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One pot synthesis of 3,5-diaryl substituted-1,2,4-oxadiazoles using *gem*-dibromomethylarenes

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Abstract: 1,2,4-oxadiazole is one of the most promising heterocyclic ring systems in medicinal chemistry. In the present paper, we are reporting the method for efficient one-pot synthesis of of 3,5-diaryl substituted 1,2,4-oxadiazoles using two-component reaction of *gem*-dibromomethylarenes with amidoximes in good yields. In this method, g*em*-dibromomethylarenes are used as benzoic acid equivalent for the efficient synthesis of aryl substituted 1,2,4-oxadiazoles. It is anticipated that this methodology will have versatile applications in the practical syntheses of various molecules of both medicinal and material chemistry importance.

Keywords: *Gem*-dibromomethylarene **;** oxadiazole **;** amidoxime.

Introduction

1,2,4-Oxadiazoles are being considered as one of the most important structural motifs in the research area for drug discovery programme. They are often considered as ester and amide bioisosteres and have been used in the design of dipeptidomimetics.[1] These *N*- and *O*- containing heterocyclic compounds are integral part of many drugs such as pleconaril,[2] verucerfont[3,4] and drug leads[5] (**Figure 1**) including the potent $S1P_1$ agonist,[6,7] mGlu5 receptor,[8] and cortical muscarinic receptor[9] for the treatment of Alzheimer's disease. They have also shown interesting biological activities such as GABA modulators,[10] anti-prostate cancer agents,[11] $5HT_3$ receptor antagonists,[12] anticonvulsant activity,[13] CNS depressant,[14] tumor-selective and apoptosis-inducing,[15] antiviral,[16] diuretic,[17] analgesic, anti-inflammatory agents, inhibitiors of cytosolic hCA II and membrane-bound hCA IX isoforms.[18]

In addition to medicinal importance, they have drawn considerable attention researchers working in the area of material science due to their exceptional electrical, thermal and optical properties. Recent reports reveals that 1,2,4-oxadiazoles are used as fabrication materials for organic solar cells[19] and light-emitting diodes.[20,21] In view of wide spread applications of 1,2,4-oxadiazoles, development of improved synthetic methodology for the synthesis of substituted 1,2,4-oxadiazoles is of prime interest.

Many synthetic methods have been reported for the preparation of 1,2,4-oxadiazole ring system.[22-27] Of the many methods reported, cyclocondensation of amidoximes, 1,3-dipolar cycloaddition of nitriles to nitrile oxides and rearrangement from other heterocycles are important methods. The most familiar method for the synthesis of 1,2,4-oxadiazoles is cyclization of amidoximes with acid chlorides/carboxylic acids and esters [28-30]. Coupling reagent such as CDI, DCC, EDC, HBTU, HOBt or TBTU are being used for their synthesis using carboxylic acids.[31] This method, although it works well fairly on straightforward substrates, it is incompatible with many functional groups. There are many other reports which arrived at synthesis of oxadiazoles using acid chlorides.[32-37] Acid chlorides are toxic, hard to store and require essential knowledge to handle. These methods suffer from drawbacks such as reactions take more time, usually reactions have to be conducted under harsh conditions, purification of

synthesized compounds are very difficult and tend to low yields accompanied with multiple by-product and high toxicity.

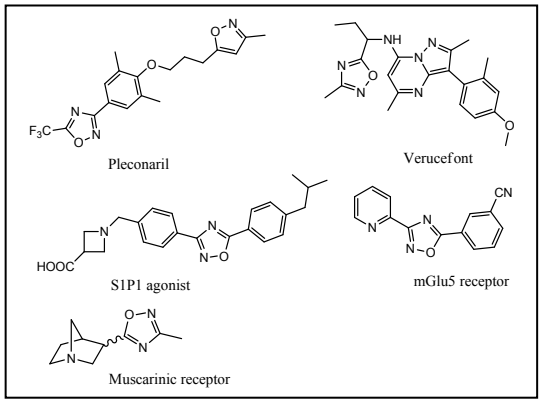


Figure-1: N and O containing heterocyclic drug molecules

Gem-dibromomethylarenes are very interesting and important starting materials in the field of synthetic organic chemistry. By using *gem*-dibromomethylarenes as synthetic carbonyl compound equivalents, various applications have been explored in synthetic organic chemistry.[38-43] In recent days, *gem*-dibromomethylarene moiety is occupying its own importance in pharmaceutical and medicinal industries. To the best of our knowledge, there is no literature available on the synthesis of 1,2,4-oxadiazoles starting from *gem*-dihalomethylarenes. Though the synthesis of 1,2,4-oxadiazoles has been extensively documented, substitution of the carboxylic acid and their derivatives component with an alternative functional group has not been documented. Therefore, development of a simple and stable substitute by using inexpensive and readily available reagents would extend the scope of 1,2,4-oxadiazoles in organic synthesis.

Experimental

General procedure for the synthesis of *gem*-dibromomethylarenes 1(a-j)

To a solution of substituted methyl analogues (1.0 eq) in CCl_4 was added NBS (2.0 eq) followed by catalytic amount of benzoylperoxide (0.2 eq). The mixture was gradually heated to reflux for 8 h. Progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature, the succinimide was filtered off and the filtrate was concentrated under reduced

pressure. The residue was purified by column chromatography (hexane:ethyl acetate 10%) to afford *gem*-dibromomethylarenes. All the products were isolated and were well characterized by physical and spectral data which are in good agreement with the structure of the reported products.

General procedure for the synthesis of amidoximes 2(a-c)

Hydroxylamine hydrochloride (2.5 eq) and sodiumcarbonate (1.6 eq) was taken in water and stirred to complete dissolution. Substituted benzonitrile (1.0 eq) were dissolved in ethanol and added to the reaction mixture. The reaction mixture is allowed to stir for 5-6 h at 60 ^{0}C. Progress of the reaction was monitored by TLC. Upon completion, the solvent was removed under reduced pressure and residue was taken in water and extracted with ethyl acetate. The organic layer was dried with anhydrous sodium sulphate, the solvent was evaporated to get amidoximes. All the products were isolated in good yields and were well characterized by physical and spectral data which are in good agreement with the structure of the reported products.

General procedure for the synthesis of 3,5-diphenyl-1,2,4-oxadiazole derivatives 3(a-ad)

Substituted *gem*-dibromomethylarenes **1(a-j)** and substituted (*Z*)-*N*′-hydroxybenzimidamides **2(a-c)** was taken in pyridine which acts as both base and solvent. Then potassium *tert*-butoxide and iodine was added. The reaction mixture was allowed to stir for 8-10 h at 80 ^{0}C. Progress of reaction was monitored by TLC. Upon completion, the solvent was removed under reduced pressure and residue was taken in water and extracted with ethyl acetate. The organic layer was dried with anhydrous sodium sulphate, the solvent was evaporated and crude was purified by column chromatography (hexane and ethyl acetate) to get 3,5-diphenyl-1,2,4-oxadiazole **3(a-ad)** derivatives.

3,5-Diphenyl-1,2,4-oxadiazole (3a)

The product was obtained from (dibromomethyl)benzene (0.1 g, 0.400 mmol) **(1a)**, *(Z)-N*′-hydroxybenzimidamide (0.052 g, 0.400 mmol) **(2a)**, potassium *tert*-butoxide (0.022 g, 0.200 mmol) and iodine (0.020 g, 0.080 mmol). Mp 105–108 °C (lit[22] 106-108 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (2H, d, J = 7.8 Hz, Ar-H), 8.20 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.62 (1H, t, J = 7.1 Hz, Ar-H), d 7.51–7.58 (5H, m, Ar-H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 175.92, 169.13, 132.82, 131.96, 129.11,

129.04, 128.70, 127.89, 127.10, 124.83. IR (KBr) ν/cm^{-1}: 1611, 1563, 1412, 1359. MS (ESI) m/z: 223.241 (100.0%).

5-Phenyl-3-(*p*-tolyl)-1,2,4-oxadiazole (3b)

The product was obtained from (dibromomethyl)benzene (0.1 g, 0.400 mmol) **(1a)**, (Z)-*N'*-hydroxy-4-methylbenzimidamide (0.060 g, 0.400 mmol) **(2b)**, potassium *tert*-butoxide (0.022 g, 0.200 mmol) and iodine (0.020 g, 0.080 mmol). Mp 114–116 °C (lit[22] 113–115 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (2H, dd, J = 7.3 and J = 1.9 Hz, Ar-H), 8.11 (2H, d, J = 8.0 Hz, Ar-H), 7.50–7.69 (3H, m, Ar-H), 7.32 (2H, d, J = 8.0 Hz, Ar-H), 2.41 (3H, s, -CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.80, 168.84, 143.41, 131.09, 129.79, 128.81, 128.11, 127.48, 127.13, 121.59, 21.70. IR (KBr) ν/cm^{-1}: 2883, 1609, 1571, 1418, 1351. MS (ESI) m/z: 237.255 (100.0%).

3-(4-Methoxyphenyl)-5-phenyl-1,2,4-oxadiazole (3c)

The product was obtained from (dibromomethyl)benzene (0.1 g, 0.400 mmol) **(1a)**, *(Z)-N'*-hydroxy-4-methoxybenzimidamide (0.066 g, 0.400 mmol) **(2c)**, potassium *tert*-butoxide (0.022 g, 0.200 mmol) and iodine (0.020 g, 0.080 mmol). Mp 93–96 °C (lit[22] 94–96 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (2H, dd, J = 8.4 and J = 1.7 Hz, Ar-H), 8.15 (2H, d, J = 8.8 Hz, Ar-H), 7.49–7.58 (3H, m, Ar-H), 7.03 (2H, d, J = 8.7 Hz, Ar-H), 3.85 (3H, s, -OCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.79, 168.91, 163.29, 131.13, 130.02, 128.79, 127.51, 127.19, 116.88 114.49, 55.47. IR (KBr) ν/cm^{-1}: 1611, 1563, 1412, 1359, 1237, 1048. MS (ESI) m/z: 253.25 (100.0%).

5-(4-Chlorophenyl)-3-phenyl-1,2,4-oxadiazole (3d)

The product was obtained from 1-chloro-4-(dibromomethyl)benzene (0.1 g, 0.351 mmol) **(1b)**, (*Z*)-*N*'-hydroxybenzimidamide (0.047 g, 0.351 mmol) **(2a)**, potassium *tert*-butoxide (0.019 g, 0.175 mmol) and iodine (0.017 g, 0.070 mmol). Mp 118–120 °C (lit[22] 118–119 °C) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (2H, d, J = 7.8 Hz, Ar-H), 8.18 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.49-7.56 (5H, m, J = 8.7 Hz, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.81, 168.71, 134.68, 131.45, 129.68, 129.14, 128.55, 127.04, 126.22, 122.03. IR (KBr) ν/cm^{-1}: 1601, 1550, 1411, 1352, 1091, 810. MS (ESI) m/z: 257.681 (100.0%).

5-(4-Chlorophenyl)-3-(p-tolyl)-1,2,4-oxadiazole (3e)

The product was obtained from 1-chloro-4-(dibromomethyl)benzene (0.1 g, 0.351 mmol) **(1b)**, *(Z)-N′*-hydroxy-4-methylbenzimidamide (0.052 g, 0.351 mmol) **(2b)**, potassium *tert*-butoxide (0.019 g, 0.175 mmol) and iodine (0.017 g, 0.070 mmol). Mp 137–140 °C (lit[22] 138–140 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (2H, d, J = 7.8 Hz, Ar-H), 8.21 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.65 (2H, d, Ar-H), 7.58 (2H, d, 2H), 2.32 (s, 3H, -CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.83, 168.91, 134.43, 131.90, 129.88, 129.08, 128.40, 125.62, 123.54, 122.35, 21.44. IR (KBr) ν/cm^{-1}: 1612, 1546, 1418, 1342, 828. MS (ESI) m/z: 271.704, (100.0%).

5-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (3f)

The product was obtained from 1-chloro-4-(dibromomethyl)benzene (0.1 g, 0.351 mmol) **(1b)**, *(Z)-N′*-hydroxy-4-methoxybenzimidamide (0.058 g, 0.351 mmol) **(2c)**, potassium *tert*-butoxide (0.019 g, 0.175 mmol) and iodine (0.017 g, 0.070 mmol). Mp 138–140 °C (lit[45] 138–139 °C) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (2H, d, J = 7.8 Hz, Ar-H), 8.18 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.71 (2H, d, Ar-H), 7.65 (2H, d, 2H), 3.83 (s, 3H, -OCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.93, 168.78, 160.84, 134.58, 129.96, 129.01, 125.67, 122.38, 118.52, 114.96, 55.88. IR (KBr) ν/cm^{-1}: 2893, 1620, 1559, 1410, 1352, 819, 741. MS (ESI) m/z: 287.724 (100.0%).

5-(4-Bromophenyl)-3-phenyl-1,2,4-oxadiazole (3g)

The product was obtained from 1-bromo-4-(dibromomethyl)benzene (0.1 g, 0.304 mmol) **(1c)**, (Z)-*N′*-hydroxybenzimidamide (0.041 g, 0.304 mmol) **(2a)**, potassium *tert*-butoxide (0.017 g, 0.152 mmol) and iodine (0.015 g, 0.068 mmol). Mp 113–114 °C (lit[45] 112–114 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (2H, d, J = 7.8 Hz, Ar-H), 8.12 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.57-7.52 (3H, m, Ar-H), 7.38 (2H, d, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.90, 168.92, 132.18, 131.03, 129.98, 129.04, 127.84, 126.39, 123.32. IR (KBr) ν/cm^{-1}: 1606, 1555, 1408, 1355, 734. MS (ESI) m/z: 302.128, (100.0%).

5-(4-Bromophenyl)-3-(*p*-tolyl)-1,2,4-oxadiazole (3h)

The product was obtained from 1-bromo-4-(dibromomethyl)benzene (0.1 g, 0.304 mmol) **(1c)**, *(Z)-N′*-hydroxy-4-methylbenzimidamide (0.045 g, 0.304 mmol) **(2b)**, potassium *tert*-butoxide (0.017 g, 0.152

mmol) and iodine (0.015 g, 0.068 mmol). Mp 118–120 °C (lit[46] not given). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (2H, d, J = 7.8 Hz, Ar-H), 8.14 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.57 (2H, d, Ar-H), 7.45 (2H, d, Ar-H), 2.32 (s, 3H, -CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ δ 175.89, 168.79, 132.55, 131.71, 129.96, 129.15, 128.40, 125.71, 123.04, 21.38. IR (KBr) v/cm^{-1}: 2892, 1601, 1550, 1411, 1352, 738. MS (ESI) m/z: 316.209, (100.0%).

5-(4-Bromophenyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (3i)

The product was obtained from 1-bromo-4-(dibromomethyl)benzene (0.1 g, 0.304 mmol) **(1c)**, *(Z)-N′*-hydroxy-4-methoxybenzimidamide (0.050 g, 0.304 mmol) **(2c)**, potassium *tert*-butoxide (0.017 g, 0.152 mmol) and iodine (0.015 g, 0.068 mmol). Mp 110–112 °C (lit[46] not given). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (2H, d, J = 7.8 Hz, Ar-H), 8.15 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.55 (2H, d, Ar-H), 7.47 (2H, d, Ar-H), 3.79 (s, 3H, -OCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.84, 168.81, 160.62, 132.38, 129.87, 125.58, 123.77, 118.63, 114.79, 55.92. IR (KBr) v/cm^{-1}: 2884, 1608, 1561, 1407, 1350, 1125, 732. MS (ESI) m/z: 331.164, (100.0%).

5-(4-Fluorophenyl)-3-phenyl-1,2,4-oxadiazole (3j)

The product was obtained from 1-(dibromomethyl)-4-fluorobenzene (0.1 g, 0.373 mmol) **(1d)**, *(Z)-N′*-hydroxybenzimidamide (0.050 g, 0.373 mmol) **(2a)**, potassium *tert*-butoxide (0.020 g, 0.186 mmol) and iodine (0.018 g, 0.074 mmol). Mp 116–118 °C (lit[47] 116-117 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (2H, d, J = 7.8 Hz, Ar-H), 8.18 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.42-7.49 (5H, m, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.88, 168.82, 163.05, 131.25, 129.28, 129.10, 127.22, 126.22 119.82, 116.13. IR (KBr) v/cm^{-1}: 1625, 1571, 1421, 1371, 1210. MS (ESI) m/z: 241.239, (100.0%).

5-(4-Fluorophenyl)-3-(p-tolyl)-1,2,4-oxadiazole (3k)

The product was obtained from 1-(dibromomethyl)-4-fluorobenzene (0.1 g, 0.373 mmol) **(1d)**, *(Z)-N′*-hydroxy-4-methylbenzimidamide (0.056 g, 0.373 mmol) **(2b)**, potassium *tert*-butoxide (0.020 g, 0.186 mmol) and iodine (0.018 g, 0.074 mmol). Mp 122–124 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (2H, d, J = 7.8 Hz, Ar-H), 8.13 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.49 (2H, d, Ar-H), 7.38 (2H, d, Ar-H), 2.38 (3H, s, -CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.94, 168.82, 163.07, 131.75, 129.98, 129.08,

125.70, 123.09, 116.07, 119.83, 21.41. IR (KBr) ν/cm^{-1}: 2891, 1610, 1542, 1412, 1371, 1219, 761. MS (ESI) m/z: 255.263, (100.0%).

5-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (3l)

The product was obtained from 1-(dibromomethyl)-4-fluorobenzene (0.1 g, 0.373 mmol) **(1d)**, (Z)-*N'*-hydroxy-4-methoxybenzimidamide (0.062 g, 0.373 mmol) **(2c)**, potassium *tert*-butoxide (0.020 g, 0.186 mmol) and iodine (0.018 g, 0.074 mmol). Mp 150–152 °C (lit[48] 151-152 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (2H, d, J = 7.8 Hz, Ar-H), 8.15 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.51 (2H, d, Ar-H), 7.36 (2H, d, Ar-H), 3.84 (3H, s, -OCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.90, 168.79, 163.01, 160.85, 129.19, 125.89, 119.79, 118.03, 116.12, 114.99, 55.95. IR (KBr) ν/cm^{-1}: 1612, 1548, 1412, 1363, 1253, 1217, 1048. MS (ESI) m/z: 271.264, (100.0%).

5-(2-Chloro-6-fluorophenyl)-3-phenyl-1,2,4-oxadiazole (3m)

The product was obtained from 1-chloro-2-(dibromomethyl)-3-fluorobenzene (0.1 g, 0.330 mmol) **(1e)**, (Z)-*N'*-hydroxybenzimidamide (0.045 g, 0.330 mmol) **(2a)**, potassium *tert*-butoxide (0.018 g, 0.165 mmol) and iodine (0.016 g, 0.066 mmol). Mp 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.50 (2H, t, Ar-H), 7.45 (1H, t, Ar-H), 7.37 (1H, d, Ar-H), 7.30 (1H, d, Ar-H), 7.25 (1H, t, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.93, 166.79, 159.95, 133.91, 131.92, 131.02, 129.31, 127.42, 126.18, 124.92, 123.95, 112.93. IR (KBr) ν/cm^{-1}: 1624, 1581, 1430, 1363, 1273, 1095, 827. MS (ESI) m/z: 275.682, (100.0%).

5-(2-Chloro-6-fluorophenyl)-3-(p-tolyl)-1,2,4-oxadiazole (3n)

The product was obtained from 1-chloro-2-(dibromomethyl)-3-fluorobenzene (0.1 g, 0.330 mmol) **(1e)**, *(Z)-N'*-hydroxy-4-methylbenzimidamide (0.049 g, 0.330 mmol) **(2b)**, potassium *tert*-butoxide (0.018 g, 0.165 mmol) and iodine (0.016 g, 0.066 mmol). Mp 119–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.52 (2H, t, Ar-H), 7.40 (1H, d, Ar-H), 7.34 (1H, d, Ar-H), 7.28 (1H, t, Ar-H), 2.36 (3H, s, -CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.80, 168.91, 159.84, 133.92, 131.87, 129.66, 125.93, 124.95, 123.98, 123.12, 112.91, 21.55. IR (KBr): 2907, 1613, 1560, 1454, 1371, 1265, 1089, 840, 769. MS (ESI) m/z ν/cm^{-1}: 289.904, (100.0%).

5-(2-Chloro-6-fluorophenyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (3o)

The product was obtained from 1-chloro-2-(dibromomethyl)-3-fluorobenzene (0.1 g, 0.330 mmol) **(1e)**, *(Z)-N′*-hydroxy-4-methoxybenzimidamide (0.054 g, 0.330 mmol) **(2c)**, potassium *tert*-butoxide (0.018 g, 0.165 mmol) and iodine (0.016 g, 0.066 mmol). Mp 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.54 (2H, t, Ar-H), 7.39 (1H, d, Ar-H), 7.34 (1H, d, Ar-H), 7.27 (1H, t, Ar-H), 3.78 (3H, s, -OCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.91, 168.93, 160.71, 159.81, 133.85, 131.88, 125.99, 124.99, 123.95, 118.81, 114.91, 112.99, 55.92. IR (KBr) ν/cm^{-1}: 1608, 1574, 1423, 1358, 1260, 1243, 1088, 1066, 841. MS (ESI) m/z: 305.724, (100.0%).

4-(3-Phenyl-1,2,4-oxadiazol-5-yl)benzonitrile (3p)

The product was obtained from 4-(dibromomethyl)benzonitrile (0.1 g, 0.363 mmol) **(1f)**, *(Z)-N′*-hydroxybenzimidamide (0.049 g, 0.363 mmol) **(2a)**, potassium *tert*-butoxide (0.020 g, 0.181 mmol) and iodine (0.018 g, 0.072 mmol). Mp 160–162 °C (lit[49] 161-162 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (2H, d, J = 7.8 Hz, Ar-H), 8.13 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.92 (2H, d, Ar-H), 7.50 (2H, t, J = 7.1 Hz, Ar-H), 7.42 (1H, d, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.95, 168.91, 132.88, 131.15, 129.38, 128.99, 128.03, 127.62, 126.13, 118.91, 112.79. IR (KBr) ν/cm^{-1}: 2236, 1622, 1570, 1424, 1367. MS (ESI) m/z: 248.241, (100.0%).

4-(3-(*p*-Tolyl)-1,2,4-oxadiazol-5-yl)benzonitrile (3q)

The product was obtained from 4-(dibromomethyl)benzonitrile (0.1 g, 0.363 mmol) **(1f)**, (*Z*)-*N′*-hydroxy-4-methylbenzimidamide (0.054 g, 0.363 mmol) **(2b)**, potassium *tert*-butoxide (0.020 g, 0.181 mmol) and iodine (0.018 g, 0.072 mmol). Mp 128–130 °C (lit[46] not reported[I]). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (2H, d, J = 7.8 Hz, Ar-H), 8.09 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.92 (2H, d, Ar-H), 7.35 (2H, t, J = 7.1 Hz, Ar-H), 2.32 (3H, s, -CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.89, 168.93, 132.84, 131.81, 130.00, 128.39, 128.59, 125.89, 123.27, 118.74, 112.63, 21.55. IR (KBr) ν/cm^{-1}: 2877, 2242, 1610, 1559, 1437, 1356, 761. MS (ESI) m/z: 262.50, (100.0%).

4-(3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl)benzonitrile (3r)

The product was obtained from 4-(dibromomethyl)benzonitrile (0.1 g, 0.363 mmol) **(1f)**, *(Z)-N′*-hydroxy-4-methoxybenzimidamide (0.060 g, 0.363 mmol) **(2c)**, potassium *tert*-butoxide (0.020 g, 0.181 mmol) and iodine (0.018 g, 0.072 mmol). Mp 108–110 °C (lit[46] not reported). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (2H, d, J = 7.8 Hz, Ar-H), 8.13 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.90 (2H, d, Ar-H), 7.38 (2H, t, J = 7.1 Hz, Ar-H), 3.83 (3H, s, -OCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.97, 168.83, 160.79, 132.89, 128.99, 128.03, 125.77, 119.00, 118.01, 114.91, 112.71, 55.85. IR (KBr) ν/cm^{-1}: 2241, 1634, 1561, 1430, 1353, 1246, 1038. MS (ESI) m/z: 278.267, (100.0%).

3-Phenyl-5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3s)

The product was obtained from 1-(dibromomethyl)-4-(trifluoromethyl)benzene (0.1 g, 0.314 mmol) **(1g)**, *(Z)-N′*-hydroxybenzimidamide (0.042 g, 0.314 mmol) **(2a)**, potassium *tert*-butoxide (0.017 g, 0.157 mmol) and iodine (0.016 g, 0.062 mmol). Mp 130–132 °C (lit[46] not reported). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (2H, d, J = 7.8 Hz, Ar-H), 8.11 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.85 (2H, d, Ar-H), 7.53 (2H, t, J = 7.1 Hz, Ar-H), 7.45 (1H, d, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.88, 168.93, 131.90, 131.02, 129.99, 127.97, 127.01, 127.00, 126.22, 125.89, 124.32. IR (KBr) ν/cm^{-1}: 1619, 1549, 1424, 1351, 1317, 1273, 1142, 641. MS (ESI) m/z: 291.252, (100.0%).

3-(*p*-Tolyl)-5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3t)

The product was obtained from 1-(dibromomethyl)-4-(trifluoromethyl)benzene (0.1 g, 0.314 mmol) **(1g)**, *(Z)-N′*-hydroxy-4-methylbenzimidamide (0.047 g, 0.314 mmol) **(2b)**, potassium *tert*-butoxide (0.017 g, 0.157 mmol) and iodine (0.016 g, 0.062 mmol). Mp 132–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (2H, d, J = 7.8 Hz, Ar-H), 8.13 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.87 (2H, d, Ar-H), 7.50 (2H, t, J = 7.1 Hz, Ar-H), 2.36 (3H, s, -CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.91, 168.90, 131.98, 131.01, 129.97, 127.89, 127.01, 125.94, 125.12, 124.32, 123.12, 21.41. IR (KBr) ν/cm^{-1}: 2886, 1624, 1557, 1432, 1363, 1321, 1278, 1151, 742, 636. MS (ESI) m/z: 305.272, (100.0%).

3-(4-Methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3u)

The product was obtained from 1-(dibromomethyl)-4-(trifluoromethyl)benzene (0.1 g, 0.314 mmol) **(1g)**, *(Z)-N′*-hydroxy-4-methoxybenzimidamide (0.052 g, 0.314 mmol) **(2c)**, potassium *tert*-butoxide

(0.017 g, 0.157 mmol) and iodine (0.016 g, 0.062 mmol). Mp 120–122 °C (lit[50] not reported). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (2H, d, J = 7.8 Hz, Ar-H), 8.10 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.83 (2H, d, Ar-H), 7.47 (2H, t, J = 7.1 Hz, Ar-H), 3.78 (3H, s, -OCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.86, 168.93, 160.71, 131.09, 127.99, 127.02, 125.68, 125.50, 124.30, 118.51, 114.96, 55.89. IR (KBr) ν/cm^{-1}: 1615, 1542, 1428, 1357, 1310, 1278, 1197, 1145, 1046, 648. MS (ESI) m/z: 321.233, (100.0%).

3-Phenyl-5-(thiophen-2-yl)-1,2,4-oxadiazole (3v)

The product was obtained from 2-(dibromomethyl)thiophene (0.1 g, 0.390 mmol) **(1h)**, (Z)-*N′*-hydroxybenzimidamide (0.053 g, 0.390 mmol) **(2a)**, potassium *tert*-butoxide (0.023 g, 0.195 mmol) and iodine (0.019 g, 0.078 mmol). Mp 108–110 °C (lit[51] not reported). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.53 (2H, d, Ar-H), 7.40 (1H, t, J = 7.1 Hz, Ar-H), 7.35–7.33 (1H, d, J = 7.8 Hz, Ar-H), 7.22–7.20 (1H, d, Ar-H), 7.13 (1H, t, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.72, 164.69, 132.23, 131.53, 131.02, 129.62, 128.72, 128.06, 127.88, 126.25. IR (KBr) ν/cm^{-1}: 1622, 1570, 1527, 1423, 1384, 1366, 1236, 847. MS (ESI) m/z: 229.327, (100.0%).

5-(Thiophen-2-yl)-3-(p-tolyl)-1,2,4-oxadiazole (3w)

The product was obtained from 2-(dibromomethyl)thiophene (0.1 g, 0.390 mmol) **(1h)**, *(Z)-N′*-hydroxy-4-methylbenzimidamide (0.058 g, 0.390 mmol) **(2b)**, potassium *tert*-butoxide (0.023 g, 0.195 mmol) and iodine (0.019 g, 0.078 mmol). Mp 112–114 °C (lit[51] not reported). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.48 (2H, d, Ar-H), 7.36–7.34 (1H, d, J = 7.8 Hz, Ar-H), 7.25–7.23 (1H, d, Ar-H), 7.15 (1H, t, Ar-H), 2.31 (3H, s, -CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.94, 164.72, 132.45, 131.95, 131.08, 129.71, 128.96, 128.11, 125.93, 21.31. IR (KBr) ν/cm^{-1}: 2858, 1620, 1575, 1521, 1420, 1389, 1371, 1242, 840, 746. MS (ESI) m/z: 243.384, (100.0%).

3-(4-Methoxyphenyl)-5-(thiophen-2-yl)-1,2,4-oxadiazole (3x)

The product was obtained from 2-(dibromomethyl)thiophene (0.1 g, 0.390 mmol) **(1h)**, *(Z)-N′*-hydroxy-4-methoxybenzimidamide (0.064 g, 0.390 mmol) **(2c)**, potassium *tert*-butoxide (0.023 g, 0.195 mmol)

and iodine (0.019 g, 0.078 mmol). Mp 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.50 (2H, d, Ar-H), 7.34–7.31 (1H, d, J = 7.8 Hz, Ar-H), 7.25–7.23 (1H, d, Ar-H), 7.15 (1H, t, Ar-H), 3.83 (3H, s, -OCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.82, 164.80, 160.58, 132.05, 131.12, 129.00, 128.22, 125.77, 118.52, 114.91, 55.91. IR (KBr): 1614, 1563, 1531, 1430, 1365, 1351, 1244, 1231, 1042, 840. MS (ESI) m/z v/cm^{-1}: 258.375, (100.0%).

5-(5-Bromothiophen-2-yl)-3-phenyl-1,2,4-oxadiazole (3y)

The product was obtained from 2-bromo-5-(dibromomethyl)thiophene (0.1 g, 0.298 mmol) **(1i)**, *(Z)-N′*-hydroxybenzimidamide (0.040 g, 0.298 mmol) **(2a)**, potassium *tert*-butoxide (0.016 g, 0.149 mmol) and iodine (0.015 g, 0.059 mmol). Mp 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.56 (2H, d, Ar-H), 7.40 (1H, t, Ar-H) 7.38–7.35 (1H, d, J = 7.8 Hz, Ar-H), 7.25–7.23 (1H, d, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.81, 164.82, 134.93, 131.22, 129.92, 127.78, 126.23, 111.79. IR (KBr) v/cm^{-1}: 1618, 1564, 1534, 1423, 1372, 1351, 1225, 841, 805. MS (ESI) m/z: 307.631, (100.0%).

5-(5-Bromothiophen-2-yl)-3-(*p*-tolyl)-1,2,4-oxadiazole (3z)

The product was obtained from 2-bromo-5-(dibromomethyl)thiophene (0.1 g, 0.298 mmol) **(1i)**, *(Z)-N′*-hydroxy-4-methylbenzimidamide (0.044 g, 0.298 mmol) **(2b)**, potassium *tert*-butoxide (0.016 g, 0.149 mmol) and iodine (0.015 g, 0.059 mmol). Mp 114–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.53 (2H, d, Ar-H), 7.34–7.31 (1H, d, J = 7.8 Hz, Ar-H), 7.23–7.21 (1H, d, Ar-H), 2.33 (3H, s, -CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.74, 164.55, 134.85, 131.99, 131.12, 129.94, 129.13, 125.82, 123.21, 111.88, 21.42. IR (KBr) v/cm^{-1}: 2864, 1623, 1571, 1541, 1432, 1363, 1351, 1217, 838, 801, 732. MS (ESI) m/z: 321.233, (100.0%).

5-(5-Bromothiophen-2-yl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (3aa)

The product was obtained from 2-bromo-5-(dibromomethyl)thiophene (0.1 g, 0.298 mmol) **(1i)**, *(Z)-N′*-hydroxy-4-methoxybenzimidamide (0.049 g, 0.298 mmol) **(2c)**, potassium *tert*-butoxide (0.016 g, 0.149 mmol) and iodine (0.015 g, 0.059 mmol). Mp 100–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.56 (2H, d, Ar-H), 7.33–7.30 (1H, d, J = 7.8 Hz, Ar-H), 7.22–7.19 (1H, d,

Ar-H), 3.79 (3H, s, -OCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.91, 164.81, 160.81, 134.79, 131.22, 129.08, 125.75, 118.55, 114.88, 111.71, 55.88. IR (KBr) ν/cm^{-1}: 1614, 1571, 1540, 1423, 1365, 1350, 1262, 1218, 1044, 835, 808. MS (ESI) m/z: 337.299, (100.0%).

3-Phenyl-5-(pyridin-4-yl)-1,2,4-oxadiazole (3ab)

The product was obtained from 4-(dibromomethyl)pyridine (0.1 g, 0.398 mmol) **(1j)**, *(Z)-N′*-hydroxybenzimidamide (0.054 g, 0.398 mmol) **(2a)**, potassium *tert*-butoxide (0.022 g, 0.199 mmol) and iodine (0.020 g, 0.079 mmol). Mp 154–157 °C (lit[47] 155-157 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (2H, d, Ar-H), 8.21 (2H, d, J = 7.8 Hz, Ar-H), 8.14 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.60 (1H, t, J = 7.1 Hz, Ar-H), 7.53–7.56 (2H, dd, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.91, 168.86, 150.01, 131.22, 129.32, 12781, 126.18, 121.65, 143.78. IR (KBr) ν/cm^{-1}: 1628, 1575, 1521, 1424, 1354. MS (ESI) m/z: 224.367, (100.0%).

5-(Pyridin-4-yl)-3-(p-tolyl)-1,2,4-oxadiazole (3ac)

The product was obtained from 4-(dibromomethyl)pyridine (0.1 g, 0.398 mmol) **(1j)**, *(Z)-N′*-hydroxy-4-methylbenzimidamide (0.059 g, 0.398 mmol) **(2b)**, potassium *tert*-butoxide (0.022 g, 0.199 mmol) and iodine (0.020 g, 0.079 mmol). Mp 157–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (2H, d, Ar-H), 8.24 (2H, d, J = 7.8 Hz, Ar-H), 8.08 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.50–7.53 (2H, dd, Ar-H), 2.45 (3H, s, -CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.91, 168.79, 149.91, 143.95, 131.81, 129.81, 125.78, 123.29, 121.45, 21.49. IR (KBr) ν/cm^{-1}: 2931, 1612, 1576, 1535, 1518, 1358, 763. MS (ESI) m/z: 238.273, (100.0%).

3-(4-Methoxyphenyl)-5-(pyridin-4-yl)-1,2,4-oxadiazole (3ad)

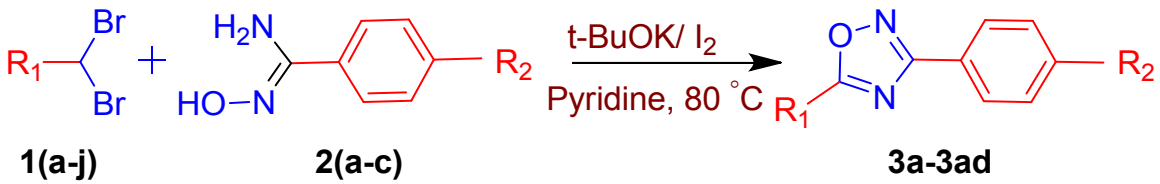
The product was obtained from 4-(dibromomethyl)pyridine (0.1 g, 0.398 mmol) **(1j)**, **)**, *(Z)-N′*-hydroxy-4-methoxybenzimidamide (0.066 g, 0.398 mmol) **(2c)**, potassium *tert*-butoxide (0.022 g, 0.199 mmol) and iodine (0.020 g, 0.079 mmol). Mp 148–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (2H, d, Ar-H), 8.25 (2H, d, J = 7.8 Hz, Ar-H), 8.13 (2H, dd, J = 7.5 and J = 1.5 Hz, Ar-H), 7.52–7.55 (2H, dd, Ar-H), 3.85 (3H, s, -OCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.89, 168.82, 160.71, 149.94, 143.81, 125.88,

121.68, 118.59, 114.92, 55.96. IR (KBr) ν/cm^{-1}: 1620, 1554, 1534, 1435, 1340, 1263, 1023. MS (ESI) m/z: 254.283, (100.0%).

Results and Discussion

In connection with above studies and in continuation of our previous research works, the present paper reports the new, rapid and efficient method for the one-pot synthesis of 3,5-aryl substituted 1,2,4-oxadiazoles from *gem*-dibromomethylarenes/ *gem*-dibromomethyl-hetero-arenes and amidoximes (**Scheme 1**). In this synthetic approach, *gem*-dibromomethylarenes were generated starting from the easily accessible methyl analogs using radical bromination.[31] The obtained *gem*-dibromomethylarenes were treated with different amidoximes[44] in presence of potassium *tert*-butoxide and iodine in pyridine to yield 3,5-aryl substituted-1,2,4-oxadiazoles. As mentioned above, various coupling reagents are used for the synthesis of 3,5-substituted-1,2,4-oxadiazoles to achieve a good yield and purity of the obtained products. Of which pyridine catalyzed reaction ended up with good expected yield in 8 h, whereas the other bases did not promote this reaction.

Conditions were optimized for synthesis of 1,2,4-oxadiazoles by varying reaction temperature and time to get good yield. The obtained results showed that the reaction using a 1:1 ratio of *gem*-dibromomethylarene **1** and amidaoxime **2** in a one-pot reaction proceeded with highest yield in shorter reaction times (**Table 1, entry 9**). One equivalent of pyridine with respect to the *gem*-dibromomethylarene is sufficient for complete conversion of the starting materials.



Scheme 1. Scheme for synthesis of 3,5-substituted-1,2,4-oxadiazoles 3a-3ad

Table 1. Optimization of the synthesis of 3,5-substituted-1,2,4-oxadiazoles.

Sl.No[a]	Time(h)	Temperature (°C)	Yield (%)
1	6	30	26
2	7	30	38
3	8	30	31
4	6	55	44
5	7	55	58
6	8	55	78
7	6	80	70
8	7	80	81
9	8	80	93
10	6	100	72
11	7	100	77
12	8	100	85

A wide variety of base catalysts including DBU, triethylamine, DABCO, K_2CO_3, Cs_2CO_3, and piperidine were employed to improve the yield for the synthesis of 3,4-dihydropyrimidin-2-ones/thiones. While pyridine catalysed the reaction in presence of potassium *tert*-butoxide (*t*-BuOK) and iodine to give quantitative yield in 8-10 h, the other bases did not promote this reaction. Under the above reaction conditions, *gem*-dibromomethylarene proved to be an excellent substrate for the synthesis of 1,2,4-oxadiazoles and various functional groups like fluro, chloro, bromo, cyano, trifluromethyl, methoxy groups are survived in this reaction (**Table 2**).

Gem-dibromomethylarenes being stable and readily accessible alternates for noncommercial and some of the unstable carboxylic acid and its derivatives, this transformation would extend the scope in organic synthesis. In addition, it is fascinating to note that aromatic *gem*-dibromomethylarenes bearing various functionalities such as chloro, bromo, nitrile, methoxy and trifluoromethyl groups survived the reaction and provided high yields of corresponding products.

Table 2. 3,5-substituted-1,2,4-oxadiazoles results

Entry	R_1	R_2	Product (3a-3ad)	Time (h)	Yield (3) [a,b] (%)
1	**1a**	-H	**3a**	8	89[22]
2	**1a**	$-CH_3$	**3b**	10	88[22]
3	**1a**	$-OCH_3$	**3c**	10	91[22]
4	**1b**	-H	**3d**	8	85[22]
5	**1b**	$-CH_3$	**3e**	9	87[22]
6	**1b**	$-OCH_3$	**3f**	9	92[45]
7	**1c**	-H	**3g**	8	90[45]
8	**1c**	$-CH_3$	**3h**	9	87[46]
9	**1c**	$-OCH_3$	**3i**	9	91[46]
10	**1d**	-H	**3j**	8	90[47]
11	**1d**	$-CH_3$	**3k**	9	93
12	**1d**	$-OCH_3$	**3l**	9	88[48]
13	**1e**	-H	**3m**	8	86
14	**1e**	$-CH_3$	**3n**	9	93
15	**1e**	$-OCH_3$	**3o**	9	94
16	**1f**	-H	**3p**	8	88[49]
17	**1f**	$-CH_3$	**3q**	9	89[46]
18	**1f**	$-OCH_3$	**3r**	10	84[46]
19	**1g**	-H	**3s**	8	85[46]
20	**1g**	$-CH_3$	**3t**	8	88
21	**1g**	$-OCH_3$	**3u**	9	90[50]
22	**1h**	-H	**3v**	9	89[51]
23	**1h**	$-CH_3$	**3w**	10	90[51]
24	**1h**	$-OCH_3$	**3x**	10	85
25	**1i**	-H	**3y**	8	88
26	**1i**	$-CH_3$	**3z**	9	84
27	**1i**	$-OCH_3$	**3aa**	10	86
28	**1j**	-H	**3ab**	9	87[47]
29	**1j**	$-CH_3$	**3ac**	10	89
30	**1j**	$-OCH_3$	**3ad**	10	90

[a] Isolated yields of product. [b] Literature reported compounds.

Conclusion

In summary, *gem*-dibromomethylarenes have been identified and exploited as excellent starting material substrate for the cyclocondensation in the synthesis of 1,2,4-oxadiazoles in high yield. Accessibility of a large number of *gem*-dibromomethylarenes for synthesis of substituent varied 1,2,4-oxadiazoles synthesis is one of the main advantages of this method compared to the other methods for the synthesis of title compounds. More importantly, this improved method is compatible with many functional groups. It is anticipated that this methodology will have versatile applications in the practical syntheses of medicinal and material science important molecules.

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Supporting Information

Supplementary information is available with the article through the journal Web site.

References

[1].a) Borg S.; Estenne-Bouhtou, G.; Luthman, K.; Csoeregh, I.; Hesselink, W.; Hacksell, U. *J. Org. Chem.* **1995**, *60,* 3112. (b) Sureshbabu, V. V.; Hemantha, H. P.; Naik, S. A. *Tet. Lett.* **2008**, *49*, 5133;

[2]. Rotbart, H. A.; Webster, A. D. *Clinical Infectious Diseases*, **2001**, *32*, 228.

[3]. Schwandt, M. L.; Cortes, C. R.; Kwako, L. E.; George, D. T.; Momenan, R.; Sinha, R.; Grigoriadis, D. E.; Pich, E. M.; Leggi, L.; Heilig, M. *Neuropsychopharmacology*, **2016***, 41*, 2818.

[4]. Tellew, J. E.; Lanier, M.; Moorjani, M.; Lin, E.; Luo, Z.; Slee, D. H.; Zhang, X.; Hoare, S. R.; Grigoriadis, D. E.; St Denis, Y.; Di Fabio, R.; Di Modugno, E.; Saunders, J.; Williams, J. P. *Bioorg. Med. Chem. Lett*. **2010,** *20*, 7259.

[5]. Borg, S.; Vollinga, R. C.; Labarre, M.; Payza, K.; Terenius. L.; Luthman, K. *J. Med. Chem*. **1999,** *42,* 4331.

[6]. Bolli, M. H.; Müller, C.; Mathys, B.; Abele, S.; Birker, M.; Bravo, R.; Bur, D.; Hess, P.; Kohl, C.; Lehmann, D.; Nayler, O.; Rey, M.; Meyer, S.; Scherz, M.; Schmidt, G.; Steiner, B.; Treiber, A.; Velker, J.; Weller, T.; *J. Med. Chem.* **2013,** *56*, 9737.

[7]. Li, Z.; Chen, W.; Hale, J. J.; Lynch, C. L.; Mills, S. G.; Hajdu, R.; Keohane, C. A.; Rosenbach, M. J.; Milligan, J. A.; Shei, G.-J.; Chrebet, G.; Parent, S. A.; Bergstrom, J.; Card, D.; Forrest, M.; Quackenbush, E. J.; Wickham, L. A.; Vargas, H.; Evans, R. M.; Rosen, H.; Mandala, S. *J. Med. Chem.* **2005,** *48,* 6169.

[8]. a) Stauffer, S. R. *ACS. Chem. Neurosci.* **2011,** *2,* 450. b) Packiarajan, M.; Mazza Ferreira, C. G.; Hong, S. P.; White, A. D.; Chandrasena, G.; Pu, X.; Brodbeck, R. M.; Robichaud, A. J. . *Bioorg. Med. Chem. Lett*. **2012**, 22, 6469.

[9]. Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; MacLeod, A. M.; Merchant, K. J.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B.; Harley, E. A. *J. Med. Chem*. **1990,** *33,* 2690.

[10]. Lankau, H. J.; Unverferth, K.; Grunwald, C.; Hartenhauer, H.; Heinecke, K.; Bernoster, K.; Dost, R.; Egerland, U.; Rundfeldt, C. *Eur. J. Med. Chem*. **2007,** *42,* 873.

[11]. Khatik, G. L.; Kaur, J.; Kumar, V.; Tikoo, K.; Nair, V. A. *Bioorg. Med. Chem. Lett*. **2012**, 22, 1912.

[12]. Swain, C. J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E. M.; Stevenson, G .; Beer, M.; Stanton, J.; Watling, K. *J. Med. Chem*. **1991**, *34*, 140.

[13]. a) Almasirad, A.; Tabatabai, S. A.; Faizi, M.; Kebriaeezadeh, A.; Mehrabi, N.; Dalvandi, A.; Shafiee, A. *Bioorg. Med. Chem. Lett*. **2004,** *14*, 6057. b) Mohammadi-Khanaposhtani, M.; Shabani, M.; Faizi, M.; Aghaei, I.; Jahani, R.; Sharafi, Z.; Zafarghandi, N. S.; Mahdavi, M.; Akbarzadeh, T.; Emami, S.; Shafiee, A. *Eur. J. Med. Chem.*. **2016,** *112*, 91.

[14]. Cavalleri, B.; Volpe, G.; Del Turco, B. R.; Diena, A. *Farmaco. Edizione. Scientifica*. **1976,** *31*, 393.

[15]. a) Jessen, K. A.; English, N. M.; Yu Wang, J.; Maliartchouk, S.; Archer, S. P.; Qiu, L.; Brand, R.; Kuemmerle, J.; Zhang, H. Z.; Gehlsen, K.; Drewe, J.; Tseng, B.; Cai, S. X.; Kasibhatla, S. *Mol. Cancer. Ther.* **2005,** *4*, 761. b) Rao, A. S.; Vardhan, M. V.; Reddy, N. S.; Reddy, T. S.; Shaik, S. P.; Bagul, C.; Kamal, A. *Bioorg. Chem.,* **2016,** 69, 7.

[16]. a) Pratap, R.; Yarovenko, V. N. *Nucleosides. Nucleotides. & nucleic acids*. **2000,** *19*, 845. b) Wang, P. Y.; Chen, L.; Zhou, J.; Fang, H.; Wu, Z. B.; Song, B. A.; Yang, S. *J. Saudi. Chem. Soc.* **2017,** *21,* 315.

[17]. Watthey, J. W.; Desai, M.; Rutledge, R.; Dotson, R. *J. Med. Chem*. **1980,** *23* 690.

[18]. a) Farooqui, M.; Bora, R.; Patil, C. R. *Eur. J. Med. Chem*. **2009,** *44*, 794. b) Krasavin. M.; Shetnev, A.; Sharonova, T.; Baykov, S.; Tuccinardi, T.; Kalinin, S.; Angeli, A.; Supuran, C.T. *Bioorg. Chem*. **2018,** *76,* 88.

[19]. Agneeswari, R.; Tamilavan, V.; Song, M.; Kang, J. W.; Jin, S. H.; Hyun, M. H. *J. Polym. Sci. A Polym. Chem.* **2013,** *51*, 2131.

[20]. Chang, Y. T.; Chang, J. K.; Lee, Y. T.; Wang, P. S.; Wu, J. L.; Hsu, C. C.; Wu, I. W.; Tseng, W. H.; Pi, T. W.; Chen, C. T.; Wu, C. I. *ACS . Appl. Mater. Inte.* **2013,** *5*, 10614.

[21]. Li, Q.; Cui, L. S.; Zhong, C.; Yuan, X. D.; Dong, S. C. ; Jiang, Z. Q. ; Liao L. S. *Dyes and Pigments.* **2014,** *101*, 142.

[22]. Adib, M. ; Jahromi, A. H.; Tavoosi, N.; Mahdavi, M.; Bijanzadeh, H. R. *Tet. Lett.* **2006,** *47*, 2965.

[23]. a) Augustine, J. K.; Vairaperumal, V.; Narasimhan, S.; Alagarsamy, P.; Radhakrishnan, A. *Tetrahedron*. **2009,** *65*, 9989; b) Wang, W.; Xu, H.; Xu, Y.; Ding, T.; Zhang, W.; Ren, Y.; Chang, H. *Org. Biomol. Chem.*, **2016**, *14*, 9814.

[24]. a) Gangloff, A. R.; Litvak, J.; Shelton, E. J.; Sperandio, D.; Wang, V. R.; Rice, K. D. *Tet. Lett.* **2001,** *42*, 1441; b) Asad, M.; Gupta, P. K.; Jaiswal, S. K.; Hajela, K. *ChemistrySelect* **2016**, *16*, 4753.

[25]. a) Wang, Y. R.; Miller, L.; Sauer, D. R.; Djuric, S. W. *Org. Lett*. **2005,** *7*, 925. b) Liew, S. K.; Holownia, A.; Diaz, D. B.; Cistrone, P.A.; Dawson, P. E.; Yudin, A. K. *Chem. Commun.* **2017**, *53*, 11237.

[26]. a) Santagada, V.; Frecentese, F.; Perissutti, E.; Cirillo, D.; Terracciano, S.; Caliendo, G.; *Bioorg. Med. Chem. Lett*. **2004**, *14*, 4491. b) Guo, W.; Huang, K.; Ji, F.; Wua, W.; Jiang, H. *Chem. Commun.* **2015**, *51*, 8857.

[27]. Evans, M. D.; Ring, J.; Schoen, A.; Bell, A.; Edwards, P.; Berthelot, D.; Nicewonger, R.; Baldino, C. M. *Tet. Lett.* **2003**, *44*, 9337.

[28]. a) Poulain, R. F.; Tartar, A. L.; Déprez, B. P. *Tet. Lett.* **2001,** *42*, 1495; b) Adib, M.; Mahdavi, M.; Mahmoodi, N.; Pirelahi, H.; Bijanzadeh, H. R. *Synlett,* **2006**, 1765.

[29]. a) Milcent, R.; Barbier, G. *J. Heterocyclic. Chem.* **1983,** *20***,** 77; b) Zhang, F. L.; Wang, Y. F.; Chiba, S. *Org. Biomol. Chem*. **2013**, *11*, 6003.

[30]. a) Eloy, F.; Lenaers, R. *Chemical. Rev.* **1962**, *62*, 155. b) Baykov, S.; Sharonova, T.; Shetnev, A.; Rozhkov, S.; Kalinin, S.; Smirnov, A. V. *Tetrahedron* **2017,** *73*, 945.

[31]. Mandal, A. B.; Augustine, J. K.; Quattropani, A.; Bombrun, A. *Tet. Lett.* **2005,** *46*, 6033.

[32]. Mangarao, N.; Mahaboob Basha, G.; Ramu, T.; Srinuvasarao, R.; Prasanthi, S.; Siddaiah, V. *Tet. Lett.* **2014,** *55*, 177.

[33]. Kaboudin, B.; Malekzadeh, L. *Tet. Lett.* **2011,** 52*,* 6424.

[34]. Kivrak, A.; Zora, M. *Tetrahedron*, **2014,** *70***,** 817.

[35]. Li, Q.; Cui, L. S.; Zhong, C.; Jiang, Z. Q.; Liao. L. S. *Org. Lett.* **2014,** *16*, 1622.

[36]. Xu, L. L.; Zhu, J. F.; Xu, X. L.; Zhu, J.; Li, L.; Xi, M. Y.; Jiang, Z. Y.; Zhang, M. Y.; Liu, F.; Lu, M. C.; Bao, Q. C.; Li, Q.; Zhang, C.; Wei, J. L.; Zhang, X. J.; Zhang, L. S.; You, Q. D.; Sun, H. P. *J. Med. Chem.* **2015,** *58*, 5419.

[37]. Subrao, M.; Potukuchi, D. M.; Sharada Ramachandra, G.; Bhagavath, P.; Bhat, S. G.; Maddasani, S. *Beilstein. J. Org. Chem.* **2015,** *11*, 233.

[38]. Siddappa, C.; Umashankara, M.; Kambappa, V.; Ananda Kumar, C. S.; Rangappa, K. S. *Tet. Lett.* **2012,** *53***,** 2632.

[39]. Siddappa, C.; Kambappa, V.; Umashankara, M.; Rangappa, K. S. *Tet. Lett.* **2011,** *52* 5474.

[40]. Siddappa, C.; Kambappa, V.; Siddegowda, A. K. C.; Rangappa, K. S. *Tetrahedron Lett*, **2010,** *51*, 6493.

[41]. Narasimhamurthy, K. H.; Chandrappa, S.; Sharath Kumar, K. S.; Harsha, K. B.; Ananda, H.; Rangappa, K. S. *RSC. Advances*. **2014,** *4*, 34479.

[42]. Augustine, J. K.; Naik, Y. A.; Mandal, A. B.; Chowdappa, N.; Praveen, V. B. *J. Org. Chem*, **2007,** *72*, 9854.

[43]. Augustine, J. K.; Naik Y. A.; Poojari, S.; Chowdappa, N.; Sherigara, B. S.; Areppa, K. *Synthesis*. **2009,** 2349.

[44]. Augustine, J. K.; Akabote, V.; Hegde, S. G.; Alagarsamy, P. *J. Org. Chem*. **2009,** *74*, 5640.

[45]. Zhou, T.; Chen, Z. C. *Syn. Comm.* **2002**, *32*, 887.

[46]. Deegan, T. L.; Nitz, T. J.; Cebzanov, D.; Pufko, D. E.; Porco Jr, J. A. *Bioorg. Med. Chem. Lett.* **1999,** *9*, 209.

[47]. Guo, W.; Huang, K.; Ji, F.; Wu, W.; Jiang, H. *Chem. Comm.* **2015**, *51***,** 8857.

[48]. Kandre, S.; Bhagat, P. R.; Sharma, R.; Gupte A. *Tet. Lett.* **2013,** *54* 3526.

[49]. Buscemi, S.; Pace, A.; Vivona, N.; Caronna, T.; Galia, A. *J. Org. Chem.* **1999,** *64*, 7028.

[50]. Lin, Y. I.; Hlavka, J. J.; Bitha, P.; Lang, S. A. *J. Heterocyclic. Chem*. **1983,** 20, 1693.

[51]. Feng, L.; Reynisdóttir, I.; Reynisson, J. *Eur. J. Med. Chem*. **2012,** *54*, 463.