A PRACTICAL SYNTHESIS OF UREAS FROM 2-AMINOPICOLINES USING MICROWAVE IRRADIATION

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Abstract: Several symemetrically disubstituted ureas are synthesized by heating of urea with 2-aminopicoline analogues under enviromentally benign conditions without any solvent in a conventional microwave oven.

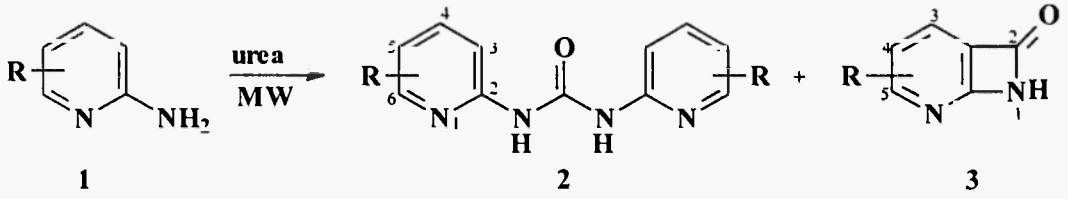
Introduction

Substituted ureas have received considerable attention due to their wide range of applications, e. g. for use as HIV-1 integrase inhibitors, anticancer, antihelminthic, antidiabetic and tranquillising drugs, antioxidants in gasoline, corrosion inhibitors, pesticides and plant growth regulators (1). Although the synthesis of mono and disubstituted ureas has been extensively documented, many of these methods have limitations in their general applications (2). Recently the preparations of symmetrically substituted ureas were reported by the reductive alkylation of aromatic aldehydes (3), by the reaction of aliphatic and aromatic amines with ethyl acetoacetate (4), and of aromatic amines with urea using microwave irradiation (5).

Microwave irradiation has opened new perspectives in synthetic organic chemistry, not only in terms of yield and selectivity, but also ease of the reaction conditions (6). In view of the above, and in conjunction with recent work on microwave-assisted reactions under solvent-free conditions (5-7), we report preliminary results of our study on the synthesis of symmetrical dipyridylureas under environmentally benign conditions, using a microwave oven, without any solvent or solid support (scheme 1).

The reaction of a 2-aminopicolines with urea in a conventional microwave oven produced symmetrically disubstituted ureas **2a-e**, easily isolated after addition of water to the final reaction mixture, removing the solid product by filtration, and washing with diethyl ether. The isolated yields of **2a-e** were good (see **Table 1**),

Scheme 1. Coupling reaction between 2-aminopicoline analogues and urea.



1 **2** **3**

a) R= H b) R= 3-CH_3 c) R= 4-CH_3 d) R= 5-CH_3 e) R= 6-CH_3

because only small amounts of β-lactams (**3a, 3c-e**) were formed (15, 10, 8 and 12% respectively) as by products. The mixture was separated by thin layer chromatography using chloroform:diethyl ether 3:1. In the case of product **2b**, only the 3-methylpyridyl urea was detected. The ureas were characterised by ^{1}H NMR, ^{13}C NMR, COSY, HETCOR, IR, elemental analysis and mass spectra.

In summary, we have shown that direct heating of 2-aminopicoline derivatives with urea leads to an efficient synthesis of symmetric N,N-disubstituted ureas; it is a very simple method which seems to be particularly valuable from both an economic and an environmental point of view.

Experimental

A White-Westinghouse microwave oven equipped with a turntable and operating 2450 MHz was used at its full power, 750 W, for all the experiments. An Alumina batch (Aluminium oxide 60 G neutral, type E, Merck: 50g; batch 4.0 cm diameter) was used as a sink inside the MW oven to irradiate the reaction mixture. Melting points (uncorrected) were recorded on a Thomas Scientific capillary melting point apparatus. IR spectra were determined as KBr pellets on a Shimadzu model 470 spectrophotometer. ^{1}H, ^{13}C and TD NMR spectra were recorded on a Jeol Eclipse 270 MHz spectrometer and are reported in ppm dowenfield from TMS as internal standard. Elemental analysis were performed by Atlantic Microlab, Inc., Norcross, GA. Mass spectra were determined on a Varian Saturn 2000 GC. MS. instrument.

TABLE 1. Physical, Analytical and Spectral Data for Compounds 2a-d and 3a, 3c-e

Cmpd	Yield (%)	mp (°C)	Time (min)	IR (cm^{-1}) NH	IR (cm^{-1}) CO	^1H, ^{13}C NMR (δ)/ $CDCl_3$; MS m/z; Analysis %
2a	61	246-248	3	3104	1696	6.83(m, 4H, $H_{3,5}$); 7.56(m, 2H, H_4); 8.18(dd, 2H, H_5 J: 5.6Hz); 8.84(brs, 2H NH); 112.15, 117.27, 138.39, 146.40, 153.02, 157.29 (CO); MS: m/z (%) 215 (M^+ 37); *Anal.* Calcd(Found): C, 61.67 (61.84); H, 4.71 (4.68); N, 26.15 (25.93).
2b	78	108-110	2.5	3128	1690	2.22(s, 3H, CH_3); 6.84(dd, 2H H_3, J_1: 5.21, J_2: 5.18 Hz); 7.43(dd, 2H, H_4, J_1: 5.36, J_2: 1.3 Hz); 8.05(dd, 2H, H_5, J_1:5.18, J_2:1.24 Hz); 9.53(brs, 2H, NH); 16.91(CH_3), 117.30, 118.98, 139.07, 144.03, 151.15, 156.16 (CO), MS. m/z (%) 243 (M^+ 46),); *Anal.* Calcd(Found): C, 64.45 (64.27); H, 5.82 (5.82); N, 23.13 (23.18).
2c	51	212-213	6	3112	1683	2.29(s, 3H, CH_3); 5.56(s, 2H, H_3); 6.72(d, 2H, H_5, J: 5.21); 8.01(d, 2H, H_6, J:5.21Hz); 8.35(brs, 2H, NH); 21.07(CH_3), 109.06, 115.67, 147.63, 149.30, 156.18, 159.12 (CO); MS: m/z (%) 243 (M^+ 42); *Anal.* Calcd(Found): C, 64.45 (64.45); H, 5.82 (5.80); N,23.13 (23.33)
2d	56	202-204	3.5	3132	1685	2.29(s, 3H, CH_3); 6.73(d 2H, H_3, J: 8.16 Hz); 7.39(dd, 2H, H_4, J_1: 8.16, J_2: 2.23Hz); 7.99(d, 2H, H_6, J:2.20Hz); 8.51(brs, 2H, NH); 23.31(CH_3), 109.86, 116.67, 148.63, 149.39, 155.18, 158.12 (CO); MS: m/z (%) 243 (M^+ 38); *Anal.* Calcd(Found): C, 64.45 (64.49); H, 5.82 (5.79); N, 23.13 (23.15).
2e	67	207-208	4.5	3108	1691	2.52(s, 3H, CH_3), 6.61(d, 2H, H_3, J_1: 8.15Hz); 7.45(d, 2H, H_5, J: 7.91 Hz); 7.52(dd, 2H, H_4 J_1:7.86 J_2:7.91Hz); 8.76(brs, 2H, NH); 24.23(CH_3), 108.88, 116.47, 138.52, 151.96, 155.62, 157.34 (CO); MS: m/z (%) 243 (M^+ 45); *Anal.* Calcd(Found): C, 64.45 (64.38); H, 5.82 (5.82); N, 23.13 (23.07).
3a	15	165-166	3	3072	1710	6.97(dd, 1H, H_4 J:4.95 Hz); 7.67(m, 1H, H_3); 7.56(brs, 1H, NH); 8.35(dd, 1H, H_5 J:1.24 Hz); 113.19; 118.30; 138.42; 147.36; 152.51; 153.39 (CO); MS: m/z (%) 121 (M^+ 35).
3c	10	178-180	6	3080	1712	2.34(s, 3H, CH_3); 6.79(d, 1H, H_3 J:5.21Hz); 7.81(brs, 1H, NH); 8.19(d, 1H, H_5 J:5.21Hz); 21.07; 109.06; 115.67; 147.63; 149.30; 152.31; 156.28(CO); MS: m/z (%) 135 (M^+ 76%).
3d	8	167-168	3.5	3070	1708	2.24(s, 3H, CH_3); 7.98(s, 1H, H_3); 8.14(s, 1H, H_5); 22.70(CH_3); 108.19; 115.33; 150.29; 152.17; 152.98; 156.17(CO); MS: m/z (%) 135 (M^+ 63).
3e	12	157-158	4.5	3080	1715	2.43(s, 3H, CH_3); 6.71(d, 1H, H_3 J:7.24Hz); 6.80(d, 1H, H_4 J:7.24Hz); 7.35(brs, 1H, NH); 24.23(CH_3); 108.88; 116.47; 138.64; 152.37; 153.41; 155.62(CO); MS: m/z (%) 135 (M^+ 71).

General Procedure for the Preparation of Disubstituted Ureas **2a-e.**

A 2-aminopicoline analogues (2.5 mmol) was mixed throughly with urea (0.12 g, 2.0 mmol) in a 10 mL PYREX® round bottom centrifuge tube. Then the tube was placed in a conventional microwave oven until the mixture became liquid. The time required for each reaction is indicated in the Table. To remove the unreacted urea, water (5 mL) was added to the reaction mixture and the insoluble product was collected. The recovered solid material was separated by thin layer chromatography using chloroform:diethyle ther (3:1).

Acknowledgements

This work was supported by grants from IIF-UCV, CDCH-UCV (grant IIF. 02/2000, PG. 06-30-4590-2000) and CONICIT (grant LAB. 97000665). The authors thank L. Vasquez, Facultad de Farmacia, Universidad Central de Venezuela for helping with the mass spectras.

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Received on April 12, 2001