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Transition metal-free, base-promoted hydroalkoxylation: Synthesis of substituted imidazo[2,1-c][1,4]oxazines

MUTHUPANDI NAGARAJ and SHANMUGAM MUTHUSUBRAMANIAN*
Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India
e-mail: muthumanian2001@yahoo.com

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Abstract. An efficient, transition metal-free method to synthesize substituted imidazo[2,1-c][1,4]oxazine derivatives *via* hydroalkoxylation of 1,5-alkynyl alcohol has been described. The reaction proceeds regioselectively with exclusive formation of 6-*exo-dig* product.

Keywords. 1,4-Oxazines; hydroalkoxylation; 6-*exo-dig*; regioselectivity; 1,5-alkynyl alcohol.

1. Introduction

Novel fused heterocyclic ring systems are often considered as important scaffolds in medicinal chemistry. Synthetic and naturally occurring fused bicyclic imidazoles have been found to display a wide range of biological activities,[1] thus assuming clinical importance as drugs.[2] Obviously, efficient and combinatorial methodologies towards the convenient synthesis of fused imidazole frameworks are being explored by both organic and medicinal chemists. Recently, nitroimidazooxazine (PA-824)[3] (figure 1) has been shown to exhibit good *in vitro* and *in vivo* activities against *Mycobacterium* tuberculosis in both active and persistent forms.[4] GSK588045 also exhibits outstanding profile with in *vivo* activity in different animal models of anxiety and depression[5] and is being processed as a clinical candidate.

Hydroalkoxylation of alkynes is an efficient approach to construct C–O bonds towards the synthetic intermediates of natural products.[6] The catalytic addition of alcohols to alkynes can be performed achieving 100% atom efficiency with negligible waste formation[7] paving way for many useful oxygen containing organic compounds. The importance of intermolecular hydroalkoxylation in the synthesis of ethers has been widely recognized and exploited.[8]

Metals or Lewis acids or bases have been employed as catalysts to effect exocylic as well as endocyclic ring formation from different starting materials.[9] Normally metals catalyze the *exo* mode cyclization,[10] though bases such as sodium amide and sodium hydride have also been employed[11] for this transformation. Nevertheless, *endo* mode of cyclization is also noticed with alkynyl alcohols using metal catalysts.[12]

2. Experimental

2.1 *General*

Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ using TMS as internal standard. Chemical shifts are reported in parts per million (δ), coupling constants (J values) are reported in Hertz (Hz). The hydroxyl hydrogen signal is not visible in most of the cases. ^{13}C NMR spectra were routinely run with broadband decoupling. Melting points were determined on a melting point apparatus (Inlab Pvt. Ltd., India) equipped with a thermometer and were uncorrected. Column chromatography was carried out in silica gel (60–120 mesh) using pet ether-ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 series II Elemental CHNS analyzer.

2.2 *General procedure for the preparation of aryl(4-aryl-1-(3-arylprop-2-ynyl)-1H-imidazol-2-yl)methanol (**1**)*

Terminal 1,5-alkyne-alcohol imidazole derivatives were synthesized following a literature procedure.[13a] Aryl halide (1 equiv.) in dry acetonitrile (10 mL) under nitrogen atmosphere was added with $PdCl_2(PPh_3)_2$ (3 mol%), CuI (6 mol%), Et_3N (5 equiv.) and terminal-1,5 alkyne-alcohol imidazole derivative (1.0 equiv.). The resulting mixture was refluxed for 30 min. The solvent was evaporated under reduced pressure and

*For correspondence

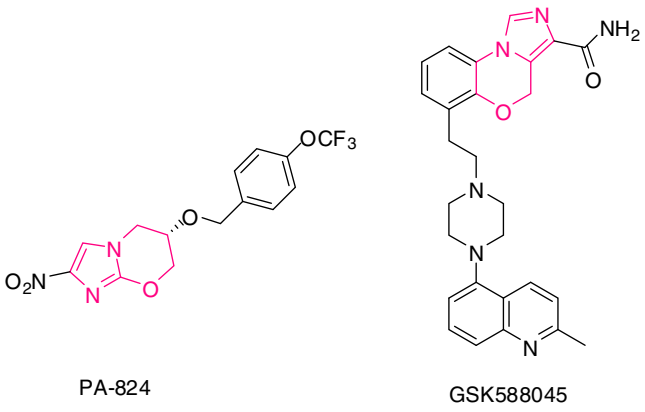


Figure 1. Biologically active compounds containing imidazooxazine scaffold.

the crude material was then purified by flash chromatography to yield non-terminal alkyne (Ethyl acetate/petroleum ether 1:4). Terminal 1,5-alkyne-alcohol imidazole derivatives (**1a–i**) have already been reported.[13a]

2.2a *Phenyl(4-phenyl-1-(3-phenylprop-2-ynyl)-1H-imidazol-2-yl)methanol (**1j**)*: Colorless solid; M.p. 148–150°C; ^{1}H NMR (300 MHz, $CDCl_3$) = 4.42 (d, J = 17.7 Hz, 1H), 4.51 (d, J = 17.7 Hz, 1H), 6.15 (s, 1H), 7.22–7.23 (m, 8H), 7.32–7.44 (m, 6H), 7.73 (dd, J = 7.5 Hz, 1.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 36.6, 69.4, 81.8, 85.7, 116.4, 121.9, 124.9, 126.4, 126.9, 127.8, 128.3, 128.6, 128.6, 128.8, 131.7, 133.7, 139.6, 140.1, 148.7; Anal. Calcd. (%) for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found (%): C, 82.26; H, 5.42; N, 7.59.

2.2b *(1-(3-(4-Chlorophenyl)prop-2-ynyl)-4-phenyl-1H-imidazol-2-yl)(phenyl)methanol(**1k**)*: Colorless solid; M.p. 152–154°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.37 (d, J = 18.0 Hz, 1H), 4.52 (d, J = 18.0 Hz, 1H), 6.16 (s, 1H), 7.15–7.27 (m, 7H), 7.30 (d, J = 8.1 Hz, 2H), 7.34–7.43 (m, 4H), 7.72 (dd, J = 7.8 Hz, 1.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 36.4, 69.1, 82.8, 84.2, 116.3, 120.3, 124.8, 126.1, 126.9, 127.6, 128.4, 128.5, 128.6, 132.9, 133.4, 134.8, 139.4, 139.9, 148.8; Anal. Calcd. (%) for $C_{25}H_{19}ClN_2O$: C, 75.28; H, 4.80; N, 7.02. Found (%): C, 75.09; H, 4.72; N, 6.91.

2.2c *Phenyl(4-phenyl-1-(3-(3-(trifluoromethyl)phenyl) prop-2-ynyl)-1H-imidazol-2-yl) methanol (**1l**)*: Colorless solid; M.p. 124–126°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.31 (d, J = 18.0 Hz, 1H), 4.60 (d, J = 18.0 Hz, 1H), 6.22 (s, 1H), 7.12 (s, 1H), 7.22 (d, J = 6.9 Hz, 2H), 7.29–7.37 (m, 5H), 7.43–7.53 (m, 5H), 7.71 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 36.2, 68.9, 82.8, 83.6, 116.2, 121.8, 122.8, 124.8, 125.2, 125.3, 125.9, 126.9, 127.5, 128.4, 128.6, 128.7, 130.8, 133.3, 134.7, 139.4, 139.9, 149.0; Anal. Calcd. (%) for $C_{26}H_{19}F_3N_2O$: C, 72.21; H, 4.43; N, 6.48. Found (%): C, 72.08; H, 4.36; N, 6.39.

2.2d *(1-(3-Phenylprop-2-ynyl)-4-p-tolyl-1H-imidazol-2-yl)(p-tolyl)methanol (**1m**)*: Colorless solid; M.p. 157–159°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.28 (s, 3H), 2.35 (s, 3H), 4.45 (d, J = 18.0 Hz, 1H), 4.53 (d, J = 18.0 Hz, 1H), 6.06 (s, 1H), 7.12 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.22 (s, 1H), 7.29–7.33 (m, 7H), 7.64 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.1, 21.2, 36.5, 69.3, 81.8, 83.8, 115.9, 121.9, 124.7, 126.4, 128.2, 128.7, 129.3, 130.8,* 131.7, 136.4, 137.1, 137.5, 139.5, 148.6; Anal. Calcd. (%) for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14. Found (%): C, 82.51; H, 6.07; N, 7.05. *Two carbon signals are merged together.

2.2e *(1-(3-(4-Chlorophenyl)prop-2-ynyl)-4-p-tolyl-1H-imidazol-2-yl)(p-tolyl)methanol (**1n**)*: Colorless solid; M.p. 139–141°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.26 (s, 3H), 2.33 (s, 3H), 4.37 (d, J = 18.0 Hz, 1H), 4.54 (d, J = 18.0 Hz, 1H), 6.11 (s, 1H), 7.08–7.14 (m, 3H), 7.16–7.18 (m, 4H), 7.23 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.0, 21.2, 36.3, 68.9, 83.1, 84.1, 115.8, 120.4, 124.7, 126.0, 128.5, 129.1, 129.2, 130.1, 132.9, 134.7, 136.4, 137.0, 138.7, 139.4, 148.8; Anal. Calcd. (%) for $C_{27}H_{23}ClN_2O$: C, 75.96; H, 5.43; N, 6.56. Found (%): C, 75.82; H, 5.36; N, 6.48.

2.2f *p-Tolyl(4-p-tolyl-1-(3-(3-(trifluoromethyl)phenyl) prop-2-ynyl)-1H-imidazol-2-yl)methanol (**1o**)*: Colorless solid; M.p. 126–128°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.24 (s, 3H), 2.34 (s, 3H), 4.37 (d, J = 18.0 Hz, 1H), 4.60 (d, J = 18.0 Hz, 1H), 6.13 (s, 1H), 7.09–7.12 (m, 2H), 7.18 (d, J = 7.8 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.38–7.40 (m, 2H), 7.49 (s, 1H), 7.52–7.54 (m, 2H), 7.61 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 20.7, 20.9, 36.0, 69.0, 77.2, 83.5, 115.6, 122.8, 124.6, 125.0, 126.0, 128.3, 128.5, 128.9, 129.0, 130.6, 131.0, 134.6, 136.3, 136.9, 137.2, 139.6, 139.9, 148.6; Anal. Calcd. (%) for $C_{28}H_{23}F_3N_2O$: C, 73.03; H, 5.03; N, 6.08. Found (%): C, 72.94; H, 4.98; N, 5.99.

2.3 *General procedure for the preparation of substituted imidazo[2,1-c][1,4]oxazine (**2**)*

Aryl(4-aryl-1-(prop-2-ynyl)-1H-imidazol-2-yl)methanol **1** (1 mmol) was dissolved in DMF (5.0 mL) taken in a 10 mL microwave vial. To this, LiOtBu (7.4 mmol)

was added and the reaction mixture was subjected to microwave irradiation (CEM-DISCOVER model no. 908010) at 80°C for 10 min in 120 W microwave power. Completion of the reaction was confirmed by TLC. The reaction mixture was then poured into ice-cold water and extracted with dichloromethane. The solvent was evaporated under reduced pressure and the crude material was then purified by flash chromatography to yield **2**.

2.3a *6-Methyl-2,8-diphenyl-[2,1-c][1,4]-8H-imidazooxazine (**2a**)*: Colorless solid; M.p. 118–120°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.89 (s, 3H), 6.23 (s, 1H), 6.38 (s, 1H), 7.16 (s, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.33–7.38 (m, 7H), 7.65 (d, J = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.4, 75.5, 101.9, 110.5, 124.8, 126.8, 127.1, 128.4, 128.5, 128.7, 133.8, 137.5, 138.9, 141.7, 142.3; Anal. Calcd. (%) for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found (%): C, 79.01; H, 5.52; N, 9.64.

2.3b *2,8-Bis(4-chlorophenyl)-6-methyl-8H-imidazo[2,1-c][1,4]oxazine (**2b**)*: Colorless solid; M.p. 113–115°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.89 (s, 3H), 6.24 (s, 1H), 6.30 (s, 1H), 7.13 (s, 1H), 7.25–7.32 (m, 6H), 7.65 (d, J = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.3, 74.8, 101.8, 110.7, 126.1, 128.5, 128.6, 128.7, 132.2, 132.4, 134.7, 135.8, 138.6, 140.8, 147.6; Anal. Calcd. (%) for $C_{19}H_{14}Cl_2N_2O$: C, 63.88; H, 3.95; N, 7.84. Found (%): C, 63.72; H, 3.82; N, 7.77.

2.3c *2,8-Bis(4-bromophenyl)-6-methyl-8H-imidazo[2,1-c][1,4]oxazine (**2c**)*: Colorless solid; M.p. 141–143°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.90 (s, 3H), 6.24 (s, 1H), 6.29 (s, 1H), 7.15 (s, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.44–7.50 (m, 4H), 7.59 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.3, 74.9, 101.8, 110.8, 120.5, 122.9, 126.4, 128.8, 131.6, 131.7, 132.7, 136.3, 138.6, 140.9, 142.6; MS (M+1) 447.16; Anal. Calcd. (%) for $C_{19}H_{14}Br_2N_2O$: C, 51.15; H, 3.16; N, 6.28. Found (%): C, 51.02; H, 3.08; N, 6.22.

2.3d *2,8-Bis(4-flourophenyl)-6-methyl-8H-imidazo[2,1-c][1,4]oxazine (**2d**)*: Colorless solid; M.p. 84–86°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.88 (s, 3H), 6.24 (s, 1H), 6.30 (s, 1H), 7.01–7.10 (m, 5H), 7.35 (t, J = 6.6 Hz, 2H), 7.68 (t, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.2, 74.9, 101.8, 110.3, 115.3, 115.5, 126.4, 129.2, 129.9, 133.2, 138.7, 140.9, 142.5, 160.8, 164.1; Anal. Calcd. (%) for $C_{19}H_{14}F_2N_2O$: C, 70.36; H, 4.35; N, 8.64. Found (%): C, 70.22; H, 4.23; N, 8.54.

2.3e *6-Methyl-2,8-dip-tolyl-8H-imidazo[2,1-c][1,4]oxazine (**2e**)*: Colorless solid; M.p. 118–120°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.88 (s, 3H), 2.33 (s, 3H), 2.34 (s, 3H), 6.22 (s, 1H), 6.34 (s, 1H), 7.11 (s, 1H), 7.15–7.17 (m, 4H), 7.24 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.1, 20.9,* 75.3, 101.6, 109.8, 124.6, 126.9, 128.9, 129.0, 131.0, 134.5, 136.2, 138.2, 138.8, 141.7, 142.0; Anal. Calcd. (%) for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found (%): C, 79.61; H, 6.29; N, 8.74. *Two carbons are mereged together.

2.3f *2,8-Bis(4-methoxyphenyl)-6-methyl-8H-imidazo[2,1-c][1,4]oxazine (**2f**)*: Colorless solid; M.p. 123–125°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.88 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 6.24 (s, 1H), 6.30 (s, 1H), 6.87 (d, J = 6.9 Hz, 2H), 6.89 (d, J = 6.9 Hz, 2H), 7.07 (s, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.4, 55.2, 55.3, 75.3, 101.8, 109.4, 113.8, 113.9, 126.1, 126.8, 128.7, 129.7, 138.9, 141.6, 142.2, 158.7, 159.9; MS (M+1) 349.22; Anal. Calcd. (%) for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found (%): C, 72.31; H, 5.72; N, 7.96.

2.3g *6-Methyl-2,8-di(naphthalen-2-yl)-8H-imidazo[2,1-c][1,4]oxazine (**2g**)*: Colorless solid; M.p. 181–183°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.85 (s, 3H), 6.17 (s, 1H), 6.54 (s, 1H), 7.22 (s, 1H), 7.41–7.79 (m, 13H), 8.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.3, 75.7, 101.9, 111.1, 122.9, 123.5, 124.5, 124.7, 125.4, 126.1, 126.2, 126.4, 127.6, 128.0, 128.1, 128.3, 128.5, 131.1,* 132.6,* 133.4, 133.7, 134.8, 139.1, 141.7, 142.5; Anal. Calcd. (%) for $C_{27}H_{20}N_2O$: C, 83.48; H, 5.19; N, 7.21. Found (%): C, 83.32; H, 5.11; N, 7.13. *Two carbons are merged together.

2.3h *2,8-Di(biphenyl-4-yl)-6-methyl-8H-imidazo[2,1-c][1,4]oxazine (**2h**)*: Colorless solid; M.p. 203–205°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.92 (s, 3H), 6.26 (s, 1H), 6.43 (s, 1H), 7.20 (s, 1H), 7.32–7.35 (m, 3H), 7.40 (d, J = 7.2 Hz, 2H), 7.45 (d, J = 7.8 Hz, 2H), 7.56–7.61 (m, 9H), 7.83 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.4, 75.4, 101.9, 110.7, 125.3, 126.8, 127.1, 127.2, 127.3, 127.5, 127.6, 128.7, 128.8,* 132.9, 136.5, 139.0, 139.5, 140.6, 140.9, 141.5, 141.6, 142.5; Anal. Calcd. (%) for $C_{31}H_{24}N_2O$: C, 84.52; H, 5.49; N, 6.36. Found (%): C, 84.41; H, 5.39; N, 6.28. *Two carbons are merged together.

2.3i *6-Methyl-2,8-di(thiophen-2-yl)-8H-imidazo[2,1-c][1,4]oxazine (**2i**)*: Viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.87 (s, 3H), 6.23 (s, 1H), 6.57 (s, 1H), 6.91–6.93 (m, 2H), 7.00 (t, J = 5.1 Hz, 1H), 7.06

(s, 1H), 7.17 (d, J = 5.1 Hz, 1H), 7.26 (d, J = 4.2 Hz, 1H), 7.30 (d, J = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.3, 71.2, 101.8, 110.0, 122.1, 123.3, 126.6, 126.7, 126.9, 127.4, 136.8, 137.3, 138.2, 140.4, 142.2; Anal. Calcd. (%) for $C_{15}H_{12}N_2OS_2$: C, 59.97; H, 4.03; N, 9.33; S, 21.35. Found (%): C, 59.85; H, 3.98; N, 9.27; S, 21.22.

2.3j *6-Benzyl-2,8-diphenyl-8H-imidazo[2,1-c][1,4]oxazine* ***(2j)***: Colorless solid; M.p. 87–89°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.47 (s, 2H), 6.16 (s, 1H), 6.40 (s, 1H), 7.14–7.17 (m, 3H), 7.25–7.39 (m, 11H), 7.76 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 37.8, 75.6, 102.8, 110.6, 124.8, 126.8, 127.1, 128.3, 128.4, 128.5,* 128.6, 129.0, 133.7, 135.8, 137.2, 138.8, 141.8, 144.9; Anal. Calcd. (%) for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found (%): C, 82.22; H, 5.44; N, 7.58. *Two carbons are merged together.

2.3k *6-(4-Chlorobenzyl)-2,8-diphenyl-8H-imidazo[2,1-c][1,4]oxazine* ***(2k)***: Colorless solid; M.p. 140–142°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.40 (s, 2H), 6.22 (s, 1H), 6.36 (s, 1H), 7.01 (d, J = 8.1 Hz, 2H), 7.12–7.19 (m, 5H), 7.22–7.30 (m, 4H), 7.35 (d, J = 7.5 Hz, 2H), 7.73 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 37.2, 75.6, 102.9, 110.6, 124.8, 126.9, 127.2, 128.3, 128.5, 128.7,* 130.3, 132.6, 133.6, 134.4, 136.9, 138.8, 141.9, 144.2; Anal. Calcd. (%) for $C_{25}H_{19}ClN_2O$: C, 75.28; H, 4.80; N, 7.02. Found (%): C, 75.12; H, 4.72; N, 6.93. *Two carbons are merged together.

2.3l *2,8-Diphenyl-6-(3-(trifluoromethyl)benzyl)-8H-imidazo[2,1-c][1,4]oxazine* ***(2l)***: Viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.47 (s, 2H), 6.28 (s, 1H), 6.36 (s, 1H), 7.09 (d, J = 7.8 Hz, 2H), 7.16–7.28 (m, 5H), 7.27–7.38 (m, 4H), 7.46 (d, J = 7.2 Hz, 2H), 7.73 (dd, J = 7.5 Hz, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 37.6, 75.7, 103.0, 110.7, 122.2, 123.7,* 124.9, 125.7, 126.9, 127.2, 128.3, 128.6, 128.7, 128.9, 132.3, 133.6, 136.8, 136.9, 138.8, 142.0, 143.7; Anal. Calcd. (%) for $C_{26}H_{19}F_3N_2O$: C, 72.21; H, 4.43; N, 6.48. Found (%): C, 72.08; H, 4.38; N, 6.42. *Two carbons are merged together.

2.3m *6-Benzyl-2,8-dip-tolyl-8H-imidazo[2,1-c][1,4]oxazine* ***(2m)***: Colorless solid; M.p. 112–114°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.31 (s, 3H), 2.33 (s, 3H), 3.44 (s, 2H), 6.14 (s, 1H), 6.33 (s, 1H), 7.05–7.10 (m, 4H), 7.11–7.16 (m, 4H), 7.24–7.30 (m, 4H), 7.61 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.1,* 37.9, 75.6, 102.8, 110.1, 124.7, 126.7, 127.1, 128.4, 129.0, 129.1, 129.2, 130.9, 134.3, 135.9, 136.4, 138.3, 138.9, 141.9, 144.8; Anal. Calcd. (%) for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14. Found (%): C, 82.51; H, 6.09; N, 7.08. *Two carbons are merged together.

2.3n *6-(4-Chlorobenzyl)-2,8-dip-tolyl-8H-imidazo[2,1-c][1,4]oxazine* ***(2n)***: Colorless solid; M.p. 126–128°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.32 (s, 3H), 2.34 (s, 3H), 3.37 (s, 2H), 6.20 (s, 1H), 6.30 (s, 1H), 6.99–7.02 (m, 5H), 7.12–7.26 (m, 6H), 7.62 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 20.9,* 37.0, 75.4, 102.8, 110.0, 124.6, 126.7, 127.1, 128.8, 129.0, 129.4, 130.1, 130.7, 132.4, 134.3, 136.4, 138.4, 138.7, 141.8, 143.9; Anal. Calcd. (%) for $C_{27}H_{23}ClN_2O$: C, 75.96; H, 5.43; N, 6.56. Found (%): C, 75.82; H, 5.36; N, 6.48. *Two carbons are merged together.

2.3o *2,8-Di-p-tolyl-6-(3-(trifluoromethyl)benzyl)-8H-imidazo[2,1-c][1,4]oxazine* ***(2o)***: Viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.26 (s, 3H), 2.32 (s, 3H), 3.42 (s, 2H), 6.24 (s, 1H), 6.30 (s, 1H), 6.94–6.97 (m, 3H), 7.12–7.13 (m, 2H), 7.16 (s, 1H), 7.27 (d, J = 7.8 Hz, 2H), 7.35 (s, 1H), 7.44 (d, J = 7.2 Hz, 2H), 7.62 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.0, 21.1, 37.6, 75.6, 103.0, 110.2, 123.6, 124.8, 125.6, 127.1, 128.7, 128.9, 129.2,* 130.8,* 132.3, 133.9, 136.6, 137.1, 138.5, 138.8, 142.0, 143.5; MS (M+1) 461.37; Anal. Calcd. (%) for $C_{28}H_{23}F_3N_2O$: C, 73.03; H, 5.03; N, 6.08. Found (%): C, 72.94; H, 4.98; N, 5.99. **Two carbons are merged together.

2.4 *General procedure for the preparation of* ***4***

Aryl halide (1 equiv.) was added to dry acetonitrile (10 mL) under nitrogen atmosphere. $PdCl_2(PPh_3)_2$ (3 mol%), CuI (6 mol%), Et_3N (5 equiv.) and terminal-1,5-alkyne-carbonyl imidazole derivative (1.0 equiv.) were added to the above solution and refluxed for 30 min. After evaporating the solvent under reduced pressure, the crude material was purified by flash chromatography (Ethyl acetate/pet ether, 1:20).

2.4a *(4-Chlorophenyl)(4-(4-chlorophenyl)-1-(3-phenylprop-2-ynyl)-1H-imidazol-2-yl)methanone* ***(4a)***: Colorless solid; M.p. 136–138°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.53 (s, 2H), 7.34–7.36 (m, 5H), 7.45–7.48 (m, 4H), 7.75 (d, J = 7.2 Hz, 2H), 7.80 (s, 1H), 8.43 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 39.6, 81.8, 86.8, 121.0, 121.7, 126.4, 128.3, 128.4, 128.8, 129.0, 131.5, 131.8, 132.6, 133.3, 135.2, 139.5, 140.7, 141.8, 182.1; Anal. Calcd. (%) for $C_{25}H_{16}Cl_2N_2O$: C, 69.62; H, 3.74; N, 6.49. Found (%): C, 69.51; H, 3.68; N, 6.41.

2.4b *(4-Chlorophenyl)(4-(4-chlorophenyl)-1-(3-(4-chlorophenyl)prop-2-ynyl)-1H-imidazol-2-yl)methanone* ***(4b)***: Colorless solid; M.p. 142–144°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.55 (s, 2H), 7.32–7.47 (m, 7H), 7.62 (d, J = 7.2 Hz, 2H), 7.75 (d, J = 7.8 Hz, 2H), 8.45 (d, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 39.8, 81.6, 86.5, 121.1, 121.6, 126.5, 128.3, 128.4, 128.9, 129.1, 131.5, 131.8, 132.7, 133.4, 135.2, 139.5, 140.5, 142.1, 182.3; Anal. Calcd. (%) for $C_{25}H_{15}Cl_3N_2O$: C, 64.47; H, 3.25; N, 6.01. Found (%): C, 64.36; H, 3.18; N, 5.92.

2.4c *6-Benzyl-2,8-bis(4-chlorophenyl)-8H-imidazo[2,1-c][1,4]oxazine* ***(2p)***: Viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.44 (s, 2H), 5.92 (s, 1H), 6.08 (s, 1H), 6.90 (s, 1H), 7.01 (d, J = 7.5 Hz, 2H), 7.12–7.20 (m, 3H), 7.28–7.35 (m, 6H), 7.58 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 36.6, 68.4, 116.4, 116.6, 121.6, 125.4, 126.0, 127.4, 127.7, 128.3, 128.5, 128.6, 128.7, 131.7, 132.4, 133.6, 135.4, 138.3, 148.5; Anal. Calcd. (%) for $C_{25}H_{18}Cl_2N_2O$: C, 69.29; H, 4.19; N, 6.46. Found (%): C, 69.19; H, 4.11; N, 6.39.

2.4d *6-(4-Chlorobenzyl)-2,8-bis(4-chlorophenyl)-8H-imidazo[2,1-c][1,4]oxazine* ***(2q)***: Viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.42 (s, 2H), 5.96 (s, 1H), 6.11 (s, 1H), 6.92 (s, 1H), 7.12 (d, J = 7.5 Hz, 2H), 7.14–7.28 (m, 6H), 7.42 (d, J = 7.8 Hz, 2H), 7.62 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 36.8, 68.5, 116.2, 116.5, 121.7, 125.4, 126.1, 127.2, 127.8, 128.3, 128.5, 128.8, 128.9, 131.8, 132.4, 133.8, 135.7, 138.6, 148.3; Anal. Calcd. (%) for $C_{25}H_{17}Cl_3N_2O$: C, 64.19; H, 3.66; N, 5.99. Found (%): C, 64.08; H, 3.62; N, 5.91.

2.5 *Preparation of 1-(1-(prop-2-ynyl)-1H-pyrrol-2-yl) ethanol* ***(5)***

The pyrrole derivative **5** was obtained by the usual procedure of *N*-propargylation of 2-acetylpyrrole. The resulting crude product was dissolved in methanol and sodium borohydride was added slowly. After completion of the reduction, reaction mixture was poured in to ice-cold water and extracted with dichloromethane. The resulting crude product was purified by column chromatography.

Viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.15 (d, J = 6.0 Hz, 3H), 2.37 (t, J = 2.4 Hz, 1H), 4.72 (d, J = 2.4 Hz, 1H), 4.77 (d, J = 2.4 Hz, 1H), 4.85 (q, J = 6.0 Hz, 1H), 6.06–6.09 (m, 2H), 6.78 (t, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 22.0, 35.8, 62.0, 73.0, 78.7, 106.2, 107.5, 121.8, 134.9; Anal. Calcd. (%) for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found (%): C, 72.35; H, 7.35; N, 9.28.

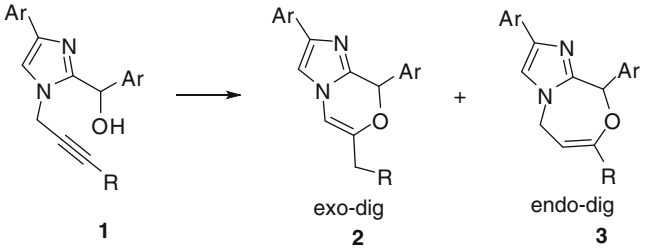
2.6 *Preparation of 1,3-dimethyl-1H-pyrrolo[2,1-c][1,4]oxazine* ***(6)***

1-(1-(Prop-2-ynyl)-1*H*-pyrrol-2-yl)ethanol **5** (0.1g, 0.67 mmol) was taken in a 10 mL microwave vial and dissolved in DMF (5.0 mL). To this, LiO^tBu (0.67 mmol) was added and the reaction mixture was subjected to microwave irradiation at 80°C for 5 min in 120 W microwave power. Completion of the reaction was confirmed by TLC. The crude material was then purified by flash chromatography (5% ethyl acetate/pet ether).

Viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.63 (d, J = 6.3 Hz, 3H), 1.85 (s, 3H), 2.37 (t, J = 2.4 Hz, 1H), 5.08 (q, J = 6.3 Hz, 1H), 5.89 (s, 1H), 6.14 (bs, 1H), 6.21 (bs, 1H), 6.85 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 18.3, 29.5, 69.9, 101.9, 103.7, 108.0,* 116.2, 140.8; Anal. Calcd. (%) for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found (%): C, 72.32; H, 7.38; N, 9.26. *Two carbons are merged together.

3. Results and Discussion

We have reported the synthesis of different imidazo [1,2-x]heterocycles with a bridgehead nitrogen atom from propargyl derivatives of imidazole.[13] In continuation, it has been planned to synthesize imidazo[2,1-c] [1,4]oxazine derivatives *via* hydroalkoxylation of 1,5-alkynyl alcohol. Although these hydroalkoxylation reactions have been extensively studied by different research groups, the reactions were all transition metal catalyzed. The present investigation involves a metal free, base promoted regioselective synthesis of imidazo [2,1-c][1,4]oxazine by *exo-dig* mode of addition. This core of imidazooxazine has not been reported widely in literature with only limited references. To the best of our knowledge, the bases like t-butoxide have not been employed so far for the hydroalkoxylation of 1,5-alkynyl alcohol. The importance of this method is further augmented by the fact that the starting materials used



Scheme 1. Possible modes of addition.

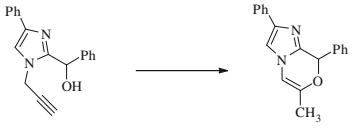
are quite common and inexpensive. For intramolecular hydroalkoxylations in alkynyl alcohol, two possible products can be expected as exemplified by the exo- and endo-enol ether formations (scheme 1). According to Baldwin rule, these two products – a six membered ring **2** and/or a seven membered ring **3** - could be formed with ease.[14]

The reaction of phenyl(4-phenyl-1-(prop-2-ynyl)-1H-imidazol-2-yl)methanol **1** (Ar = Ph, R = H)[13a] has been tested with various bases in order to choose the best base for the proposed ring closure. Lithium t-butoxide has been found to be the best choice as the base for this reaction. Other organic bases, alkali hydroxides and potassium carbonate resulted in lower yield and after optimization, it was found that when **1** (Ar = Ph, R = H) (0.4 mmol) and LiOtBu (0.4 mmol) in DMF was irradiated at 80°C with 120 W microwave for 10 minutes, 2,8-diphenyl-6-methyl-8H-imidazo[2,1-c][1,4]oxazine **2a** was obtained in excellent yield after purification by a short silica gel column (table 1).

It must be mentioned that, recently, related reactions have been carried out *via* gold catalyzed/base-promoted cyclization of 1-alkynylimidazoles.[15] Very recently, Wang *et al.*, reported the synthesis of 1,4-oxazine via sodium hydride promoted regioselective cyclization of 1,5-alkyne alcohol system.[11c] The chemistry described in this investigation employs an alkali hydroxide as the base and a new set of imidazooxazines – a bicyclic system with bridge head nitrogen – has been generated, thus extending the work of Wang *et al.*[11c]

The scope of the reaction was extended with various aryl substituted propargyl derivatives of imidazole **1** under the optimized reaction condition to get **2a** – **2i** (table 2). The structure of **2** has been unambiguously assigned by spectral and analytical data, and that of **2f**

Table 1. Screening of bases and solvents for the cyclization of **1** (Ar = Ph, R = H). All reactions were carried out under microwaves at 80°C except entry #8.

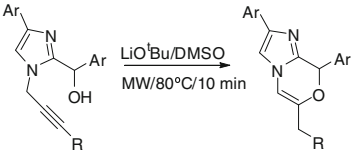


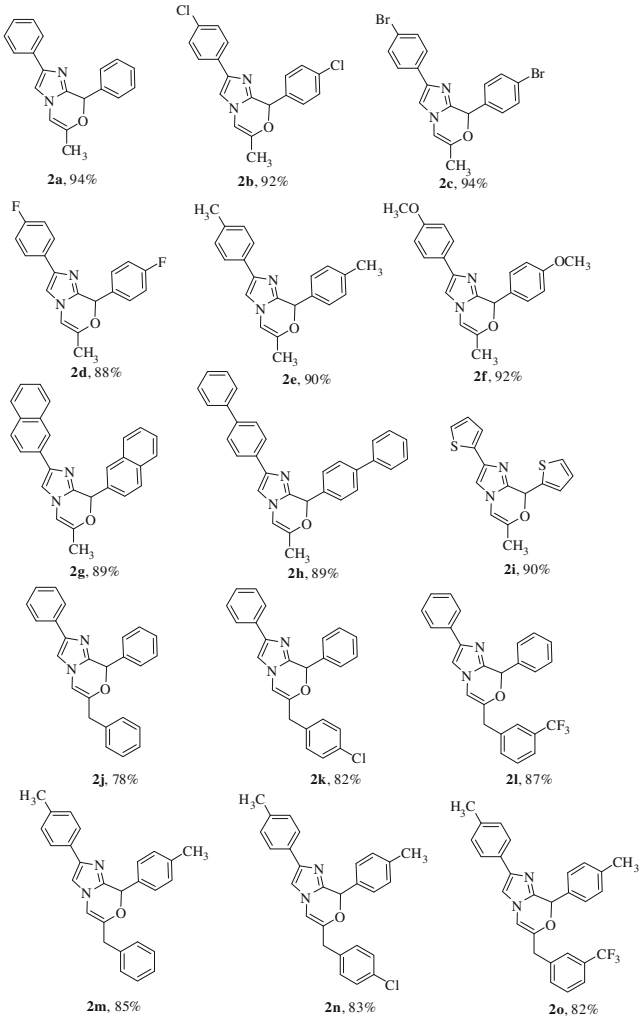
2a

Sl No	Base	Solvent	Reaction time	Yield(%)
1	Sodium carbonate	DMF	2 h	Trace
2	Sodium hydroxide	DMF	1 h	26
3	Potassium hydroxide	DMF	1 h	28
4	Lithium hydroxide	DMF	1 h	25
5	Sodium hydride	-	30 min	62
6	Sodium hydride	DMF	30 min	78
7	Lithium t-butoxide	-	30 min	76
8*	Lithium t-butoxide	DMF	1 h	40
9	**Lithium t-butoxide**	**DMF**	**5 min**	**93**
10	Lithium t-butoxide	DMSO	10 min	81
11	Lithium t-butoxide	Dioxan	10 min	63
12	Lithium t-butoxide	THF	30 min	25
13	Lithium t-butoxide	Toluene	1 h	Trace
14	Lithium t-butoxide	CH_3CN	30 min	33
15	Sodium t-butoxide	DMF	10 min	86
16	Sodium t-butoxide	DMSO	10 min	82
17	Potassium t-butoxide	DMF	10 min	87
18	Potassium t-butoxide	DMSO	10 min	83
19	DEA	DME	1 h	Trace
20	DABCO	DME	1 h	18
21	DMP	DME	1 h	15

*The reaction in Entry 8 was carried out under thermal condition (80°C).

Table 2. Synthesis of substituted imidazo[2,1-*c*][1,4]oxazine **2** (with isolated yields).





has been confirmed by single crystal X-ray analysis (figure 2).[16] It can be noticed that only **2** has been formed in this manipulation with no trace of **3**. It must be mentioned that the reaction did not yield the product quantitatively (table 1, Entry 8) under thermal conditions in the absence of microwaves.

To check the validity of this reaction in non-terminal alkynes, a set of non terminal alkynes **1** (R = Ar) has been prepared by the Sonogashira coupling of the terminal alkyne alcohol **1** (R = H) with different aryl iodides. The reaction of these internal 1,5-alkyne alcohol - imidazole derivatives has also been investigated, which afforded the corresponding substituted imidazo[2,1-c][1,4]oxazine derivatives (**2j** – **2o**) in excellent yields (78–94%) (table 2). The reaction is not effective when R is an alkyl group.

Encouraged by these results, we were curious to know whether borohydride reduction can promote the cyclization of 1,5-alkyne-carbonyl compound **4** directly to **2**. Interestingly, the reaction led to sequential reduction followed by cyclization with internal alkyne with good yield (78–80%). However, in the case of terminal alkynes, cyclization did not proceed as expected (scheme 2) and the reaction stopped after the initial reduction of carbonyl group ending up in **1**. The alkyne carbon getting attacked by OH may not be electrophilic enough when R = H.

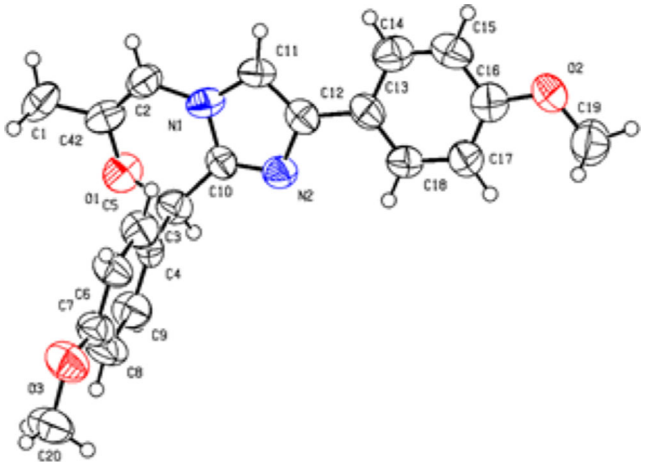
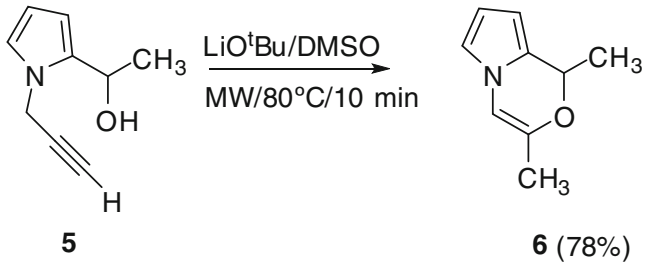


Figure 2. ORTEP diagram of **2f**.



Scheme 3. Synthesis of 1,3-dimethyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazine.

Next, the scope of the present transformation was extended to propargyl derivative of pyrrole. The pyrrole derivative **5**, obtained by the usual procedure of N-propaglylation of 2-acetylpyrrole followed by sodium borohydride reduction, has been subjected to hydroalkoxyation. As expected, the corresponding substituted pyrrolo[2,1-c][1,4]oxazine **6** was obtained in good yield (scheme 3).

4. Conclusions

An effective base-promoted intramolecular hydroalkoxylation of various 1,5-alkynyl-alcohol derivative of imidazole leading to the regioselective synthesis of substituted imidazo[2,1-c][1,4]oxazine has ben developed. The cyclization provided the exo-enol ethers in 78–94% yield with complete regioselectivity.

Supporting Information (SI)

^{1}H and ^{13}C NMR and Mass Spectra of compounds **1**, **2**, **4**, **5** and **6** can be found in the Supplementary Information available at www.ias.ac.in/chemsci.

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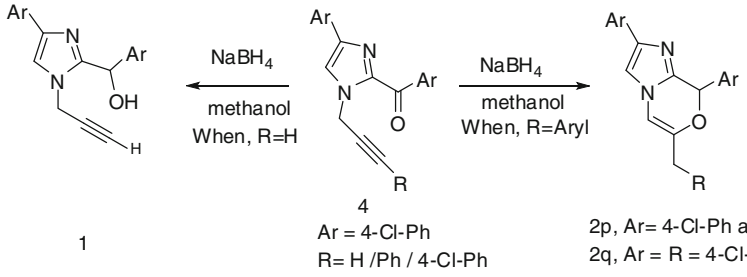

Scheme 2. Reduction of 1,5-alkyne-carbonyl system.

NMR facility. M.N. thanks Council of Scientific and Industrial Research (CSIR), New Delhi for JRF.

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