Synthesis of Imidazo[1,2-a]pyridines and Pyrido[1,2-a]pyrimidines in Water and their SnAr Cyclizations

Langpoklakpam Gellina Chanu, Thokchom Prasanta Singh, Yong Ju Jang,† Yong-Jin Yoon,† Okram Mukherjee Singh,* and Sang-Gyeong Lee†,*

Department of Chemistry, Manipur University, Canchipur-795003, Manipur, India. *E-mail: ok_mukherjee@yahoo.co.in
†Department of Chemistry and Research Institute of Life Science, Graduate School for Molecular Materials and Nanochemistry, Gyeongsang National University, Jinju 660-701, Korea. E-mail: leesang@gnu.ac.kr

Received September 4, 2013, Accepted October 11, 2013

Synthesis of tetrahydroimidazo[1,2-a]pyridines and tetrahydropyrido[1,2-a]pyrimidines by a one-pot and three component reaction of \(\alpha\)-oxoketenedithioacetals, diamines and DMAD in water has been described. Different routes for accessing the desired compounds were examined and a few specially designed-substrates have been utilized further to afford the new imidazo and pyrido fused [1,8] naphthyridine tetracyclic compound by SnAr intramolecular cyclization.

Key Words: Tetrahydroimidazo[1,2-a]pyridines, Tetrahydropyrido[1,2-a]pyrimidines, Imidazo and pyrido fused [1,8] naphthyridine tetracyclic, One-pot and multicomponent

Introduction

Synthetic routes for bioactive heterocycles involving environmentally benign media are attracting the interests of synthetic and medicinal chemists in recent years. Among the heterocyclic compounds, bicyclic pyridines containing a ring-junction nitrogen are considered as the privileged fragments in many natural products particularly alkaloids and other pharmacologically active compounds. Certain tetrahydroimidazo[1,2-a]pyridines are patented as analgesic and anti-inflammatory agents. Further, many of their analogues exhibit a broad range of biological activities such as antiviral, antibacterial, antitumor (NSC649900, I) and GABAA receptor modulators (II). On the other hand, pyrido[1,2-a]pyrimidines structural motif is present in the tranquilizer pirenperone, the antiallergic agent ramastine (III), an anti-asthmatic (IV) and anti-HIV-1 agents (IV). Ever since, Huang et al. reported the synthesis of imidazo[1,2-a]pyridine and pyrido[1,2-a]pyrimidine derivatives using keteneaminals, the development of novel and efficient routes for rapid access to such functionalized bicyclic pyridines/pyrimidines under mild condition is of high demand.

On the basis of the above considerations and in the context of our efforts on developing strategies towards bioactive heterocycles, herein we wish to present an efficient method for synthesis of tetrahydroimidazo[1,2-a]pyridines and tetrahydropyrido[1,2-a]pyrimidines by a one-pot, three-component reaction of \(\alpha\)-oxoketenedithioacetals, diamines and DMAD.

Results and Discussion

Initially, the solution of three substrates, ketenedithioacetals (2 mmol), diamines (2 mmol), and DMAD (2 mmol) was stirring at 100 °C. An intractable tarry mixture was obtained. On another set of conditions, the condensation product 3a of benzoyl ketenedithioacetals (1a; 2 mmol) and diaminethanol (2a/b; 2 mmol) was stirred at 0 °C with DMAD under different organic solvents such as acetonitrile, dimethylformamide (DMF), dimethylsulfoxide (DMSO) and ethanol which ends up in yielding inseparable mixture. In our successive efforts, benzoyl ketenedithioacetals (1a; 2 mmol) and diamine (2a/b; 2 mmol) were refluxed for about 4-5 h in water, then HKA 3 was isolated by normal extraction procedure using dichloromethane. In the next step, the isolated...
HKAs were treated with DMAD followed by the addition of water (10 mL) at room temperature and stirred for only 10 minutes. After 10 min, the product was isolated and characterized either as imidazo[1,2-a]pyridines (when n = 1) or the pyrido[1,2-a]pyrimidines (n = 2) corresponding to the diamines. However as the overall reaction involves the release of obnoxious and unfavorable odors of gases like thiophenol, the isolation process is tedious and work up of the reaction mixture needs lots of extra reagents to maintain the neutral conditions. In view of these observations, we have designed a one pot and three-component direct method as shown in Scheme 1, which generates HKAs in situ and trapped with DMAD. Using aroylketene dithioacetal 1a as the model substrate and refluxing it with the respective diamino compounds in water for 4 h, the corresponding HKAs 3a or 4a were generated and cooled at room temperature. Then DMAD was added and stirred the reaction mixtures at either 0 °C or room temperature for 5-10 minutes (monitored by TLC) to afford the products 6a or 7a.

Our various trial experiments for optimization of the yield of the bicyclic compounds were initially based on the use of different solvents and bases like triethylamine, sodium hydride and sodium tertiary butoxide with anticipation that displacement of methylthio groups from ketene dithioacetals and successive Michael addition reactions may require strong bases. However after finding satisfactory yields in presence of water without any other catalytic agents, we have performed all the experiments under aqueous medium either at ambient temperature or ice-cold conditions. The complete conversion took only 10 min under aqueous medium (Table 1, entry 10) and if the reaction was kept longer unwanted side products were found to develop in TLC (Table 1).

With this optimized condition in hand, we next explored the generality of the reaction by employing variously substituted aryl and heteroaryl ketene dithioacetals 1a-i (Table 2). The corresponding bicyclic compounds 6b-i/7b-i were obtained in good yields (85-92%) and the structures of the newly synthesized compounds were established with the help of spectral and analytical data.

When HKA 3a-i generated in situ was directly treated with DMAD and stirring for only 10 mins yielded imidazopyridines 6a-i in 85-92% yield (Table 2, entries 1-9). Further, HKAs 4a-i generated in situ were directly treated with DMAD for 10 min only to yield the desired pyrido[1,2-a]pyrimidines 7a-i in 85-95% yield (Table 2, entries 10-18).

A plausible mechanism of this tandem reaction is depicted in Scheme 2. The steps involved in situ generation of HKA by 1,4 addition reaction with S,S-acetals, Michael addition, intramolecular imine-enamine tautomerization (A&B), followed by cyclocondensation.

Furthermore, imidazopyridine 6h-i and pyridopyrimidine 7h-i were utilized to afford the corresponding new imidazo and pyrido fused [1,8] naphthyridine tetracyclic compounds 8a-d via S,Ar intramolecular cyclization reaction (Scheme 3). Heterocyclic ketene aminals with enamine moiety (HN-C=) are found to act as ambident nucleophiles in these reactions and due to their conjugation effect of the electron-donating amino groups and the electron withdrawing substituents, the double bond is highly polarized which makes it convenient to apply in the Michael addition reactions with DMAD. Moreover among the benzyolketene N,N-acetals, ortho-halo group substituted ones broadens the scope of this reaction to diversity oriented synthesis by further intramolecular tandem annihilations.

**Experimental**

**General Procedure for the Preparation of Compound (6a-i and 7a-i).**

**Method A:** One-pot three component: To a reaction mixture of o xo ketenedithioacetal 1 (1 mmol) and diamino compound 2a or 2b (1.5 mmol), water (20 mL) was added and the mixture refluxed for 2-4 h. The mixture was then brought to room temperature (after TLC monitored) and DMAD (1 mmol) was added and stirred for 5-10 minutes. Some of the reaction mixtures were exothermic and vigor-
Table 2. Synthesis of tetrahydroimidazo[1,2-\(a\)]pyridines 6 and tetrahydropyrido [1,2-\(a\)] pyrimidines 7 under aqueous medium

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>2 Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>C(_6)H(_5)</td>
<td>2a</td>
<td>85</td>
</tr>
<tr>
<td>1b</td>
<td>4-BrC(_6)H(_4)</td>
<td>2a</td>
<td>86</td>
</tr>
<tr>
<td>1c</td>
<td>4-ClC(_6)H(_4)</td>
<td>2a</td>
<td>92</td>
</tr>
<tr>
<td>1d</td>
<td>4-MeC(_6)H(_4)</td>
<td>2a</td>
<td>89</td>
</tr>
<tr>
<td>1e</td>
<td>4-MeOC(_6)H(_4)</td>
<td>2a</td>
<td>90</td>
</tr>
<tr>
<td>1f</td>
<td>2-thienyl</td>
<td>2a</td>
<td>87</td>
</tr>
<tr>
<td>1g</td>
<td>2-furyl</td>
<td>2a</td>
<td>85</td>
</tr>
<tr>
<td>1h</td>
<td>2-ClC(_6)H(_4)</td>
<td>2a</td>
<td>86</td>
</tr>
<tr>
<td>1i</td>
<td>2,4-Cl(_2)C(_6)H(_3)</td>
<td>2a</td>
<td>85</td>
</tr>
</tbody>
</table>

Isolated yields after silica gel chromatography
Methyl-8-(4-chlorobenzoyl)-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridine-7-carboxylate (6c): Yellow amorphous solid, 0.305 g, 92% yield; mp 148-150 °C; 1H NMR (300 MHz, CDCl₃) δ 2.90 (s, 3H, CH₃), 3.63 (t, J = 11.7 Hz, 2H), 3.73 (t, J = 11.4 Hz, 2H), 6.19 (s, 1H), 7.40 (d, J = 5.4 Hz, 2H), 7.74 (d, J = 5.7 Hz, 2H), 8.93 (br s, NH); 13C NMR (75 MHz, CDCl₃) δ 37.0, 39.6, 51.0, 90.6, 109.3, 128.4, 129.8, 135.3, 136.4, 140.6, 160.7, 166.9, 168.0 and 187.7; IR (KBr) 1600, 1635, 1725, 2140, 3014, 3305 cm⁻¹; MS m/z 332 (M⁺). Anal. Calc. for C₁₇H₁₂ClN₂O₂: C, 57.75; H, 3.94; Cl, 10.65; N, 8.42; O, 19.23. Found: C, 57.34; H, 3.65; Cl, 10.43; N, 8.39; O, 19.11.

Methyl-8-(4-methoxybenzoyl)-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridine-7-carboxylate (6d): Yellow crystal, 0.277 g, 89% yield; mp 183-185 °C; 1H NMR (300 MHz, CDCl₃) δ 2.32 (s, 3H), 3.26 (s, 3H), 4.02 (dd, J = 8.7 Hz, J = 6.6 Hz, 2H) and 4.32 (dd, J = 6.3 Hz, J = 4.8 Hz, 2H), 6.12 (s, 1H), 7.22 (d, J = 5.4 Hz, 2H), 7.40 (d, J = 4.5 Hz, 2H), 8.32 (br s, NH); 13C NMR (75 MHz, CDCl₃) δ 21.5, 42.8, 43.7, 52.0, 94.5, 108.9, 127.9, 130.4, 138.0, 141.9, 145.8, 157.1, 161.2, 167.1 and 179.2; IR (KBr) 1605, 1658, 1746, 2953, 3025, 3338 cm⁻¹; MS m/z 312 (M⁺). Anal. Calc. for C₁₇H₁₄O₂N₂: C, 65.8; H, 5.16; N, 8.97; O, 20.49. Found: C, 65.23; H, 5.10; N, 8.54; O, 20.21.

Method B: Direct synthesis from HKA (3 or 4); 10 mL of water was added to a solution of either arylmethyleneimidazolidine 3a or the arylmethylenimidazopyrimidines 4a (2 mmol) and DMAD (2 mmol). The reaction mixture was stirred for 5 min at 0 °C. After the completion of the reaction (as monitored by TLC), the residue was purified by column chromatography to give pure compound as bright yellow solid.

Methyl-8-benzoyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridine-7-carboxylate (6a): Yellow solid, 0.258 g, 85% yield; mp 176-178 °C (180-181 °C) [11]; 1H NMR (300 MHz, CDCl₃) δ 3.10 (s, 3H, CH₃), 4.00 (dd, J = 9.6 Hz, J = 3.0 Hz, 2H), 4.30 (dd, J = 8.4 Hz, J = 7.5 Hz, 2H), 6.10 (s, 1H), 7.32-7.40 (m, 3H, aromatic), 7.53 (d, J = 4.5 Hz, 2H), 8.31 (br s, NH); 13C NMR (75 MHz, CDCl₃) δ 42.8, 43.7, 52.0, 94.3, 109.1, 127.6, 128.4, 131.3, 140.7, 145.8, 157.3, 160.2, 167.0 and 192.7; IR (KBr) 1600, 1644, 1730, 2951, 3015, 3304 cm⁻¹; MS m/z 298 (M⁺). Anal. Calc. for C₁₅H₁₄N₂O₂: C, 64.42; H, 4.73; N, 9.39; O, 21.45. Found: C, 64.31; H, 4.45; N, 9.13 O, 21.12.

Methyl-8-(4-bromobenzoyl)-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridine-7-carboxylate (6b): Yellow crystal, 0.323 g, 86% yield: mp 135-137 °C; 1H NMR (300 MHz, CDCl₃) δ 3.19 (s, 3H, CH₃), 4.00 (t, J = 12.6 Hz, 2H) and 4.29 (t, J = 12 Hz, 2H), 6.09 (s, 1H), 7.40 (d, J = 5.4 Hz, 2H), 7.53 (d, J = 5.7 Hz, 2H), 8.31 (br s, NH); 13C NMR (75 MHz, CDCl₃) δ 42.9, 43.7, 52.2, 94.0, 109.3, 125.9, 129.1, 131.6, 139.5, 145.4, 157.3, 160.1, 166.9 and 191.3; IR (KBr) 1601, 1640, 1720, 2145, 3010, 3300 cm⁻¹; MS m/z 376 (M⁺). Anal. Calc. for C₁₆H₁₂BrN₂O₂: C, 50.95; H, 3.47; Br, 21.18; N, 7.43; O, 16.97. Found: C, 50.85; H, 3.25; Br, 21.10; N, 7.32; O, 16.56.


Method A: 1,2,3-triazol-4-ylmethylenemolecules were cyclized using the intramolecular cyclization reaction. (Image 55x592 to 282x745)
solid, 0.318 g, 92% yield: mp 186-188 °C (187-188 °C); 1H NMR (300 MHz, CDCl₃) δ 2.16-2.23 (m, 2H), 3.15 (s, 3H), 3.61 (t, J = 9.9 Hz, J = 10.5 Hz, 2H), 3.81 (t, J = 9.9 Hz, J = 10.5 Hz, 2H), 6.18 (s, 1H), 7.35 (d, J = 6.0 Hz, 2H), 7.53 (d, J = 6.3 Hz, 2H), 9.80 (br s, NH); 13C NMR (75 MHz, CDCl₃) δ 19.9, 37.0, 39.2, 50.9, 50.9, 90.3, 109.6, 122.5, 128.4, 135.3, 136.3, 140.2, 160.1, 167.8, 169.0, 187.6; IR (KBr) 1615, 1657, 1725, 2931, 3015, 3273 cm⁻¹; MS m/z 346 (M⁺).

Methyl-(4-bromobenzoyle)-6-oxo-2,3,4,6-tetrahydro-1H-pyrido[1,2-α]pyrimidine-8-carboxylic acid (7c): Yellow solid, 0.259 g, 86% yield: mp 128-130 °C; 1H NMR (300 MHz, CDCl₃) δ 2.10-2.18 (m, 2H), 3.23 (s, 3H), 3.67 (dd, J = 6.9 Hz, J = 4.8 Hz, 2H), 3.78 (dd, J = 7.5 Hz, J = 5.7 Hz, 2H), 6.33 (s, 1H), 6.90 (t, J = 11.1 Hz, 1H), 7.20 (d, J = 5.1 Hz, 1H), 7.36 (d, J = 6.3 Hz, 1H), 9.20 (br s, NH); 13C NMR (75 MHz, CDCl₃) δ 19.9, 37.0, 39.2, 52.1, 90.1, 113.6, 130.1, 132.9, 138.3, 146.6, 155.5, 160.2, 187.8; IR (KBr) 1615, 1657, 1725, 2931, 3015, 3273 cm⁻¹; MS m/z 346 (M⁺).
126.7, 128.6, 130.6, 135.2, 135.5, 138.4, 158.6, 160.7, 185.3; IR (KBr) 1550, 1645, 1740, 2934, 3018, 3235 cm⁻¹; MS m/z 302 (M)⁺. Anal. Calcld for C₁₉H₁₆N₂O₃: C, 59.60; H, 4.67; N, 9.27; O, 26.46. Found: C, 59.43; H, 4.24; N, 9.12; O, 26.27.

Methyl-9-(2-chlorobenzoyl)-6-oxo-2,3,4,6-tetrahydro-1H-pyrido[1,2-α]pyrimidine-8-carboxylic acid (7a): Yellow crystal, 0.287 g, 85% yield; ¹H NMR (300 MHz, CDCl₃) δ 7.21 (d, J = 8.3 Hz, 2H), 7.41-7.48 (m, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.81-7.85 (m, 2H), 8.29; O, 19.35. Found: C, 58.01; H, 3.21; Cl, 10.53; N, 8.29; O, 19.19.

Methyl-5,8-dioxo-2,3,5,8-tetrahydro-1H-benzo-[b]pyrimido[1,2-α]-[1,8]naphthyridine-7-carboxylic acid (8c): White solid, 0.257 g, 83% yield. ¹H NMR (300 MHz, CDCl₃) δ 3.27 (s, 3H), 3.62 (dd, J = 10.5 Hz, 2H), 3.96 (t, J = 4.5 Hz, 1H), 4.36 (t, J = 4.2 Hz, 1H), 6.00 (s, 1H), 7.12 (t, J = 5.1 Hz, 1H), 7.75 (d, J = 9.9 Hz, 2H) 13C NMR (75 MHz, CDCl₃) δ 19.3, 37.0, 39.2, 50.9, 90.3, 109.6, 125.2, 128.5, 133.5, 136.3, 140.2, 144.0, 145.5, 160.1, 166.8, 180.5; IR (KBr) 1555, 1655, 1737, 2937, 3020, 3230 cm⁻¹; MS m/z 436 (M)⁺. Anal. Calcld for C₁₉H₁₅N₂O₃: C, 58.88; H, 4.36; Cl, 10.22; N, 8.08; O, 18.46. Found: C, 58.75; H, 4.29; Cl, 10.14; N, 8.01; O, 18.40.

General Procedure for the Preparation of Compound (8a-d): 10 mL of DMF was added to the mixture of K₂CO₃ (2 mmol) and compound 6h-i or 7h-i (2 mmol). The reaction mixture was refluxed at 80 °C for about 2 h. After the completion of the reaction, DMF was evaporated and the residue was extracted from CHCl₃ to give pure compound 8a-d as white solids, which was recrystallized from hot benzene.

Methyl-4,7-dioxo-1,2,4,7-tetrahydrobenzo[6-oxoimidazo[1,2-α]-[1,8]naphthyridine-6-carboxylate (8a): White solid, 0.323 g, 85% yield; ¹H NMR (300 MHz, CDCl₃) δ 3.27 (s, 3H), 3.62 (dd, J = 5.4 Hz, 2H), 3.75 (dd, J = 8.4 Hz, 6.6 Hz, 2H), 6.18 (s, 1H), 7.34 (s, 1H), 7.26 (d, J = 4.5 Hz, 1H), 7.47 (d, J = 6.3 Hz, 1H), 9.90 (brs, 1H); ¹C NMR (75 MHz, CDCl₃) δ 19.9, 37.0, 39.2, 50.9, 90.3, 109.5, 126.3, 128.5, 133.5, 136.3, 140.1, 144.0, 145.5, 160.1, 166.8, 180.5; IR (KBr) 1515, 1555, 1747, 2937, 3020, 3230 cm⁻¹; MS m/z 436 (M)⁺. Anal. Calcld for C₁₉H₁₅N₂O₃: C, 58.88; H, 4.36; Cl, 10.22; N, 8.08; O, 18.46. Found: C, 58.75; H, 4.29; Cl, 10.14; N, 8.01; O, 18.40.

Conclusion

In summary, a facile synthesis of tetrahydropyrimidinones and tetrahydroimidazopyridines by one-pot, triple-component tandem annulation from readily accessible α-oxoketene S,S-acetals has been described. Consequently, a library of bicyclic pyridine derivatives with nitrogen at ring junction was constructed from readily available starting materials under mild and environmentally benign reaction conditions. The strategy involves the formation of three new C-N bonds and one C-C bond leading to the formation of two heterocyclic systems. On further reaction, the ortho-chlorine substituted bicyclic products give rise to novel tetra cyclic compounds.

Acknowledgements

One of the author T. P. Singh is grateful to DST, New Delhi for INSPIRE Fellowship. O.M. Singh is thankful to DBT and CSIR (New Delhi) for financial assistance. Lee is thanks to NRF funded partly by the ministry of Education, Science and Technology (Grant Number: 2010-0023775).

References


