Intramolecular cyclocondensation of *α*-oxoketene *N,N*-, *N,S*- and *N,O*-acetals : synthesis of novel pyrido[1,2-*a*]pyrimidinium tetrafluoroborates

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Abstract

A facile regioselective synthesis of substituted pyrido[1,2-*a*]pyrimidinium salts **5a-f** from *α*-oxo-ketene *N,S*-acetals **2a-f**, **6a-d** from *N,N*-acetals **3a-d**, **7b-c** from *N,O*-acetals **4b-c**, and **8a-c** from *N,S*-acetals **2a-c** is described. The scope and mechanisms of these reactions have been investigated.

Keywords: Oxoketene, ring cyclization, pyrido pyrimidine, cyclocondensation

Introduction

α-Oxoketene *N,S*-, *N,N*- and *N,O*- acetals are useful intermediates for the synthesis of a wide range of five and six membered heterocycles.[1-3] These compounds can behave either as enaminones providing C-C-N component in the product heterocycles[4] or act as 1,3-bielectrophilic component in their reactions with bifunctional heteronucleophiles furnishing various annulated heterocycles.[5]

We have reported earlier, a synthetic route to certain functionalized ketene *N,S*-, *N,N*- and *N,O*- acetals.[6] In the subsequent work, we further demonstrated the synthetic elaboration of some of these ketene aminals derived from 2-aminopyridine for the construction of imidazo[1,2-*a*] pyridines by cupric chloride induced oxidative cyclization.[7] In continuation of our studies on these ketene aminals, we now report acid induced intramolecular cyclocondensation of some of these intermediates (*α*-oxoketene aminals from 2-aminopyridines) providing a new route to pyrido[1,2-*a*]primidinium salts.

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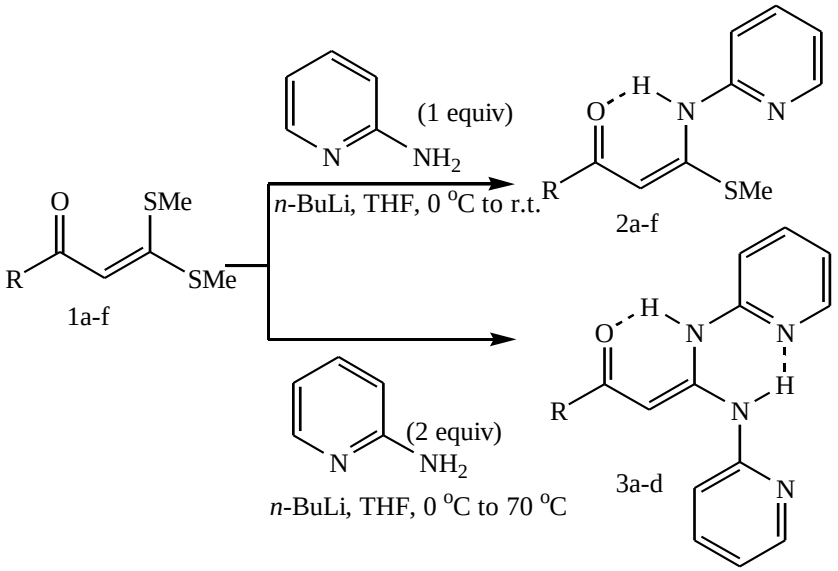
Pyrido[1,2-*a*]pyrimidines constitute a class of bioactive heterocycles bearing bridgehead nitrogen atoms.[8] This structural motif is present in the tranquilizer pirenperone,[9a] the antiallergic agent ramastine,[9b] an antiulcerative agent,[9c] an antiasthmatic [9d] and antiparasitic agent.[9e] They are also used as synthetic intermediates or as additives to photographic materials and dyes.[8a]

There are several reports of synthesis of pyrido[1,2-*a*]pyrimidine-2- and -4-ones by reaction of 2-aminopyridines with a variety of acetylenic esters and β–ketoesters,[10-11] however only a few reports[12-13] concerning pyrido[1,2-*a*]pyrimidinium salts not bearing oxo or imino substituents have appeared in the literature. Various 1,3-bielectrophilic compounds used for annulation of 2-aminopyridine to give pyrido[1,2-*a*]pyrimidine salts are restricted only to β–ketoaldehyde, β–diketones and their dimethoxyacetals, β–chlorovinylic ketones and propargylic ketones.[12,13]

In view of these limited studies, a systematic investigation into development of general synthetic routes for these class of bioactive heterocycles and related compounds is desirable. We herein report a direct one step route for these compounds via intramolecular cyclocondensation of *α*-oxoketene *N,S*-, *N,N*- and *N,O*- acetals derived from 2-aminopyridine.

Results and Discussion

The desired *N,S*-, *N,N*-acetals **2a**–**f** and **3a**–**d** required for this transformations were prepared according to our earlier reported[6] procedure via displacement on α- oxoketene *S,S*-acetals **1a**–**f** by 2-aminopyridine in presence of *n*-butyllithium (Scheme **1**). The corresponding *N,O*-acetals **4a**–**b** were similarly obtained by replacement of methylthio group in *N,S*-acetals **2b**–**c** by methoxy group in presence of sodium methoxide in refluxing methanol (Scheme **2**).[7]



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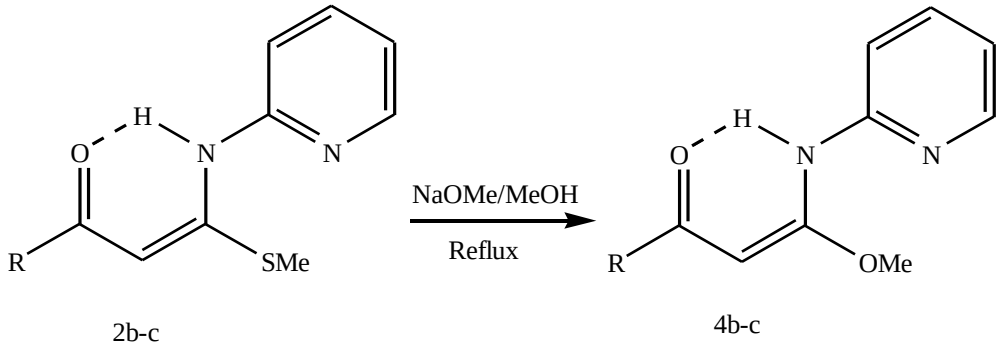
Scheme 1. Synthesis of ketene *N,S*- and *N,N*-acetals.

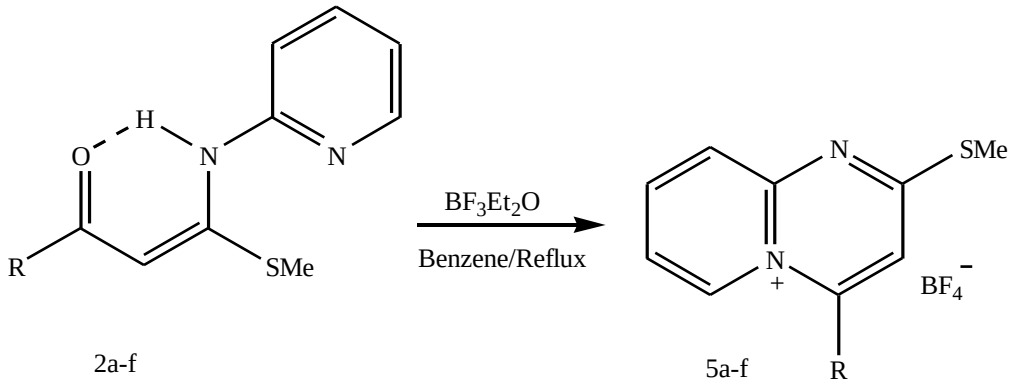


2b-c 4b-c

Scheme 2. Synthesis of *N,O*-acetals.

Regioselective synthesis of 2-(methylthio)/2-(2-aminopyridyl)/2-(methoxy)-4-arylpyrido-[1,2-a]pyrimidinium fluoroborates (Schemes 3–5).

The *N,S*-acetals **2a**–**f** were then subjected to acid induced intramolecular ring closure in presence of a mineral acid (HBr, $HClO_4$, or HBF_4) or a Lewis acid ($BF_3.Et_2O$) (Scheme **3**). Best results were obtained when $BF_3.Et_2O$ was employed in refluxing benzene (1h) yielding the corresponding 2-(methylthio)pyrido pyrimidinium fluoroborates **5a**–**f** as well defined crystalline solid products in 70-85% overall yields.



2a-f 5a-f

Scheme 3. Cyclocondensations of *N,S*-acetals

Similarly the corresponding ketene *N,N*-ketene aminals **3a**–**d** underwent smooth intramolecular cyclization under identical conditions to furnish the respective 2-(2-pyridylamino) pyrido[1,2-*a*]pyrimidinium tetrafluoroborates **6a**–**d** in 70-76% overall yields (Scheme **4**). The spectral and analytical data of the product **5a**–**f** & **6a**–**d** were in conformity with the assigned structures.

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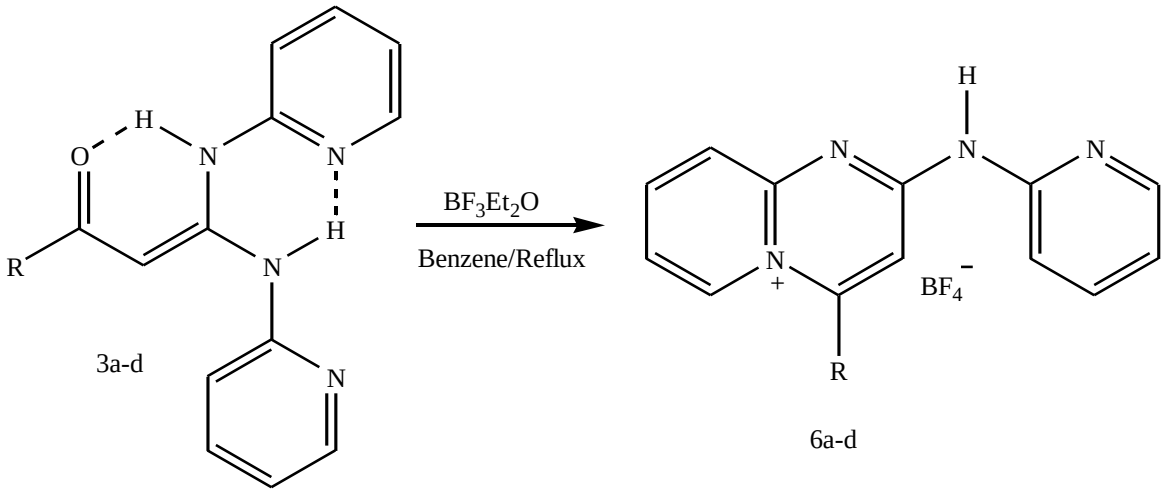
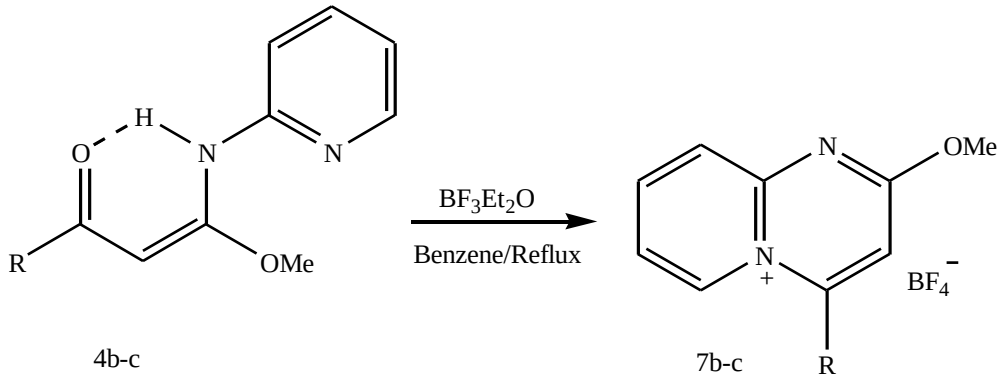


Scheme 4. Cyclocondensations of *N*,*N*-acetals

This intramolecular cyclization was equally facile with *N*,*O*-acetals **4b**–**c** which afforded the corresponding 2-(methoxy)pyridopyrimidinium salts **7b**–**c** in high yields on treatment with BF_3Et_2O in refluxing benzene (Scheme **5**).



Scheme 5. Cyclocondensations of *N*,*O*-acetals

The use of perchloric acid as the cyclizing agent generally gave lower yields (60-62%) of perchlorates **8a**–**c** from **2a**–**c** (Scheme **6,** Table **2**) which were found to be less stable than the corresponding tetrafluoroborates **5a**–**c** (Scheme **3**). Thus these perchlorate salts **8a**–**c** underwent hydrolysis and ring opening under alkaline conditions (40% NaOH, rt) yielding the starting *N*, *S*-acetals **2a**–**c** as the sole products (Scheme **6**) whereas the corresponding fluoroborate salts remained unaffected under these conditions.

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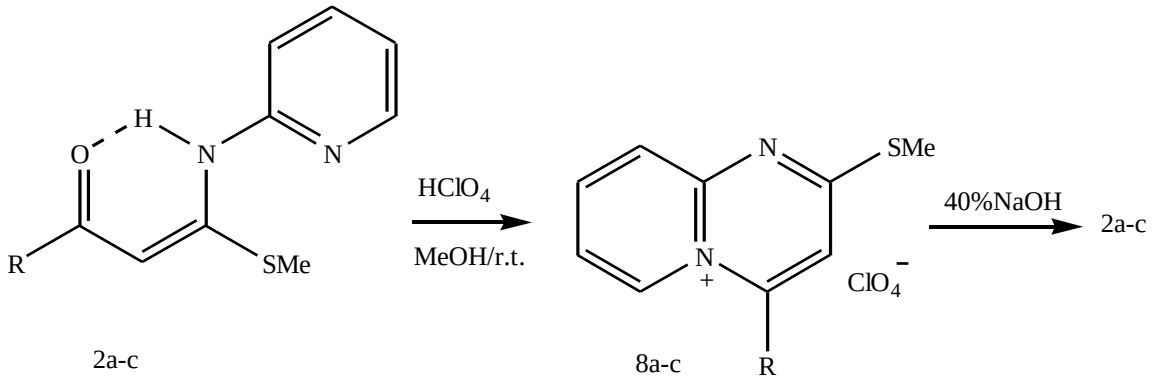

Scheme 6. Perchloric acid catalysed cyclizations of *N*,*S*-acetals and hydrolysis of the cyclized products.

Table 1. Products **2**, **3, 4, 5, 6, 7** & **8** with different **R** substituents

1	R	2	3	4	5	6	7	8
1a	C_6H_5	**2a**	**3a**		**5a**	**6a**		**8a**
1b	4-$MeOC_6H_4$	**2b**	**3b**	**4b**	**5b**	**6b**	**7b**	**8b**
1c	4-ClC_6H_4	**2c**	**3c**	**4c**	**5c**	**6c**	**7c**	**8c**
1d	4-MeC_6H_4	**2d**	**3d**		**5d**	**6d**		
1e	2-Furyl	**2e**			**5e**			
1f	2-Thienyl	**2f**			**5f**			

Mechanistic pathway

A possible mechanism for the formation of substituted pyridopyrimidines **5**,**6**,**7** and **8** from **2**–**4** is shown in the Scheme 7 involving the following steps: (1) conformational rearrangement of enaminone **2** to **2A**; (2) BF_3Et_2O assisted intramolecular ring closure of the intermediate **2A** through participation of pyridine ring nitrogen to give cyclized intermediate **2B** and, (3) aromatization of the intermediate **2B** to products **5**–**7** via nitrogen lone pair electron assisted elimination of boron coordinated oxygen. The formation of other regioisomeric product i.e 1,8-naphthyridines **3B** via intramolecular cyclization on pyridine ring was not observed under these reaction conditions.[14-16] Our efforts to isolate 1,8-naphthyridines such as **9** from **2** under varying conditions were not successful.

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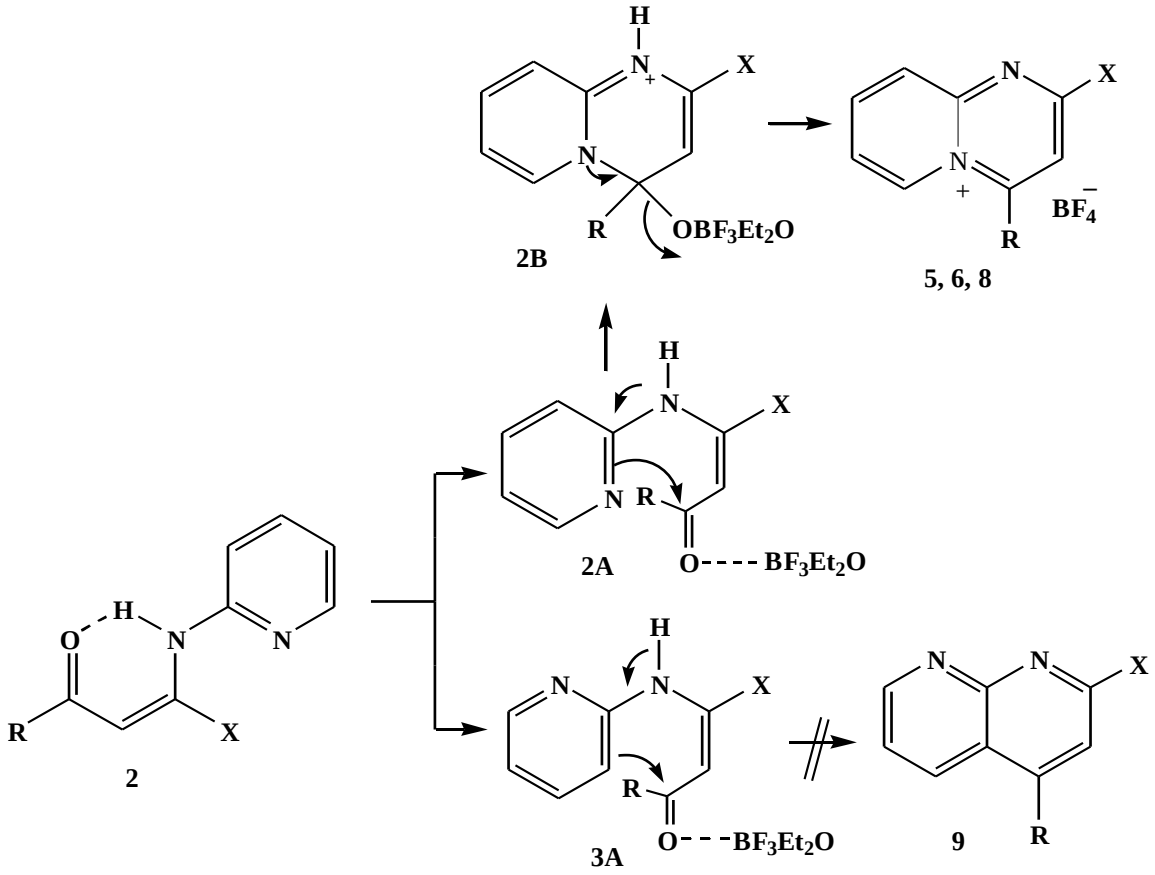

Scheme 7. Probable mechanistic pathways for regioselective ring cyclizations to obtain pyrido[1,2-*a*]pyrimidinium salts.

Conclusion

In summary we have developed an efficient general synthesis of pyrido[1,2-*a*]pyrimidinium salts by acid induced intramolecular cyclocondensation of α-oxoketene *N,S*-, *N,N*-, and *O,N*-acetals derived from 2-aminopyridine. In view of easy availability of starting materials the methodology is useful to generate libraries of these biologically important bridgehead heterocycles for probing their biological activities.

Experimental

Melting points were determined on a "Thomas-Hoover" capillary melting point apparatus and were uncorrected. The IR spectra were recorded on a Perkin-Elmer 983 spectrometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker ACF 300 operating in a field strength of 300 and 75.5 MHz, respectively. Chemical shifts were reported in parts per million (δ) and coupling

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constants (*J*) in Hertz, using in the case of ^{1}H NMR, tetramethylsilane (TMS) as internal standard and setting, in the case of ^{13}C NMR, the references at the signal of the solvent (77.0 ppm for $CDCl_3$ and 39.5 ppm for DMSO-d_6). Mass measurements were carried out with Jeol JMS D-300 spectrometer. Masses (MS) were reported in unit of mass over charge (m/z), the molecular or base peaks and relative intensities were indicated by (M) and (%) respectively. Elemental analyses were performed on a Heraeus CHN-O- Rapid Analyzer. Dry benzene was obtained by washing with concentrated sulfuric acid followed by azeotropic distillation and stored over sodium wire. THF was distilled over sodium benzophenone ketyl prior to use. Dry ether was obtained by keeping over calcium chloride (fused) and stored over sodium wire. $BF_3.Et_2O$ was redistilled before use.

All the α-oxoketene *N,S*-acetals **2a**–**f,** *N,N*-acetals **3a**–**d** and *N,O*-acetals **4b**–**c** were prepared according to our earlier reported procedure.[6,7]

Cyclization of the *N,S*-acetals 2a–f, *N,O*-acetals 4b–c and *N,N*-acetals 3a–d: General procedure for the synthesis of pyrido[1,2-*a*] pyrimidinium fluoroborates (5a–f, 6a–d, and 7b–c). To a solution of *N,S-/N,O-/N,N*-acetals (10 mmol) in dry benzene (30 mL), boron trifluoride etherate (3 mL) was added and the reaction mixture was refluxed with stirring for 45min – 1 hour. The reaction mixture was then cooled; benzene layer was separated and distilled off under reduced pressure. The remaining residue was dissolved in minimum amount of acetone, neutralized with saturated sodium bicarbonate solution (20 mL) and the solid separated was collected by filtration, washed with water (50 mL) and then with ether (2x10 mL). Analytically pure products were obtained by recrystallization from glacial acetic acid. The structures of **5a**–**f** were fully established from their spectral and analytical data which are given below.

2-Methylthio-4-phenylpyrido[1,2-*a*]pyrimidin-5-ium tetrafluoroborate (5a). Colourless crystals (AcOH); mp 155^{0}C; yield 83%; IR (KBr): 3033, 1619 (C=N^{+}), 1147, 1093, 1039 (BF_4^-) cm^{-1}; ^{1}H NMR (300 MHz, DMSO- d_6) δ 2.90 (s, 3H), 7.77-7.89 (m, 5H, ArH), 7.91 (dd, 1H, *J* = 6.5, 7.5 Hz, H-7), 8.20 (s, 1H, H-3), 8.22 (d, 1H, *J* = 9 Hz, H-9), 8.60 (dd, 1H, *J* = 7.5, 8.0 Hz, H-8), 8.75 (dd, 1H, *J* = 1.0, 6.5 Hz, H-6); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.6, 119.2, 122.1, 126.9, 128.3, 129, 130, 132.21, 132.5, 142.5, 148.9, 149.1, 174.1; MS m/z (%) 253 (M^+-BF_4, 22), 238 (M-102, 7.6), 87(6), 77 (100); Anal. Calcd for $C_{15}H_{13}N_2S$ .BF_4 (340.14) C, 52.9; H, 3.8; N, 8.23. Found: C, 52.83; H, 3.86; N, 8.30.

2-Methylthio-4-(4-methoxyphenyl)pyrido[1,2-*a*]pyrimidin-5-ium tetrafluoroborate (5b). Colourless crystals (AcOH); mp 130^{0}C; yield 84%; IR (KBr) 3325, 1617, 1105, 1072, 1030 (BF_4^-) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.88 (s, 3H), 3.96 (s, 3H), 7.19 (d, 2H, *J* = 9 Hz, ArH), 7.65 (d, 2H, *J* = 9 Hz, ArH), 7.76 (s, 1H, H-3), 7.80 (dd, 1H, *J* = 7.0, 7.4, 0.6 Hz, H-7), 8.29 (dd, 1H, *J* = 8.6, 0.6 Hz, H-9), 8.79 (dd, 1H, *J* = 7.4, 8.6 Hz, H-8), 8.80 (dd, 1H, *J* = 7.0, 0.6 Hz, H-6) [typical ABMX pattern]; ^{13}C NMR (300 MHz, DMSO-d_6) δ 13.4, 55.5, 115.3, 119.0, 120.2, 121.8, 126.7, 130.78, 132.7, 142.7, 142.2, 149.0, 150.1, 162.3, 174.1; MS m/z (%) 283

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(M^+-BF_4, 8), 253(10), 87(5), 67(100); Anal. Calcd for $C_{16}H_{15}N_2OS$ .BF_4 (370.17) C, 51.8; H, 4.0; N, 7.5. Found : C, 52.1; H, 4.1; N, 6.9.

2-Methylthio-4-(4-chlorophenyl)pyrido[1,2-*a*]pyrimidin-5-ium tetrafluoroborate (5c). Colourless crystals (EtOH); mp 140^0C; yield 84%; IR (KBr): 3230, 1623 (C=N^+), 1150, 1081, 1035 (BF_4^-) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.84 (s, 3H), 7.65(d, 2H, *J* = 9Hz, ArH), 7.68 (s, 1H, H-3), 7.70 (d, 2H, *J* = 9 Hz, ArH), 7.78 (dd , 1H, *J* = 6.6, 7.4 Hz, H-7), 8.26 (d, 1H, *J* = 9 Hz, H-9), 8.45 (dd, 1H, *J* = 7.4, 1.0 Hz, H-8), 8.62 (dd, 1H, *J* = 6.6, 1.0 Hz, H-6). [IncludesABMX].^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.6, 119.3, 122.1, 126.9, 129, 130.2, 131.2, 132.6, 136.3, 142.4, 146, 148, 174.4; MS m/z (%) 287 (M^+-BF_4, 10.7), 272 (M-102, 12.8%), 87(8) Anal.Calcd for $C_{15}H_{12}N_2$ SCl.BF_4(374.58) C, 48.1; H, 3.2; N, 7.4. Found: C, 48.3; H, 3.1; N 7.5.

2-Methylthio-4-(4-methylphenyl)pyrido[1,2-*a*]pyrimidin-5-ium tetrafluoroborate (5d). Colourless crystals (AcOH); mp 150^0C; yield 86%; IR (KBr) 3372, 1616 (C=N^+), 1150, 1063 (BF_4^-), 1034 cm^{-1}; ^{1}H NMR(300 MHz, DMSO-d_6) δ 2.50 (s, 3H), 2.82 (s, 3H), 7.47 (d, 2H, *J* = 9 Hz, ArH), 7.55 (s, 1H, H-3), 7.57(d, 2H, *J* = 9 Hz, ArH), 7.75 (dd, 1H, *J* = 6.5, 7.0 Hz, H-7), 8.25 (d, 1H, *J* = 8.9 Hz, H-9), 8.45 (dd, 1H, *J* = 7.0, 8.3 Hz, H-8), 8.66 (dd, 1H, *J* = 6.5, 0.5 Hz, H-6); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.6, 21.5, 110, 122.0, 125.3, 126.9, 129.27, 130.6, 132.45, 142.4, 143.0, 148.9, 149.4, 174.1; MS m/z (%) 267 (M^+-BF_4, 21), 252 (M^+-102, 2.1), 87(7), 41(100); Anal. Calcd for $C_{16}H_{15}N_2S.BF_4$ (354.17) C, 54.2; H, 4.2; N, 7.9. Found: C, 54.3; H, 4.3; N, 7.70.

2-Methylthio-4-(2-furyl)-pyrido[1,2-*a*]pyrimidin-5-ium tetrafluoroborate (5e). Yellow crystals (AcOH); mp 200^0C; yield 80%; IR (KBr) 3448, 1602 (C=N^+), 1152, 1056 (BF_4^-) cm^{-1}; ^{1}H NMR(90 MHz, DMSO-d_6) δ 2.70 (s, 3H), 6.90 (dd, 1H, *J* = 3.5, 1.5 Hz, H-4 furyl), 7.80 (d, 1H, *J* = 3 Hz, H-3 furyl), 8.10 (dd, 1H, *J* = 6.0, 7.0 Hz, H-7), 8.21 (s, 1H, H-3), 8.30 (d, 1H, *J* = 1.4 Hz, H-5, furyl), 8.50 (dd, 1H, *J* = 1.0, 8.1 Hz, H-9), 8.61 (dd, 1H, *J* = 8.0, 6.9 Hz, H-8), 9.50 (dd, 1H, *J* = 7.5, 1.5 Hz, H-6); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.9, 105.2, 107.1, 116.9, 118.5, 128.3, 129, 130, 142.5, 146.0, 147.1, 154, 172.5; MS: m/z (%) 243 (M^+-BF_4,15); Anal. Calcd for $C_{13}H_{11}N_2OS.BF_4$ (330.10) C, 47.2; H, 3.3; N, 8.4. Found: C, 47.3; H, 3. 2; N, 8.50.

2-Methylthio-4-(2-thienyl)pyrido[1,2-*a*]pyrimidin-5-ium tetrafluoroborate (5f). Yellow crystals (AcOH); mp 170^0C; yield 70%;IR (KBr) 3424, 1601 (C=N^+), 1148, 1085 (BF_4^-), 1067 cm^{-1}; ^{1}H NMR (90 MHz, DMSO-d_6) δ 2.80 (s, 3H), 7.50 (dd, 1H, *J* = 4.5, 1.5 Hz, H-4 furyl), 7.86 (d, 1H, *J* = 3 Hz, H-3 furyl), 8.25 (s, 1H, H-3), 8.26-8.56 (m, 3H, H-7, H-9, H-5 furyl), 8.70 (dd, 1H, *J* = 8.5, 6.6 Hz, H-8), 9.30 (dd, 1H, *J* = 7.5, 1.5 Hz, H-6); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.6, 117.2, 118.9, 122.1, 126.9, 128.3, 129, 130, 132.2, 142.5, 148.9, 159.1, 172.1; Anal.Calcd for $C_{13}H_{11}N_2S_2$ .BF_4 (346.16) C, 45.01; H, 3.1; N, 8.0.Found : C, 45.3; H, 3.05; N, 8.26.

2-(2-pyridylamino)-4-phenylpyrido[1,2-*a*]pyrimidin-5-ium tetrafluoroborate (6a). Colorless crystals (EtOH); mp 201^0C; yield 72%; IR (KBr) δ 3437, 3299, 1644 (C=N^+), 1582, 1072 (BF_4^-), 1021 cm^{-1} ; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.30 (dd, 1H, *J* = 7.6, 6.0Hz, H-5 of pyridyl); 7.51 (m, 3H), 7.70-7.89 (m, 6H), 7.90-8.25 (m, 2H), 8.31 (dd, 1H, *J* = 9.5, 8.6 Hz, H-8), 8.43 (dd, 1H,

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J = 8.2 and 1.5 Hz, H-6), 8.80 (brs, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) 105.5, 113.1, 119.6, 120.5, 121.2, 125.8, 130.9, 132.3, 137, 140, 148, 150.2, 155.1, 160, 165.5, 168.7; MS m/z (%) 299 (M^+-BF_4, 20; Anal.Calcd for $C_{19}H_{15}N_4$ .BF_4 (386) C, 59.06; H, 3.8; N, 14.50. Found: C, 59.5; H, 3.2; N, 14.31.

2-(2-Pyridylamino)-4-(4-methoxyphenyl)pyrido[1,2-*a*]pyrimidin-5-ium tetrafluoroborate (6b). Colorless crystals (EtOH); mp 200^{0}C; yield 76%; IR (KBr) 3471, 3114, 1620, 1082 (BF_4^-) cm^1; ^{1}H NMR (300MHz, DMSO-d_6) δ 3.90 (s, 3H), 6.60 (brs, NH), 7.25 (d, 2H, *J* = 9 Hz, ArH), 7.35 (s, 1H, H-3), 7.60 (d, 2H, *J* = 9 Hz, ArH), 7.65 (dd, 1H, *J* = 6.6, 7.4 Hz, H-7), 8.08 (dd , 1H, *J* = 7.6, 7.4 Hz, H-9), 8.24-8.35 (m, 4H), 8.51 (d, *J* = 8 Hz, H-6 of pyridyl), 8.60 (dd, 1H, *J* = 6.6, 1.5 Hz, H-6). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 55.9, 105.4, 115.1, 119.6, 120.5, 121.2, 125.8, 130.9, 132.3, 137, 140, 148, 150.2, 155.1, 160, 162.5, 166.7; MS m/z (%) 329 (M^+-BF_4, 11); Anal.Calcd for $C_{20}H_{17}N_4O$ .BF_4 (416) C, 57.69; H, 4.08; N, 13.96. Found: C, 57.50; H, 4.15; N, 13.60.

2-(2-Pyridylamino)-4-(4-chlorophenyl)pyrido[1,2-*a*]pyrimidin-5-ium tetrafluoroborate (6c). Colorless crystals (EtOH); mp 209^{0}C; yield 75%; IR (KBr) 3475, 3110, 1630, 1080 (BF_4^-) cm^{-1}; ^{1}H NMR (300MHz, DMSO-d_6) δ 6.60 (brs, NH), 7.25 (s, 1H, H-3), 7.55 (d, 2H, *J* = 9 Hz, ArH), 7.55 (dd, 1H, *J* = 6.6, 7.4 Hz, H-7), 7.60 (d, 2H, *J* = 9 Hz, ArH), 8.08 (ddd, 1H, *J* = 7.6, 7.4, 1.0 Hz, H-9), 8.24-8.35 (m, 4H), 8.51 (d, 1H, *J* = 8 Hz, H-6 of pyridyl), 8.90 (dd, 1H, *J* = 6.6, 1.5 Hz, H-6). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 107.4, 110.1, 115.9, 119.6, 120.5, 121.2, 125.8, 130, 132.3, 137, 141, 143, 150.2, 152.1, 155, 166.9; MS m/z (%) 333 (M^+-BF_4, 8); Anal.Calcd for $C_{19}H_{14}N_4Cl$ .BF_4 (420) C, 54.26; H, 3.36; N, 13.32. Found: C, 54.50; H, 3.15; N, 13.40.

2-(2-Pyridylamino)-4-(4-methylphenyl)pyrido[1,2-*a*]pyrimidin-5-ium tetrafluoroborate (6d). Colorless crystals (EtOH); mp 220^{0}C; yield 70%; IR (KBr) 3471, 3112, 1605, 1088 (BF_4^-) cm^{-1}; ^{1}H NMR (300MHz, DMSO-d_6) δ 3.90 (s, 3H), 6.60 (brs, NH), 7.25 (d, 2H, *J* = 9 Hz, ArH), 7.35 (s, 1H, H-3), 7.60 (d, 2H, *J* = 9 Hz, ArH), 7.65 (dd, *J* = 6.6, 7.4 Hz, H-7), 8.08 (dd, 1H, *J* = 7.6, 7.4 Hz, H-9), 8.24-8.35 (m, 4H), 8.51 (d, 1H, *J* = 8 Hz, H-6 of pyridyl), 8.65 (dd, 1H, *J* = 6.6, 1.5 Hz, H-6). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 21.8, 107.4, 110.1, 115.9, 119.6, 120.5, 121.2, 125.8, 130.9, 132.3, 137, 141, 150.2, 152.1, 155, 163.9, 166.2; MS m/z (%) 329 (M^+-BF_4, 11); Anal.Calcd for $C_{20}H_{17}N_4O$ .BF_4 (416) C, 57.69; H, 4.08; N, 13.96. Found: C, 57.50; H, 4.15; N, 13.60.

2-Methoxy-4-(4-methoxyphenyl)pyrido[1,2-*a*]pyrimidin-5-ium tetrafluoroborate (7b). Colourless crystals (AcOH); mp 205^{0}C; yield 81%; IR (KBr) 3033, 1619 (C=N$^+$), 1147, 1093, 1039 (BF_4^-) cm^{-1}; ^{1}H NMR (300MHz, DMSO-d_6) δ 3.85 (s, 3H), 3.90 (s, 3H), 7.05 (d, 2H, *J* = 9 Hz, ArH), 7.10 (ddd, 1H, *J* = 6.5, 7.5, 1.0 Hz), 7.55(d, 2H, *J* = 9 Hz, ArH), 8.20 (s, 1H, H-3), 8.22 (d, 1H, *J* = 9 Hz), 8.60 (dd, 1H, *J* = 7.5, 8.0 Hz), 8.75 (dd, *J* = 1.0, 6.5 Hz, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 54.5, 55.8, 112.2, 114.1, 115.0, 126.9, 128.3, 129, 132.2, 132.5, 152.5, 160.9, 169.1, 174.1 (C-10); Anal. calcd for $C_{16}H_{15}N_2O_2$ .BF_4 (354) C, 54.2; H, 4.2; N, 7.9. Found: C, 54.8; H, 4.0; N, 8.1.

2-Methoxy-4-(4-chlorophenyl)pyrido[1,2-*a*]pyrimidin-5-ium tetrafluoroborate (7c). Colourless crystals (AcOH); mp 175^{0}C; yield 80%; IR (KBr) 3035, 1618 (C=N$^+$), 1140, 1095,

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1038 (BF_4^-) cm^{-1}; ^1H NMR (300MHz, DMSO-d_6) δ 3.90 (s, 3H), 7.35 (dd, 1H, *J* = 6.5, 7.5 Hz), 7.55(d, 2H, *J* = 9Hz, ArH), 7.85(d, 2H, *J* = 9Hz, ArH), 8.10 (s, 1H, H-3), 8.22 (d, *J* = 9 Hz, 1H), 8.60 (dd, 1H, *J* = 7.5, 8.0 Hz), 8.95 (dd, 1H, *J* = 1.0, 6.5 Hz, H-6); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 55.1, 112.2, 114.1, 114.9, 126.3, 127, 130, 132.21, 137.4, 156.5, 158.9, 169.16, 174.15 (C-10); Anal. calcd for $C_{15}H_{12}ClN_2O$. BF_4 (358) C, 50.2; H, 3.3; N, 7.8. Found: C, 50.8; H, 3.0; N, 8.0.

General procedure for the synthesis of pyrido[1,2-*a*] pyrimidinium perchlorates 8a–c.

N,*S*–acetal **2a**–**c** (10 mmol) was dissolved in 20 mL of dry methanol and stirred for 15 min. Then 60% perchloric acid (3 mL) was added slowly and the reaction mixture was stirred for 2–3 h. The milky colour solution precipitated slowly. The separated solid was filtered and washed with 10 mL of ether and dried. The crude products were recrystallized from hot ethanol.

2-Methylthio-4-phenylpyrido[1,2-*a*]pyrimidin-5-ium perchlorate salt (8a). Colourless crystals (AcOH); mp 200^0C; yield 60%; IR (KBr): 3030, 1630 ($C=N^+$), 1143, 1102 (ClO_4^-) cm^{-1}; ^1H NMR (300 MHz, DMSO- d_6) δ 2.80 (s, 3H), 7.70-7.80 (m, 5H, ArH), 7.91 (dd , 1H, *J* = 6.5, 7.5 Hz), 8.10 (s, 1H, H-3), 8.15 (d, 1H, *J* = 9 Hz), 8.50 (m, 1H), 8.55 (dd, 1H, *J* = 1.0, 6.5 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.3, 118.2, 121.1, 125.9, 127.3, 128, 131, 132.2, 132.5, 142.5, 148.9, 150.1, 173.15 (C-10); Anal.Calcd for $C_{15}H_{13}N_2S$. ClO_4 (352.7) C, 51.0; H, 3.7; N, 7.9. Found: C, 51. 3;H, 3.8; N, 7.3.

2-Methylthio-4-(4-methoxyphenyl)pyrido[1,2-*a*]pyrimidin-5-ium perchlorate (8b). Colourless crystals (AcOH); mp 130^0C; yield 62%; IR (KBr) 3325, 1617, 1105 (ClO_4^-) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.88 (s, 3H), 3.96 (s, 3H), 7.19 (d, 2H, *J* = 9 Hz, ArH), 7.65 (d, 2H, *J* = 9 Hz, ArH), 7.76 (s, 1H, H-3), 7.80 (dd, 1H, *J* =7.0, 0.6 Hz, H-7), 8.29 (dd, 1H, *J* = 8.6, 0.6 Hz, H-9), 8.79 (dd, 1H, *J* = 7.4, 8.6 Hz, H-8), 8.80 (dd, 1H, *J* = 7.0, 0.6 Hz, H6) [typical ABMX pattern]; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.4, 55.5, 115.3, 119.0, 120.2, 121.8, 126.7, 130.78, 132.7, 142.2, 142.7, 149.0, 150.1, 162.3, 174.1 (C-10); Anal. Calcd for $C_{16}H_{15}N_2OS$. ClO_4 (382.8) C, 50.2; H, 3.9; N, 7.3. Found : C, 50.1; H, 3.7; N, 7.0.

2-Methylthio-4-(4-chlorophenyl)pyrido[1,2-*a*]pyrimidine-5-ium perchlorate (8c). Colourless crystals (EtOH); mp 140^0C; yield 60%; IR (KBr): 3230, 1613 ($C=N^+$), 1150, 1100 (ClO_4^-) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.84 (s, 3H), 7.65(d, 2H, *J* = 9 Hz, ArH), 7.68 (s, 1H, H-3), 7.70 (d, 2H, *J* = 9 Hz, ArH), 7.78 (ddd, 1H, *J* = 6.6, 7.4, 1.0 Hz, H-7), 8.26 (d, 1H, *J* = 9 Hz, H-9), 8.45 (dd, 1H, *J* = 8, 1.0 Hz, H-8), 8.62 (dd, 1H, *J* = 6.6, 1.0 Hz, H-6). [Includes ABMX].^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.6, 119.3, 122.1, 126.9, 129, 130.2, 131.2, 132.6, 136.3, 142.4, 146, 148, 174.4 (C-10); MS m/z (%) 287 (M^+-ClO_4, 10.7), 272 (M-102, 12.8%), 99(100) Anal.Calcd for $C_{15}H_{12}ClN_2S.ClO_4$(387) C, 46.5; H, 3.1; N, 7.2. Found: C, 46.3; H, 3.1; N 7.5.

Basic hydrolysis of 2-Methylthio-4-aryl[1,2-*a*]pyrimidin-5-ium perchlorate salts 8a–c.

To a stirred solution of **8a**–**c** (10 mmol) in 10 mL of methanol, 40% NaOH solution (20 mL) was added and continued the stirring for 4 h. Then it was poured to 100 mL of water and extracted with 50 mL of chloroform. The organic layer was dried over sodium sulfate and evaporation of the solvent affords the crude products **2a**–**c,** which were purified by column chromatography.

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(*E*)-3-Methylthio-1-phenyl-3-(pyridine-2-ylamino)prop-2-en-1-one (2a). Light yellow crystals; mp 90ºC; yield 54%; IR (KBr) 3496 and 3351(NH), 1588, 1537 and 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H, SCH_3), 5.93 (s, 1H, vinylic), 6.85 (m, 1H, 5-H pyridyl), 6.93 (d, 1H, *J* = 9 Hz, 3-H pyridyl), 7.38-7.42 (m, 3H, ArH), 7.53 (dd, 1H, *J* = 1.5, 6.9 and 8.7 Hz, 4-H pyridyl), 7.86-7.89 (m, 2H, ArH), 8.27 (dt, 1H, *J* =1.5 and 6.6 Hz, 6-H pyridyl) and 14.64 (s, 1H, NH, exchanges D_2O); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 15.9 (SCH_3), 90.63 (=CH), 113.6, 118.0 (C-5 and C -3 of pyridyl), 127.0, 128.5 and 131.4 (C-2′, -3′ and -4′ of Ar), 137.6 (C-4 pyridyl), 139.8 (C-1′ Ar), 146.6 (C-6 pyridyl), 152.2, 165.8 and 185.67 (C=O); Anal.Calcd for $C_{15}H_{14}N_2OS$ (270) C, 66.66; H, 5.18; N, 10.37**.** Found; C, 66.69; H, 5.15; N, 10.38.

(*E*)-1-(4-Methoxyphenyl)-3-methylthio-3-(pyridin-2-ylamino)prop-2-en-1-one (2b). Yellow crystals; mp 105ºC; yield 55%; IR (KBr) 3491, 3325 (NH), 1580, 1534 and 1238 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43(s, 3H, SCH_3), 3.82 (s, 3H, OCH_3), 5.92 (s, 1H, vinylic), 6.91 (d, 2H, *J* = 9 Hz, ArH), 6.93-6.98 (m, 2H, 6-and 3-H pyridyl), 7.59 (dd, 1H, *J* = 7.8 and 8.7 Hz, 4-H pyridyl), 7.88-7.91 (d, 2H, *J* = 9 Hz, ArH), 8.32 (dt, 1H, *J* = 1.8 and 6.9 Hz, 6-H pyridyl) and 14.56 (s, 1H, NH, exchanges D_2O); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.10 (SCH_3), 55.3 (OCH_3), 90.5 (=CH), 113.61 (C-2′Ar), 113.84 and 118.13 (C-5 and -3 pyridyl), 129.08 (C-3′ Ar), 132.46 (C-1′ Ar), 137.96 and 146.81 (C-4 and -6 pyridyl), 152.50, 162.19 (C-4′ Ar) and 165.13 and 185.25 (C=0); Anal.Calcd for $C_{16}H_{16}N_2OS$ (300) C, 63.97; H, 5.33; N, 9.33**.** Found; C, 63.95; H, 5.29; N, 9.50.

(*E*)-1-(4-Chlorophenyl)-3-methylthio-3-(pyridin-2-ylamino)prop-2-en-1-one (2c). Bright yellow crystals, mp 116ºC; yield 50%; IR (KBr) 3498, 3347 (NH), 1579, 1538 and 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H, SCH_3), 5.91 (s, 1H, vinylic), 6.91-7.10 (m, 2H, 5- and 3-H pyridyl), 7.49 (d, 2H, *J* = 9 Hz, ArH), 7.59 (dd, 1H, *J* =7.9 and 8.7 Hz, 4-H pyridyl), 8.00 (d, 2H, *J*=9Hz, ArH), 8.32 (dt, 1H, *J* = 1.8 and 6.9 Hz, 6-H pyridyl) and 14.6 (s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.6 (SCH_3), 90.6 (=CH), 114.5, 118.5 (C-5 and -3 pyridyl), 128.5, 128.59 and 137.28 (C-2′, -3′ and -1′ of Ar), 138.03 (C-4 pyridyl), 138.35 (C-4′ Ar), 146.0 (C-6 pyridyl), 152.2, 166.58 and 184.52 (C=O); Anal. Calcd for $C_{15}H_{13}ClN_2OS$ (304.6) C, 59.06; H, 4.2; N, 9.12. Found; C, 59.13; H, 4.1; N, 9.10.

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