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One step synthesis of imidazole and benzimidazole acycloaromatic nucleoside analogs

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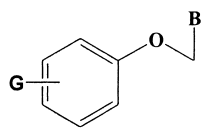
Abstract—A facile and rapid method for the synthesis of novel imidazole and benzimidazole aromatic acyclic nucleosides is described. Synchronous *N*-alkylation of imidazole or benzimidazole and potassium aryloxide with methylene iodide in the presence of triethylamine and a catalytic amount of tetrabutylammonium bromide (TBAB) in dry acetonitrile or acetone gave moderate yields of the acycloaromatic nucleoside analogs.

1. Introduction

Given the significance of imidazole and benzimidazole as a part of the purine nucleobase framework, drug design based on imidazole or benzimidazole is an interesting topic for synthetic medicinal chemists. The unique biological activity of *N*-alkylated imidazoles and benzimidazoles on remedying diseases such as protozoal infections, like trichomoniasis[1,2] as well as nucleoside analogs in inhibiting viral infections, like TCRB[3–5] and ribovirin[6] encouraged us to prepare novel derivatives which could show useful pharmaceutical properties. In continuation of our previous work on the synthesis of aromatic acyclic nucleosides with miscellaneous purine and pyrimidine nucleobases[7] (**1**) which led to introduction of 1-(phenoxymethyl)-6-azauracil (**2**) as an active chemotherapeutic agents for inhibiting the growth of myeloid cell and useful in the treatment of leukemia.[8] This synthesis[7] had a number of drawbacks including multi-step synthesis sequence, harmful reagents and intermediates, poor yield, tedious workups and harsh reaction conditions. Here we describe a simple and rapid method for the one step synthesis of acyclic nucleoside analogs.



G=Cl, Br,OBn, Me,...
B=Purine or Pyrimidine Nucleobases

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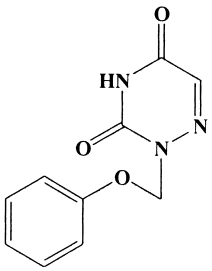

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2. Results and discussion

The synthesis of compounds (**3**) and (**4**) was achieved using 1 equiv. of each of methylene iodide, potassium aryloxide, imidazole (Scheme 1) or benzimidazole (Scheme 2), triethylamine and catalytic tetrabutylammonium bromide (TBAB) in dry acetonitrile or acetone and refluxed for 1.5–2.5 h.

Reaction of potassium aryloxide with methylene iodide and imidazole (Scheme 1) or benzimidazole (Scheme 2) was expected to give three products in each case. In the case of imidazole, the reaction gave compound (**3**) as major product and a trace amount of 1-(phenoxymethoxy) benzene (<%6) but it did not give the third possible product namely 1-(1*H*-imidazol-1-ylmethyl)-1*H*-imidazole. For benzimidazole (Scheme 2) compound (**4**) was obtained as the main product but in contrast to imidazole (Scheme 1) a trace amount of 1-(1*H*-benzimidazol-1-ylmethyl)-1*H*-benzimdazole was observed but not 1-(phenoxymethoxy) benzene. The reason for this difference is not fully understood. Semi-empirical quantum mechanic calculations (MNDO/3) gave a mechanistic point of view. The calculated data have illustrated a negative value for the heat of formation for in situ generated 1-(iodomethoxy) benzene ($E=-0.02346$ kcal/mol) with respect to other possible intermediates such as nucleophilic *N*-alkylation of imidazole or benzimidazole with methyleneiodide, although formation of 1-(iodomethoxy) benzene was not detected through the reaction progress.

Keywords: imidazole; benzimidazole; acycloaromatic nucleosides.
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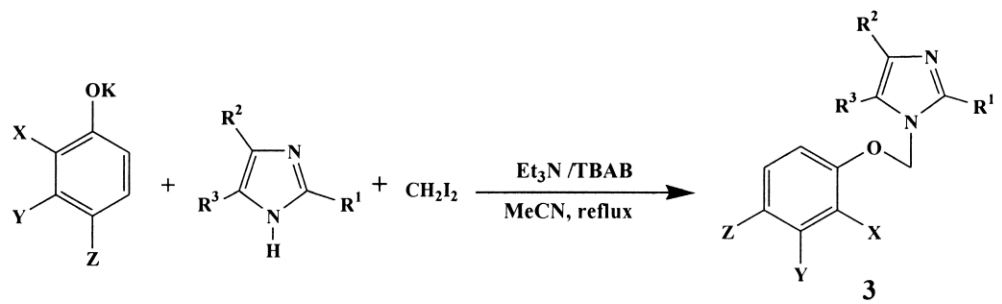
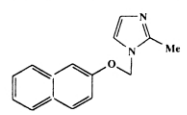
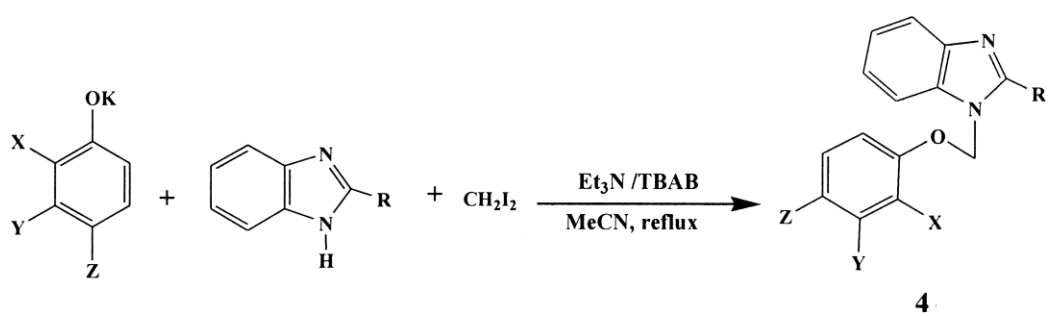


Compounds	X	Y	Z	R^1	R^2	R^3
3a	H	H	H	H	H	H
3b	H	H	Cl	H	H	H
3c	Cl	H	Cl	H	H	H
3d	Cl	Cl	H	H	H	H
3e	H	H	Me	H	H	H
3f	H	Me	Cl	H	H	H
3g	MeO	H	Allyl	H	H	H
3h	H	H	H	Me	NO_2	H
3i	H	H	Ph	H	Me	H
3j*	-	-	-	Me	H	H

*3j 

Scheme 1.

Because of the low solubility of imidazole in non-nucleophilic solvents, polar protic solvents are usually used but these solvents themselves can act as nucleophiles in the reaction with active substrates. Phase transfer catalyst (PTC) systems are often advantageous in these cases and such a system has been employed for imidazole[9] therefore using non-nucleophile solvents are possible for this purpose. So, for this reason TBAB was used as PTC in dry acetonitrile or acetone. The one step synthesis of imidazole acycloaromatic nucleosides with non-symmetrical imidazoles (4 or 5 substituted) are usually accompanied with the formation of multiple by-products.



Compounds	X	Y	Z	R
4a	H	H	H	H
4b	MeO	H	H	H
4c	H	H	Me	H
4d	H	H	Me	Me

Scheme 2.

In the case of 2-methyl-4(5)-nitroimidazole derivatives which possess considerable medical and potential agricultural interest as chemotherapeutic agents and potential biocides, compound (**3h**) was synthesized. Analyzing the spectroscopic data[10] has revealed to us the formation of 2-methyl-4-nitro-1-phenoxymethyl-1*H*-imidazole (**3h**) as the main product and trace amounts of the 5-nitro isomer (<5%). This is completely in agreement with the literature,[11] where the 1-alkyl-2-methyl-4-nitro derivative is obtained under basic conditions, while the 1-alkyl-2-methyl-5-nitro derivative is the major product under neutral or acidic conditions.[12] The same results were also obtained for 4(5)-methylimidazole, entry (**3i**).

3. Conclusion

The one step synthesis of imidazole or benzimidazole acycloaromatic nucleosides in which the sugar moiety is replaced by an aromatic side-chain may show interesting biological activity. The explained method has superiority with respect to the previous methods. Glycoside linkage i.e. $O-CH_2-N$ as a part of nucleosides is directly interacted with aromatic π-electron systems and this special case may create interesting biological activity.

4. Experimental

4.1. General

The chemicals were obtained from Fluka or Merck chemical companies except for potassium aryloxides that were prepared using 1 equiv. of KOH and 1 equiv. of related phenols in a minimum amount of distilled water, which is evaporated to dryness under vacuum. Purification and dehydration of solvents were done using the reported methods[13] and stored over molecular sieves. TLC using silica gel SILG/UV 254 plates followed reaction progress. IR spectra were run on a Perkin–Elmer 781 Spectrophotometer. The ^1H NMR spectra were run on a Bruker Advanced DPX-250, FT-NMR spectrometer. Mass spectra were recorded on a Shimadzu GC MS-QP 1000EX. Microanalyses were performed on a Perkin–Elmer 240-B microanalyzer. Melting points were determined on a Büchi 510 in open capillary tubes and are uncorrected.

4.1.1. 1-Phenoxymethyl-1*H*-imidazole (3a). In a round bottomed flask (100 mL) a mixture of imidazole (0.68 g, 0.01 mol), methylene iodide (2.68 g, 0.01 mol), potassium phenoxide (1.32 g, 0.01 mol), dry triethylamine (1.01 g, 0.01 mol) and catalytic amount of TBAB (0.1 g) were dissolved in dry acetonitrile (40 mL). The solution was refluxed for 2 h. Evaporation of solvent gave an oil, which was dissolved in $CHCl_3$ (150 mL) and washed with water (2×200 mL). The organic layer was dried with anhydrous sodium sulfate, filtered and evaporated to give an oily crude product. Using column chromatography on silica gel and EtOAc as eluent gave a brown–yellow, syrupy product (0.99 g, 57%); R_f (EtOH) 0.7; IR (potassium bromide): ν_{max} 3150, 2980, 1620–1500, 1200, 1150 cm^{-1}; MS: *m/z* (%) 174 (M^+, 58.2); δ_H (250 MHz, $CDCl_3$) 7.69 (1H, s, C(2), imidazole), 7.60–7.04 (7H, m, aromatic), 5.79 (2H, s, OCH_2N). Anal. calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.87; H, 5.86; N, 16.19.

4.1.2. 1-(4-Chloro-phenoxymethyl)-1*H*-imidazole (3b). Column chromatography on silica gel elution with EtOAc gave pale yellow crystals (1.27 g, 61%); R_f (EtOH) 0.8; mp 72–73°C; IR (potassium bromide): ν_{max} 3100, 2900, 1600–1540, 1220, 1160, 750 cm^{-1}; MS: *m/z* (%) 208 (M^+, 12.1); δ_H (250 MHz, $CDCl_3$) 7.70 (1H, s, C(2), imidazole), 7.50–6.80 (6H, m, aromatic), 5.80 (2H, s, OCH_2N). Anal. calcd for $C_{10}H_9N_2O$: C, 57.57; H, 4.35; N, 13.43. Found: C, 57.44; H, 4.36; N, 13.36.

4.1.3. 1-[(2,4-Dichloro-phenoxy) methyl]-1*H*-imidazole (3c). Column chromatography on silica gel elution with EtOAc/EtOH (5:2) gave pale yellow crystals (1.43 g, 59%); R_f (EtOH) 0.83; mp 80–82°C; IR (potassium bromide): ν_{max} 3130, 2900, 1620–1540, 1210, 1140, 800–650 cm^{-1}; MS: *m/z* (%) 243 (M^+, 29.1); δ_H (250 MHz, $CDCl_3$) 7.73 (1H, s, C(2), imidazole), 7.50–6.80 (5H, m, aromatic), 5.78 (2H, s, OCH_2N). Anal. calcd for $C_{10}H_8Cl_2N_2O$: C, 49.41; H, 3.32; N, 11.52. Found: C, 49.58; H, 3.21; N, 11.40.

4.1.4. 1-(2,3-Dichloro-phenoxymethyl-1*H*-imidazole (3d). Column chromatography on silica gel elution with EtOAc/EtOH (5:2) gave pale yellow crystals (1.45 g, 60%); R_f (EtOH) 0.81; mp 70–72°C; IR (potassium bromide): ν_{max} 3130, 2900, 1620–1540, 1210, 1140, 800–650 cm^{-1}; MS: *m/z* (%) 243 (M^+, 29.1); δ_H (250 MHz, $CDCl_3$) 7.58 (1H, s, C(2), imidazole), 7.46–6.74 (5H, m, aromatic), 5.79 (2H, s, OCH_2N). Anal. calcd for $C_{10}H_8Cl_2N_2O$: C, 49.41; H, 3.32; N, 11.52. Found: C, 49.29; H, 3.24; N, 11.38.

4.1.5. 1-*p*-Tolyloxymethyl-1*H*-imidazole (3e). Column chromatography on silica gel elution with EtOAc gave white crystals (1.01 g, 54%); R_f (EtOH) 0.73; mp 70–71°C; IR (potassium bromide): ν_{max} 3100, 2960, 1600–1500, 1200, 1040 cm^{-1}; MS: *m/z* (%) 188 (M^+, 32.6); δ_H (250 MHz, $CDCl_3$) 7.48 (1H, s, C(2), imidazole), 7.19–6.71 (6H, m, aromatic), 5.75 (2H, s, OCH_2N), 2.21 (3H, s, Me). Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.05; H, 6.33; N, 14.68.

4.1.6. 1-(4-Chloro-3-methyl-phenoxymethyl)-1*H*-imidazole (3f). Column chromatography on silica gel elution with EtOAc/EtOH (5:2) gave pale yellow crystals (1.37 g, 62%); R_f (EtOH) 0.76; mp 68–72°C; IR (potassium bromide): ν_{max} 3130, 2900, 1600–1530, 1140, 690 cm^{-1}; MS: *m/z* (%) 243 (M^+, 29.1); δ_H (250 MHz, $CDCl_3$) 7.57 (1H, s, C(2), imidazole), 7.57–7.03 (5H, m, aromatic), 6.04 (2H, s, OCH_2N), 2.21 (3H, s, Me). Anal. calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.29; H, 5.08; N, 12.68.

4.1.7. 1-(4-Allyl-2-methoxy-phenoxymethyl)-1*H*-imidazole (3g). Column chromatography on silica gel elution with EtOAc gave a yellow oily product (1.58 g, 65%); R_f (EtOH) 0.84; IR (potassium bromide): ν_{max} 3200, 2900, 1600–1500, 1240–1210, 1100 cm^{-1}; MS: *m/z* (%) 245 (M^+, 60.3); δ_H (250 MHz, $CDCl_3$) 7.80 (1H, s, C(2), imidazole), 7.20–6.50 (5H, m, aromatic), 6.02–5.81 (1H, m, vinylic), 5.80 (2H, s, OCH_2N), 5.21–4.9 (2H, dd, vinylic, *J*=10.3, 16.8 Hz), 3.91 (3H, s, OCH_3), 3.43 (2H, d,

allylic, J=6.6 Hz). Anal. calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.91; H, 6.71; N, 11.59.

4.1.8. 2-Methyl-4-nitro-1-phenoxymethyl-1*H*-imidazole (3h). Column chromatography on silica gel elution with EtOAc/EtOH (5:3) gave pale yellow crystals (1.32 g, 57%); R_f (EtOH) 0.85; mp 91–93°C; IR (potassium bromide): ν_{max} 3100, 2890, 1600–1560, 1550–1350 (two bands), 1200, 1100 cm^{-1}; MS: m/z (%) 233 (M^+, 41.8); δ_H (250 MHz, $CDCl_3$) 7.82 (1H, s, C(5), imidazole), 7.42–6.71 (5H, m, aromatic), 5.80 (2H, s, OCH_2N), 2.62 (3H, s, Me). Anal. calcd for $C_{11}H_{11}N_3O_3$: C, 56.85; H, 4.75; N, 18.02. Found: C, 56.93; H, 4.88; N, 17.94.

4.1.9. 1-(4-Phenyl-phenoxymethyl)-4-methyl-1*H*-imidazole (3i). Column chromatography on silica gel elution with EtOAc/EtOH (5:2) gave white crystals (1.37 g, 53%); R_f (EtOH) 0.5; mp 120–125°C; IR (potassium bromide): ν_{max} 3100, 2890, 1600–1500, 1210, 1100 cm^{-1}; MS: m/z (%) 264 (M^+, 24.9); δ_H (250 MHz, $CDCl_3$) 7.43 (1H, s, C(2), imidazole), 7.43–6.87 (12H, m, aromatic), 5.66 (2H, s, OCH_2N), 2.09 (3H, s, Me). Anal. calcd for $C_{17}H_{16}N_2O$: C, 77.27; H, 6.06; N, 10.60. Found: C, 77.21; H, 5.98; N, 10.63.

4.1.10. 2-Methyl-1-β-naphthoxymethyl-1*H*-imidazole (3j). Column chromatography on silica gel elution with EtOAc/EtOH (5:2) gave white crystals (1.23 g, 52%); R_f (EtOH) 0.7; mp 109–111°C; IR (potassium bromide): ν_{max} 3100, 2900, 1600–1550, 1200, 1140 cm^{-1}; MS: m/z (%) 238 (M^+, 35.8); δ_H (250 MHz, $CDCl_3$) 8.06–7.02 (9H, m, aromatic), 5.89 (2H, s, OCH_2N), 2.65 (3H, s, Me). Anal. calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.72; H, 6.07; N, 11.84.

4.1.11. 1-Phenoxymethyl-1*H*-benzimidazole (4a). In a round bottomed flask (100 mL) a mixture of benzimidazole (1.18 g, 0.01 mol), methylene iodide (2.68 g, 0.01 mol), potassium phenoxide (1.32 g, 0.01 mol), dry triethylamine (1.01 g, 0.01 mol) and catalytic amount of TBAB (0.1 g) were dissolved in dry acetonitrile (40 mL). The solution was refluxed for 2.5 h. Evaporation, dissolving in $CHCl_3$ (150 mL) washing with water (2×200 mL) afforded the crude solid product which, purified with column chromatography on silica gel EtOAc/EtOH (8:1) gave white crystals (1.18 g, 53%); R_f (EtOH) 0.76; mp 105–107°C; IR (potassium bromide): ν_{max} 3180, 2800, 1610–1500, 1200, 1160 cm^{-1}; MS: m/z (%) 224 (M^+, 34.2); δ_H (250 MHz, $CDCl_3$) 8.33 (1H, s, C(2), benzimidazole), 7.92–6.92 (9H, m, aromatic), 5.99 (2H, s, OCH_2N). Anal. calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.07; H, 5.46; N, 12.57.

4.1.12. 1-(2-Methoxy-phenoxymethyl)-1*H*-benzimidazole (4b). Column chromatography on silica gel elution with EtOAc gave a bright brown oil (1.27 g, 50%); R_f (EtOH) 0.84; IR (potassium bromide): ν_{max} 3150, 2900, 1600–1550, 1240–1210, 1100 cm^{-1}; MS: m/z (%) 254 (M^+, 20.3); δ_H (250 MHz, $CDCl_3$) 7.96 (1H, s, C(2), benzimidazole), 7.70–6.71 (8H, m, aromatic), 5.93 (2H, s, OCH_2N), 3.64 (3H, s, OCH_3). Anal. calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.81; H, 5.60; N, 10.96.

4.1.13. 1-(*p*-Tolyloxymethyl)-1*H*-benzimidazole (4c). Column chromatography on silica gel elution with EtOAc gave white crystals (1.10 g, 49%); R_f (EtOH) 0.73; mp 101–112°C; IR (potassium bromide): ν_{max} 3100, 2900, 1600–1500, 1200, 1100 cm^{-1}; MS: m/z (%) 238 (M^+, 40.1); δ_H (250 MHz, $CDCl_3$) 8.13 (1H, s, C(2), benzimidazole), 7.86–7.26 (8H, m, aromatic), 6.77 (2H, s, OCH_2N), 2.26 (3H, s, CH_3). Anal. calcd for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.46; N, 11.83. Found: C, 75.54; H, 5.39; N, 11.96.

4.1.14. 1-(*p*-Tolyloxymethyl)-2-methyl-1*H*-benzimidazole (4d). Column chromatography on silica gel elution with EtOAc gave white crystals (1.36 g, 54%); R_f (EtOH) 0.71; mp 92–94°C; IR (potassium bromide): ν_{max} 3100, 2850, 1600–1500, 1210, 1100 cm^{-1}; MS: m/z (%) 252 (M^+, 35.3); δ_H (250 MHz, $CDCl_3$) 7.08–6.51 (8H, m, aromatic), 5.92 (2H, s, OCH_2N), 2.50 (3H, s, C(2), CH_3), 2.20 (3H, s, CH_3 (aryl)). Anal. calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.21; H, 6.46; N, 11.29.

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