DOI 10.1515/hc-2013-0059 — Heterocycl. Commun. 2013; 19(5): 327–330

Preliminary Communication

Yuan-Yuan Xing*, Chuanxiang Liu and Fanhong Wu*

Efficient synthesis of substituted imidazo[4,5-*b*]pyridines

Abstract: An efficient approach to the synthesis of 1-methylimidazo[4,5-*b*]pyridine derivatives **5–10** of biological interest has been developed. The key intermediate product **4** is obtained by cyclization of 2-amino-3-methylaminopyridine (**3**) with phenylacetic acid.

Keywords: cyclization; imidazo[4,5-*b*]pyridine; synthesis.

***Corresponding authors: Yuan-Yuan Xing and Fanhong Wu,** School of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai 201418, P.R. China, e-mail: yuanyuanxing@sit.edu.cn; wfh@sit.edu.cn
Chuanxiang Liu: School of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai 201418, P.R. China

Among heterocyclic compounds, imidazo[4,5-*b*]pyridines represent a class of useful precursors for preparation of a variety of drugs [1, 2]. Previous studies have shown that substituted imidazo[4,5-*b*]pyridines are, for example, anticancer [3], inotropic [4], antimitotic [5], and selective antihistamine agents [6]. A survey of previous reports indicates that introduction of a methyl group at the *N*1-position increases bioactivity of imidazo[4,5-*b*]pyridines [7, 8]. Hence, it is of interest to prepare new 1-methyl-substituted imidazo[4,5-*b*]pyridine derivatives for the development of bioactive heterocyclic compounds.

It is difficult to prepare *N*1-substituted imidazo[4,5-*b*]pyridines in a regioselective manner by direct alkylation of unsubstituted imidazo[4,5-*b*]pyridines because this reaction is not selective [9]. Successful attempts to circumvent this problem include a low-yield synthesis of methyl-substituted azabenzimidazoles [8] and Pd-catalyzed coupling of amides and 3-amino-2-chloropyridines to prepare 1-substituted imidazo[4,5-*b*]pyridines [9]. Although good to excellent yields have been obtained for the latter reaction, expensive Pd catalyst and phosphine ligand are required. Herein, we report a novel approach to the desired 1-methylimidazo[4,5-*b*]pyridines, in which a pyridine moiety with a pre-introduced *N*-methyl group undergoes cyclization with phenylacetic acid.

The synthetic route is shown in Scheme 1, where the key step is the use of pyridine **3** with a pre-introduced *N*-methyl group in the ring closure reaction to the desired intermediate product **4**. Synthesis of **3** was achieved in two simple steps starting with commercially available 3-methoxy-2-nitropyridine (**1**) [8]. Cyclization reaction of **3** with phenylacetic acid was conducted in the presence of *N*,*N*′-carbonyldiimidazole (CDI) in 51% yield. Oxidation of **4** with H_2O_2 gave **5** [10], which was then treated with $POCl_3$ to produce the chloro-substituted product **6** in 54% yield [11]. The targeted 1-methyl-imidazo[4,5-*b*]pyridines **7–10** functionalized at the 7 position were then prepared by a nucleophilic displacement of chloride in **6**. Removal of the benzyl group in **7** with CAN gave the free amine **8** [12].

A concise and highly efficient approach to the preparation of substituted imidazo[4,5-*b*]pyridines has been successfully developed.

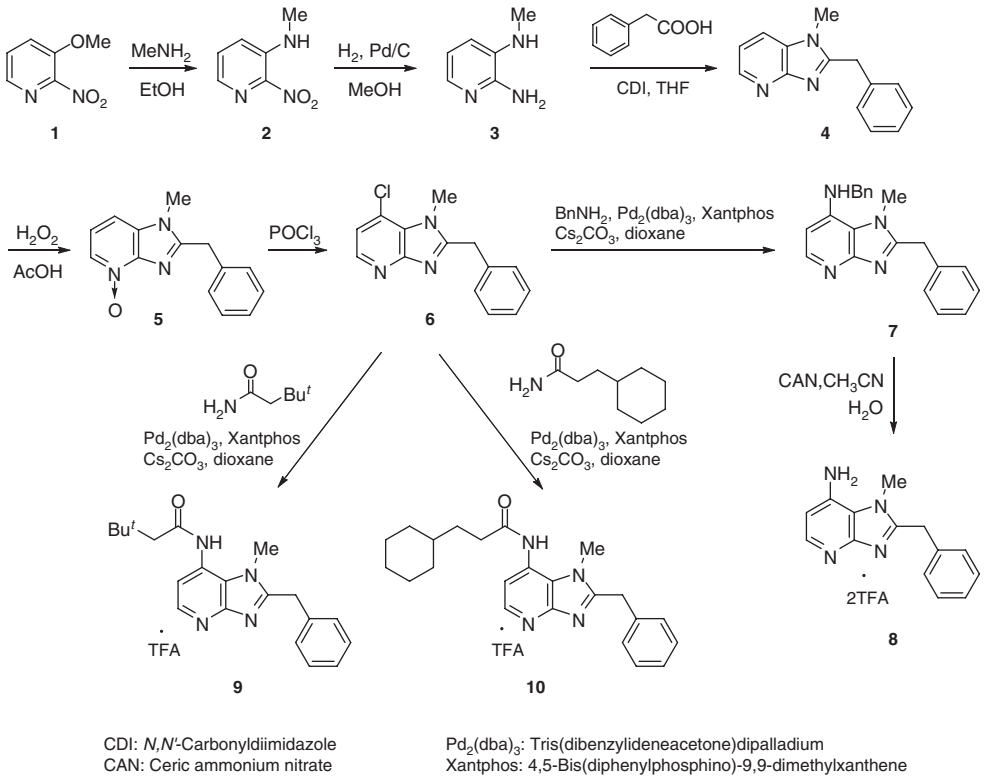
Experimental

Melting points are uncorrected. Commercial reagents were used directly without further purification. Solvents were treated according to standard methods prior to use. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer. Mass spectra were obtained on a Shimadzu LCMS instrument. High resolution mass spectra (HRMS) were recorded on a KE465 LCT Premier/XE spectrometer. Elemental analyses were performed on an Elementar Vario EL III instrument. Prep-HPLC was performed on a Shimadzu instrument with a Fuji C18 (300 × 25) column; wavelength: 220 nm; mobile phase A, CH_3CN (0.1% trifluoroacetic acid); B, water (0.1% trifluoroacetic acid).

3-Methylamino-2-nitropyridine (2)

To a stirred solution of 30% $MeNH_2$ in EtOH (550 mL) was added 3-methoxy-2-nitropyridine (**1**, 50.0 g, 0.32 mol). The mixture was heated under reflux overnight, allowed to cool to room temperature, and concentrated under reduced pressure. The residue was purified by silica gel chromatography with petroleum ether/ethyl acetate

Brought to you by | Dip Matematica e Applicazioni Sezione di Ingegneria
Authenticated | 134.99.128.41
Download Date | 10/8/13 3:02 PM



Scheme 1

(19:1) as eluent to give 29.6 g (59%) of **2** as yellow solid, mp 108–110°C [lit. mp 109–110°C] [13]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.95 (d, J = 5 Hz, 3H), 7.53–7.81 (m, 3H), 7.90 (br, 1H).

2-Amino-3-methylaminopyridine (3)

To a stirred solution of compound **2** (28.0 g, 0.18 mol) in anhydrous methanol (450 mL) was added 10% Pd/C (5.8 g) and the mixture was hydrogenated under 1 atm at 5°C while stirring overnight. The catalyst was filtered off through celite and the filtrate was concentrated under reduced pressure to afford 22.0 g (98%) of **3** as a brown solid, mp 124–125°C [lit. mp 124–125°C] [13]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.69 (d, J = 5 Hz, 3H), 4.88 (d, J = 4 Hz, 1H), 5.41 (s, 2H), 6.46–6.53 (m, 2H), 7.28 (dd, J = 5 Hz, 2 Hz, 1H).

2-Benzyl-1-methyl-1*H*-imidazo[4,5-*b*] pyridine (4)

To a suspension of phenylacetic acid (32.0 g, 0.24 mol) in tetrahydrofuran (THF) (300 mL) was added CDI (39.0 g, 0.24 mmol) at 0°C, and the mixture was stirred at 60°C for 1 h. Then compound **3** (20.0 g, 0.16 mmol) was added, and the mixture was stirred at 60°C overnight. After cooling, the mixture was concentrated and the residue dissolved in ethyl acetate (400 mL). The solution was washed successively with saturated aqueous $NaHCO_3$ (150 mL × 5), brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography with dichloromethane/methanol (50:1) as eluent to afford a crude product with impurity of imidazole, identified by ^{1}H NMR. The crude product was washed with saturated aqueous $NaHCO_3$ (150 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 18.2 g (51%) of compound **4** as a brown solid, mp 124–126°C [lit. mp 123–125°C] [14]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.73 (s, 3H), 4.36 (s, 2H), 7.20–7.35 (m, 6H), 7.93 (m, 1H), 8.35 (m, 1H).

2-Benzyl-1-methyl-1*H*-imidazo[4,5-*b*] pyridine-4-oxide (5)

To a stirred solution of compound **4** (18.0 g, 0.08 mol) in acetic acid (200 mL) was added dropwise 30% aqueous H_2O_2 (20 mL, 0.17 mol), and the mixture was stirred at 70°C overnight. After cooling, the mixture was treated with Na_2SO_3 (11.3 g, 0.09 mmol) and stirred for an additional 10 min. Solid material was filtered off and the filtrate was concentrated. The residue was dissolved in ethyl acetate (800 mL) and the solution washed with 10% NaOH (200 mL × 2) and then brine (200 mL × 2). The ethyl acetate phase was dried over Na_2SO_4, filtered, concentrated, and the residue was purified by silica gel chromatography with dichloromethane/methanol (10:1) as eluent to afford 9.2 g (48%) of compound **5** as a yellow solid, mp 143–145°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.77 (s, 3H), 4.35 (s, 2H), 7.16–7.37 (m, 6H), 7.58 (d, J = 8 Hz, 1H), 8.13 (d, J = 6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 146.3, 144.7, 136.7, 135.2, 130.6, 129.3, 126.3, 122.8, 121.7,

Brought to you by | Dip Matematica e Applicazioni Sezione di Ingegneria
Authenticated | 134.99.128.41
Download Date | 10/8/13 3:02 PM

119.9, 31.2, 29.3; HRMS (ESI) m/z calcd for $C_{14}H_{14}N_3O$ $(M+H)^+$: 240.1137, found: 240.1139.

2-Benzyl-7-chloro-1-methyl-1*H*-imidazo [4,5-*b*]pyridine (6)

Compound **5** (9.0 g, 37.6 mmol) was dissolved in $POCl_3$ (160 mL) and the solution stirred under reflux overnight. After cooling, the mixture was concentrated and the residue dissolved in ethyl acetate (600 mL). The solution was washed with saturated aqueous $NaHCO_3$ (200 mL × 2) and brine (200 mL × 2), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography with petroleum ether/ethyl acetate (1:2) as eluent to afford 5.2 g (54%) of compound **6** as a yellow solid, mp 168–170°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.96 (s, 3H), 4.37 (s, 2H), 7.24–7.36 (m, 6H), 8.27 (d, J = 5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.1, 149.8, 144.7, 139.5, 133.6, 129.3, 128.8, 126.2, 124.7, 120.3, 32.2, 31.5; HRMS (ESI) m/z calcd for $C_{14}H_{13}ClN_3$ $(M+H)^+$: 258.0798, found: 258.0793.

2-Benzyl-7-benzylamino-1-methyl-1*H*-imidazo[4,5-*b*]pyridine (7)

To a solution of **6** (1.0 g, 3.9 mmol), benzylamine (0.46 g, 4.3 mmol) and $Pd_2(dba)_3$ (0.36 g, 0.39 mmol) in 1,4-dioxane (25 mL) was added Cs_2CO_3 (1.9 g, 0.59 mmol) and xantphos (0.67 g, 1.16 mmol) under nitrogen atmosphere. The mixture was stirred at 90–100°C for 16 h. After cooling, the mixture was concentrated and the residue was purified by flash column chromatography with dichloromethane/methanol (10:1) as eluent to afford 1.2 g (94%) of compound **7** as a yellow solid, mp 203–205°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.98 (s, 3H), 4.27 (s, 2H), 4.44 (d, J = 6 Hz, 2H), 6.17 (d, J = 6 Hz, 1H), 6.75 (t, J = 5 Hz, 1H), 7.20–7.42 (m, 10H), 7.83 (d, J = 6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.3, 152.2, 146.4, 140.2, 137.2, 128.6, 127.6, 127.3, 127.1, 126.8, 126.1, 125.8, 118.9, 116.2, 58.2, 33.0, 31.8; LC-MS: m/z 329.2 $(M+1)^+$; HRMS (ESI) m/z calcd for $C_{21}H_{21}N_4$ $(M+H)^+$: 329.1766, found: 329.1762.

2-Benzyl-1-methyl-1*H*-imidazo[4,5-*b*] pyridine-7-amine, a salt with trifluoroacetic acid (8)

To a solution of **7** (0.6 g, 1.8 mmol) in a mixture of MeCN (10 mL) and H_2O (2 mL) was added CAN (3.0 g, 5.5 mmol), and the mixture was stirred at 8–14°C overnight. The mixture was concentrated and the residue was treated with water (10 mL) and dichloromethane (10 mL). The resultant solid was filtered, suspended in methanol (30 mL), and the mixture was stirred for 10 min. After filtration the filtrate was collected and then concentrated. The residue was purified by preparative HPLC with 0.1% trifluoroacetic acid as additive to afford 0.19 g (44%) of **8** as a yellow salt with trifluoroacetic acid, mp 186–188°C (dec); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.01 (s, 3H), 4.35 (s, 2H), 6.61 (d, J = 7 Hz, 1H), 7.25–7.36 (m, 5H), 7.95–8.01 (m, 3H), 14.03 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.1, 149.4, 146.2, 137.3, 127.6, 127.3, 127.1, 126.2, 118.6, 115.3, 33.2, 31.4; LC-MS: m/z 239.2 $(M+1)^+$; HRMS (ESI) m/z calcd for $C_{14}H_{15}N_4$ $(M+H)^+$: 239.1297. Found: 239.1299. Anal. Calcd for $C_{14}H_{14}N_4 \cdot 2C_2HF_3O_2$: C, 46.36; H, 3.46; N, 12.01. Found: C, 46.23; H, 3.50; N, 12.18.

N-(2-Benzyl-1-methyl-1*H*-imidazo[4,5-*b*] pyridine-7-yl)-3,3-dimethylbutanamide, a salt with trifluoroacetic acid (9)

To a solution of **6** (200 mg, 0.78 mmol), 3,3-dimethylbutanamide (104 mg, 0.9 mmol) and $Pd_2(dba)_3$ (13 mg, 0.01 mmol) in 1,4-dioxane (7 mL) was added Cs_2CO_3 (507 mg, 1.56 mmol) and xantphos (9 mg, 0.01 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 110°C for 16 h. After cooling, the mixture was concentrated and the residue was dissolved in ethyl acetate (150 mL), and the solution washed with brine (30 mL × 3), dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by preparative HPLC with 0.1% trifluoroacetic acid as additive to afford 61 mg (23%) of **9** as an off-white salt with trifluoroacetic acid, mp 192–194°C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 2.49 (s, 2H), 3.91 (s, 3H), 4.23 (s, 2H), 7.14–7.33 (m, 5H), 7.59–7.71 (m, 2H), 8.62 (br, 1H), 10.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 149.7, 145.4, 138.6, 137.0, 127.5, 127.1, 126.7, 126.1, 117.9, 115.2, 52.5, 33.1, 31.8, 31.3, 29.2; LC-MS: m/z 336.5 $(M)^+$; HRMS (ESI) m/z calcd for $C_{20}H_{25}N_4O$ $(M+H)^+$: 337.2028, found: 337.2022. Anal. Calcd for $C_{20}H_{24}N_4O \cdot C_2HF_3O_2$: C, 58.66; H, 5.59; N, 12.44. Found: C, 58.78; H, 5.71; N, 12.52.

N-(2-Benzyl-1-methyl-1*H*-imidazo[4,5-b] pyridine-7-yl)-3-cyclohexylpropanamide, a salt with trifluoroacetic acid (10)

To a solution of **6** (200 mg, 0.76 mmol), 3-cyclohexylpropanamide (118 mg, 0.76 mmol) and $Pd_2(dba)_3$ (14 mg, 0.01 mmol) in 1,4-dioxane (5 mL) was added Cs_2CO_3 (493 mg, 1.52 mmol) and xantphos (9 mg, 0.01 mmol) under nitrogen atmosphere. The mixture was stirred at 110°C for 16 h. After cooling, the mixture was concentrated and the residue was dissolved in ethyl acetate (150 mL). The solution was washed with brine (30 mL × 3), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by preparative HPLC with 0.1% trifluoroacetic acid as additive to afford 81 mg (28%) of **10** as a yellow salt with trifluoroacetic acid, mp 197–199°C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78–0.86 (m, 2H), 1.03–1.18 (m, 5H), 1.50–1.63 (m, 6H), 2.51 (m, 2H), 3.85 (s, 3H), 4.22 (s, 2H), 7.06–7.22 (m, 5H), 7.65 (s, 1H), 7.92 (s, 1H), 10.14 (br, 1H), 10.53 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 150.1, 146.3, 138.3, 137.2, 127.4, 127.1, 126.7, 125.9, 116.8, 115.4, 36.8, 34.6, 32.9, 32.7, 32.3, 31.6, 26.1. 25.7; LC-MS: m/z 376.9 $(M+1)^+$; HRMS (ESI) m/z calcd for $C_{23}H_{29}N_4O$ $(M+H)^+$: 377.2341, found: 377.2337. Anal. Calcd for $C_{23}H_{28}N_4O \cdot C_2HF_3O_2$: C, 61.21; H, 5.96; N, 11.42. Found: C, 61.35; H, 6.06; N, 11.53.

Acknowledgment: We are grateful for the financial support from Shanghai Training Program Foundation for the Talents (yyy11026).

Received April 10, 2013; accepted May 24, 2013

Brought to you by | Dip Matematica e Applicazioni Sezione di Ingegneria
Authenticated | 134.99.128.41
Download Date | 10/8/13 3:02 PM

References

[1] He, X.-P.; Xie, J.; Tang, Y.; Li, J.; Chen, G.-R. CuAAC Click chemistry accelerates the discovery of novel chemical scaffolds as promising protein tyrosine phosphatases inhibitors. *Curr. Med. Chem.* **2012**, *19*, 2399–2405.

[2] Kale, R. P.; Shaikh, M. U.; Jadhav, G. R.; Gill, C. H. Eco-friendly and facile synthesis of 2-substituted-1*H*-imidazo[4,5-*b*]pyridine in aqueous medium by air oxidation. *Tetrahedron Lett.* **2009**, *50*, 1780–1782.

[3] Temple, C., Jr.; Rose, J. D.; Comber, R. N.; Rener, G. A. Synthesis of potential anticancer agents: imidazo[4,5-*c*]pyridines and imidazo[4,5-*b*]pyridines. *J. Med. Chem.* **1987**, *30*, 1746–1751.

[4] Barraclough, P.; Black, J. W.; Cambridge, D.; Collard, D.; Firmin, D.; Gerskowitch, V. P.; Glen, R. C.; Giles, H.; Hill, A. P.; Hull, R. et al. Inotropic 'A' ring substituted sulmazole and isomazole analogs. *J. Med. Chem.* **1990**, *33*, 2231–2239.

[5] Temple, C., Jr. Antimitotic agents. Synthesis of imidazo[4,5-*c*] pyridin-6-ylcarbamates and imidazo[4,5-*b*]pyridin-5-ylcarbamates. *J. Med. Chem.* **1990**, *33*, 656–661.

[6] Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. New antihistaminic *N*-heterocyclic 4-piperidinamines. 3. Synthesis and antihistaminic activity of *N*-(4-piperidinyl)-3*H*-imidazo[4,5-*b*]pyridin-2-amines. *J. Med. Chem.* **1985**, *28*, 1943–1947.

[7] Yoshizawa, H.; Itani, H.; Ishikura, K.; Irie, T.; Yokoo, K.; Kubota, T.; Minami, K.; Iwaki, T.; Miwa, H.; Nishitani, Y. S-3578, a new broad spectrum parenteral cephalosporin exhibiting potent activity against both methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* synthesis and structure-activity relationships. *J. Antibiotics* **2002**, *55*, 975–992.

[8] Zhang, L.; Rogers, B. N.; Duplantier, A. J.; McHardy, S. F.; Efremov, I.; Berke, H.; Qian, W.; Zhang, A. Q.; Maklad, N.; Candler, J.; et al. 3-(Imidazolyl methyl)-3-aza-bicyclo[3.1.0] hexan-6-yl)methyl ethers: a novel series of mGluR2 positive allosteric modulators. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5493–5496.

[9] Rosenberg, A. J.; Zhao, J.; Clark, D. A. Synthesis of imidazo [4,5-*b*]pyridines and imidazo[4,5-*b*]pyrazines by palladium catalyzed amidation of 2-chloro-3-amino-heterocycles. *Org. Lett.* **2012**, *14*, 1764–1767.

[10] Zeinyeh, W.; Xia, H.; Lawton, P.; Radix, S.; Marminon, C.; Nebois, P.; Walchshofer, N. Synthesis and modulation properties of imidazo[4,5-*b*]pyridin-7-one and indazole-4,7-dione derivatives towards the *Cryptosporidium parvum* CpABC3 transporter. *Eur. J. Med. Chem.* **2010**, *45*, 2480–2488.

[11] Itoh, T.; Ono, K.; Sugawara, T.; Mizuno, Y. Studies on the chemical synthesis of potential antimetabolites. 30. Regioselective introduction of a chlorine atom into the imidazo[4,5-*b*] pyridine nucleus. *J. Heterocycl. Chem.* **1982**, *19*, 513–517.

[12] Bull, S. D.; Davies, S. G.; Kelly, P. M.; Gianotti, M.; Smith, A. D. Orthogonal *N,N*-deprotection strategies of β-amino esters. *J. Chem. Soc. Perkin Trans. 1*, **2001**, *23*, 3106–3111.

[13] Clark-Lewis, J. W.; Thompson, M. J. Methylation of 3-aminopyridines and preparation of 2-amino-3-methylaminopyridine and 2: 3-diaminopyridine. *J. Chem. Soc.* **1957**, 442–446.

[14] Berner, D. H.; Reinshagen, H. Ein biologischer Vergleich zwischen Benzol und Pyridin in kondensierten Ringsystemen. *Monatshef. Chem.* **1975**, *106*, 1059–1069.

Brought to you by | Dip Matematica e Applicazioni Sezione di Ingegneria
Authenticated | 134.99.128.41
Download Date | 10/8/13 3:02 PM