Notes

Practicable Synthesis of 1-(1-Phenylethyl)-1*H*-pyrido[2,3-*b*][1,4]oxazine†

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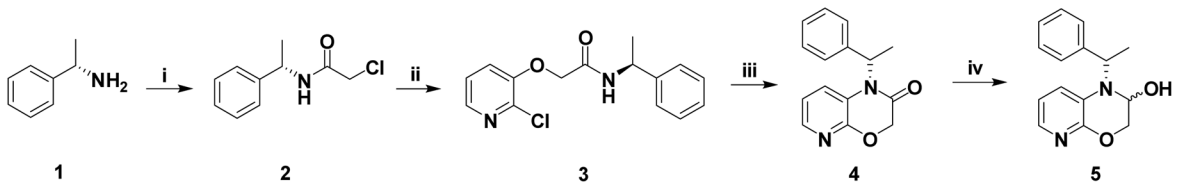
The benzo[1,4]-oxazine ring system executing an important template has attracted considerable interest in the search for novel pharmaceutical compounds,[1-3] but their pyridine derivatives were rarely mentioned in the literature. Only very few like synthesis of 2*H*-pyrido[3,2-*b*][1,4]oxazine,[4] pyrido[4,3-*b*][1,4]oxazine[5] and 4-acetyl-3(*R*)- and 3(*S*)-(hydroxymethyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]oxazine[6] were reported. On the other hand most of the compounds reported in the literatures possess [1,4]-oxazinone moieties.[7-9] Thus the reported methods demonstrated the synthesis of pyrido[3,2-*b*][1,4]-oxazine derivatives but there is no synthetic approach valuable for the synthesis of its isomer pyrido[2,3-*b*][1,4]-oxazine series having the nitrogen of pyridine and *N* of oxazine in trans fashion. It is known that 2-amino-3-pyridol is liable to *O*-alkylation rendering the formation of pyrido [3,2-*b*][1,4]oxazine. The selection of 2-hydroxy pyridine is less liable and more problematic for the *O*-alkylation to obtain [1,4]-oxazine. We have earlier reported the reaction of 2-chloro-3-pyridol with chloroacetamides could undergo Smiles rearrangement to afford pyrido[2,3-*b*][1,4]oxazinones.[10] In this paper we outline the approach to synthesize pyrido[2,3-*b*][1,4]oxazine as potential scaffold for bioactive compounds.

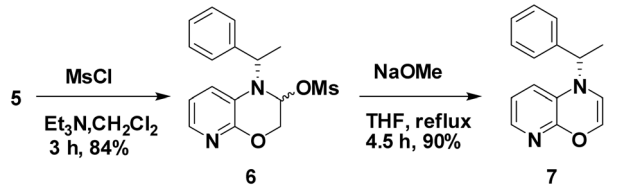
Endlessly, benzo[1,4]oxazines and pyrido[3,2-*b*][1,4]oxazines are prepared by direct cyclization of 2-haloacetyl halides or alkyl 2-halopropionates with 2-aminophenol or 2-amino-3-hydroxypyridine.[5] A similar approach, however, is not directly applicable to the pyrido[2,3-*b*][1,4]oxazine ring system. Nevertheless it was felt that the Smiles rearrangement could be exploited to circumvent this limitation. Since the Smiles rearrangement necessitates an electron-deficient center to proceed at a reasonable rate, we selected 2-haloacetamide and 2-halo-3-hydroxypyridine as the reaction partners. The reduction of the lactam function with metal hydrides was found to be promising but it was found that sodium borohydride was better reagent for reduction of pyrido[2,3-*b*][1,4]oxazinone. In order to form the oxazine the hydroxy group was replaced with mesyl group by reacting with mesyl chloride and the mesyl ester thus obtained was removed with sodium methoxide to afford pyrido[2,3-*b*][1,4]-oxazines. The use of three-step reaction condition in converting the oxazine by reduction of lactam, converting to *O*-Ms and the removal of *O*-Ms by base afforded pyridooxazines. Moreover the regioselective formation of pyrido-[3,2-*b*][1,4]oxazine could be understood by this and it can be applied for the synthesis of large number of heterocycles by Diels-Alder or Aza Diels-Alder reactions to synthesize a various kinds of scaffold for new drug development.

In an demonstrative experiment, reaction of 2-chloro-3-hydroxy pyridine with (*S*)-2-chloro-*N*-(1-phenylethyl) acetamide **2** in the presence of potassium carbonate furnished (*S*)-2-(2-chloropyridin-3-yloxy)-*N*-(1-phenylethyl) acetamide **3** as the major product in 96% yield (Scheme 1). The 2-chloro-*N*-(1-phenylethyl) acetamide **2** was prepared by known procedures[10a] using chloroacetyl chloride with (*S*)-(–)-α-methyl benzylamine **1** in the presence of potassium carbonate (95% yield). The subsequent exposure of **3** with cesium carbonate afforded cyclized product, (*S*)-1-(1-

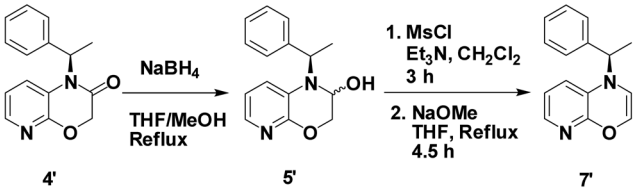


Scheme 1. Reagents and conditions: i) 2-Chloroacetyl chloride, K_2CO_3, CH_2Cl_2, reflux, 95%. ii) 2-Chloro-3-hydroxypyridine, K_2CO_3, CH_3CN, reflux, 96%. iii) Cs_2CO_3, CH_3CN, reflux, 96%. iv) $NaBH_4$, THF/MeOH, reflux, 88%.

†Dedicated to Professor Sang Chul Shim on the occasion of his honorable retirement.



Scheme 2



Scheme 3

phenylethyl)-1*H*-pyrido[2,3-*b*][1,4]oxazin-2(3*H*)-one **4** in quantitative yield. The formation of **4** is best explained by the utilization of Smiles rearrangement. We also investigated the base and solvent effects on the synthesis of **4** and according to our observation, cesium carbonate was found to be the most effective system with acetonitrile as solvent (96% yield). Whereas, it was found the yield of **4** was lower in the case of using bases such as NaOH and K_2CO_3 than cesium carbonate in acetonitrile as solvent. On the other hand, the use of cesium carbonate in DMF was found to afford **4** in good yield (90%) while the use of THF did not undergo any reaction with K_2CO_3 or Cs_2CO_3 as base. The reduction of **4** with sodium borohydride in THF and methanol gave (*S*)-1-(1-phenylethyl)-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-ol **5** in good yield (88%). The spectral and physical data of these compounds confirmed the formation of compound **5**.

It was not possible to convert the pyrido [2,3-*b*] 1,4-oxazine from the pyrido oxazinone directly. In order to extend the synthetic strategy it was planned to convert the hydroxy group to mesyl ester and removal of mesyl group with NaOMe to afford the oxazines. Compound **5** was first treated with methanesulfonyl chloride in dichloromethane in the presence of triethylamine to furnish methanesulfonic ester **6**. The reaction was tried with different bases in various temperatures, and the triethylamine at 4 °C was found to be the best giving 84% of yield. The removal of mesyl ester by treatment with NaOMe in THF under refluxing condition gave (*S*)-1-(1-phenylethyl)-1*H*-pyrido[2,3-*b*][1,4] oxazine **7** in 90% yield. (Scheme 2).[11] We were able to synthesis (*R*)-1-(1-phenylethyl)-1*H*-pyrido[2,3-*b*][1,4] oxazine **7'** from (*R*)-(+)-α-methyl benzylamine with the same synthetic route which was developed to synthesize (*S*)-**7** as moderative yield (Scheme 3).

In summary we have demonstrated a convenient and practical method for the synthesis of chiral pyrido [2,3-*b*] 1,4-oxazines ((S)-**7**, (R)-**7'**) *via* Smiles rearrangement. The obtained products, variety of fused oxazine derivatives is useful in Diels-Alder and aza Diels-Alder reactions and also have wide application in synthetic and biological point of view. The synthesis of other types of fused heterocyclic moieties and their chemical and biological transformations are underway in our laboratory.

Experimental Section

The compounds (*S*)-2-chloro-*N*-(1-phenyl-ethyl) acetamide **2**, (*S*)-2-(2-chloropyridin-3-yloxy)-*N*-(1-phenylethyl) acetamide **3** and (*S*)-1-(1-phenylethyl)-1*H*-pyrido[2,3-*b*][1,4]oxazin-2(3*H*)-one **4** were prepared according to the literature procedure.[10a]

Synthesis of (*S*)-1-(1-phenylethyl)-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-ol (5): To a stirred solution of (*S*)-1-(1- phenylethyl)-1*H*-pyrido[2,3-*b*][1,4]oxazin-2(3*H*)-one **4** (3 g, 11.80 mmol) in THF/MeOH (70 mL, 30:1) was added $NaBH_4$ (0.49 g, 12.98 mmol) in ice bath, and then stirred for 1 h. Then the reaction mixture was removed from the ice bath, reaction temperature was increased at room temperature and refluxed for 5 h. After the completion of the reaction, the solvent was removed at reduced pressure and the residue was treated with water. The pH of the solution was adjusted to 6, extracted with CH_2Cl_2 and dried over anhydrous $MgSO_4$. The CH_2Cl_2 extract was purified by column chromatography and (*S*)-1-(1-phenylethyl)-2,3-dihydro-1*H*-pyrido[2,3-*b*] [1,4]oxazin-2-ol **5** was obtained (2.66 g, 88%). R_f = 0.32 (hexane: ethyl acetate = 2:1); IR (KBr, cm^{-1}): 3396, 3060, 2960; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (d, J = 8.0 Hz, 3H), 3.98 (dd, J = 2.0, 0.4 Hz, 2H), 4.43 (d, J = 6.8 Hz, 1H), 4.42-4.59 (m, J = 0.8, 1.6, 2.0 Hz, 2H), 6.46 (d, J = 1.6 Hz, 1H), 6.62 (dd, J = 5.2, 2.4 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.32-7.36 (m, J = 1.6 Hz, 3.6 Hz, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 52.7, 63.3, 70.2, 119.0, 126.6, 128.2, 129.8, 131.1, 132.4, 133.0, 152.1.

Synthesis of (*R*)-1-(1-phenylethyl)-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-ol (5'): R_f= 0.32 (hexane : ethyl acetate = 2:1); Yield: 80%; IR (KBr, cm^{-1}): 3396, 3060, 2960; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (d, J = 8.0 Hz, 3H), 3.97-3.99 (m, 2H), 4.40-4.45 (q, J = 6.8 Hz, 1H), 4.56-4.58 (m, 2H), 6.44-6.46 (dd, J = 1.2, 6.4 Hz, 1H), 6.61-6.64 (dd, J = 5.2, 1.2 Hz, 1H), 7.24-7.26 (m, 1H), 7.32-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 53.2, 63.1, 70.0, 116.7, 118.0, 125.7, 127.1, 128.8, 131.8, 132.2, 144.3, 152.0.

Synthesis of (*S*)-1-(1-Phenylethyl)-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-yl methanesulfonate (6): A solution of (*S*)-1-(1-phenylethyl)-2,3-dihydro-1*H*-pyrido-[2,3-*b*] [1,4] oxazin-2-ol **5** (2 g, 7.81 mmol) and Et_3N (1.20 mL, 8.59 mmol) in CH_2Cl_2 (70 mL) was treated with methanesulfonyl chloride (0.7 mL, 8.59 mmol) in ice bath and stirred for 3 h. After the completion of the reaction, the solvent was removed at reduced pressure and the residue was added to water. The water layer was extracted with dichloromethane (50 mL × 2) and dried over $MgSO_4$. The combined extracts were evaporated and thus the solid was purified by column chromatography (hexane:ethyl acetate = 2:1) to yield desired product (*S*)-1-(1-phenylethyl)-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-yl methanesulfonate **6** (2.19 g, 84%). R_f = 0.38 (hexane:ethyl acetate = 2:1); IR

(KBr, cm^{-1}): 3010, 2980, 1762, 1654; ^1H NMR (400 MHz, $CDCl_3$): δ 1.57 (d, J = 6.8 Hz, 3H), 3.88 (s, 2H), 4.16-4.22 (q, J = 8 Hz, 1H), 4.36 (d, J = 6.8 Hz, 2H), 5.97 (t, J = 2.8 Hz, 1H), 6.63 (dd, J = 3.2, 2.4 Hz, 1H), 7.26-7.33 (m, J = 1.6, 3.6 Hz, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.6, 42.0, 52.3, 76.9, 77.2, 106.3, 108.0, 125.3, 126.5, 126.8, 128.0, 129.7, 137.6, 144.2.

Synthesis of (*S*)-1-(1-phenylethyl)-1*H*-pyrido[2,3-*b*]-[1,4]oxazine (7): The solution of (*S*)-1-(1-phenylethyl)-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-yl methane sulfonate **6** (1.82 g, 5.44 mmol) in THF (50 mL) was treated with NaOMe (1.23 mL, 5.44 mmol) and refluxed for 4.5 h. After the completion of the reaction, the solvent was removed at reduced pressure and the residue was treated with water. The water layer was extracted with dichloromethane and the extract was dried over $MgSO_4$. The solvent was removed at reduced pressure and purified by column chromatography (hexane:ethyl acetate = 2:1) to afford the desired product (*S*)-1-(1-phenylethyl)-1*H*-pyrido[2,3-*b*]-[1,4]oxazine **7** (1.15 g, 90%). R_f = 0.40 (hexane:ethyl acetate = 2:1); ^1H NMR (300 MHz, $CDCl_3$): δ 1.54 (d, J = 6.6 Hz, 3H), 4.31-4.39 (m, J = 6.3, 5.5 Hz, 1H), 5.22 (d, J = 15 Hz, 1H), 5.83 (d, J = 6.9 Hz, 1H), 5.98 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 7.2 Hz, 1H), 7.19-7.26 (m, J = 4.5, 4.2, 3.9 Hz, 5H), 7.30 (d, J = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 53.2, 102.9, 107.0, 107.8, 117.2, 125.6, 126.9, 128.6, 132.1, 137.8, 144.0, 156.7.

Synthesis of (*R*)-1-(1-phenylethyl)-1*H*-pyrido[2,3-*b*]-[1,4]oxazine (7'): R_f = 0.32 (hexane:ethyl acetate = 2:1); Yield: 72% (overall yield from (R)-**5'**); ^1H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, J = 6.8 Hz, 3H), 4.34-4.39 (q, J = 6.8 Hz, 1H), 5.00-5.02 (dd, J = 1.6, 3.6 Hz, 1H), 5.21-5.25 (dd, J = 1.2, 14.8 Hz, 1H) 5.83 (t, J = 1.2 Hz, 1H), 6.00 (t, J = 3.2 Hz, 1H), 6.84 (t, J = 3.2 Hz, 1H), 7.23-7.32 (m, 5H), 7.30 (q, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 53.3, 103.1, 107.2, 107.9, 117.3, 125.7, 127.1, 128.7, 132.2, 137.9, 144.1, 156.8.

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