), 3.32 (t, \(J = 9.2\) Hz, 2H), 3.12 (s, 3H), 2.81 (t, \(J = 10.8\) Hz, 2H); MS (ESI) m/z 262.2 ([M+H]+).

Notes