HL **ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)**
http://heteroletters.org **Vol. 3: (4), 2013, 427-430**

SYNTHESIS OF 2,3 -DISUBSTITUTED PYRIDINE DERIVATIVES* WITH MICROWAVE

Lv Zhao-ping, Li Jin-huan, Lou Shan-ning, Liv Dao-hui, Huang meng.*

Department of Applied Chemistry , College of Materials Science and Engineering, Nanjing University of Aeronautics and Astronautics, Nanjing 210016, China

ABSTRACT

Seven novel 2,3-disubstituted pyridine derivatives**(a~g)** are designed and synthesized in high yield with microwave. The chemical structure has been confirmed by spectral (^{1}HNMR, ^{13}C NMR) analysis and elemental analysis.

INTRODUCTION

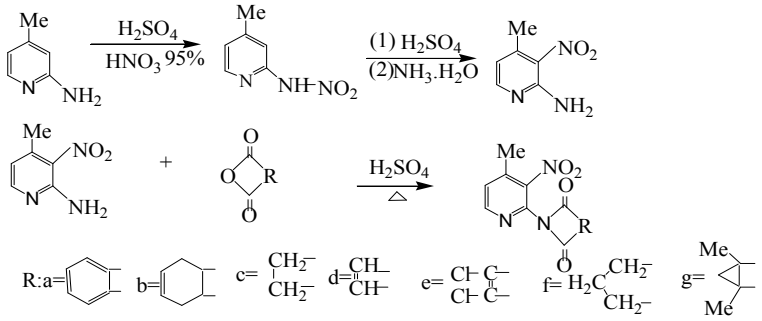
Ample evidence suggests that nitration of pyridine derivative possesses an unique functionality, which can act both as a push electron donor and a pull electron acceptor group.[1] This strong push-pull property has an essential consequence, Nitro substituent of pyridine derivative can be used as biological activity intermediates and auxiliary agents in synthesis of some heterocyclic pyridine products.[2,3] It has been suggested that the presence of the nitro substituent is essential for any significant antifungal activity of these compounds.[4,5] In previous papers, we reported the insecticidal activities of nitration.[6,7,8] With this interest, in this report, we have designed and synthesized compounds containing 2-dicarbonylimideyl-3-nitro-4-methylpyridine derivative (**a-g**) with normal synthesis procedure(method A) and microwave-assisted synthesis method(method B).

RESULTS AND DISCUSSION

The 2-amino-4-methyl-3-nitropyridine is important intermediates for the synthesis of nitration of 2,3-disubstituted pyridines derivative **(a~g)**. The synthesis[9,10]of 2-amino-4-methyl-3-nitropyridine is given through two steps of reactions. The first one includes the reaction of 2-amino-4-methylpyridine with concentrated sulfuric acid and 95% nitric acid, leading to the intermediate of 2-nitramino-4-methylpyridine. The second referred to the reaction

*Project supported by the National Natural Science Foundation of China (No. 29522002); Current Address: Department of Applied Chemistry, College of Material Science and Engineering, Nanjing University of Aeronautics and Astronautics, Nanjing 210016, China; E-mail: *nhzplv@nuaa.edu.cn.*

of 2-nitramino-4-methylpyridine with concentrated sulfuric acid. 2-Amino-4-methyl-3-nitropyridine reacted with raw anhydride gave 2-dicarbonylimidyl-4-methyl-3-nitropyridine **(a-g)** as presented Scheme.



Scheme: Synthesis of 2-dicarbonylimidyl-4-methyl-3-nitropyridin

Seven novel 2,3-disubstituted pyridine derivatives**(a~g)** are analyzed under normal synthesis method and microwave-assisted synthesis method. The contrast result shows that the microwave-assisted synthesis method(method B) can be carried on with shorter reaction time and gave higher yield than the normal synthesis procedure(method A).The synthetic results and elemental analysis and spectral data are summarized in Tables I-II **.**

Table I

The Characteristics of the Target Compounds (**a-g**)

Compound	R	Yield, % /Time, minite		Empirical	Found,% /Calculated,%		
		Method A	Method B	Formula	C	H	N
a		85.5/360	98.5/20	$C_{14}H_9N_3O_4$	59.33 / 59.42	3.16 / 3.19	14.87 / 14.82
b		71.6/300	95.4/20	$C_{14}H_{13}N_3O_4$	58.53 / 58.59	4.63 / 4.55	14.59 / 14.61
c		67.3/300	90.2/15	$C_{10}H_9N_3O_4$	51.90 / 50.98	3.89 / 3.85	17.87 / 17.84
d		70.6/300	93.7/15	$C_{10}H_7N_3O_4$	50.42 / 51.51	3.08 / 3.02	18.10 / 18.02
e		65.8/300	97.8/20	$C_{10}H_5N_3O_4Cl_2$	39.84 / 39.76	1.72 / 1.67	13.96 / 13.91
f		71.8/300	92.6/20	$C_{11}H_{11}N_3O_4$	53.08 / 53.01	4.42 / 4.44	16.78 / 16.86
g		64.5/300	95.8/20	$C_{13}H_{13}N_3O_4$	56.62 / 56.73	4.82 / 4.75	15.29 / 15.27

Tables II

The Spectral Characteristics of the Compounds (**a-g**)(^{13}C NMR,and ^{1}H NMR)

Compound	R	^{13}C NMR Data, δ, ppm		^{1}H NMR Data δ, ppm , (H_Z)
		C=O	C_1- C_5(pyridine)	
a		167.14	138.93,141.96, 145.83,146.01,147.42	2.27(3H, s, CH_3), 5.86 (4H, s, Ph-H), 7.31(1H,d, Py-H) ,7.42 (1H, s, Py-H)
b		164.37	117.49,128.64, 139.83,140.56,141.37	2.17(3H,s,CH_3),4.35(8H,m,CH-CH_2),7.12(1H,d, Py-H) ,7.35 (1H, s, Py-H)
c		176.41	112.56,116.94, 137.52,152.87,157.36	1.82(3H,s,CH_3),2.29(4H,s,2CH_2),6.41(1H,d , Py-H) ,7.33 (1H, s, Py-H)
d		178.40	113.43,117.63, 138.66,154.39,158.82	1.95(3H,s,CH_3),2.32(2H,dd,2CH),6.53(1H, d, Py-H) ,7.39(1H, s, Py-H)
e		179.34	128.43,140.56, 141.47,143.81,144.36	1.92(3H,s,CH_3),6.57(1H,d,Py-H) ,7.27(1H, s, Py-H)
f		177.86	127.67,132.76, 138.84,145.01,148.62	1.78(6H,s,CH_2),6.39(1H,d,Py-H) ,7.36(1H, s, Py-H)
g		175.90	110.98,114.21, 132.87,151.47,156.85	1.13 (6H, s, 2CH_3), 2.06(2H,s,CH_2), 6.62 (1H,d,Py-H) ,7.48(1H, s, Py-H)

EXPERIMENTAL

Melting points are determined on a WRS-IA capillary melting point apparatus. Elemental analyses are recorded for C, H and N on Vario-EL III from vacuum-dried samples. NMR spectra are obtained on a JEOL AC−500E (500MHz) instrument at room temperature with TMS as internal standard. Microwave-assisted synthesis are carried out on MAS-1(1430W) microwave apparatus. Thin layer chromatography (TLC) plates are coated with silica gel G and spots are visualized by exposing the dry plates in iodine vapors to check the purity as well as the progress of reaction.

Synthesis of the intermediate 2-Amino-4-methyl-3-nitropyridine [9,10]

The solution is heated on a steam bath for 20 minutes, and cooled to 0°C. The mixture is neutralized with concentrated ammonium hydroxide below 20°C for 2 hours. The 2-amino-4-methyl-3-nitropyridine is recrystallized from a mixture of ethanol and water to yield

71%, m. p. of 211°C.

General procedure for the nitration of 2, 4-disubstituted pyridine derivatives (a-g)

Raw anhydride(1.02mol), 2-amino-4-methyl-3-nitropyridine (0.80mol) and 3~5 drops of concentrated sulfuric acid are mixed thoroughly. The mixed content is heated at 120°C, monitoring reaction with TLC. The reaction mixture is cooled to room temperature, the reaction mixture is washed with 2.5M Na_2CO_3(aq) and recrystallized with anhydrous EtOH to give target product **(a-g)** .

Microwave procedure for the nitration of 2, 4-disubstituted pyridine derivatives (a-g) [11]

Raw anhydride(1.02mol), 2-amino-4-methyl-3-nitropyridine (0.80mol) and 3~5 drops of concentrated sulfuric acid are mixed thoroughly. The mixed contents are kept to 120°C under microwave oven and irradiated at 1430W (100% of supplying power), monitoring reaction with TLC. The reaction mixture is cooled to room temperature, the reaction mixture is washed with 2.5M Na_2CO_3(aq) and recrystallized with anhydrous EtOH to give target product **(a-g)**.

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Received on July17, 2013.