IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Phase Transfer Catalysis In A Toluene-Water Biphasic System: A 1,3-Dipolar Cycloaddition Approach For The Synthesis Of Bis-Isoxazoles

Raksha P. Dhankar*

[a*]Assistant Professor, Institution of Higher Learning, Research and Specialised Studies, Department of Chemistry, Sardar Patel Mahavidyalaya, Chandrapur, 442402, Maharashtra, India

Abstract

A forthright method for the synthesis of bis isoxazoles has been investigated through 1,3 dipolar cycloaddition reactions involving isoxazole-4- carbaldehyde oximes and alkynes. TBAB (tetrabutylammonium bromide) serves as a PTC (phase transfer catalyst) in biphasic system of toluene and water. The process offers notable advantages, including mild reaction conditions, accelerated reaction rates, better atom economy, increased overall efficiency the use of cost-effective catalyst, an environment friendly solvent and lesser reaction time periods. The versatility of this technology has been demonstrated through its applicability to the synthesis of various chemical hybrids.

Keywords: Cycloaddition reaction, tetrabutylammonium bromide, dipole, dipolarphile

1. INTRUDUCTION

In a quest for a sustainable approach to organically synthesise valued isoxazoles by employing a resourceful method based on 1,3 dipolar cycloaddition (1 ,3 DC) of dipolarophiles and dipoles; have endeavoured to formulate a method that is both efficient and cost-effective in synthesising them. Achieving a synthetic protocol that aligns with all the principles of green chemistry is a challenging task. However, the closer a protocol adheres to these principles, the closer it gets to more environmentally process.

Isoxazole derivatives represents a distinctive category of aza-oxo heterocycles. A major focus continues to be on synthesis of novel isooxazoline derivatives because of their diverse pharmacological activities. A considerable amount of research effort has been directed towards developing new derivatives of isoxazole compounds as a result of their versatility as an effective chemotherapeutic agent. A variety of activities have been reported for isoxazole derivatives, including analgesic[1], antimicrobial[2], insecticidal[3], and antioxidant[4] properties. These derivatives have been identified as promising structural moiety for drug design with reported anticonvulsant[5], antibacterial[6], antitumor[7], and anti-inflammatory[8], actions.

A considerable number of pharmacologically active heterocyclic compounds can be synthesized from isoxazoline derivatives.

The 1,3 dipolar cycloaddition stands out as a most versatile pathway for synthesizing isoxazoles. The pioneering studies from previous years have extensively documented a range of catalysts for the synthesis of isoxazoles via 1,3 dipolar cycloaddition reactions involving both dipoles with electron electron – defficient and electron rich alkenes or alkynes, respectively. [9-15]

Furthermore, some researchers have employed surfactants in organised aqueous media for the alkylation of oximes to generate nitrone and facilitate their in situ cycloaddition with olefins [16]. There is an increasing interest in developing catalytic green chemical processes, particularly under phase transfer catalysis, as a means to eliminate the use of corrosive and hazardous organic solvents. The pursuit of innovative and exceptional catalysts has led many to consider phase transfer catalysts (PTCs). The advantages of PTCs include the elimination of organic solvents and the need for the hazardous and expensive bases. This approach is characterised by its procedural simplicity, high yields and product purity. It is particularly appealing in the light of the growing number of environmental regulations, as PTC processes typically result in significantly less industrial wastes and lower energy consumption compared to traditional methods. [17-21]

The synthesis of bis isoxazoles through both conventional and non-conventional methods focusing on the generation of a diverse library of new isoxazole derivatives utilising phase transfer catalysis (PTC) was undertaken. Our preferred methods involved 1,3 cycloadditions, with formyl isoxazole incorporating the formyl functionality at C-4 position, subsequently subjected to oxime formation. In pursuit of more efficient processes, we explored a synthetic pathway for the production of biologically active bis-isoxazoles catalysed by tetrabutylammonium bromide (TBAB) in a toluene-water biphasic system at ambient temperature, maintaining constant stirring for 4 hours. The reaction was systematically optimised by experimenting with various solvent systems, also incorporating didecyldimethylammonium bromide (DDAB) as a surfactant. Among the tested conditions TBAB demonstrated optimal conversions and highest reaction efficiencies as illustrated in Table 1.

2 EXPERIMENTAL

2.1 Methods and Materials

Differently substituted isoxazoles were made by using analytical grade p-cresol, resorcinol, p-chlorophenol, acetic anhydride and substituted aldehydes (S.D.Fine Chemicals, 98%). $POCl_3$, DMF and hydroxylamine hydrochloride were purchased from Qualigen India Ltd. Mumbai. Didecyldimethylammonium bromide (DDAB), Tetrabutylammonium bromide (TBAB) and diphenyl acetylene were purchased from Across Ltd, Belgium.

2.2 Apparatus

Silica gel G was employed for thin layer chromatography and melting points were determined using open capillary method. Infrared (IR) spectra were recorded with Shimadzu FT-IR spectrometer utilising the KBr pettets. Gas chromatography/ mass spectrometry (GS/MS) analysis was conductedbon a Shimadzu gas

chromatograph coupled with QP 5050 spectrometer at 1-1.5eV. Proton and Carbon nuclear magnetic resonance (NMR) spectra were captured on a Brucker AVII FT-NMR spectrometer operating at 400 MHz for the entire samples.

2.3 Synthesis of 3-(2- hydroxyl-5 substituted phenyl)-5- substituted isoxazole-4-carbaldehyde (2a-i)

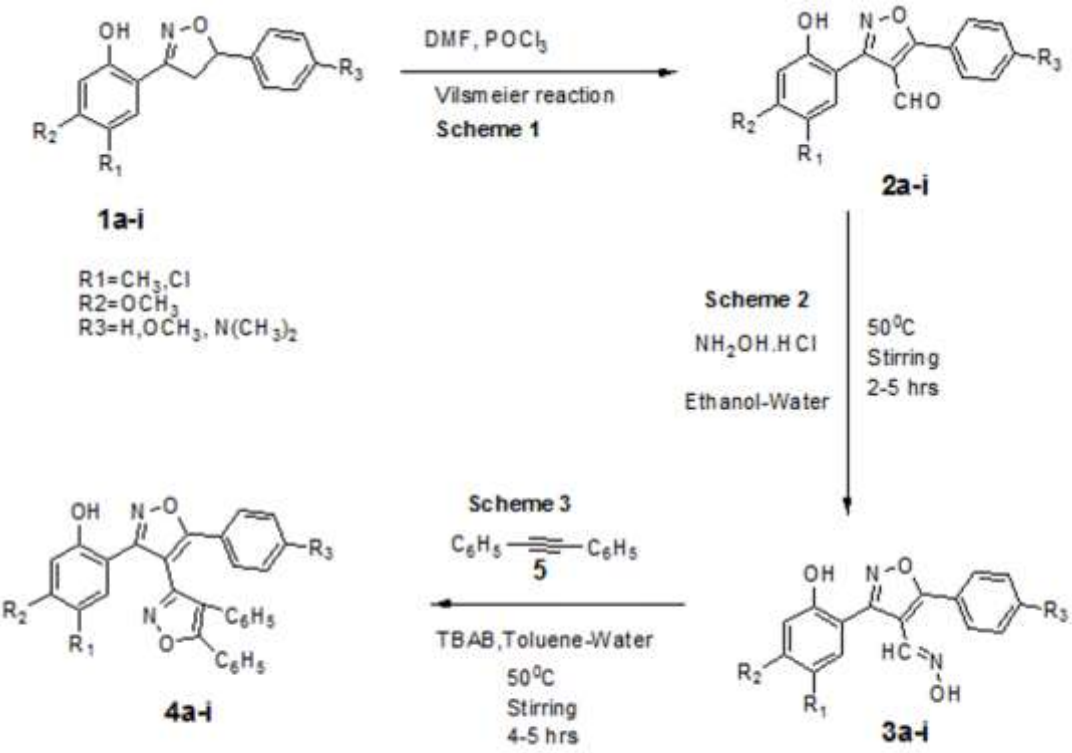
In dry DMF (4 mmoles, 0.6 mL) at 0-5^{0}C, $POCl_3$ (8 mmoles, 1.6 mL) was added dropwise with constant stirring**.** This addition is performed very slowly. After complete addition of $POCl_3$ the stirring was continued for the next half an hour. Subsequently the compounds 4-substituted-2-(5- phenyl isoxazole-3-yl) phenol (1mmole, 1g) were added and stirred at 50-60^{0}C for 4-8 hours. This reaction mixture was cooled with ice cold water and stirring was continued for 5 minutes. The product obtained was filtered, washed several times with water, dried and recrystallized with ethanol. (Scheme 1)

2.4 Synthesis of 3-(2- hydroxyl-5 substituted phenyl)-5- substituted isoxazole-4-carbaldehyde oximes (3a-i)

In a reaction vessel equipped with a dropping funnel was charged with a solution of hydroxylamine hydrochloride (20mmole, 0.140g) in 10 ml of water and 3-(2- hydroxyl-5 substituted phenyl)-5-substituted isoxazole-4-carbaldehyde (20mmole) dissolved in ethanol. A solution of $NaHCO_3$ (20 mmoles, 0.166g) was added continuously dropwise to the reaction mixture with constant stirring at 36^{0}C till it reaches to the pH of 7-8. This stirring continued at an elevated temperature of 50-60^{0}C ranging from 2-5 hrs. The product was then chromatographed in 7:3 hexane – ethyl acetate eluent. (Scheme 2)

2.5 Synthesis of 4-substituted-2-(-5-substituted-4-(4,5-diphenylisoxazol-3-yl)isoxazol-3yl) phenol (4a-i)

3-(2- hydroxyl-5 substituted phenyl)-5- substituted isoxazole-4-carbaldehyde oximes **3a-i**(1mmole) was dissolved in water in the presence of phase transfer catalyst, tetrabutyl ammonium chloride (25mole%, 0.080g). Diphenyl acetylene (1mmole, 0.217g) dissolved in toluene was added to above solution and stirred at at 50^{0}C for 4 hrs. The reaction was monitored until the complete consumption of oxime. Then organic layer of reaction mixture was extracted with diethyl acetate (3x 20 mL) and dried over $CaCl_2$ and separated by column in 1:1 hexane-ethyl acetate eluent. (Scheme 3)



3-(2-hydroxy-5-methylphenyl)-5-phenylisoxazole-4-carbaldehyde (2a)

Light brown; Yield 74%, m.p.102^{0}C, [$C_{17}H_{13}NO_3$]; ^{13}C NMR (75MHz, $CDCl_3$) : δ = 24.06, 100.6, 116.3, 120.4, 127.10, 128.6, 129.4, 130.8, 131.5, 152.2, 160.7, 168.5, 191.1; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm) = 2.28(s, 3H, CH_3), 7.2-7.8(m, 7H, aromatic region), 9.4(s,1H,-OH),10.1(s, 1H, -CHO); IR(KBr) 3053, 2730, 2806, 1340 cm^{-1} ; GC-MS (70 eV): m/z = 279[M+].

3-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl) isoxazole-4-carbaldehyde (2b)

Brown; Yield 78% m.p.105^{0}C, [$C_{18}H_{15}NO_4$]; ^{13}C NMR(75MHz, $CDCl_3$) : δ = 21.2, 56.2, 104.5, 112.6, 114.1, 119.3, 123.6, 130.0, 130.6, 130.8, 137.5, 150.0, 152, 156.9, 164.5, 192.0; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm) = 2.28(s, 3H,CH_3), 3.7(s,3H,-OCH_3), 6.6-7.7(m,7H,aromatic region), 9.6(s,1H,-OH),10.4(s,1H,-CHO); IR(KBr) 3046, 2721, 2805, 1343 cm^{-1} ; GC-MS (70 eV): m/z = 303[M+].

3-(2-hydroxy-5-methylphenyl)-5-(4-dimethylamino) phenyl) isoxazole-4-carbaldehyde (2c)

Reddish brown; Yield 82% m.p. 115^{0}C, [$C_{19}H_{18}N_2O_3$]; ^{13}C CNMR (75MHz,$CDCl_3$): δ = 21.3, 43.6, 100.5, 111.6, 113.1, 116.5, 117.9, 129.1, 129.3, 130.6, 130.9, 145.0, 150.0, 152.8, 158.9, 170.9, 191.0; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm) = 2.28 (s,3H,CH_3) 2.8 (s, 6H, $N(CH_3)_2$), 7.4-7.9 (m,7H, aromatic region), 9.1 (s,1H,-OH), 9.9 (s,1H,-CHO); IR (KBr) 3039, 2723, 2808, 1360, cm^{-1}; GC-MS(70 eV): m/z =322[M+].

3-(5-chloro-2-hydroxyphenyl)-5-phenylisoxazole-4-carbaldehyde(2d)

Yellowish brown ; Yield 72% m.p. 124^{0}C [$C_{16}H_{10}ClNO_3$]; ^{13}C NMR (75MHz,$CDCl_3$): δ = 99.5, 117.6, 125.1, 126.9, 127.0, 128.5, 128.8, 129.0, 130.0, 136.5, 137.5, 150.0, 153.0, 159.9, 190.1; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm) = 6.7-7.6 (m,7H,aromatic region), 9.1 (s, 1H, -OH)9.4(s,1H, -CHO); IR(KBr) 3139, 2720, 2812, 1349 cm^{-1}; GC-MS (70 eV): m/z = 299[M+].

3-(5-chloro-2hyroxyphenyl)-5-(4-methoxyphenyl) isoxazole-4-carbaldehyde (2e)

Yellowish brown; Yield 75% m.p.145^{0}C, [$C_{17}H_{12}ClNO_4$]; ^{13}C NMR (75MHz, $CDCl_3$): δ = 56.0, 100.5, 112.6, 114.1, 117.6, 119.3, 125.1, 126.9, 128.8, 130.0, 130.3, 137.5, 150.0, 158.9, 162.5, 190.0; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm) = 3.7(s,3H,-OCH_3), 7.1-8.7(m, 7H, aromatic region),9.4(s,1H,-OH), 10.1(s,1H,-CHO); IR(KBr) 3150, 2710, 2815, 1329 cm^{-1}; GC-MS(70 eV): m/z = 329[M+].

3-(5-chloro-2hyroxyphenyl)-5-(4-dimethylamino)phenyl) isoxazole-4-carbaldehyde (2f)

Dark red; Yield 87% m.p. 129^{o}C, [$C_{18}H_{15}ClN_2O_3$];); ^{13}C NMR (75MHz, $CDCL_3$):δ =43.6, 100.7, 111.6, 113.1, 116.5, 117.6, 125.1, 126.9, 12.8, 129.9, 130.3, 137.4, 145.1, 150.1, 153.9, 158.9, 193.0; ^{1}HNMR(400MHz, $CDCl_3$) δ(ppm) = 2.85(s,6H,-$N(CH_3)_2$), 6.8-7.6(m,7H,aromatic region), 9.4(s,1H,-OH), 10.2(s,1H,-CHO); IR(KBr) 3154, 2707, 2812,1336cm^{-1}; GC- MS(70eV): m/z = 342[M+].

3-(2-hydroxy-4methoxyphenyl)-5-phenyl isoxazole-4-carbaldehyde (2g)

Off white; Yield 85% m.p. 162^{0}C , [$C_{17}H_{13}NO_4$]; ^{13}C NMR (75MHz, $CDCl_3$): δ = 56.0, 100.3, 101.8, 107.2, 116.0, 127.0, 128.5, 129.0, 129.4, 136.5, 150.0, 156.8, 158.9, 163.4, 187.9; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm) = 3.7(s,3H,-OCH_3), 7.2-7.(m,7H,aromatic region), 9.7(s,1H, -OH),10.3(s,1H,-CHO); IR(KBr) 3267, 2703, 2809 ,1341 cm^{-1}; GC-MS(70 eV): m/z = [M+].

2-hydroxy-4methoxyphenyl)-5-(4-methoxyphenyl) isoxazole-4-carbaldehyde (2h)

Brown; Yield 81% m.p.130^{0}C, [$C^{18}H^{15}NO^5$]; ^{13}C NMR (75MHz, $CDCl_3$): δ = 56.5, 100,2, 101.6, 107.2, 112.6, 114.1, 116.0, 119.3, 129.4, 130.0, 137.5, 150.0, 156.8, 158.9, 162.5, 163.4, 191.0; ^{1}HNMR(400MHz, $CDCl_3$) δ(ppm) = 3.7(s,3H,-OCH_3), 4.1(s,3H,-OCH_3), 7.2-7.8(m, 7H, aromatic region), 9.2(s,1H,-OH), 10.3(s,1H, -CHO); IR(KBr) 3256,2711, 2815,1356 cm^{-1}; GC-MS(70 eV): m/z = 325[M+].

3-(2-hydroxy-4methoxyphenyl)-5-(4-dimethylamino)phenyl) isoxazole-4-carbaldehyde (2i)

Dark brown; Yield 76% m.p. 126^{o}C, [$C_{19}H_{18}N_2O_4$]; ^{13}C NMR (75MHz, $CDCl_3$): δ = 43.6, 56.7,100.2, 101.8, 107.2, 111.6, 113.1, 116.0, 116.5, 129.4, 129.9, 137.4, 145.0, 150.0, 156.8, 158.9, 163.4, 190.0; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm) = 2.85(s,6H,$N(CH_3)_2$), 3.6(s,3H,-OCH_3), 6.7-7.6(m,7H,aromatic region), 9.1(s,1H,-OH), 9.4(s,1H,-CHO); IR(KBr) 3114,2704,2813,1346 cm^{-1}; GC-MS (70 eV): m/z =338[M+].

3-(2-hydroxy-5-methylphenyl)-5-phenylisoxazole-4-carbaldehyde oxime (3a)

Off white; Yield 76% m.p. 137^{o}C, [$C_{17}H_{14}N_2O_3$]; ^{13}C NMR (75MHz, $CDCl_3$):δ = 24.1, 29.6, 86.1, 115.5, 117.9, 126.2, 130.1, 132.1, 140.1, 152.0, 160.5; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)= 2.29(s,3H,CH_3), 7.1-7.6(m, 7H, aromatic region0, 9.0(s,1H, CH=N), 9.3(s,1H,-OH of oxime), 9.6(s,1H,-OH); IR(KBr) 1646, 3033, 976 cm^{-1}; GC-MS (70 eV): m/z = 279[M+].

3-(2-hydroxy-5-methylphenyl)-5-(4methoxyphenyl) isoxazole-4-carbaldehyde oxime (3b)

Yellowish white; Yield 72% m.p. 239^{o}C, [$C_{18}H_{16}N_2O_4$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7, 31.6, 53.7, 86.9, 110.6, 114.2, 115.8, 127.2, 128.8, 129.1, 141.6, 152.4, 158.8, 165.0; ; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)= 2.49(s,3H,CH_3) 3.4 (s, 3H, methoxy), 7.2-7.6(m, 7H, aromatic region), 8.5(s,1H,CH=N), 9.2(s,1H,-OH of oxime), 9.7(s, 1H, -OH); IR(KBr) 1648, 3029, 969 cm^{-1}GC-MS (70 eV): m/z =324[M+].

3-(2-hydroxy-5-methylphenyl)-5-(4-dimethylamono)phenyl) isoxazole-4-carbaldehyde oxime (3c)

Dark brown; Yield 82% m.p. 168ºC, [$C_{19}H_{19}N_3O_3$]; ^{13}C NMR(75MHz, $CDCl_3$):δ = 12.0, 14.5, 41.2, 83.7, 114.2, 117.6, 118.1, 119.0, 129.4, 130.1, 132.9, 141.3, 152.1, 154.8, 159.6; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm) = 2.3(s,3H,CH_3), 3.07(s,06H,N(CH_3)$_2$), 7.1-7.9(m, 7H, aromatic region), 9.2(s,1H,CH=N), 9.5(s,1H,-OH of oxime), 10.1(s,1H,-OH); IR(KBr) 1634, 3083, 971 cm^{-1}; GC-MS (70 eV): m/z = 324[M+].

3-(5-chloro-2-hydroxyphenyl)-5-phenylisoxazole-4-carbaldehyde oxime (3d)

Yellow; Yield 67% m.p. 173ºC, [$C_{16}H_{11}ClN_2O_3$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.1, 85.5, 114.2, 123.6, 127.1, 127.2, 127.4, 128.6, 129, 150.8, 159.8; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)=7.1-7.9(m, 7H, aromatic region), 8.5(s, 1H, CH=N), 9.2(s, 1H, -OH of oxime), 9.4(s, 1H, -OH); IR(KBr) 1636, 3023, 975cm^{-1}; GC-MS (70eV): m/z = 314[M+].

3-(5-chloro-2hyroxyphenyl)-5-(4-methoxyphenyl) isoxazole-4-carbaldehyde oxime (3e)

Yellowish white; Yield 76% m.p. 165ºC [$C_{17}H_{13}ClN_2O_4$]; ^{13}C NMR (75MHz, $CDCl_3$): δ = 31.6, 49.0, 83.0, 117.9, 118.0, 119.0, 127.0, 133.6, 135.1, 141.8, 150.6, 157.6, 171.0; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)=3.8 (s,3H,-OCH_3), 7.3-8.2(m,7H,aromatic region), 8.3(s, 1H,CH=N), 9.4(s,1H,-OH of oxime), 10.3(s,1H,Y-OH); IR(KBr) 1630, 3026, 967cm^{-1}; GC-MS (70 eV): m/z = 344[M+].

3-(5-chloro-2hyroxyphenyl)-5-(4-dimethylamino) phenyl) isoxazole-4-carbaldehyde oxime (3f)

Dark red; Yield 78% m.p. 197ºC, [$C_{18}H_{16}ClN_3O_3$]; ^{13}C NMR (75MHz, $CDCl_3$): δ = 12.0, 14.7, 35.6, 40.1, 54.4, 56.0, 85.6, 112.5, 113.4, 114.0, 119.6, 127.5, 128.0, 132.1, 141.9, 147.5, 154.8, 163.6; ; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)= 3.1 (s,6H,N(CH_3)$_2$), 7.1-7.9(m,7H,aromatic region), 8.8(s,1H, CH=N), 9.8(s,1H,-OH of oxime), 10.3(s,1H,-OH); IR(KBr) 1656, 3031, 965cm^{-1}; GC-MS (70 eV): m/z = 357[M+].

3-(2-hydroxy-4methoxyphenyl)-5-phenyl isoxazole-4-carbaldehyde oxime (3g)

White; Yield 67% m.p. 225ºC, [$C_{17}H_{14}N_2O_4$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7, 53.7, 65.9, 86.2, 102.2, 106.6, 111.8, 129.1, 132.6, 141.6, 146.6, 147.6, 148.8, 163.2, 165.0; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)= 3.7 (s,3H,-OCH_3), 6.9-7.6(m,7H,aromatic region), 8.5(s,1H,CH=N), 9.1(s,1H,-OH of oxime), 10.1(s,1H,-OH); IR(KBr) 1666, 3034, 981cm^{-1};

GC-MS (70 eV): m/z = 310[M+].

3-(2-hydroxy-4methoxyphenyl)-5-(4-methoxyphenyl) isoxazole-4-carbaldehyde oxime (3h)

Yellow; Yield 79% m.p. 156ºC, [$C_{18}H_{16}N_2O_5$]; ^{13}C NMR (75 MHz,$CDCl_3$): δ= 29.6, 50.3, 61.1, 86.1, 101.8, 106.1, 115.7, 119.5, 129.1, 130.8, 141.0, 150.6, 156.8, 159.1, 163.3, 167.8; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)= 3.75(s,3H,-OCH_3), 3.85(s,3H,-OCH_3), 7.1-7.7(m,7H, aromatic region), 8.9(s,1H,CH=N), 9.3(s,1H,-OH of oxime), 10.4(s,1H,-OH); IR(KBr) 1653, 3028, 968cm^{-1}; GC-MS (70 eV): m/z = 340[M+].

3-(2-hydroxy-4methoxyphenyl)-5-(4-dimethylamino) phenyl) isoxazole-4-carbaldehyde oxime (3i)

Brown; Yield 81% m.p. 178ºC, [$C_{19}H_{19}N_3O_4$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ =27.0, 50.3, 53.7, 84.2, 106.6, 111.6, 112.0, 112.8, 115.6, 129.1, 132.6, 141.6, 146.6, 147.6, 148.8, 165.0; ^{1}HNMR (400MHz ,$CDCl_3$) δ(ppm) 3.1 (s,6H,$N(CH_3)_2$), 3.7(s,3H.–OCH_3), 7.1-7.9(m,7H, aromatic region), 8.9(s,1H,CH=N), 9.6(s,1H,-OH of oxime), 10.3(s,1H,-OH); IR(KBr) 1676, 3038, 978cm^{-1}; GC-MS (70 eV): m/z =353[M+].

4 methyl-2-(5-phenyl-4-(4, 5-diphenylisoxazol-3-yl)isoxazol-3-yl) phenol (4a)

Yellow; Yield 61% m.p. 157ºC, [$C_{31}H_{22}N_2O_3$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ =21.2, 100.5, 116.1, 123.6, 127.0, 128.5, 129.0, 130.6, 131.8, 136.5, 150.0, 152.8, 158; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)= 2.26(s, 3H, CH_3), 6.8-7.5(m,17H, aromatic region), 9.5(s, 1H, -OH); IR(KBr) 3400, 1602, 745,683cm^{-1}; GC-MS (70 eV): m/z = 470[M+].

2-(5-(4-methoxyphenyl)-4-(4,5-diphenylisoxazol-3-yl)isoxazol-3-yl)-4methoxyphenyl phenol (4b)

Yellow; Yield 67% m.p. 142ºC, [$C_{32}H_{24}N_2O_4$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.2, 56.0, 101.5, 114.6, 116.1, 122.6, 122.6,125.0, 128.6, 129.6, 129.9, 131.2, 135.4, 136.5, 152.9, 154.2, 162.0, 163.4; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)= 2.32(s, 3H, CH_3), 3.8(s, 3H, -OCH_3), 7.1-8.2(m,17H, aromatic region), 9.7(s, 1H, -OH); IR(KBr) 3405, 1609, 747,685cm^{-1}; GC-MS (70 eV): m/z =500[M+].

2-(5-(4-dimethylaminophenyl)-4-(4, 5-diphenylisoxazol-3-yl)isoxazol-3-yl)-4methoxy phenol (4c)

Yellow; Yield 62% m.p. 194ºC, [$C_{32}H_{22}N_3O_3$];); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.6, 43.6, 100.2, 113.6, 116.1, 123.6, 126.0, 127.0, 127.9, 128.5, 129.0, 130.6, 132.8, 136.5, 144.5, 150.0, 152.8, 158.4; ^{1}HNMR (400MHz,$CDCl_3$) δ(ppm)= 2.35(s, 3H, CH_3), 3.2 (s, 6H, $N(CH_3)_2$), 6.6-7.9 (m,17H, aromatic region), 9.5(s, 1H, -OH); IR(KBr) 3412, 1605, 748,689 cm^{-1}; GC-MS (70 eV): m/z = 513[M+].

4-chloro-2-(5-phenyl-4-(4, 5-diphenylisoxazol-3-yl)isoxazol-3-yl)phenol (4d)

Dirty yellow; Yield 68% m.p. 128ºC, [$C_{30}H_{19}ClN_2O_3$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ =100.5, 117.6, 125.1, 127.0, 128.5, 128.8, 129.0, 130.3, 136.5, 150.0, 153.9, 158.6; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)=7.1-7.5(m,17H, aromatic region), 9.3(s, 1H, -OH); IR(KBr) 3410, 1608, 743, 688 cm^{-1} GC-MS (70 eV): m/z = 490[M+].

4-chloro-2-(5-(4-methoxyphenyl)-4-(4, 5-diphenylisoxazol-3-yl) isoxazol-3-yl)phenol (4e)

Yellowish white; Yield 66% m.p. 177ºC, [$C_{31}H_{21}ClN_2O_4$]; ^{13}C NMR (75 MHz,$CDCl_3$):δ =56.0, 100.3, 114.6, 117.6, 125.1, 127.0, 128.5, 128.8, 128.9,129.0 130.3,136.5, 151.2, 153.5, 158.7, 162.0; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)=7.3-8.3(m,17H, aromatic region), 9.8(s, 1H, -OH), 3.4(s, 3H, -OCH_3); IR(KBr) 3412, 1601, 742,687 cm^{-1}; GC-MS (70 eV): m/z = 520[M+].

4-chloro-2-(5-(4-dimethylaminoyphenyl)-4-(4, 5-diphenylisoxazol-3-yl) isoxazol-3-yl)phenol (4f)

Brownish yellow; Yield 62% m.p. 229ºC, [$C_{32}H_{24}ClN_3O_3$^{13}C NMR (75 MHz, $CDCl_3$): δ=42.1, 101.9, 113.6, 117.8, 125.9, 126.3, 127.9, 128.5, 129.0, 130.3, 136.5, 144.5, 152.3, 154.6,158.9; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm) = 3.1 (s, 6H, $N(CH_3)_2$), 7.2-7.8(m,17H, aromatic region), 10.1(s, 1H, -OH);]; IR(KBr) 3404, 1607, 749, 688 cm^{-1}; GC-MS (70 eV): m/z = 533[M+].

5-methoxy-2-(5-phenyl-4-(4, 5diphenylisoxazol-3-yl) isoxazol-3-yl) phenol (4g)

Brownish yellow; Yield 69% m.p. 192ºC, [$C_{31}H_{22}N_3O_4$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ =54.2, 102.3, 115.6, 120.8, 122.9, 124.5, 127.6, 128.9, 142.3, 149.7, 150.3, 159.2; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)= 3.67 (s, 3H. –OCH_3), 6.7-7.2 (m, 17H, aromatic region), 9.32 (s, 1H, -OH); IR(KBr) 3415, 1602, 745,684 cm^{-1}; GC-MS (70 eV): m/z = 468[M+].

5-methoxy-2-(5-(4-methoxy phenyl)-4-(4, 5diphenylisoxazol-3-yl) isoxazol-3-yl) phenol (4h)

Yellow; Yield 72% m.p. 167ºC, [$C_{32}H_{24}N_2O_5$]; ^{13}C NMR (75 MHz, $CDCl_3$):δ =56.0, 56.3, 102.5, 114.6, 115.5, 120.7, 122.6, 124.7, 127.0, 128.0, 128.5, 128.9, 136.5, 141.6, 147.7, 150.0, 158.9, 162.0; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)=3.6(s, 3H –OCH_3), 3.9(s, 3H, -OCH_3), 6.9-7.5(m, 17H, aromatic region), 9.6(s, 1H, -OH); IR(KBr) 3409, 1609,749,684 cm^{-1}; GC-MS (70 eV): m/z = 516[M+].

5-methoxy-2-(5-(4-dimethylamino) phenyl)-4-(4, 5diphenylisoxazol-3-yl) isoxazol-3-yl) phenol (4i)

Reddish Yellow; Yield 66% m.p. 163ºC, [$C_{33}H_{27}N_3O_4$]; ^{13}C NMR (75MHz, $CDCl_3$) δ=43.6, 56.9, 100.2, 113.6, 115.7, 119.2, 123.4, 126.0,127.8, 18.9, 129.2, 130.1, 131.2, 136.5, 141.9, 143.7, 150.4, 160.9; ^{1}HNMR (400MHz, $CDCl_3$) δ(ppm)= 3.1(s,6H,N(CH_3)$_2$), 3.7(s,3H.–OCH_3), 3.86(s,3H,-OCH_3), 7.3-8.5(m,17H, aromatic region), 9.2(s,1H,-OH); IR(KBr) 3408,1610,743,683 cm^{-1} ; XGC-MS (70 eV): m/z = 529[M+].

3 RESULT

3.1 Intermolecular pathway

To begin with, a model reaction was chosen between **3a** (2- hydroxyl-5 substituted phenyl)-5- substituted isoxazole-4-carbaldehyde oxime) and diphenyl acetylene to give bis-isoxazolines, forming 2-(5-(4-methoxyphenyl)-4-(4, 5-diphenylisoxazol-3-yl) isoxazol-3-yl)-4methoxyphenyl phenol **(4b**) (Scheme 3). Further, in order to optimize the reaction conditions the compound **3a** was exposed to alkyne in diverse solvents and for varying durations, resulting in the synthesis of the respective bis isoxazole **4b** (Table 1). Under room temperature conditions, the reaction of 3b and alkyne in CH_2Cl_2-water with the catalytic amount of TBAB was concluded in 18 hours, yielding 4b with a minimal isolated yield of 12%. (Table 1, entry 1). The reaction time and temperature were carefully regulated to avoid the formation of by-products. In S2 DDAB-water solvent system, no conversion of the reactants was observed (entry 2). The efficacy of the reaction was noticeably affected by adding TBAB to DDAB-water solvent system (Entry 3) indicating a preference for phase transfer catalysis mechanism to 1-3 dipolar addition reaction. Further, the reaction in toluene-water and CH_2Cl_2– water at 50º C for 20-25 hours resulted negligible conversion of reactant to products (Table 1, entries 5 and 6, respectively); however, using the toluene-water solvent system with TBAB, the yield obtained was dramatically enhanced (Entry 4).

Table 1 Reaction Conditions Optimization for the synthesis of 4-substituted-2(-5-sunstituted-4-(4,5-diphenylisoxazol-3-yl)isoxazol-3yl)phenol(4a-i)

Sr. No.	Solvent system	Solvent/Catalyst	Time	Yield %
1	S1	CH_2Cl_2+TBAB+Water	18 hrs	12
2	S2	Water + DDAB	15 hrs	No adduct
3	S3	BBAB+Water+TBAB	10 hrs	38%
4	S4	Toluence+water+TBAB	4 hrs	67%
5	S5	Toluence+water	20 hrs	No adduct
6	S6	CH_2Cl_2+water	25 hrs	No adduct

The use of TBAB (entries 3 and 4) led significantly faster reaction rates as compared to those observed in the other solvent systems (entries 1-3 and 5–6). Notably, it was observed that the reaction of substrate 3b exhibited better improvement in the performance in the presence of TBAB (entries 3, 4) as compared to in typical organic solvents. (entries 1, 2, 5 and 6). Undoubtedly, the reaction in TBAB demonstrated superior efficacy and atom economy when contrasted with reactions in alternative solvents. The optimization of the amount of the catalyst was meticulously carried out in the process. Initiating with 2.5 mole % of catalyst till 10 mole% and accomplishing the 37% of yield in latter case. The further increase in the catalytic amount upto 25 mole % resulted in 67% of yield. Above this catalytic amount the there was no further increase in the yield percentage.

Furthermore, incorporating water as a secondary solvent in both protic and aprotic systems enhanced isolated yields. Consequently, the solvent's nature specifically increased hydrophilicity of the reaction mixture, significantly impacted the efficiency of the reaction , leading to an improvement in the isolated yield. Table 1 briefly presents the findings, distinctly highlighting the superiority of the tolune-water biphasic system incorporating TBAB over an organic solvent-water system. The progression of the reaction was tracked through thin layer chromatography.

Elemental analysis was performed on the purified compounds and the yields were determined by calculating the quantities of these products. Further, the investigation was carried out to the reactions of the other substates by substituting to rings A and C of molecular framework of 2 (Table2) and the yield obtained were moderate to good ranging from 61-72%. It was noted that the substituent's nature in the oxime moiety played a crucial role in shaping the reactions outcome. In general, the electron donating substituents yielded superior results as they augmented nucleophilicity of the oxime nitrogen atom, consequently facilitating the ene-like reaction. Additionally, it was observed that all substituted oximes were obtained as single product without formation of any stereoisomers

Remarkably, tetrabutyl ammonium bromide (TBAB) in toluene -water system demonstrated notable effectiveness in enhancing the reaction's efficiency. The pivotal role of tetraalkylammonium salts(Q^+X^-) in the reaction occurring between two immiscible phases is to expedite the reaction by facilitating the availability of the substrate at the interfacial boundaries.

The predicted plausible mechanism can be depicted as follows: The solubilities of the two reactants i.e. 3b and diphenyl acetylene are dissimilar. The oxime (3b) is water soluble at 500C in the presence of PTC under thermal agitation and hydrophilic in nature while alkyne is soluble in toluene. The disparate solvent solubilities of the two reactants impede the reaction.

The borderline of the two mutually immiscible liquids in not a fixed geometric surface. Owing to the thermal motion, diphenyl acetylene from organic phase enters the aqueous phase and vice versa. Consequently, the interfacial region can be regarded as third anisotropic phase where the reaction takes place.

The advocated pathway at the interfacial mechanism is first the formation of nitrones in situ (reactant A i.e. oxime) at aqueous phase. This is followed by extraction of these ions at the interface catalysed by tetrabutyl ammonium chloride where reactant B (diphenyl acetylene) is available due to thermal agitation. Since the product formed was immiscible in water, the extraction of organic layer was carried out by ethyl acetate (3x20mL) followed by further purification methods.

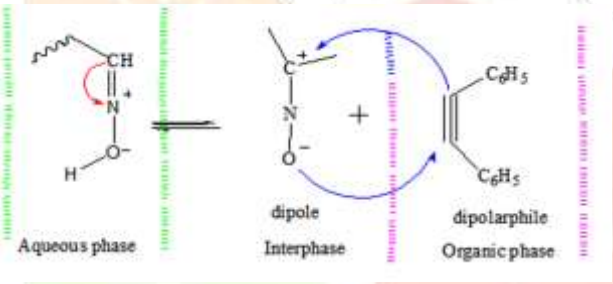


Fig 1: Plausible mechanism of 1,3 dipolar cycloaddition of dipole and dipolarphile

3.2 Chemistry

The interaction between N,N disubstituted formamide like DMF or N-methylformamide and acid chlorides such as phosphoryl chlorides or phosgene results in the formation of adducts commonly called as Vilsmeier reagents. These reagents are extensively applied in synthetic organic chemistry particularly for the formylation of the electron-rich aromatic compounds and olefin. We have incorporated the Vilsmeier reagent (Scheme 1) for the formylation of 4(5) substituted-2-(5 substituted phenyl isoxazol-3-yl) phenol (**1a-i)** leading to the formation of 3-(2-hydroxy -5(4) substituted phenyl)-5subtituted isoxazol-4-carbaldehydes (**2a-i).** Furthermore **2a-i** were subjected to oximation at 50^{o}C with constant stirring for 2 hours to obtain **3a-i**.

Table 2 Physical constants of 2a-i, 3a-i and 4a-i

Sr. No.	Entry	R_1	R_2	R_3	Yield (%)	Melting points
1	**2a**	CH_3	H	H	74	102
2	**2b**	CH_3	H	OCH_3	78	105
3	**2c**	CH_3	H	$N(CH_3)_2$	82	115
4	**2d**	Cl	H	H	72	124
5	**2e**	Cl	H	OCH_3	75	145
6	**2f**	Cl	H	$N(CH_3)_2$	87	129
7	**2g**	H	OCH_3	H	85	162
8	**2h**	H	OCH_3	OCH_3	81	130
9	**2i**	H	OCH_3	$N(CH_3)_2$	76	126
10	**3a**	CH_3	H	H	76	137
11	**3b**	CH_3	H	OCH_3	72	239
12	**3c**	CH_3	H	$N(CH_3)_2$	82	168
13	**3d**	Cl	H	H	67	173
14	**3e**	Cl	H	OCH_3	76	165
15	**3f**	Cl	H	$N(CH_3)_2$	78	197
16	**3g**	H	OCH_3	H	67	225
17	**3h**	H	OCH_3	OCH_3	79	156
18	**3i**	H	OCH_3	$N(CH_3)_2$	81	178
19	**4a**	CH_3	H	H	61	157
20	**4b**	CH_3	H	OCH_3	67	142
21	**4c**	CH_3	H	$N(CH_3)_2$	62	194
22	**4d**	Cl	H	H	68	128
23	**4e**	Cl	H	OCH_3	66	177
24	**4f**	Cl	H	$N(CH_3)_2$	62	229
25	**4g**	H	OCH_3	H	69	192
26	**4h**	H	OCH_3	OCH_3	72	167
27	**4i**	H	OCH_3	$N(CH_3)_2$	66	163

A straightforward method for synthesizing bis isoxazoles **4a-i**, involved 1,3 dipolar cycloaddition reactions between isoxazole-4-carbaldehyde oximes and alkynes. The reactions were catalysed by TBAB

(tetrabutylammonium bromide) serving as PTC (phase transfer catalyst) in the biphasic system of toluene and water.

To elucidate the structure of compounds **2a-i** (Table 2), the infrared spectra showed peaks at 828-835 and 968-974 cm^{-1} because of N-O and C-O-N stretching, respectively of the isoxazole ring and peak at 1643-1647 cm^{-1} owing to C=O of formyl group at C-4 of the isoxazole ring.

The two characteristic weak bands of CHO appeared at 2806-2809 and 2730-2734 cm^{-1}. A broad band appeared at 3053-3039 cm^{-1} resembled for Ar-OH. The ^{1}HNMR spectra of compounds 2a-i showed two singlets at δ 9.4-9.7 ppm and δ 10.12-10.4 ppm owing to the Ar-OH proton and –CHO at C-4 respectively. The multiplets at δ 6.82-7.9 ppm accorded for aromatic protons. ^{1}H NMR spectra for compounds **2a, 2b, and 2c** showed the singlets at δ 2.28 ppm referring to the three protons of Ar-CH_3 respectively. In addition, for compounds **2b, 2e and 2h,** the singlets appeared at δ 3.7-3.78 ppm for Ar-OCH_3 respectively. The six protons of $N(CH_3)_2$ in compounds **2c, 2f** and **2i** resonated as singlets at δ 2.8-3.08 ppm.

The product's structures were further substantiated through ^{13}C NMR spectral analysis where signals at δ 190 ppm corresponding to C=O and signals at δ 127-135 ppm indicated the incorporation of an isoxazole ring into the aromatic ring. Compounds 2a-i exhibited satisfactory elemental analyses and assigned structures were supported by the mass spectral data.

The desired structures of substituted 3-(2-hydroxy phenyl)-5-phenylisoxazole-4-carbaldehyde oximes **(3a-i)** have been confirmed by IR spectral data with stretching bands respectively at 3030 cm^{-1} and 3036 cm^{-1} for C=N-OH and O-H bonding. A characteristics band was observed for C=N bonding at 968-978 cm^{-1}.

The two different peaks at δ 9.2-9.6 ppm and at δ 9.6-10.3 ppm for C=N-OH and Ar-OH respectively confirmed the structures of **3a-i** in ^{1}HNMR spectra.The singlets at δ 2.29-2.49 ppm confirming the presence of three protons of methyl groups in **3a-c** respectively. The three protons resonated at δ3.85-3.89 ppm demonstrated the presence of -OCH_3 in the compounds **3b,3e,and 3h**. The singlets of six protons derived from -$N(CH_3)_2$ of compounds **3c, 3f, 3i** appeared at δ3.1-3.5 ppm. The multiplets resonated at δ 6.9-8.2 ppm assigned the aromatic protons in **3a-i**.

Intense fingerprint region appeared at 770-730 and 720-680 cm^{-1} assingned for two additional phenyl rings in **4a-i.** In ^{1}HNMR of **4a-i** disappearance of the singlets of C=N-OH at δ 9.2-9.6 ppm and appearance of new multiplets at δ 6.6-8.5 ppm integrating protons from aromatic region confirmed the formation of bis-isoxazoles **4a-i.**. A regular pattern for Ar–OH in **4a-i** exhibited at δ 9.2-9.7ppm and the other peaks in compounds **4a-c** at δ 2.29-2.49, for **4b,e, h** at δ 3.85-3.89 ppm and for compounds **4c, f, i** at δ 3.02-3.07 ppm confirmed the assigned structure. The various peaks for the aromatic carbon of isoxazoles which confirmed the assigned structure were obtained at δ131.56-130.8ppm and δ127-135 ppm for ^{13}CNMR spectra. The products **4a-i** were subjected for elemental analysis. The fragmentation pattern exhibited in mass spectra confirmed the assigned structure.

4 CONCLUSIONS

The toluene-water/TBAB combination demonstrated remarkable efficiency as a biphasic solvent system for synthesizing bis isoxazole derivatives at room temperature within a four-hour time framework. This protocol is notable for a brief reaction period, its environmentally friendly nature and straightforward operation involving a convenient workup, , and yielding products in the range of good to excellent. The reaction dynamics are influenced by the aqueous co-solvent; the organic phase solvates the hydrophobic reactant, such as diphenyl acetylene, while the phase transfer catalyst (PTC) in the aqueous solvates oximes at 50^0C. The reaction is presumed to take place at the interface of these two immiscible phases.

ACKNOWLEDGMENT

The author takes this opportunity to express her gratitude to the (SAIF) Sophisticated Analytical Instrumentation Facility, Chandigarh for ^{1}HNMR analysis, the Department of Pharmacy, Nagpur for IR spectral analysis, and University of Pune for mass analysis and ^{13}CNMR data.

References

1. K. Chikkula, and R. Sundararajan, Med Chem Res. **26**, 3026 (2017). https://doi.org/10.1007/s00044-017-2000-0
2. M. Aarjane, S. Slassi, B. Tazi and A. Amine, Archiv der Pharmazie. **1**, 1 (2020). https://doi.org/10.1002/ardp.202000261
3. Z. Yang, Y. Zhao, P. Li and Y. He, J Heterocyclic Chem. **56** 3042 **(**2019). https://doi.org/10.1002/jhet.3699Ci
4. M. Hawash, N. Jaradat, M. Abualhasan, M. Thaher, R. Sawalhi, N. Younes, A. Shanna, M. Nuseirat and A. Mousa, Sci Rep. **12** 18223 (2022). https://doi.org/10.1038/s41598-022-23050-x
5. A. Oluwaseye, A. Uzairu, G. A. Shallangwa and S. E Abechi, Journal of King Saud University – Science. **32**, 116 (2020). https://doi.org/10.1016/j.jksus.2018.03.022
6. M. B. Bommagani, J. R. Yerrabelly, M. Chitneni, G. Thalari, N. R. Vadiyala, S. K. Boda, and P. R. Chitneni, Chem. Data Collect. **31,** 100629 (2021). https://doi.org/10.1016/j.cdc.2020.100629
7. G. C. Arya, K. Kaur, and V. Jaitak European Journal of Medicinal Chemistry. **221,** 113511 (2021). https://doi.org/10.1016/j.ejmech.2021.113511
8. M. Mączyński, J. Artym, M. Kocięba, I. Kochanowska, S. Ryng and M. Zimecki, Pharmacol. Rep. **68**, 894 (2016). https://doi.org/10.1016/j.pharep.2016.04.017
9. J. Plumet, Chem Plus Chem. **85,** 225 (2020). https://doi.org/10.1002/cplu.202000448
10. S. Roscales, J. Plumet, Org. Biomol. Chem. **16**, 8446 (2018). https://doi.org/10.1039/c8ob02072h
11. F. Hu, M. Szostak, Adv. Synth.Catal. **357**, 2583 (2015). https://doi.org/10.1002/adsc.201500319
12. S. Thakur, A.Das, T. Das, New Journal of Chem., **45**, 11420 (2021). https://doi.org/10.1039/d1nj02023d
13. L. Maiuolo, V. Algieri, F. Olivito, A.D. Nino, Catalysts **10,** 65 (2020). http://dx.doi.org/10.3390/catal10010065
14. A. I. Mironova, V. G. Nenajdenko, P. S. Postnikov, A. Saito , M. S. Yusubov and A. Yoshimura Molecules, **27(12),** 3860 (2022). https://doi.org/10.3390/molecules26123491
15. S. Das and K. Chanda RSC Adv. **11,** 32680 (2021). https://doi.org/10.1039/d1ra04624a
16. S. K. Hota, A. Chatterjee, P. K. Bhattacharya and P. Chattopadhyay. Green Chem. **11**.169 (2009). https://doi.org/10.1039/b812290c
17. P. T. Anastas and J. C. Warner, Green Chemistry: Theory and Practice. Oxford University Press, Oxford, (2000). https://doi.org/10.1093/oso/9780198506980.001.0001
18. M. Poliakoff and P. Licence, Sustainable technology: Green Chemistry. Nature, **450**, 810 (2007). https://doi.org/10.1038/450810a

19. V. Polshettiwar and R.Varma, Pure and Applied Chemistry, **80**,777 (2008). https://doi.org/10.1351/pac200880040777
20. C.M. Starks, P.H. Washecheck, Phase Transfer Agent in Oxidation of Olefins. U.S. Patent 3547962 (1970). https://doi.org/10.1111/j.1749-6632.1980.tb53641.x
21. K. Nakama, S. Seki and S. Kanemasa, Tetrahedron Let. **42,** 6719 (2001). https://doi.org/10.1016/S0040-4039(01)01346-6