Pergamon

Tetrahedron, Vol. 53, No. 24, pp. 8269-8272, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00492-4

A Short and Facile Synthesis for Heteromine A

Carlos Peinador, José Mª. Quintela* and María J. Moreira

Departamento de Química Fundamental e Industrial. Facultad de Ciencias. Universidad de La Coruña
Campus de A Zapateira. E-15071. La Coruña. Spain.

Abstract: The first and efficient synthesis of the new purinium natural product Heteromine A, involving 5-amino-4-cyano-1-methylimidazole and *N,N*-dimethyldichlomethyleniminium chloride is reported. © 1997 Elsevier Science Ltd.

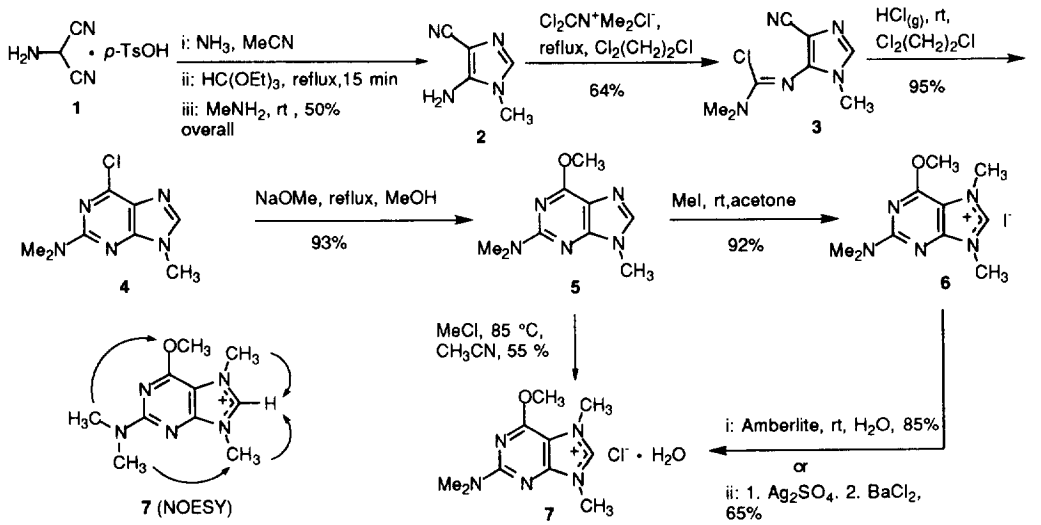
Heteromine A (6-methoxy-7,9-dimethyl-2-*N,N*-dimethylaminopurinium chloride), a new purinium natural product, has been recently isolated from the aerial parts of *Heterospemma brownii* Hay. (Asclepiadaceae).[1] This climber species, that grows at the Wen-Sun mountains of Taipei Hsien, has been used as traditional medicine for the treatment of tumors. It is also used as an expelling dampness and detoxifying agent.[2] Heteromine A showed inhibitory effect on K562 and HL-60 cell lines.[1]

The chemistry of phosgene iminium salts, which can function as a Vilsmeier or Mannich reagents has proved to be very useful in synthetic chemistry, especially in various one-step heterocyclization reactions by insertion of one carbon atom bearing a dialkylamino group.[3] Phosgeniminium chlorides are valuable strong electrophilic one carbon atom reagents. They possess three very mobile chlorine atoms and condense readily with nucleophiles to give new electrophilic synthons such as α-chloroenamines, 1,3-dichlorotrimethinecyanines, amide chlorides, etc., which react further to produce, through either inter or intramolecular processes, various types of functionalized 5, 6 and 7 membered ring systems.[4] In this context, some new methods for the preparation of polyheterocyclic compounds containing the pyrimidine ring utilizing phosgeniminium chloride and heterocyclic β-enaminonitriles have been developed in our laboratory.[5]

Herein we would like to report the first, short and convenient synthesis of the new purinium natural compound Heteromine A involving the β-enaminonitrile **2** and *N,N*-dimethyldichloromethyleniminium chloride as starting materials. Treatment of the 5-amino-4-cyano-1-methylimidazole **2**, prepared from aminomalononitrile *p*-toluenesulfonate, with phosgeniminium chloride in refluxing 1,2-dichloroethane gave the amide halide intermediate **3** which underwent smooth cyclization to the corresponding fused imidazolopyrimidine **4** *via* reaction with dry hydrogen chloride. Direct one-pot synthesis using enaminonitrile **2** and phosgenimium salt in refluxing 1,2-dichloroethane for 1 hour and subsequent treatment with hydrogen chloride provided the fused compound **4** in 57 % yield. The structure of compounds **3** and **4** were consistent with their elemental analyses and spectral data. The mass spectrum of **3** showed the expected molecular ion peak at m/z = 211 and its IR spectrum exhibited an absorption band at $\nu = 1660$ cm^{-1} due to the imino group and presented a characteristic signal at $\nu = 2220$ cm^{-1}, while the decoupled ^{13}C NMR spectrum showed one signal at $\delta = 116.35$ due to the carbon atom in the one cyano group. After cyclization, the spectra of compound **4** did not include those type of signals.

Nucleophilic displacement reaction of the chloride bearing group resulted in the formation on the corresponding 6-methoxy derivative **5** which reacted with methyl iodide to generate 6-methoxy-7,9-dimethyl-2-*N*,*N*-dimethylaminopurinium iodide **6** in 92% yield. Finally, exchange ion was achieved by treatment with Amberlite CG-400 to afford the expected Heteromine A **7** in 85% yield. Alternatively, 6-methoxy-7,9-dimethyl-2-*N*,*N*-dimethylaminopurinium **7** was prepared by reaction of purinium iodide **6** with silver sulfate and barium chloride. Furthermore, treatment of imidazolopyrimidine **5** with methyl chloride, in dry acetonitrile at 85 °C, resulted in the formation on the corresponding compound **7** in 55% yield. The ^{1}H NMR spectrum of **7** exhibited signals at $\delta = 4.10$ (3H, s) for a methoxy group, 3.99 and 3.78 (each 3H, s) for two methyl groups attached on two quaternary amines, 3.20 (6H, s) for a dimethylamino group, and 9.46 (1H, s) assigned a typical purinium base H-8.[6] The EI-MS exhibited the (M^+-Cl-1) peak at m/z(%) = 221 (97) and fragment ion peaks at 207 (55); 192 (51); 178 (43); 163 (43) and 136 (32). The above assignments were further confirmed by the NOESY experiments (Scheme 1). The molecular formula $C_9H_{14}N_5OCl{\cdot}H_2O$ was deduced from elementary analysis. Complete information about the NMR, IR, UV and mass spectra is presented in the Experimental.

Scheme 1



In conclusion, we have disclosed the facile synthesis of 6-methoxy-7,9-dimethyl-2-*N*,*N*-dimethylaminopurinium chloride (Heteromine A) from 5-amino-4-cyano-1-methylimidazole and (dichloromethylene)-dimethylammonium chloride in short five steps in an overall yield of 44 %. This route would appear to have application to the relatively simple synthesis of several other imidazolopyrimidine derivatives.

EXPERIMENTAL PART

Melting points were determined on a Büchi 510 apparatus and are uncorrected. IR spectra were recorded as potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC 200F instrument at room temperature. Mass spectra were obtained on a VG QUATTRO spectrometer. The Silica gel 60 HF_{254} used for analytical thin layer chromatography and the Silica gel 60 (230-400 mesh) employed for flash chromatography were purchased from Merck. Amberlite CG-400 strongly basic resin was prepared by thoroughly rinsing sequentially with water, 1N aq NaOH, water until neutral, 1N aq HCl, then water again until neutral. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of La Coruña.

5-Amino-4-cyano-1-methylimidazole (2):

Dry NH_3 was bubbled for 30 min through a stirred suspension of aminomalononitrile *p*-toluenesulfonate (10.0 g, 39.7 mmol) in dry CH_3CN (500 ml). After the solid that separated was filtered off, the solution was concentrated to 200 ml and triethyl orthoformate (6.6 ml, 39.7 mmol) then added. The solution was heated under reflux for 15 min. To the cooled mixture was added methylamine (4.9 ml, 39.7 mmol, 33 % in EtOH), and the solution was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by flash chromatography (CH_2Cl_2/MeOH 20:1) and recrystallized from EtOH to give **2** (2.40 g, 50 %); mp 203-205 °C, lit.[7a] 203-204 °C, lit.[7b] 196-198 °C.

5-Chlorodimethylaminomethyleneamino-4-cyano-1-methylimidazole (3):

A solution of **2** (0.50 g, 4.1 mmol) and phosgeniminium chloride (1.0 g, 6.1 mmol) in 1,2-dichloroethane (20 ml) was refluxed for 20 min. The solvent was removed under reduced pressure and the residue was partitioned between water and dichloromethane. The organic layer was washed twice with $NaHCO_3$ and then dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (dichloromethane/methanol 50:1, v/v) to afford **3** (0.52 g, 64 %); mp 119-121 °C. IR (KBr, cm^{-1}): 2220 (CN); 1660; 1540. ^1H NMR δ ($CDCl_3$): 3.20 (s, 6H, NMe_2); 3.38 (s, 3H, 1-CH_3); 7.21 (s, 1H,, H-2). ^{13}C NMR δ ($CDCl_3$): 30.40 (1-CH_3); 40.29 (NMe_2); 100.64 (C-4); 116.35 (CN); 134.66 (C-2); 143.15, 145.51 (C-5, CCl). MS (EI, m/z, %): 213 (M^++2, 22); 211 (M^+, 64); 196 (27); 176 (63); 161 (100). Anal. Calcd. for $C_8H_{10}N_5Cl$: C, 45.40 H, 4.76; N, 33.09. Found C, 45.59; H, 4.61; N, 32.93.

6-Chloro-2-dimethylamino-9-methylpurine (4):

Dry hydrogen chloride was bubbled through a stirred solution of **3** (0.41 g, 1.9 mmol) in 1,2-dichloroethane (7 ml) for 30 min. The solution was stirred at room temperature for 12 h and then partitioned between water and dichloromethane. The organic layer was washed with $NaHCO_3$ (20 ml) and water (20 ml), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was recrystallized from ethanol to give **4** (0.39 g, 95 %); mp 152-153 °C. IR (KBr, cm^{-1}): 1640; 1590; 1390; 1150. ^1H NMR δ ($CDCl_3$): 3.18 (s, 6H, NMe_2); 3.66 (s, 3H, 9-CH_3); 7.62 (s, 1H, H-8). ^{13}C NMR δ ($CDCl_3$): 29.36 (9-CH_3); 37.42 (NMe_2); 123.03 (C-5); 141.81 (C-8); 150.23, 154.07, 158.98 (C-2, C-4, C-6). MS (EI, m/z, %): 213 (M^++2, 32); 211 (M^+, 100); 196 (58); 182 (79). Anal. Calcd. for $C_8H_{10}N_5Cl$: C, 45.40; H, 4.76; N, 33.09. Found C, 45.21; H, 4.89; N, 33.19.

2-Dimethylamino-6-methoxy-9-methylpurine (5):

To a solution of sodium methoxide (0.35 g of Na, 15 mmol) in MeOH (40 ml), **4** (1.50 g, 7.1 mmol) was added. The resulting solution was refluxed for 4 h. The solvent was removed under reduced pressure and water (50 ml) was added. The solution was neutralized with 2N HCl and the solid formed was filtered off and recrystallized from ethanol to give **5** (1.4 g, 95%); mp 148-150 °C. IR (KBr, cm^{-1}): 1620; 1570; 1390; 1260. ^1H NMR δ ($CDCl_3$): 3.22 (s, 6H, NMe_2); 3.69 (s, 3H, 9-CH_3); 4.09 (s, 3H, OCH_3); 7.51 (s, 1H, H-8). ^{13}C NMR δ ($CDCl_3$/MeOD): 30.06 (9-CH_3); 37.14 (NMe_2); 53.65 (OCH_3); 107.68 (C-5); 138.59 (C-8); 153.12 (C-4); 158.89, 159.75 (C-2, C-6). MS (EI, m/z, %): 207 (M^+, 100); 192 (49); 178 (58); 163 (38). Anal. Calcd. for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.79. Found C, 51.97; H, 6.48; N, 33.97.

6-Methoxy-7,9-dimethyl-2-dimethylaminopurinium iodide (6):

A solution of **5** (101 mg, 0.49 mmol) and an excess of methyl iodide in acetone (5 ml) was stirred at rt for 24 h. The solid formed was filtered off and recrystallized from acetone/MeOH to yield **6** (156 mg, 92 %); mp 211-212 °C. IR (KBr, cm^{-1}): 1640; 1600; 1510; 1400; 1150. ^1H NMR δ (DMSO): 3.20 (s, 6H, NMe_2); 3.78 (s, 3H, 9-CH_3); 3.99 (s, 3H, 7-CH_3); 4.10 (s, 3H, OCH_3); 9.31 (s, 1H, H-8). ^{13}C NMR δ (DMSO): 31.04 (9-CH_3); 36.04 (7-CH_3); 37.04 (NMe_2); 54.56 (OCH_3); 104.00 (C-5); 140.42 (C-8); 151.93 (C-4); 157.66 (C-6); 159.61 (C-2). MS (EI, m/z, %): 221 (14); 207 (35); 192 (19); 178 (15); 163 (22); 149 (100). Anal. Calcd. for $C_{10}H_{16}N_5OI$: C, 34.39; H, 4.62; N, 20.06. Found C, 34.61; H, 4.52; N, 20.10.

6-Methoxy-7,9-dimethyl-2-dimethylaminopurinium chloride monohydrate (7):

Method A: A suspension of **6** (0.25 g, 7.2 mmol) and Amberlite CG-400 (1.0 g) in water (15 ml), was stirred at room temperature for 20 h. The resin was filtered off and the filtrate was evaporated. The residue was recrystallized from AcOEt/MeOH to give **7** (0.17 g, 85 %); mp 273 °C (decomp). UV (MeOH) λ_{max} (log ε): 254 (4.13); 315 (3.81). IR (KBr, cm^{-1}): 1640; 1610; 1560; 1510; 1150. ^1H NMR δ (DMSO): 3.20 (s, 6H, NMe_2); 3.78 (s, 3H, 9-CH_3); 3.99 (s, 3H, 7-CH_3); 4.10 (s, 3H, OCH_3); 9.46 (s, 1H, H-8). ^{13}C NMR δ (DMSO): 30.95 (9-CH_3); 35.90 (7-CH_3); 36.99 (NMe_2); 54.52 (OCH_3); 103.95 (C-5); 140.73 (C-8); 151.91 (C-4); 157.62 (C-6); 159.60 (C-2). MS (EI, m/z, %): 221 (97); 207 (55); 192 (51); 178 (43); 163 (43); 136 (32). Anal. Calcd. for $C_{10}H_{16}N_5OCl \cdot H_2O$: C, 43.54; H, 6.59; N, 25.40. Found C, 43.54; H, 6.81; N, 25.26.

Method B: To a solution of **6** (60 mg, 0.17 mmol) in water (3 ml) Ag_2SO_4 (26 mg, 0.17 mmol) in water (2 ml) was added. The solution was stirred at room temperature for 30 min. The solid formed was filtered through Celite. To the filtrate $BaCl_2 \cdot 2H_2O$ (15 mg, 0.61 mmol) was added. The solid formed was filtered through Celite and the filtrate was concentrated to give a white solid. The product was recrystallized from AcOEt/MeOH to give **7** (26 mg, 65%).

Method C: In a sealed tube a solution of **5** (0.1 g, 0.48 mmol) and $ClCH_3$ (3 ml, 3 mmol, 1 M in ethyl ether) in CH_3CN (2 ml) was heated at 85 °C for 4 d. The solution was extracted with water (3X5 ml) and the aqueous layers were combined and concentrated. The residue was recrystallized from AcOEt/MeOH to give **7** (73 mg, 55 %).

ACKNOWLEDGEMENTS

Financial support of the Xunta de Galicia project XUGA 10308B95 is gratefully acknowledged.

REFERENCES

1. Lin, Y.L.; Lee, H.P.; On, J.C.; Kuo, Y.H. *Heterocycles* **1996**, *43*, 781.
2. Chin, N.Y.; Chang, K.H. The Illustrated Medicinal Plants of Taiwan. Vol 4. **1995**, p. 183.
3. For a review see: Janousek, Z.; Viehe, H.G. Chemistry of Dichloromethyleniminium salts (Phosgeniminium salts). In *Iminium Salts in Organic Chemistry*, Vol 9, Part I, Böhme H. and Viehe, H.G., Eds.; John Wiley and Sons, Inc. New York, 1976; p. 343 and references therein.
4. a) Benahmed-Gasmi, A.S.; Frére, P.; Belyasmine, A.; Malik, K.M.A.; Hursthouse, M.B.; Moore, A.J.; Bryce, M.R.; Jubault, M.; Gorges, A. *Tetrahedron Lett.* **1993**, *34*, 2131. b) Kokel, B. *J. Heterocycl. Chem.* **1994**, *31*, 8445. c) Kokel, B. *Heterocycles* **1984**, *21*, 706. d) Pavlenko, N.G.; Kukhar, V.P. *Ukr. Khim. Zh.* **1982**, *48*, 395. e) Kokel, B.; Guillanmel, J.; Royer, R. *J. Heterocycl. Chem.* **1983**, *20*, 575. f) Kokel, B. *J. Heterocycl. Chem.* **1994**, *31*, 1185. g) Liebscher, J. *Z. Chem.* **1988**, *28*, 291
5. a) Quintela, J.M.; Moreira, M.J.; Peinador, C. *Tetrahedron* **1996**, *52*, 3037. b) Quintela, J.M.; Peinador, C.: Moreira, M.J. *Tetrahedron* **1995**, *51*, 5901. c) Peinador, C.; Veiga, M.C.; Ojea, V.; Quintela, J.M. *Heterocycles* **1994**, *38*, 2065.
6. Chenon, M.T.; Pugmire, R.J.; Grant, D.M.; Panzica, R.P.; Townsend, L.B. *J. Am. Chem. Soc.* **1975**, *97*, 4627.
7. a) Saito, T.; Asahi, S.; Nakajima, S.; Fujii, T. *Chem. Pharm. Bull.* **1994**, *42*, 2263. b) Greenhalgh, M.; Shaw, G.; Wilson, D.V.; Cusack, N.J. *J. Chem. Soc. (C)* **1969**, 2198.

(*Received in UK* 3 *April* 1997; *revised* 25 *April* 1997; *accepted* 1 *May* 1997)