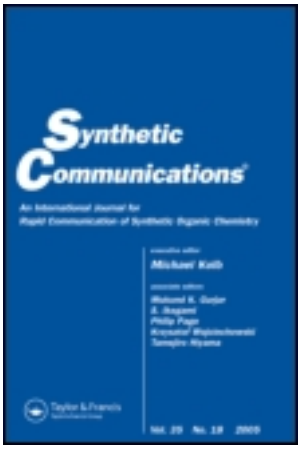
This article was downloaded by: [Duke University Libraries]
On: 24 June 2012, At: 01:02
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of 9-Methyl-11H-pyrido[2,1-b]quinazolin-11-one Using the Ullmann Condensation

Rolando F. Pellón [a], Maite L. Docampo [a], Zulfia Kunakbaeva [a], Victoria Gómez [a] & Herman Vélez-Castro [a]

[a] Center of Pharmaceutical Chemistry, Havana, Cuba

Available online: 19 Aug 2006

To cite this article: Rolando F. Pellón, Maite L. Docampo, Zulfia Kunakbaeva, Victoria Gómez & Herman Vélez-Castro (2006): Synthesis of 9-Methyl-11H-pyrido[2,1-b]quinazolin-11-one Using the Ullmann Condensation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:4, 481-485

To link to this article: http://dx.doi.org/10.1080/00397910500384566

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.tandfonline.com/page/terms-and-conditions

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Synthetic Communications®, 36: 481–485, 2006
Copyright © Taylor & Francis Group, LLC
ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500384566

Downloaded by [Duke University Libraries] at 01:02 24 June 2012

Synthesis of 9-Methyl-11H-pyrido[2,1-b] quinazolin-11-one Using the Ullmann Condensation

Rolando F. Pellón, Maite L. Docampo, Zulfia Kunakbaeva, Victoria Gómez, and Herman Vélez-Castro
Center of Pharmaceutical Chemistry, Havana, Cuba

Abstract: The Ullmann condensation between 2-chlorobenzoic acid and 2-amino-6-methyl pyridine in DMF as solvent yielded 2-[(6-methyl-2-pyridinyl)amino] benzoic acid. The cyclization of this acid gave two isomers, the 9-methyl-11H-pyrido[2,1-b] quinazolin-11-one and, in a minor quantity, 2-methylbenzo[b][1,8]naphtyridin-5(10H)-one. Using ultrasound irradiation the pyridoquinazolin-11-one was obtained as the sole product.

Keywords: 9-Methyl-11H-pyrido[2,1-b]quinazolin-11-one acid, Ullmann condensation, ultrasound irradiation

11H-pyrido[2,1-b]quinazolin-11-one (IV) was synthesized by Zeide[1] in 1924 through the condensation of 2-chlorobenzoic acid (I) with 2-aminopyridine (II) employing the dry method reported by Ullmann using copper as catalyst. Later on, a series of derivatives of this heterocycle were obtained.[2–4]

In this work the reaction between 2-chlorobenzoic acid (I) and 2-amino-6-methyl pyridine (V) was studied to obtain the 9-methyl-11H-pyrido[2,1-b] quinazolin-11-one (VII) using the conventional synthetic method and also using ultrasound irradiation.

Received in USA August 18, 2005
Address correspondence to Rolando F. Pellón, Centro de Química Farmacéutica, Calle 200 y 21, Atabey, Playa, Apartado 16042, Ciudad de La Habana, Cuba. Fax: (537) 2736471; E-mail: rolando.pellon@infomed.sld.cu

Downloaded by [Duke University Libraries] at 01:02 24 June 2012

RESULTS AND DISCUSSION

In a previous communication[5] we reported the use of N,N-dimethylformamide as a solvent in the Ullmann condensation of 2-chlorobenzoic acid (I) with 2-aminopyridine (II) for the synthesis of 11H-pyrido[2,1-b]quinazolin-11-one (IV). This reaction (Scheme 1) proceeds through the corresponding 2-(2-pyridinylamino) benzoic acid (III).

The condensation between 2-chlorobenzoic acid and 2-amino-6-methyl pyridine was studied in the present work (Scheme 2). It is noteworthy that under the conditions described earlier,[5] only 2-[(6-methyl-2-pyridinyl)amino]-benzoic acid (VI) could be isolated, which is probably due to the presence of the methyl group, which interferes with the cyclization of acid VI in the reaction medium to compound VII. The 2-[(6-methyl-2-pyridinyl)amino]benzoic acid (VI) cyclized for treatments with polyphosphoric acid to a mixture of the compounds VII and VIII, perfectly distinguished by thin-layer chromatography.

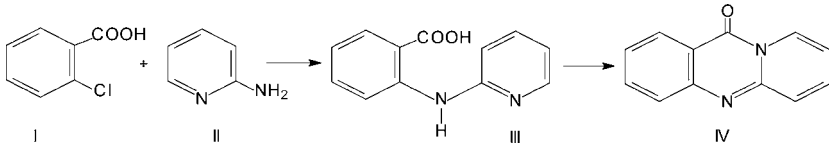
These compounds were separated via recrystallization from benzene solvent (see Experimental). The products were identified as isomers: 9-methyl-11H-pyrido[2,1-b]quinazolin-11-one (VII), which was obtained in 48% yield, and 2-methylbenzo[b][1,8]naphtyridin-5(10H)-one (VIII), in 6% yield.

In a previous communication[6] we reported the use of ultrasound irradiation in the condensation between 2-chlorobenzoic acid and 2-amino pyridine. Using the same conditions we studied the condensation between 2-chlorobenzoic acid and 2-amino-6-methyl pyridine. Various experiments were performed at different reaction times, demonstrating that at 20 min compound VII was obtained in 69%. Longer irradiation times did not increase the yield.

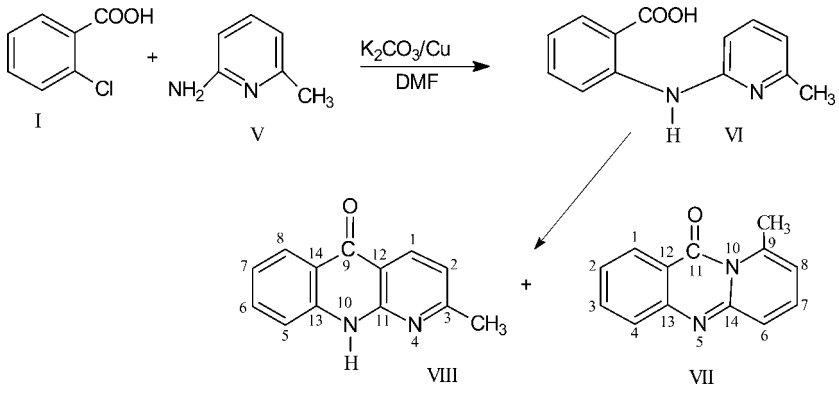
It is interesting to point out that when the condensation was performed using ultrasound, only compound VII was obtained. We believe that under these conditions the intermediate acid (VI) cyclized in the reaction medium, where ultrasound produces high temperatures[7,8] and pressures[9,10] attributed to the implosive collapse of the cavitation bubbles. For obtaining methylbenzonaphtyridin derivative (VIII), the presence of dehydrating agent is indispensable.[11]

EXPERIMENTAL

Starting materials came from commercial sources. Melting points were measured using a Gallenkanmp hot apparatus and are uncorrected. The reactions under ultrasonic irradiation were carried out in a sonic horn at



Scheme 1.



Scheme 2.

20 kHz. TLC analyses were run on 60 F254 silica-gel chromatoplates from Merck. Plates were visualized by UV light at 254 nm. UV spectra were recorded on Pharmacia LKB BIOCHROM 4060 spectrometer using a concentration of 10^{-5}mol/L. IR spectra were recorded on Phillips PU 9512 or M80 spectrometer using potassium bromide plates. ^{1}H NMR spectra were recorded on a Bruker AC 250 F spectrometer at 300 K. Chemical shifts are expressed in ppm relative to TMS as internal standard and DMSO-d_6 as solvent. Mass spectra were recorded with a TRIO 1000 Fisions Instrument spectrometer by electronic impact (EI) at 70 eV. Elemental analyses were carried out at the microanalytical unit, Instituto de Biorgánica de la Universidad de La Laguna, Tenerife, Spain.

Synthesis of 2-[(6-Methyl-2-pyridinyl)amino]benzoic Acid (VI)

A mixture of 2-chlorobenzoic acid (6.26 g, 0.04 mol), anhydrous potassium carbonate (2.76 g, 0.02 mol), 2-amino-6-methyl pyridine (8.64 g, 0.08 mol), and copper powder (0.2 g) in dimethylformamide (25 mL) was refluxed for 4 h. The mixture was poured over cold water and allowed to crystallize. It was then filtered, and the solid was washed with water. For recrystallization, the acid was dissolved in 250 mL of boiling benzene, the solution was filtered into a warm suction flask, and then it was cooled until crystallization was completed. Compound VI was obtained as a white solid (7.13 g, 78%).

Synthesis of 9-Methyl-11H-pyrido[2,1-b]quinazolin-11-one (VII) and 2-Methylbenzo[b][1,8]naphtyridin-5(10H)-one (VIII)

A mixture of VI (5.00 g) and polyphosphoric acid (50 mL) was stirred in a water bath at 100°C. After 3.5 h the mixture was poured onto ice-cold water

Downloaded by [Duke University Libraries] at 01:02 24 June 2012

Downloaded by [Duke University Libraries] at 01:02 24 June 2012

and was then basified with aqueous ammonia. The solid was precipitated, filtered, and dried. It was dissolved by refluxing in 20 mL of benzene for 30 min. The mixture was cooled and the solid crystallized. It was recrystallized from a mixture of ethanol–water (1:1) to give compound VIII as a yellow solid (0.26 g, 6%); mp 275–277°C; $R_f = 0.81$ (toluene–acetic acid, 2:1); $R_f = 0.77$ (acetone–isopropanol, 1:1). UV/Vis (C_2H_5OH) λ_{max} (lg ε): 256 nm (1.963), 377 nm (0.359). IR (KBr)/cm^{-1}: 3441 (νNH); 3134 ν(CH); 2900 ($\nu^{as}CH_3$); 2800 ($\nu^{s}CH_3$); 1621 (νC=O); 1436 (νC–N); 1273 (νC–N aromatic amine); 1032 (γC–N); 772 (γCH); 686 (γNH). ^{1}H NMR (DMSO-d_6) δ (ppm): 7.19 (d, $J_{(2,1)} = 10.08$, H_2); 7.28 (t, $J_{(6,7)} = 9.08$, $J_{(6,5)} = 9.68$, H_6); 7.63 (d, $J_{(5,6)} = 9.68$, H_5); 7.74 (t, $J_{(7,8)} = 9.58$, $J_{(7,6)} = 9.08$, H_7); 8.18 (d, $J_{(8,7)} = 9.58$, H_8); 8.45 (d, $J_{(1,2)} = 10.08$, H_1). ^{13}C NMR (DMSO-d_6) δ (ppm): 24.54 (CH_3); 113.00 (C_5); 117.62 (C_{11}); 117.91 (C_2); 120.85 (C_{14}); 121.58 (C_7); 125.82 (C_6); 133.71 (C_8); 135.68 (C_1); 140.76 (C_{13}); 150.53 (C_3); 164.13 (C_{12}); 177.07 (C_9). MS m/z (%): 210 (M^+, 100), 182 (8); 181 (13); 154 (3); 140 (4); 127 (3). Anal. calcd. for $C_{13}H_{10}N_2O$: C, 74.28; H, 4.76. Found: C, 74.15; H, 4.85.

The benzene solution was removed on a rotary evaporator, and the residual solid was extracted in boiling 95% ethanol. The solution was cooled, filtered, and the yellow solid was recrystallized from a mixture of ethanol–water (1:1) to give compound VII (2.20 g, 48%); mp 90–92°C; $R_f = 0.67$ (toluene–acetic acid, 2:1); $R_f = 0.61$ (acetone–isopropanol, 1:1). UV/Vis (C_2H_5OH) λ_{max} (lg ε): 231 nm (1.455), 365 nm (0.576). IR (KBr)/cm^{-1}: 2960 ($\nu^{as}CH_3$); 2860 ($\nu^{s}CH_3$); 1686 (νC=O); 1643 (νC=N); 1360 (νC–N); 786 (νC–H); 688 (νC–H benzene ring). ^{1}HNMR (DMSO-d_6) δ (ppm), J (Hz): 2.85 (s, CH_3); 6.56 (dd, $J_{(8,7)} = 5.96$, $J_{(8,6)} = 2.34$, H_8); 7.16 (dd, $J_{(6,7)} = 9.48$, $J_{(6,8)} = 2.34$, H_6); 7.32 (dd, $J_{(8,7)} = 5.96$, $J_{(7,6)} = 9.48$, H_7); 7.38 (dt, $J_{(2,3)} = 6.84$, $J_{(2,1)} = 8.10$, $J_{(2,4)} = 1.05$, H_2); 7.55 (dd, $J_{(4,3)} = 8.30$, $J_{(4,2)} = 1.05$, H_4); 7.76 (ddd, $J_{(3,4)} = 8.30$, $J_{(3,2)} = 6.84$, $J_{(3,1)} = 1.37$, H_3); 8.08 (dd, $J_{(1,2)} = 8.10$, $J_{(1,3)} = 1.37$, H_1). ^{13}C NMR (DMSO-d_6) δ (ppm): 23.90 (CH_3); 115.35 (C_8); 117.88 (C_{12}); 124.52 (C_2); 124.52 (C_6); 125.78 (C_4); 126.57 (C_1); 133.97 (C_7); 134.49 (C_3); 141.87 (C_9); 147.18 (C_{13}); 149.36 (C_{14}); 161.46 (C_{11}). MS m/z (%): 210 (M^+, 100); 182 (38); 181 (52); 154 (10); 92 (14); 65 (15). Anal. calcd. for $C_{13}H_{10}N_2O$: C, 74.28; H, 4.76. Found: C, 74.31; H, 4.72.

Synthesis of 9-Methyl-11H-pyrido[2,1-b]quinazolin-11-one (VII) via Ultrasound Irradiation

A mixture of 2-chlorobenzoic acid (6.26 g, 0.04 mol), anhydrous potassium carbonate (2.76 g, 0.02 mol), 2-amino-6-methyl pyridine (8.64 g, 0.08 mol), and copper powder (0.2 g) in DMF (25 mL) was irradiated for 20 min with a sonic horn at 20 kHz. The reaction mixture was slowly added to water (100 mL) and then left to stand overnight. The solid precipitated and was

purified from a mixture of ethanol–water (1:1) to give VII as a yellow solid (5.80 g, 69%), mp 90–92°C; $R_f = 0.66$ (toluene–acetic acid, 2:1); $R_f = 0.61$ (acetone–isopropanol, 1:1). The identity of the compound was checked by elemental analyses and by comparison of TLC and mp with the compound obtained using the reflux methodology. The mother liquor was concentrated and using a TLC analysis the absence of compound VIII was confirmed.

ACKNOWLEDGMENT

Financial support by the Project SECAB-CYTED is gratefully acknowledged. Thanks go to Angel Gutierrez Ravelo and Ana Estevez (University of La Laguna, Spain) for microanalysis and NMR spectra.

REFERENCES

1. Zeide, O. About the constitution of α quinolones. *Ann.* **1924**, *440*, 311–321.
2. Abdel Aziz, M. A.; Daboun, H. A.; Abdel Gawad, S. M. α-Cyanothioacetamide and its derivatives in heterocyclic synthesis: Preparation of several new 4-oxoquinazoline derivatives. *J. Prakt. Chem.* **1990**, *332* (5), 610–618.
3. Ensinger, H.; Birke, F.; Streller, I.; Schromm, K. Oxoquinazoline derivatives as cell protectants. Ger. Offen. 3,902,639, (Cl.A61K31/645), Aug. 1990.
4. Matzkies, F.; Stechert, R.; Rauber, G. Pilot study on the effect of doqualast on dietary-induced hyperuricemia in volunteers. *Jr Arzneim-Forsch.* **1989**, *39* (9), 1171–1172.
5. Pellón, R.; Carrasco, R.; Rodés, L. Synthesis of 11H-pyrido (2,1-b)quinazolin-11-one and derivatives. *Synth. Comm.* **1996**, *26* (20), 3869–3876.
6. Docampo, P. L.; Pellón, R. F. Synthesis of 11H-pyrido[2,1-b]quinazolin-11-one and derivatives using ultrasound irradiation. *Synth. Comm.* **2003**, *33* (10), 1777–1781.
7. Suslick, K. S.; Price, G. Applications of ultrasound to materials chemistry. *Annu. Rev. Matl. Sci.* **1999**, *29*, 295–326.
8. Flint, E. B.; Suslick, K. S. The temperature of cavitation. *Science* **1991**, *253*, 1397–1399.
9. Mason, T. J. Ultrasound in synthetic organic chemistry. *Chem. Soc. Rev.* **1997**, *26*, 443–451.
10. Suslick, K. S.; Didenko, Y.; Fang, M. M.; Hyeon, T.; Kolbeck, K. J.; McNamara, W. B., III; Mdleleni, M. M.; Wong, M. Acoustic cavitation and its chemical consequences. *Phil. Trans. Roy. Soc. A.* **1999**, *357*, 335–335.
11. Acheson, R. M.; Orgel, L. E. *The Chemistry of Heterocyclic Compounds, Acridines*; Interscience: New York, 1956; Vol. 9, pp. 122–145.

Downloaded by [Duke University Libraries] at 01:02 24 June 2012