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

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Synthesis of tetrahydroimidazo[1,2-*a*]pyridines and tetrahydropyrido[1,2-*a*] pyrimidines by a one-pot and three component reaction of α-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 S_NAr intramolecular cyclization.

Key Words : Tetrahydroimidazo[1,2-*a*]pyridines, Tetrahy-dropyrido[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.[1] Among the heterocyclic compounds, bicyclic pyridines containing a ring-junction nitrogen are considered as the privileged fragments in many natural products particularly alkaloids[2] and other pharmacologically active compounds. Certain tetrahydroimidazo[1,2-*a*]pyridines are patented as analgesic and anti-inflammatory agents.[3] Further, many of their analogues exhibit a broad range of biological activities such as antiviral,[4] antibacterial, [5] antitumor (NSC649900, I)[6] and GABAA receptor modulators(II).[7] On the other hand, pyrido[1,2-*a*]pyrimidines structural motif is present in the tranquilizer pirenperone,[8] the antiallergic agent ramastine(III),[9] an anti-asthmatic[10] and anti-HIV-1 agents(IV).[11] Ever since, Huang *et al.*[12] 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.[13]

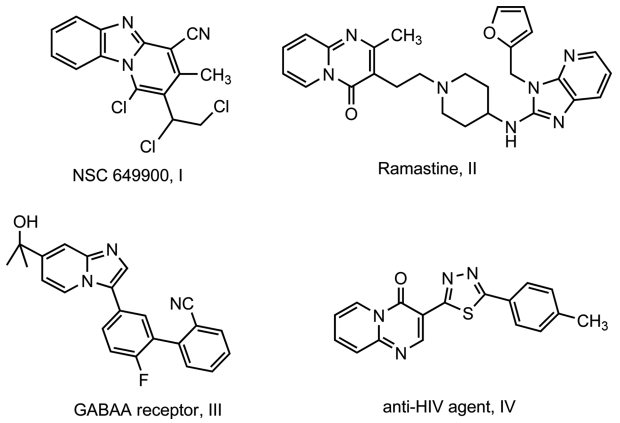
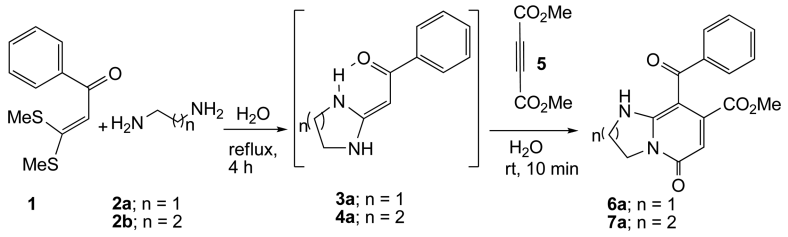


Figure 1. Biologically active tetrahydro-imidazo[1,2-*a*]pyridines and tetrahydropyrido [1,2-*a*] pyrimidines.

On the basis of the above considerations and in the context of our efforts on developing strategies towards bioactive heterocycles,[14] 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 α-oxoketenedithioacetals, diamines and dimethyl acetylenedicarboxylate (DMAD). The synthetic utility of α-oxoketenedithioacetals as versatile intermediates in organic synthesis has been well recognized, particularly, as 1,3-bielectrophilic C_3 synthons.[15] But, to the best of our knowledge, there have been no reports on the synthetic application of α-oxoketenedithioacetals with diamino bi-nucleophiles and DMAD to synthesize imidazo[1,2-*a*]pyridines, pyrido[1,2-*a*]pyrimidines and imidazo/pyrido fused [1,8]naphthyridines.

Results and Discussion

Initially, the solution of three substrates, ketenedithioacetal (2 mmol), diamines (2 mmol), 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 ketenedithioacetal (**1a**; 2 mmol) and diaminoethane (**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 ketenedithioacetal (**1a**; 2 mmol) and diamine (**2a/b**; 2 mmol) was refluxed for about 4-5 h in water, then HKA 3 was isolated by normal extraction procedure using dichloromethane.[14h] In the next step, the isolated



Scheme 1. One-pot Synthesis of imidazo[1,2-*a*]pyridines and pyrido[1,2-*a*]pyrimidines.

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 thiomethyl, 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 aroyl 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 imidazopyridine **6a-i**[16] 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 pyridopyrimidines **7a-i**[16] 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.

Table 1. Optimization of reaction conditions

Entry	Base	Solvent	Time (min)/yield of (**6a**)[a]
1	Et_3N	CH_3CN	10/(50%)
2	-	CH_3CN	10/(70%)
3	Et_3N	EtOH	10/(45%)
4	-	EtOH	10/(75%)
5	Na^{t}OBu	DMF	10/(60%)
6	Et_3N	THF	10/(65%)
7	-	DMSO	10/(60%)
8	-	DMF	10/(75%)
9	-	-	10/(77%)
10	-	H_2O	10/(85%)

[a]All reactions were performed by refluxing the mixture of **1a** (0.5 mmol) and **2a** (0.5 mmol), then further addition of DMAD (0.5 mmol) at 0-25 °C to get imidazo[1,2-*a*]pyridine **6a**

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_NAr intramolecular cyclization reaction (Scheme 3).

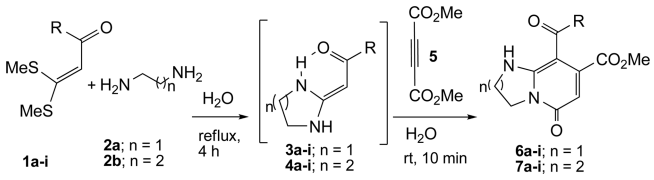
Heterocyclic ketene aminals with enamine moiety (HN-C=C) are found to act as ambident nucleophiles in these reactions and due to their conjugation effect of the electron-donating amino groups and the electron withdrawing substituents, the double bond is highly polarized which makes it convenient to apply in the Michael addition reactions with DMAD. Moreover among the benzoylketene *N*,*N*-acetals, *ortho*-halo group substituted ones broadens the scope of this reaction to diversity oriented synthesis by further intramolecular tandem annulations.

Experimental

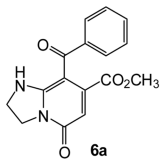
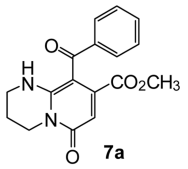
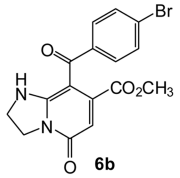
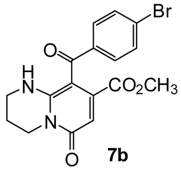
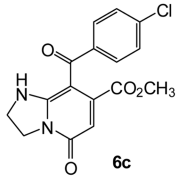
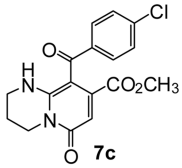
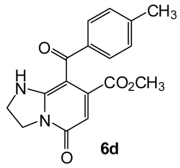
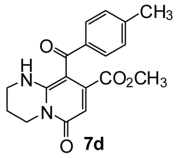
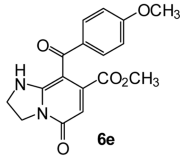
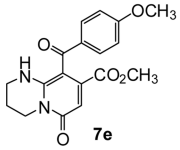
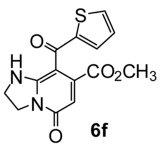
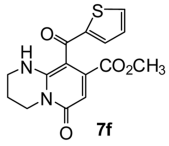
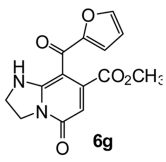
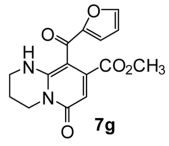
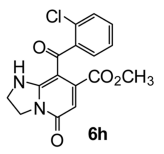
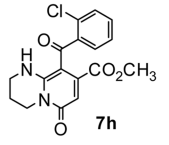
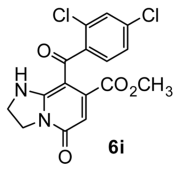
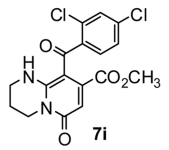
General Procedure for the Preparation of Compound (6a-i and 7a-i).

Method A: One-pot three component: To a reaction mixture of α-oxoketenedithioacetals **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-

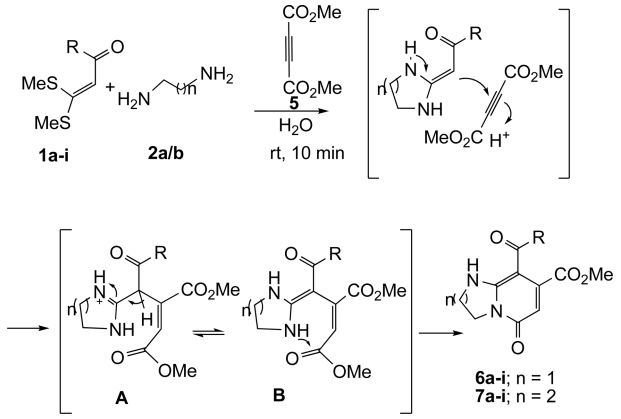
Table 2. Synthesis of tetrahydroimidazo[1,2-*a*]pyrid-ines **6** and tetrahydropyrido [1,2-*a*] pyrimidines **7** under aqueous medium



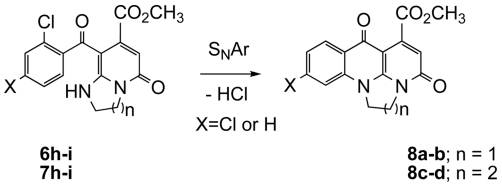
1a-i; **2a**; n = 1, **2b**; n = 2; **3a-i**; n = 1, **4a-i**; n = 2; **6a-i**; n = 1, **7a-i**; n = 2

Entry	R	2	Product	Yield (%)[a]	Entry	R	2	Product	Yield (%)[a]
1a	C_6H_5	**2a**	 **6a**	85	**1a**	C_6H_5	**2b**	 **7a**	85
1b	4-BrC_6H_4	**2a**	 **6b**	86	**1b**	4-BrC_6H_4	**2b**	 **7b**	88
1c	4-ClC_6H_4	**2a**	 **6c**	92	**1c**	4-ClC_6H_4	**2b**	 **7c**	92
1d	4-MeC_6H_4	**2a**	 **6d**	89	**1d**	4-MeC_6H_4	**2b**	 **7d**	95
1e	4-$MeOC_6H_4$	**2a**	 **6e**	90	**1e**	4-$MeOC_6H_4$	**2b**	 **7e**	87
1f	2-thienyl	**2a**	 **6f**	87	**1f**	2-thienyl	**2b**	 **7f**	88
1g	2-furyl	**2a**	 **6g**	85	**1g**	2-furyl	**2b**	 **7g**	86
1h	2-ClC_6H_4	**2a**	 **6h**	86	**1h**	2-Cl C_6H_4	**2b**	 **7h**	83
1i	2,4-$Cl_2C_6H_3$	**2a**	 **6i**	85	**1i**	2,4-Cl_2 C_6H_3	**2b**	 **7i**	85

[a]Isolated yields after silica gel chromatography



Scheme 2. Plausible reaction pathway for tandem annulations reaction.



Scheme 3. S_NAr intramolecular cyclization reaction.

ous at rt and in such cases stirring was performed at 0 °C.

Method B: Direct synthesis from HKA (**3** or **4**): 10 mL of water was added to a solution of either aroylmethyleneimidazolidine **3a** or the aroylmethyleneimidazopyrimidines **4a** (2 mmol) and DMAD (2 mmol). The reaction mixture was stirred for 5 mins 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-tetrahydroimi-dazo[1,2-*a*]pyridine-7-carboxylate (6a): Yellow solid, 0.258 g, 85% yield: mp 176-178 °C (180-181 °C)[13]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.10 (s, 3H, CH_3), 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 Calcd for $C_{16}H_{14}N_2O_4$: 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-tetrahydro-imidazo[1,2-*a*]pyridine-7-carboxylate (6b): Yellow crystal, 0.323g, 86% yield: mp 135-137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.19 (s, 3H, CH_3), 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, 5.7 Hz, 2H), 8.31 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 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 Calcd for $C_{16}H_{13}BrN_2O_4$: 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.

Methyl-8-(4-chlorobenzoyl)-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyridine-7-carboxylate (6c): Yellow amorphous solid, 0.305 g, 92% yield: mp 148-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (s, 3H, CH_3), 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), 7.48 (d, J = 5.7 Hz, 2H), 8.93 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 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 Calcd for $C_{16}H_{13}ClN_2O_4$: 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-methylbenzoyl)-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyridine-7-carboxylate (6d): Yellow crystal, 0.277g, 89% yield: mp 183-185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 42.8, 43.7, 52.0, 94.5, 108.9, 127.7, 129.0, 138.0, 141.9, 145.8, 157.1, 160.2, 167.1 and 192.6; IR (KBr) 1605, 1658, 1746, 2953, 3025, 3338 cm^{-1}; MS *m/z* 312 $(M)^+$. Anal Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97; O, 20.49. Found: C, 65.23; H, 5.10; N, 8.54 O, 20.21.

Methyl-8-(4-methoxybenzoyl)-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyridine-7-carboxylate (6e): Yellow solid, 0.295 g, 90% yield: mp 165-167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 3H), 3.22 (s, 3H), 4.05 (t, J = 18.6 Hz, 2H), 4.35 (t, J = 18.0 Hz, 2H), 6.19 (s, 1H), 7.27 (d, J = 5.7 Hz, 2H), 7.48(d, J = 6.9 Hz, 2H), 8.39 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.8, 43.8, 51.9, 53.0, 94.1, 106.8, 127.5, 129.1, 132.8, 142.1, 146.0, 155.1, 165.1, 165.3 and 195.5; IR (KBr) 1605, 1650, 1736, 2960, 3035, 3340 cm^{-1}; MS *m/z* 328 $(M)^+$. Anal Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53; O, 24.37. Found: C, 62.19; H, 4.91; N, 8.53; O, 24.37.

Methyl-5-oxo-8-(thiophene-2-carbonyl)-1,2,3,5-tetra-hydroimidazo[1,2-*a*]pyridine-7-carboxylate (6f): Yellow crystal, 0.264 g, 87% yield: mp 153-155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.97 (dd, J = 9.3 Hz, J = 9.0 Hz, 2H), 4.28 (dd, J = 9.6 Hz, J = 8.7 Hz, 2H), 6.18 (s, 1H), 7.26 (t, J = 12.6 Hz, 1H), 7.37 (d, J = 5.1 Hz, 2H), 7.46 (d, 2.7 Hz, 2H), 8.78 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.8, 43.8, 52.3, 94.7, 109.6, 127.4, 130.4, 131.7, 145.3, 147.9, 160.2, 165.2, 167.1, 176.4; IR (KBr) 1600, 1645, 1735, 2925, 3010, 3220 cm^{-1}; MS *m/z* 304 $(M)^+$. Anal Calcd for $C_{14}H_{12}N_2O_4S$: C, 55.25; H, 3.97; N, 9.21; O, 21.03; S, 10.54. Found: C, 55.13; H, 3.85; N, 9.11; O, 20.61; S, 10.17.

Methyl-8-(furan-2-carbonyl)-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyridine-7-carboxylate (6g): Yellow crystal, 0.244 g, 85% yield: mp 115-117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3H), 3.60 (dd, J = 6.6 Hz, J = 6.0 Hz, 2H) 3.82 (dd, J = 8.1 Hz, J = 3.6 Hz, 2H), 6.32 (s, 1H), 7.12 (t, J = 10.5 Hz, 1H), 7.38 (d, J = 5.7 Hz, 2H), 7.45 (d, J = 5.1 Hz, 2H), 9.17 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.2, 38.2, 51.5, 90.6, 109.3, 123.4, 128.0, 136.3, 137.6, 140.1,

162.7, 168.1, 169.7 and 182.7; IR (KBr) 1605, 1642, 1730, 2928, 3012, 3218 cm^{-1}; MS *m/z* 288 $(M)^+$. Anal Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72; O, 27.75. Found: C, 58.21; H, 4.09; N, 9.43; O, 27.32.

Methyl-8-(2-chlorobenzoyl)-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyridine-7-carboxy-late (6h): Light yellow amorphous solid 0.285 g, 83% yield: mp 193-195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 3H), 3.90 (t, *J* = 12.6 Hz, *J* = 9.9 Hz, 2H) 4.20 (t, *J* = 12.6 Hz, *J* = 9.9 Hz, 2H), 5.93 (s, 1H), 7.40-7.46 (m, ArH, 2H), 7.57 (d, *J* = 4.8 Hz, 1H) 7.62 (d, *J* = 5.1 Hz, 1H), 8.31 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.2, 43.9, 54.0, 89.3, 109.2, 118.8, 120.5, 126.9, 130.1, 132.9, 138.3, 146.6, 155.5, 158.6, 160.2, 187.8; IR (KBr) 1615, 1627, 1731, 2919, 3015, 3221 cm^{-1}; MS *m/z* 332 $(M)^+$. Anal Calcd for $C_{16}H_{13}ClN_2O_4$: C, 57.75; H, 3.94; Cl, 10.65; N, 8.42; O, 19.23 Found: C, 57.63; H, 3.89; Cl, 10.57; N, 8.36; O, 19.17.

Methyl-8-(2,4-dichlorobenzoyl)-5-oxo-1,2,3,5-tetrahydro-imidazo[1,2-*a*]pyridine-7-carboxylate (6i): Yellow amorphous solid 0.311 g, 85% yield: mp 227-228 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (s, 3H), 3.63 (t, *J* = 11.4 0 Hz, *J* = 12.0 Hz, 2H), 3.78 (t, *J* = 11.4 Hz, 12.0 Hz, 2H), 6.20 (s, 1H), 7.25 (s, 1H), 7.56 (d, *J* = 4.5 Hz, 1H), 7.72 (d, *J* = 4.8 Hz, 1H), 10.14 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.7, 42.5, 55.3, 91.6, 110.3, 126.7, 127.2, 129.2, 131.9, 137.1, 141.0, 149.3, 160.0, 163.0, 165.8,194.3; IR (KBr) 1610, 1635, 1735, 2915, 3010, 3225 cm^{-1}; MS *m/z* 366 $(M)^+$. Anal Calcd for $C_{16}H_{12}Cl_2N_2O_4$: C, 52.34; H, 3.29; Cl, 19.31; N, 7.63; O, 17.43. Found: C, 52.21; H, 3.10; Cl, 19.21; N, 7.52; O, 17.29.

Methyl-9-benzoyl-6-oxo-2,3,4,6-tetrahydro-1*H*-pyrido-[1,2-*a*]pyrimidine-8-carboxylate (7a): Yellow crystal, 0.265 g, 85% yield: mp 195-197 °C (193-194 °C);[12] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10-2.18 (m, 2H), 3.27 (s, 3H), 3.60 (t, *J* = 10.5 Hz, *J* = 13.5 Hz, 2H), 3.73 (t, *J* = 10.5 Hz, *J* = 13.5 Hz, 2H), 6.18 (s, 1H), 7.18-7.38 (m, 3H), 7.43 (d, *J* = 4.8 Hz, 2H), 8.97 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 37.0, 39.2, 52.1, 90.1, 110.8, 128.0, 131.6, 135.2, 136.6, 139.0, 156.4, 158.6, 161.7, 185.7; IR (KBr) 1615, 1655, 1745, 2955, 3015, 3270 cm^{-1}; MS *m/z* 312 $(M)^+$. Anal Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97; O, 20.49. Found: C, 65.21; H, 5.08; N, 8.84; O, 20.26.

Methyl-9-(4-bromobenzoyl)-6-oxo-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-8-carboxylate (7b): Yellow solid, 0.343 g, 88% yield: mp 168-170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19-2.28 (m, 2H), 3.15 (s, 3H), 3.62 (t, *J* = 10.8 Hz, *J* = 11.7 Hz, 2H), 3.78 (t, *J* = 10.8 Hz, *J* = 11.7 Hz, 2H), 6.18 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.7 Hz, 2H), 9.84 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 37.0, 39.2, 51.0, 91.0, 109.8, 124.8, 128.6, 131.4, 135.2, 140.6, 160.1, 167.0, 168.8, 181.9; IR (KBr) 1612, 1651, 1743, 2949, 3005, 3273 cm^{-1}; MS *m/z* 390 $(M)^+$. Anal Calcd for $C_{17}H_{15}BrN_2O_4$: C, 52.19; H, 3.86; Br, 20.42; N, 7.16; O, 16.36. Found: C, 52.05; H, 3.65; Br, 20.23; N, 7.09; O, 16.33.

Methyl-9-(4-chlorobenzoyl)-6-oxo-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-8-carboxy-late (7c): Yellow solid, 0.318 g, 92% yield: mp 186-188 °C (187-188 °C);[12] ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 37.0, 39.2, 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 $(M)^+$. Anal Calcd for$C_{17}H_{15}ClN_2O_4$: C, 58.88; H, 4.36; Cl, 10.22; N, 8.08; O, 18.46. Found: C, 58.78; H, 4.16; Cl, 10.07; N, 7.88; O, 18.32.

Methyl-9-(4-methylbenzoyl)-6-oxo-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-8-carboxy-late (7d): Yellow crystal, 0.309 g, 95% yield: mp 177-179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18-2.26 (m, 2H), 2.64 (s, 3H) 3.05 (s, 3H), 3.32 (t, *J* = 12.0 Hz, *J* = 10.8 Hz, 2H), 3.58 (t, *J* = 12.0 Hz, *J* = 10.8 Hz, 2H), 6.41 (s, 1H), 7.55 (d, *J* = 5.1 Hz, 2H), 7.66 (d, *J* = 5.1 Hz, 2H), 8.80 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 22.2, 35.4, 38.2, 51.1, 92.6, 107.8, 128.3, 130.4, 137.3, 138.3, 142.3, 162.1, 168.8, 170.0, 190.0; IR (KBr) 1610, 1650, 1720, 2925, 3012, 3275 cm^{-1}; MS *m/z* 326 $(M)^+$. Anal Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58; O, 19.61. Found: C, 66.16; H, 5.34; N, 8.32; O, 19.23.

Methyl-9-(4-methoxybenzoyl)-6-oxo-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-8-carboxy-late (7e): Yellow needle solid, 0.297 g, 87% yield: mp 170-172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65-2.73 (m, 2H), 3.70 (s, 3H) 3.90 (s, 3H), 4.63 (t, *J* = 10.2 Hz, *J* = 11.1 Hz, 2H), 4.90 (t, *J* = 10.2 Hz, *J* = 11.1 Hz, 2H), 6.23 (s, 1H), 7.37 (d, *J* = 5.1 Hz, 2H), 7.46 (d, *J* = 4.8 Hz, 2H), 8.82 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 42.8, 43.4, 52.3, 56.8, 90.9, 109.1, 126.6, 130.1, 132.9, 136.2, 145.5, 155.1, 160.5, 165.5 and 188.6; IR (KBr) 1617, 1654, 1725, 2930, 3010, 3270 cm^{-1}; MS *m/z* 342 $(M)^+$. Anal Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18; O, 23.37. Found: C, 63.02; H, 5.11; N, 8.11; O, 23.27.

Methyl-9-(thiophene-2-carbonyl)-6-oxo-2,3,4,6-tetra-hydro-1*H*-pyrido[1,2-*a*]pyrimidine-8-carbo-xylate (7f): Yellow crystal, 0.279 g, 88% yield: mp 166-168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12-2.21 (m, 2H), 3.22 (s, 3H), 3.58 (dd, *J* = 6.6, *J* = 5.1 Hz, 2H), 3.80 (dd, *J* = 6.0, *J* = 4.5 Hz, 2H), 6.22 (s, 1H), 7.00 (t, *J* =10.5 Hz, 1H), 7.50 (d, *J* = 6.0 Hz, 1H), 7.55 (d, *J* = 4.5 Hz, 1H), 9.48 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 37.0, 39.3, 51.1, 90.3, 109.5, 127.2, 128.1, 129.7, 135.2, 146.3, 159.3, 167.2, 168.0, 180.4; IR (KBr) 1600, 1652, 1745, 2945, 3025, 3245 cm^{-1}; MS *m/z* 318 $(M)^+$. Anal Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80; O, 20.10; S, 10.07. Found: C, 56.34; H, 4.22; N, 8.61; O, 20.01; S, 9.84.

Methyl-9-(furan-2-carbonyl)-6-oxo-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-8-carboxy-late (7g): Yellow solid, 0.259 g, 86% yield: mp 128-130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 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, 6.3 Hz, 1H), 9.20 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 37.0, 39.2, 52.1, 90.1, 113.6,

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 Calcd for $C_{15}H_{14}N_2O_5$: 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-1*H*-pyrido[1,2-*a*]pyrimidine-8-carboxy-late (7h): Yellow crystal, 0.287 g, 85% yield: mp 186-188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12-2.20 (m, 2H), 3.15 (s, 3H), 3.60 (t, *J* = 12.3 Hz, *J* = 10.8 Hz, 2H), 3.78 (t, *J* = 12.3 Hz, *J* = 10.8 Hz, 2H), 6.18 (s, 1H), 7.31-7.35 (m, 2H), 7.44 (d, *J* = 3.9 Hz, 1H), 7.54 (d, *J* = 4.8 Hz, 1H), 9.79 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 37.0, 39.2, 50.9, 90.3, 109.6, 125.2, 128.4, 135.3, 136.3, 140.2, 144.0, 145.2, 160.1, 166.8, 168.0, 187.6; IR (KBr) 1555, 1655, 1737, 2937, 3020, 3230 cm^{-1}; MS *m/z* 346 $(M)^+$. Anal Calcd for $C_{17}H_{15}ClN_2O_4$: 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.

Methyl-9-(2,4-dichlorobenzoyl)-6-oxo-2,3,4,6-tetrahydro-1*H*-pyrido[1,2-*a*]pyrimidine-8-carboxylate (7i): Yellow crystal, 0.323 g, 85% yield: mp 213-215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15-2.22 (m, 2H), 3.00 (s, 3H), 3.60 (t, *J* = 10.5 Hz, *J* = 11.4 Hz, 2H), 3.73 (t, *J* = 10.5 Hz, *J* = 11.4 Hz, 2H), 6.18 (s, 1H), 7.34 (s, 1H), 7.36 (d , *J* = 4.5 Hz, 1H), 7.47 (d, *J* = 6.3, 1H), 9.90 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 38.0, 39.2, 52.5, 90.1, 110.8, 124.7, 127.9, 129.5, 130.6, 133.0, 135.2, 135.6, 157.5, 159.6, 161.7, 192.7; IR (KBr) 1620, 1650, 1772, 2949, 3015, 3250 cm^{-1}; MS *m/z* 380 $(M)^+$. Anal Calcd for $C_{17}H_{14}Cl_2N_2O_4$: C, 53.56; H, 3.70; Cl, 18.60; N, 7.35; O, 16.79. Found: C, 53.43; H, 3.51; Cl, 18.47; N, 7.23; O, 16.55

General Procedure for the Preparation of Compound (8a-d): 10 mL of DMF was added to the mixture of K_2CO_3 (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 $CHCl_3$ to give pure compound **8a-d** as white solids, which was recrystallized from hot ethanol.

Methyl-4,7-dioxo-1,2,4,7-tetrahydrobenzo[*b*]-imidazo-[1,2,3-*ij*][1,8]naphthyridine-6-carboxy-late (8a): White solid, 0.251 g, 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27 (s, 3H), 3.62 (dd, *J* = 5.4 Hz, 2.1 Hz, 2H), 3.75 (dd, *J* = 8.4 Hz, 6.6 Hz, 2H), 6.18 (s, 1H), 7.33 (d, *J* = 4.8 Hz, 1H), 7.35 (d, 4.8 Hz, 1H), 7.46-7.51(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.0, 39.2, 52.1, 90.1, 110.8, 113.5, 126.7, 129.3, 130.6, 133.0, 135.2, 135.6, 138.4, 158.6, 160.7, 183.7; IR (KBr) 1634, 1665, 1772, 2935, 3016, 3240 cm^{-1}; MS *m/z* 296 $(M)^+$. Anal Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46; O, 21.60. Found: C, 64.75; H, 4.02; N, 9.39; O, 21.57.

Methyl-10-chloro-4,7-dioxo-1,2,4,7-tetrahydro-benzo-[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine-6-carboxylate (8b): White amorphous solid, 0.287 g, 87% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 3H), 4.10 (t, *J* = 8.4 Hz, 1H), 4.31 (t, *J* = 4.8 Hz, 2H), 6.23 (s, 1H), 7.29 (s, 1H), 7.35 (d, *J* = 5.1 Hz, 1H), 7.60 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.9, 43.4, 52.3, 91.3, 109.1, 118.8, 120.1, 126.6, 129.8, 130.1, 133.9, 136.3, 145.5, 158.6, 160.1, 188.6; IR (KBr) 1630, 1661, 1776, 2945, 3011, 3245 cm^{-1}; MS *m/z* 330 $(M)^+$. Anal Calcd for $C_{16}H_{11}ClN_2O_4$: C, 58.11; H, 3.35; Cl, 10.72; N, 8.47; 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-1*H*-benzo-[*b*]pyrimido[1,2,3-*ij*][1,8]naphthyridine-7-carb-oxylate (8c): White solid, 0.257 g, 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35-2.41 (m, 2H), 3.12 (s, 3H), 3.96 (t, *J* = 12.9 Hz, *J* = 12.6 Hz, 2H), 4.27 (t, *J* = 12.9 Hz, *J* = 12.6 Hz, 2H), 6.10 (s, 1H), 7.09 (d, *J* = 5.4 Hz, 1H) 7.21 (d, *J* = 6.6, 1H), 7.40-7.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 42.8, 43.7, 52.1, 94.6, 108.9, 127.7, 129.1, 137.6, 141.9, 145.9, 151.9, 157.1, 160.2, 160.2, 167.1, 182.6; IR (KBr) 1626, 1666, 1772, 2947, 3016, 3240 cm^{-1}; MS *m/z* 310 $(M)^+$. Anal Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03; O, 20.62. Found: C, 65.71; H, 4.47; N, 8.97; O, 20.54.

Methyl-11-chloro-5,8-dioxo-2,3,5,8-tetrahydro-1*H*-benzo-[*b*]pyrimido[1,2,3-*ij*][1,8]naphthy-ridine-7-carboxylate (8d): White solid, 0.303 g, 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19-2.27 (m, 2H), 3.27 (s, 3H), 4.14 (t, *J* = 10.2 Hz, *J* = 9.9 Hz, 2H), 4.36 (t, *J* = 10.2 Hz, *J* = 9.9 Hz, 2H), 6.00 (s, 1H), 7.15 (s, 1H), 7.21 (d, *J* = 4.8 Hz, 1H), 7.45 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 46.7, 47.8, 55.4, 92.9, 113.0, 119.3, 125.0, 127.5, 128.4, 129.2, 129.2, 130.0, 159.8, 162.6, 166.8, 181.8; IR (KBr) 1633, 1665, 1771, 2940, 3011, 3247 cm^{-1}; MS *m/z* 344 $(M)^+$. Anal Calcd for $C_{17}H_{13}ClN_2O_4$: C, 59.23; H, 3.80; Cl, 10.28; N, 8.13; O, 18.56. Found: C, 59.10; H, 3.64; Cl, 10.13; N, 8.05; O, 18.37.

Conclusion

In summary, a facile synthesis of tetrahydropyridopyrimidines and tetrahydroimidazopyridines by one-pot, three-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 tetracyclic compounds.

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