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A Convenient Synthesis of new Phenanthrolinone and Naphthyridinone Derivatives: Evaluation of their Biological activity

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Abstract

A novel and effective synthesis of substituted acetamide via smiles rearrangement is described. Treatment of phenols with 2-chloroacetamide in the presence of sodium hydroxide and DMA where substituted phenols, which contain electron withdrawing groups, are more reactive for smiles rearrangement. The reaction followed by cyclization of the product by E.A.A. afforded the corresponding substituted phenanthrolinone and naphthyridinone in good yields and showed higher activity against (G^- and G^+, Eschierchia coli and Staphylococcus aureus respectively) and good activity toward Aspergillius flavus and Candida albicans.

Keywords: Smiles rearrangement, phenanthrolinone and naphthyridinone.

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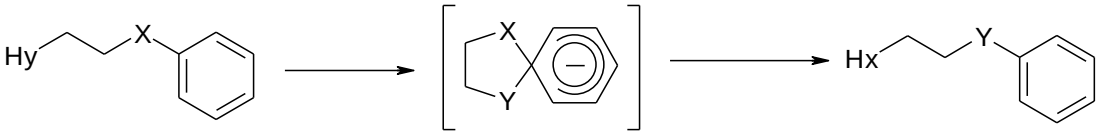
1. Introduction:

Smiles rearrangement [1] is one of the most important nucleophilic aromatic substitution reaction which attributed in the recent years in the studying of organic heterocylic compounds and the derivatives of its especially pyridine derivatives [2-7] that has a wide application and more effectiveness in medicinal chemistry and biological activity.



Scheme (1):

General smiles rearrangement

Dihydropyridine drugs, especially nifedipine, nicardipine and amalodipine, shows significant cardiovascular effect in the treatment of hypertension [8]. But, even though these drugs can be utilized, the synthesis of these compounds requires expensive reagents, organic solvents, a long reaction times and the yield result is usually unsatisfactory. Consequently, there has been focused efforts on developing effective and functional method for the implementation of the Hantzsch reaction, and there are potential researches on improved reaction conditions, consuming less reaction times and affording satisfactory yields [9-11].

Heterocyclic compounds exhibited highly biological activity as anti-bacteria, anti-fungel, anti-inflammatory, antipyretic and antihypertensive agents [12-17]. Here, in this work we synthesized phenanthrolinone and napthyridinone derivates by using either phenol or substituted phenol as starting materials which were transformed to amide derivatives and by treatment with E.A.A, the cyclization form took place to afford the substituted pyridinones. This protocol described one pot method proceeds via two-steps process through smiles rearrangement [18] to provide the desired products in good yields as in scheme (2).

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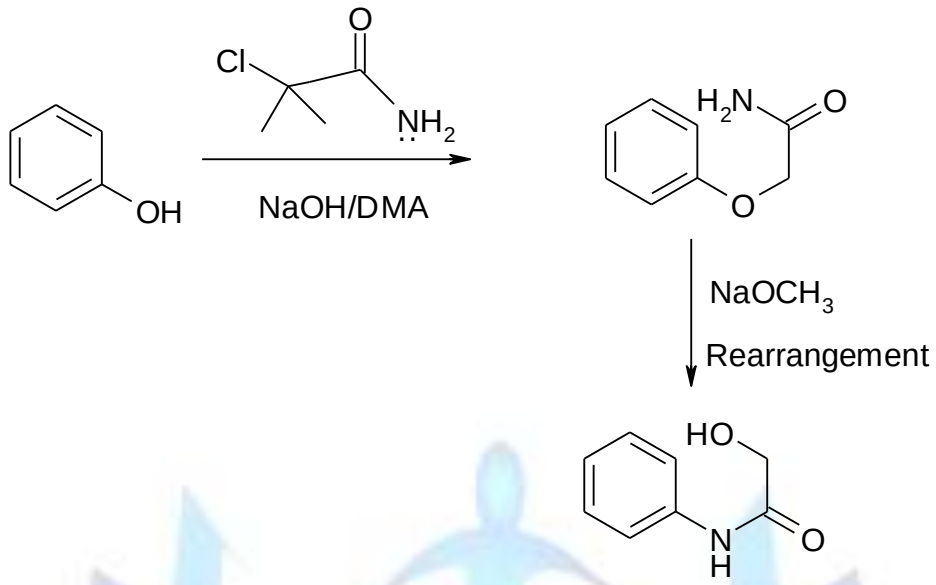
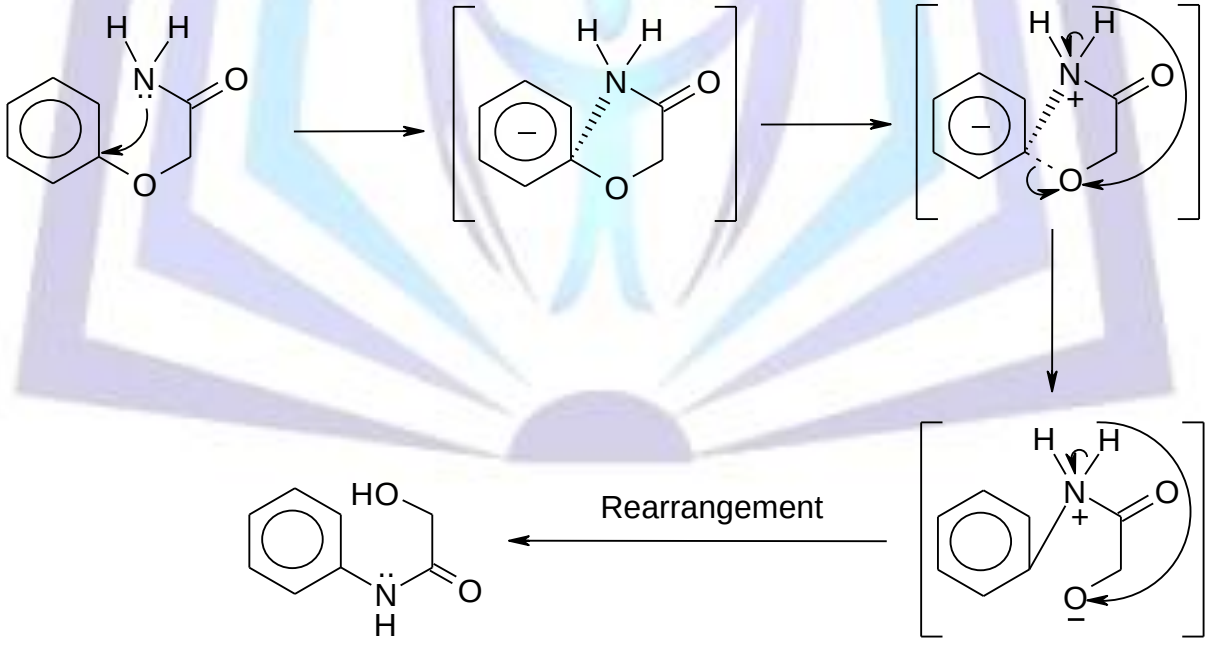
Scheme (2): Alkylation-smiles rearrangement sequence



Proposal mechanism for **scheme (2)**



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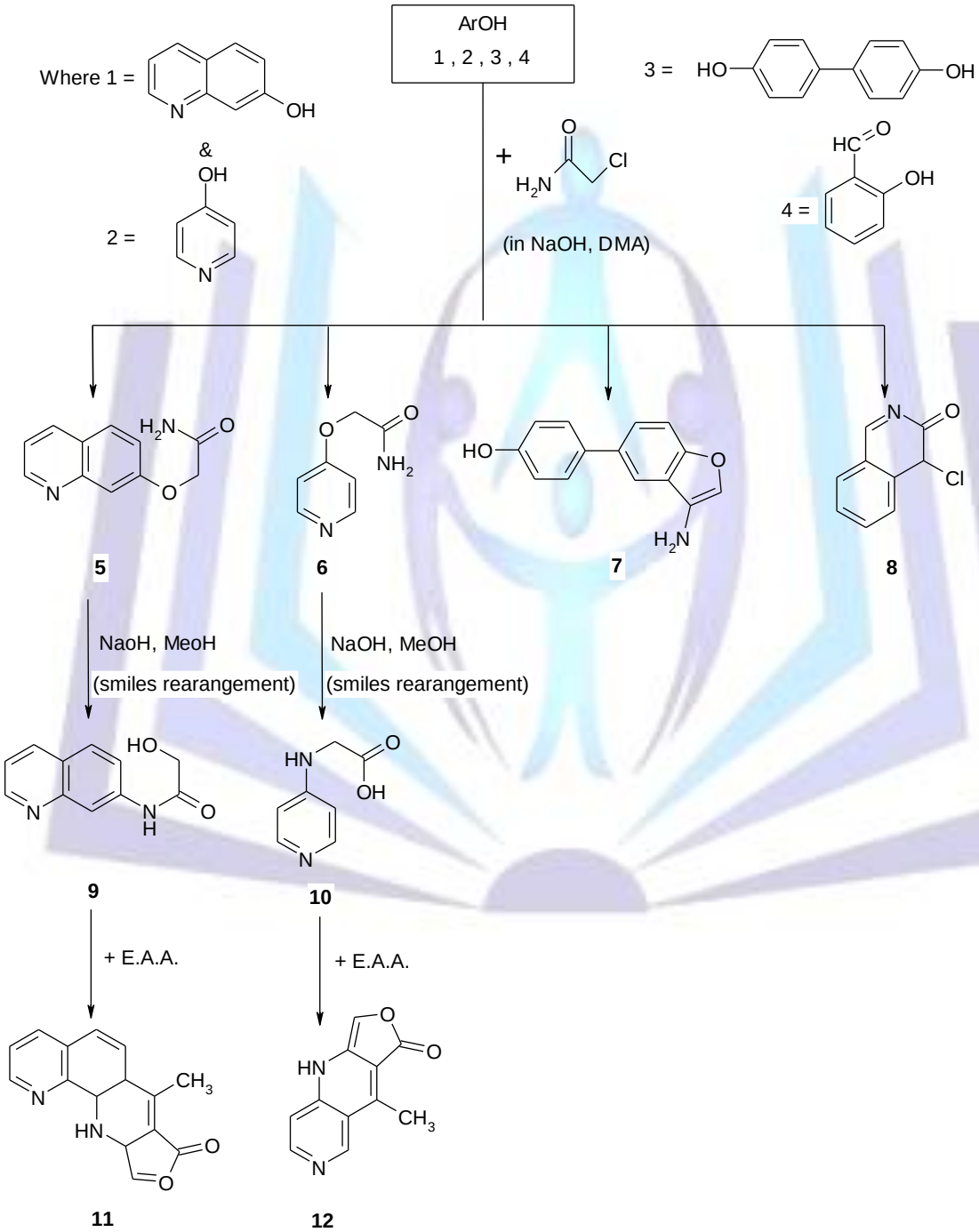
2. Results and Discussion

2.1. Chemistry

The synthetic route to prepare the different target compounds is described in scheme (3). Compound (1) and (2) afforded (9) and (10) via smiles rearrangement followed by cyclization with ethylacetoacetate to produce phenanthrolinone (11) and naphthyridinone (12) derivatives. Compound (3) and (4) also reacted to produce new compounds (7) and (8) but they failed to follow smiles rearrangement because they react with 2-chloroacetamide to produce the cyclized forms (benzofuranyl and isoquinolinone) (scheme 3) with expected biological activity similar to heterocyclic of medicinal properties and their effect on the blood pressure reduction in spontaneously hypertensive rats [19]; and their cardiotonic and renal vasodilating effects [20].

Scheme (3):



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3. Biological activity:

Disk diffusion method for filamentous fungi tested by using approved standard method (M38-A) developed by the NCCLS (2002) [21] for evaluating the susceptibilities of filamentous fungi to antifungal agents.

Disk diffusion method for yeasts developed by using approved standard method (M44-P) by the NCCLS (2003) [22].

Standard discs of tetracycline (antibacterial agent), amphotericin B (antifungal agent) served as positive controls for antimicrobial activity but filter discs impregnated with 10 µl of solvent (distilled water, chloroform, DMSO) were used as a negative control.

The agar used is Meuller-Hinton agar that is rigorously tested for composition and pH, further the depth of the agar in the plate is a factor to be considered in the disc diffusion method. This method is well documented and standard zones of inhibition have been determined for susceptible and resistant values.

Blank paper disks (Schleicher and Schuell, Spain) with a diameter of 8.0 mm were impregnated 10 µl of tested concentration of the stock solutions. When a filter paper disc impregnated with a tested chemical is placed on agar the chemical will diffuse from the disc into the agar. This diffusion will place the chemical in the agar only around the disc. The solubility of the chemical and its molecular size will determine the size of the area of chemical infiltration around the dis. If an organism is placed on the agar it will not grow in the area around the disc if it is susceptible to the chemical. This area of no growth around the disc is known as a zone of inhibition or "clear zone".

Agar-based methods such as Etest and disk diffusion can be good alternatives because they are simpler and faster than broth-based methods [23, 24].

From the results and regarding that fungi Aspergillus flavus and Candida albicans, most of the previous compounds were found inactive against them except compound (5) which exhibited very higher activity towards them compared with that of standard drugs (tetracycline and amphotericin B), in addition compound (6) which showed higher activity towards Aspergillus flavus only. Also it is interesting to point at that the compounds (9), (11), (12) attributed to good activity against Escherichia coli and staphylococcus aurues.

Compound No.		Inhibition Zone Diameter (mm/mg sample)			
		Af	**Ca**	**Ec**	**Sa**
Standard	Tetracycline antibacterial agent	–	–	33	32
	Amphotericin B antifungal agent	18	20	–	–
	5	30	20	42	47
	6	13	0.0	0.0	0.0
	9	0.0	0.0	11	12
	11	0.0	0.0	13	15
	12	0.0	0.0	9	9

Af - Aspergillus flavus, Ca - Candida albicans, Ec – Escherichia coli, Sa – Staphylococcus aureus

4. Conclusion:

In summary we have developed a novel and efficient method for the synthesis of a wide range of phenanthrolinone and naphthyridinone derivatives via the sequential smiles rearrangement followed by intramolecular cyclization in good yields and exhibit antibacterial and antifungal agents. Further work including the application, chemical transformation and biological activity is underway in our laboratory.

5. Experimental section:

5.1. General

Melting points were taken on Gallen kamp melting point apparatus and were uncorrected. Thin layer chromatography was performed with fluorescent silica gel plates HF_{254} (Merck), and plates were viewed under UV_{254} and 265 light. Infrared spectra ($v\text{-}cm^{-1}$) were recorded on Bruker vector Germany and on Mattson FT-IR 1000, using KBr disks, mass spectra were measured on GCO Finnigan MAT. ^{1}H-NMR spectra were recorded on Gemini-300 MHZ for ^{1}H and 100MHz for ^{13}C respectively, in DMSO-d_6 solution and TMS as internal standard in microanalytical center Cairo University - Egypt. Different phenols,

ethylacetoacetate and DMA were obtained from Fluka or Aldrich. The antibacterial activity was determined in microanalytical center Cairo University - Egypt.

5.2. General procedure for compounds 5, 6, 9, 10, 11, 12

The phenol (1) or (2) (1 mmol), (1 mmol) of 2-chloroacetamide and (1 mmol) of sodium hydroxide in DMA (20 ml) were refluxed with stirring for 2 hrs to produce 2-aryloxyacetamide (5) or (6). Sodium hydroxide (2 mmol) was added to this solution and then the mixture was stirred at 50 °C to produce N-aryl-2-hydroxy acetamide (9) or (10) which crystallized for each from ethyl alcohol and followed cyclized under the effect of ethylacetoacetate (1 mmol) to produce the compounds (11) or (12) respectively which showed highest inhibition zone against Escherichia coli and staphylococcus aureus, then crystallized from ethyl alcohol.

5.2.1. Compound **5:** brown ppt (yield: 56%) m.p. 262^{o}C. IR (KBr) (cm^{-1}): ν:, 3352, 3185 (NH_2), 3075 (CH, ar.), 2950 (CH_2 aliphatic), 1676 (CO-NH_2), 1559 (C=N); MS (m/z%): 202 (10.46%), 145 (100%); ^{1}H-NMR, (DMSO-d_6) δ: 4.32 (2H, CH_2), 7.09 (2H, NH_2), 7.41-8.50 (5H, ar. protons), 8.81 (CH, quinoline).

5.2.2. Compound **6:** white ppt (yield: 79%) m.p. 240^{o}C. IR (KBr) (cm^{-1}): ν: 3389-3220 (NH_2), 3060 (CH, ar.), 2928 (CH_2 aliphatic), 1648 (CO-NH_2), 1560 (C=N); MS (m/z%): 152 (54.67%), 108 (100%); ^{1}H-NMR, (DMSO-d_6) δ: 4.63 (2H, CH_2), 6.05 (2H, NH_2), 7.29-7.74 (3H, ar. protons), 8.59 (CH, pyridine).

5.2.3. Compound **9:** beige ppt (yield: 49%) m.p. 340^{o}C. IR (KBr) (cm^{-1}): ν: 3424 (OH), 3185 (NH), 3070 (CH, ar.), 2951 (CH_2, aliphatic), 1666 (C=O), 1628 (C=N), MS (m/z%): 202 (81.48%), 203 (M+1, 71.60%), 204 (M+2, 74.07%), 54 (100%), ^{1}H, NMR, (DMSO-d_6) δ: 1.96 (1H, OH), 4.69 (2H, metheline), 7.18 (1H, NH), 7.52-8.54 (5H, ar. protons), 8.82 (CH, quninoline).

5.2.4. Compound **10**: beige ppt (yield: 87%) m.p. decompose 260^{o}C. IR (KBr) (cm^{-1}): ν:3347 (OH), 3285 (NH), 3070 (CH, ar.), 2960 (CH_2, aliphatic), 1654 (C=O) 1556 (C=N); MS (m/z%): 152 (65.82%), 153 (M+1, 79.75%), 100 (100%); ^{1}H-NMR (DMSO-d_6) δ: 1.24(H, OH), 4.52 (2H,CH_2), 6.05 (1H, NH), 7.42-7.48 (3H, Ar.), 7.51 (CH, pyridine).

5.2.5. Compound **11**: deep brown ppt (yield: 52%) m.p. 150^{o}C. IR (KBr) (cm^{-1}): ν: 3435 (NHstr.), 2981 (CH, ar.), 2935 (CH, CH_3), 1725 (C=O), 1641 (NH, bend.) 1590 (C=N), 1409 (CH bend); MS (m/z%), 250 (52%), 124 (100%); ^{1}-H-NMR, (DMSO-d6) δ: 1.72 (3H, CH_3), 4.03 (1H, NH), 6.25 (1H, =CH-O), 7.25-7.36 (4H, ar.), 7.98 (CH, quninoline); ^{13}C NMR (100 MHZ, DMSO): δ 13.9, 100.4, 107.7, 110.1, 110.2, 110.4, 110.5, 124.5, 144.3, 158.6, 160.2, 168.8, 168.9, 170.7, 197.4.

5.2.6. Compound **12**: deep brown ppt (yield: 82%) m.p. 140^{o}C. IR (KBr) (cm^{-1}): ν: 3427 (NH), 2980 (CH, ar.), 2932 (CH, CH_3), 1725 (C=O), 1641 (NH bend.), 1567 (C=N), 1431 (CH, bend.); MS (m/z%): 200 (30.22%), 108 (100%); ^{1}H-NMR, (DMSO-d_6) δ: 1.52 (3H, CH_3), 4.09 (1H,NH), 6.01 (1H, =CH-O), 7.35-7.62 (2H, ar.), 9.97 (CH, pyridine); ^{13}C NMR (100 MHZ, DMSO): δ 17.7, 70.4, 71.1, 110.7, 123.5, 123.7, 123.9, 187.5, 188.6, 190.9, 208.7.

5.3. General procedure for compounds 7, 8

The phenol (3) or (4) (1 mmol), (1 mmol) of 2-chloroactamide and (1 mmol) of sodium hydroxide in DMA (20 ml) were stirring for 2 hr to produce 4- (3-amino-1-benzofuran-5-yl) phenol (7) or 4-(chloroisoquinolin-3-(4H)-one) (8) which crystallized for each from ethyl alcohol.

5.3.1. Compound **7:** white ppt (yield: 88%) m.p. 305^{o}C. IR (KBr) (cm^{-1}): ν: 3599 (OH), 3465, 3417 (NH_2), 3276-3168 (CH, ar.), 1599 (NH bend.); MS(m/z%): 225 (6.38%), 185 (100%); ^{1}H-NMR, (DMSO-d_6) δ: 4.44 (2H, NH_2), 5.14 (1H, OH), 6.98-7.56 (7H, ar.); ^{13}C NMR (100 MHZ, DMSO): δ 115.0, 115.5, 15.5, 115.6, 117.8, 126.8, 127.1, 127.1, 127.2, 132.7, 156.9, 156.9, 167.8, 169.8.

5.3.2. Compound **8**: brown ppt (yield: 95%) m.p. above 350^{o}C IR (KBr) (cm^{-1}): ν: 3415 (OH due to keto-enol form), 2927 (CH, ar.), 1675 (C=O), 1485 (C=N); MS (m/z%): 179 (2.69%), 121 (100%); ^{1}H-NMR, (DMSO-d_6) δ: 5.41 (1H, $-\overset{|}{\underset{}{CH}}-Cl$), 7.20-7.74 (4H, ar.); 8.19 (1H, pyridine); ^{13}C NMR (100 MHZ, DMSO): δ 61.2, 91.7, 113.7, 121.2, 127.8, 127.8, 130.7, 164.6, 189.8.

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