American Journal of Heterocyclic Chemistry
2018; 4(1): 26-29
http://www.sciencepublishinggroup.com/j/ajhc
doi: 10.11648/j.ajhc.20180401.13
ISSN: 2575-7059 (Print); ISSN: 2575-5722 (Online)

Synthesis of Pyridine and Phenyl Succinimides by Green Pathway and Their Antimicrobial Assay

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To cite this article:
Ravindra Dhivare, Prashant Chaudhari, Shankarsing Rajput. Synthesis of Pyridine and Phenyl Succinimides by Green Pathway and Their Antimicrobial Assay. *American Journal of Heterocyclic Chemistry*. Vol. 4, No. 1, 2018, pp. 26-29. doi: 10.11648/j.ajhc.20180401.13

Received: November 15, 2017; **Accepted**: December 6, 2017; **Published**: January 30, 2018

Abstract: A simple and clean green method was implemented for the preparation of different succinimide derivatives by means of the N-substituted anilines or N-substituted 2-aminopyridines with succinic anhydride with the heating in aqueous medium. The total synthesized 3a-j compounds were evaluated against antibacterial and antifungal species.

Keywords: N-Methylpyridin-2-yl Succinimide, N-Phenyl Succinimides, Antimicrobial Activity

1. Introduction

Cyclic imides incorporating the most familiar heterocyclic elements resembling sulphur, oxygen and nitrogen which shows their title role in the development of pharmaceutical, chemical, medicinal, biological and agricultural areas. Cyclic imides revealed the central nervous system anxiolytic and anti-depressive activities [1]. Their bio-transformations of racemic and chiral forms are susceptible on fungi [2]. They are significant regioselective [3] and stereo-selective [4], and nephrotoxicity NDHS formation [5]. Various succinimide derivatives exhibit good anticonvulsants [6-7], 5-HT1A or 5-HT7 receptors affinity [8], antimicrobial activities [9-11], in vitro bovine acetyl cholinesterase inhibitors [12], Mitochondrial and Cytotoxicity effect [13] and plant growth regulator [14], anti-mutagenic and anti-epileptic activities [15] so on. In the perspective of preparation modes; some of the novel substituted succinimides by intra-molecular cyclization using solid phase [16], CF_3SiMe_3 under fluoride ion catalysis [17], enantio-selective acylated succinimides developed by squaramide catalyst [18], ring extension method from 4-oxoazetidine-2-carbaldehydes converted into enantio-pure succinimides by using thiazolium salt pre-catalyst [19]. Certain Aryl-succinimides also been synthesized by decarboxylative oxidation of N-aryl-c-lactam-2-carboxylic acids with the dual oxidant CAN or NaBrO3 in refluxing aqueous acetonitrile [20]. Halo-succinimides were prepared by the brominating phenyl group without catalyst and solvent under the ball-mill method [21], by thionyl chloride [22], acetyl chloride [23] and DABCO catalyst [24]. Moreover the succinimide derivatives are prepared by microwave irradiated method using aqueous mixture of DMF and acetic acid as a catalyst [25].

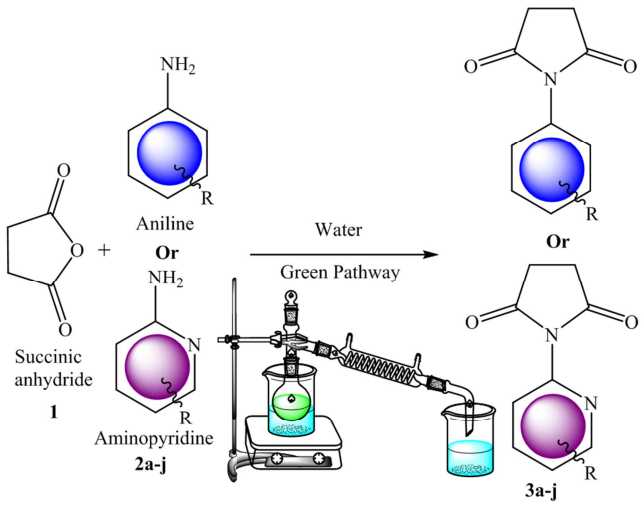
2. Material Methods

Melting points of all the synthesized compounds were recorded in an open glass capillaries and were uncorrected and converted into Kelvin scale. IR spectra were recorded on Shimadzu FTIR-8400S and ATR Brucker alpha FT-IR spectrophotometers. ^1H NMR spectra were verified on 500.13MHz by Brucker spectrophotometer. The reaction was monitored by thin layer chromatography was carried out through pre-coated silica gel aluminium plates with mixture of diethyl ether and ethyl acetate 7:3 proportion or benzene. Total compounds 3a-j was synthesized by ecofriendly green pathways in hours from N-substituted anilines, N-substituted 2-aminopyridines, succinic anhydride, alcohol and distilled water.

2.1. Experimental Section

General procedure for the preparation of substituted succinimides (3a-j):

0.02 mole of the appropriately substituted aniline or substituted 2-aminopyridine was dissolved in 20 mL of water and 0.02 mole of succinic anhydride was gradually added. The mixture was heated in an oil bath with simultaneous distillation of water. After the removal of water, then reaction temperature was increased up to 180°C which was maintained for 90 min. The crude products were recovered and recrystallized by alcohol. (Figure 1)



R = 4-methylpyridin-2-yl, 5-methylpyridin-2-yl, 6-methylpyridin-2-yl, -4CH_3, -4OCH_3,-4Br, -4Cl, -4F, -3Cl-4F, 2,4,5-Cl

Figure 1. *Synthesis of N-phenyl or N-methylpyridin-2-yl succinimides (3a-j).*

2.2. Characterization of the Synthesized Compounds (3a-j)

2.2.1. 1-(4-Methylpyridin-2-yl) Succinimide (3a)

White Solid; M. F.: $C_{10}H_{10}N_2O_2$; Yield: 63.78%; M. W.: 190.20; M. P.(K): 415-417 K; FTIR: >C=O (2-Peaks): 1700 cm^{-1} and 1670 cm^{-1}, CH_2-CH_2: 2969 cm^{-1} and 2813 cm^{-1}, cyclic imines 1301 cm^{-1}, -Ar ring (3-Peaks): 1491 cm^{-1}, 1551 cm^{-1} and 1405 cm^{-1}, -CH_3 (1-peak): 2764 cm^{-1}, -CH_3 bend (2-Peaks): 1444 cm^{-1}, 1353 cm^{-1}; Anal: C, 63.32; H, 5.51; N, 14.87; ^{1}H NMR (500.13 MHz, DMSO d^6, δ ppm): 7.16-7.19 (m, 2H, pyridine), 8.49 (d, 1H, pyridine), 2.41 (s, 3H, -CH_3 - pyridine), 2.90 (s, 4H, imide)

2.2.2. 1-(5-Methylpyridin-2-yl) Succinimide (3b)

White Solid; M. F.: $C_{10}H_{10}N_2O_2$; Yield: 66.80%; M. W.: 190.20; M. P.(K): 419-421 K; FTIR: >C=O (2-Peaks): 1709 cm^{-1} and 1675 cm^{-1}, CH_2-CH_2: 2967 cm^{-1} and 2924 cm^{-1}, cyclic imines 1356 cm^{-1}, -Ar ring (3-Peaks): 1490 cm^{-1}, 1551 cm^{-1} and 1598 cm^{-1}, -CH_3 (1-peak): 2759 cm^{-1}, -CH_3 bend (2-Peaks): 1490 cm^{-1}, 1357 cm^{-1}; Anal: C, 63.32; H, 5.51; N, 14.87; ^{1}H NMR (500.13 MHz, DMSO d^6, δ ppm): 7.85-8.47 (m, 2H, pyridine), 8.23 (d, 1H, pyridine), 2.35 (s, 3H, -CH_3 - pyridine), 2.90 (s, 4H, imide)

2.2.3. 1-(6-Methylpyridin-2-yl) Succinimide (3c)

White Solid; M. F.: $C_{10}H_{10}N_2O_2$; Yield: 70.67%; M. W.: 190.20; M. P.(K): 421-423 K; FTIR: >C=O (2-Peaks): 1689 cm^{-1} and 1640 cm^{-1}, CH_2-CH_2: 2967 cm^{-1} and 2924 cm^{-1}, cyclic imines 1309 cm^{-1}, -Ar ring (2-Peaks): 1261 cm^{-1} and 1544 cm^{-1}, -CH_3 (1-peak): 2792 cm^{-1}, -CH_3 bend (2-Peaks): 1403 cm^{-1}, 1309 cm^{-1}; Anal: C, 63.32; H, 5.51; N, 14.87; ^{1}H NMR (500.13 MHz, DMSO d^6, δ ppm): 7.22 (d, 1H, pyridine), 7.06 (d, 1H, pyridine), 7.74 (t, 1H, pyridine), 2.59 (s, 3H, -CH_3 - pyridine), 2.90 (s, 4H, imide)

2.2.4. 1-p-Tolyl Succinimide (3d)

White Crystals; M. F.: $C_{11}H_{11}NO_2$; Yield: 62.73%; M. W.: 189.21; M. P.(K): 423-425 K; FTIR: >C=O (2-Peaks): 1710 cm^{-1} and 1774 cm^{-1}, CH_2-CH_2: 2995 cm^{-1}, cyclic imines 1288 cm^{-1}, -Ar ring (3-Peaks): 1450 cm^{-1}, 1519 cm^{-1} and 1589 cm^{-1}; Anal: C, 69.13; H, 5.70; N, 7.21

2.2.5. 1-(4-Methoxyphenyl) Succinimide (3e)

Whitish Crystals; M. F.: $C_{11}H_{11}NO_3$; Yield: 78.91%; M. W.: 205.21; M. P.(K): 433-435 K; FTIR: >C=O (2-Peaks): 1708 cm^{-1} and 1770 cm^{-1}, CH_2-CH_2: 2963 cm^{-1}, cyclic imines 1302 cm^{-1}, -Ar ring (3-Peaks): 1476 cm^{-1}, 1512 cm^{-1} and 1606 cm^{-1}, Ar-OCH_3: 1178 cm^{-1}; Anal: C, 62.95; H, 4.89; N, 6.14

2.2.6. 1-(4-Bromophenyl) Succinimide (3f)

Brownish Crystals; M. F.: $C_{10}H_8BrNO_2$; Yield: 89.78%; M. W.: 254.08; M. P.(K): 447-449 K; FTIR: >C=O (2-Peaks): 1707 cm^{-1} and 1766 cm^{-1}, CH_2-CH_2: 2998 cm^{-1}, cyclic imines 1295 cm^{-1}, -Ar ring (3-Peaks): 1455 cm^{-1}, 1488 cm^{-1} and 1588 cm^{-1}, Ar-Br: 1070 cm^{-1}; Anal: C, 48.01; H, 3.59; N, 5.18

2.2.7. 1-(4-Chlorophenyl) Succinimide (3g)

Whitish Crystals; M. F.: $C_{10}H_8ClNO_2$; Yield: 76.60%; M. W.: 209.63; M. P.(K): 432-434 K; FTIR: >C=O (2-Peaks): 1711 cm^{-1} and 1773 cm^{-1}, CH_2-CH_2: 2985 cm^{-1}, cyclic imines 1302 cm^{-1}, -Ar ring (3-Peaks): 1495 cm^{-1}, 1527 cm^{-1} and 1589 cm^{-1}, Ar-Cl: 1093 cm^{-1}; Anal: C, 56.90; H, 3.70; Cl, 16.74; N, 6.23

2.2.8. 1-(4-Fluorophenyl) Succinimide (3h)

White Crystals; M. F.: $C_{10}H_8FNO_2$; Yield: 62.90%; M. W.: 193.17; M. P.(K): 449-451 K; FTIR: >C=O (2-Peaks): 1712 cm^{-1} and 1767 cm^{-1}, CH_2-CH_2: 3000 cm^{-1}, cyclic imines 1290 cm^{-1}, -Ar ring (3-Peaks): 1456 cm^{-1}, 1513 cm^{-1} and 1604 cm^{-1}, Ar-F: 1178 cm^{-1}; Anal: C, 62.38; H, 4.09; F, 9.53; N, 6.87; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.16-7.36 (m, 4H, Ar-H), 2.94 (s, 4H, imide)

2.2.9. 1-(3-Chloro-4-Fluorophenyl) Succinimide (3i)

White Solid; M. F.: $C_{10}H_7ClFNO_2$; Yield: 79.91%; M. W.: 227.62; M. P.(K): 431-433 K; FTIR: >C=O (2-Peaks): 1698 cm^{-1} and 1776 cm^{-1}, CH_2-CH_2: 2937 cm^{-1}, cyclic imines 1294 cm^{-1}, -Ar ring (3-Peaks): 1490 cm^{-1}, 1502 cm^{-1} and 1595 cm^{-1}, Ar-Br: 1070 cm^{-1}, Ar-*p*-F: 1173 cm^{-1} and *m*-Cl: 1059 cm^{-1}; Anal: C, 53.01; H, 3.32; Cl, 15.15; F, 8.47; N, 6.20; ^{1}H NMR (500.13 MHz, $CDCl_3$, δ ppm): 7.25-7.44 (m, 3H, Ar-H), 2.92 (s, 4H, imide)

2.2.10. 1-(2, 4, 5-Trichlorophenyl) Succinimide (3j)

White Solid; M. F.: $C_{10}H_6Cl_3NO_2$; Yield: 75.56%; M. W.: 278.52; M. P.(K): 469-471 K; FTIR: >C=O (2-Peaks): 1660 cm^{-1} and 1700 cm^{-1}, CH_2-CH_2: 2993 cm^{-1}, cyclic imines 1356 cm^{-1}, -Ar ring (3-Peaks): 1454 cm^{-1}, 1508 cm^{-1} and 1570 cm^{-1}, Ar-2, 4, 5 Cl_3: 1072 cm^{-1}; Anal: C, 43.04; H, 3.01; Cl, 38.15; N, 5.27; ^{1}H NMR (500.13 MHz, $CDCl_3$, δ ppm): 7.28-7.57 (m, 2H, Ar-H), 2.27 (s, 4H, imide)

3. Antimicrobial Activities and Statistical Analysis

All the results of compound series 3a-j were carried out by the triplicate method N=3 with Mean±SD statistical analysis calculated in the Table 1.

Table 1. *Antimicrobial activities of 3a-j compounds by Mean±SD method.*

Compd Code	Zone of diameter calculated in mm by (Mean±S. D.)			
	Bacillus subtilis	*Escherichia coli*	*Candida albicans*	*Aspergillus niger*
	100 µg/ml	**100 µg/ml**	**100 µg/ml**	**100 µg/ml**
3a	---	11.77±0.31	---	---
3b	7.64± 0.21	07.48±0.34	---	---
3c	10.2± 0.07	12.05±0.06	---	---
3d	11.33±0.57	11.66±1.15	---	---
3e	13±1	13±1	---	---
3f	11.33±0.57	11.33±0.57	---	---
3g	12.66±0.57	12.66±0.57	---	---
3h	12.66±0.57	12.66±0.57	13.19 ± 0.15	16.41 ± 0.42
3i	12.33±0.57	12.33±0.57	14.68 ± 0.18	15.56 ± 0.37
3j	12±1	12±1	7.41 ± 0.27	-
Ctrl	0.0±0.0	0.0±0.0	0.0 ± 0.0	0.0 ± 0.0
Std	28.43± 0.29	24.09±0.10	NA	NA
	NA	NA	12.40 ± 0.43	10.45 ± 0.11

Keynote: Zone of inhibition measured in mm (Mean±S. D.) (N=3) ('---' means no zone).

Some of the compound showed moderate to good activities against antimicrobial species shown in the Figure 2;

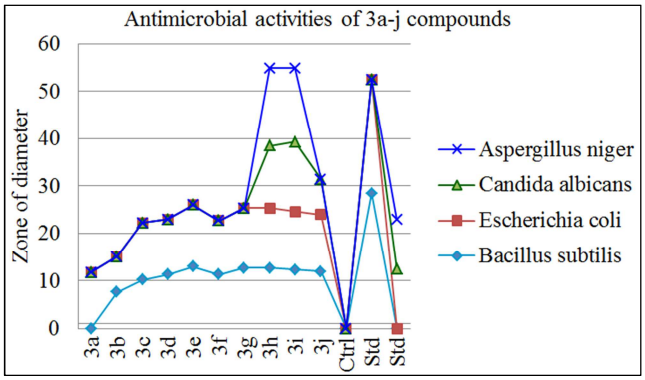


Figure 2. *Antimicrobial activities of 3a-j compounds.*

4. Result and Discussion

Chemistry:

The series of cyclic imides 3 a-j were prepared by the reaction of succinic anhydride and primary aromatic amines by distillation pathway and reasonable yield is obtained. The formation of five membered cyclic imides was confirmed by IR, ^{1}HNMR and elemental analysis.

Antimicrobial protocol:

All synthesized compounds 3a-j were screened for their antibacterial activity against gram positive bacteria *Bacillus subtilis* (NCIM 2250) and gram negative bacteria *Escherichia coli* (NCIM 2109) using DMSO and DMF solvents. Also screened against Fungi (Yeast) *Candida albicans* (NCIM 3471) and *Aspergillus niger* (NCIM 545). Ampicillin and Chloramphenicol were used as standard drugs against antibacterial testing and Amphotericin-B was used for antifungal activities by using disc diffusion method.

5. Conclusion

Syntheses of succinimides 3a-j were developed by green method with good yield. All these compounds were characterized by their spectral analysis. Most of the compound showed moderate to good activity against *Bacillus Subtilis* and *Escherichia coli*. The compound 3h, 3i and 3j exhibited good antifungal activities against *Candida albicans* and *Aspergillus niger*. The synthesized compounds may be used for preparation of various heterocyclic systems.

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