An efficient one-pot synthesis of 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles under solvent-free conditions

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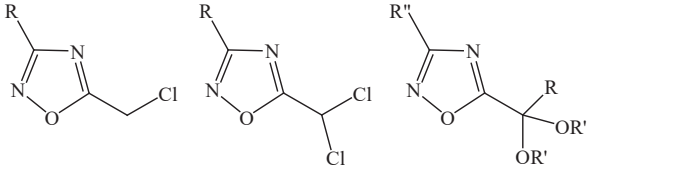
An efficient and simple synthesis of 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles is described. The *in situ* prepared amidoximes from the reaction between nitriles and hydroxylamine are condensed with alkyl 2,2-dialkoxyacetates under solvent-free conditions to produce the title compounds in excellent yields.

Keywords: 1,2,4-oxadiazoles, aryl nitriles, amidoximes, alkyl 2,2-dialkoxyacetates, one-pot reaction, solvent-free synthesis

1,2,4-Oxadiazoles, an important class of heterocyclic compounds, are of interest because of their wide range of pharmacological and therapeutic activities.[1,2] They have received considerable attention as heterocyclic amide and ester bioisosteres.[3,4] Thus designing new synthetic approaches for the preparation of 1,2,4-oxadiazoles has attracted much attention.[5,6]

In recent years, some 1,2,4-oxadiazoles syntheses have been reported. Amidoximes treated with chloroacetyl chloride to produce 5-(chloromethyl)-1,2,4-oxadiazole (**1**, Fig. 1).[7–12] Reaction between amidoximes and dichloroacetic acid derivatives (acid, chloride, ester, anhydride or nitrile) afforded 5-dichloromethyl-1,2,4-oxadiazoles (**2**, Fig. 1).[13–19] Treatment of 2,2-diethoxypropionamide and dimethylacetamide dimethyl acetal gave *N*-[1-(dimethylamino) ethylidene]-2,2-dimethoxypropanamide which upon reaction with hydroxylamine followed by treatment with acetic acid produced 5-(1,1-diethoxyethyl)-3-methyl-1,2,4-oxadiazole (**3a**, Fig. 1).[20,21] *p*-Nitrophenyl 3-bromo-2,2-diethoxypropionate treated with acetamidoxime to give the corresponding *O*-acyl acetamidoxime, the latter on treatment with *p*-TsOH in refluxing toluene cyclised to 5-(2-bromo-1,1-diethoxyethyl)-3-methyl-1,2,4-oxadiazole (**3b**, Fig. 1).[20]

Considering the above reports in conjunction with our previous works on synthesis of 1,2,4-oxadiazoles[22–24] and other heterocyclic compounds and pursuing our studies on multi-component reactions,[25–30] herein, we would like to report a simple, efficient and one-pot method for the preparation of 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles under solvent-free conditions. Thus a mixture of an arylnitrile **4** and hydroxylamine in the presence of a catalytic amount of acetic acid stirred at 150 °C for 40 min under solvent-free conditions to produce the corresponding amidoxime **5**. After nearly complete conversion to the corresponding amidoxime, as was indicated by TLC monitoring, an alkyl 2,2-dialkoxyacetate **6** and potassium carbonate were added to the reaction mixture which was further stirred at 100 °C for 6 h to afford 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles **7a–l** in 90–96% yields. TLC and NMR spectroscopic analysis of the reaction mixtures clearly indicated formation of the corresponding 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles **7**. NMR spectroscopy showed **7** as the only product. A range of 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles **7a–l** were synthesised from the reaction between arylnitriles **4a–f**, hydroxylamine, and methyl 2,2-dimethoxyacetate (**6a**) or ethyl 2,2-diethoxyacetate (**6b**) (Scheme 1, Table 1).



1 **2** **3a:** R = R'' = CH_3, R' = C_2H_5
3b: R = CH_2Br, R' = C_2H_5, R''= CH_3

Fig. 1 Some reported 1,2,4-oxadiazoles.

The structures of the isolated products were deduced on the basis of IR, ^1H and ^{13}C NMR spectroscopy and mass spectrometry. The mass spectrum of **7h** displayed the molecular ion (M^+) peaks at *m/z* 284 and 282, which was consistent with the 1:1:1 adduct of 4-chlorobenzonitrile **4d**, hydroxylamine and ethyl 2,2-diethoxyacetate **6b** with the loss of water and an ethanol molecule. The ^1H NMR spectrum of **7h** exhibited a triplet (δ = 1.31 ppm, J = 7.2 Hz) arising from the two enantiotopic methyl groups, as well as two doublets of quartets at (3.77 and 3.81 ppm; ^2J = 10.4, ^3J = 7.2 Hz) for the two diastereotopic H-atoms of the two methylene moieties. A sharp singlet was observed at 5.82 ppm due to the acetal H-atom, along with two doublets at 7.46 and 8.06 ppm (J = 8.4 Hz) for the four H-atoms of the 4-chlorophenyl substituent. The ^1H-decoupled ^{13}C NMR spectrum of **7h** showed two signals

Table 1 Synthesis of 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles **7a–l**

Product	Ar	R	%Yield[a]
7a	C_6H_5	Me	93
7b	C_6H_5	Et	92
7c	4-MeC_6H_4	Me	96
7d	4-MeC_6H_4	Et	96
7e	4-FC_6H_4	Me	91
7f	4-FC_6H_4	Et	92
7g	4-ClC_6H_4	Me	95
7h	4-ClC_6H_4	Et	96
7i	3-BrC_6H_4	Me	91
7j	3-BrC_6H_4	Et	90
7k	3-MeC_6H_4	Me	93
7l	3-MeC_6H_4	Et	94

[a]Isolated yields.

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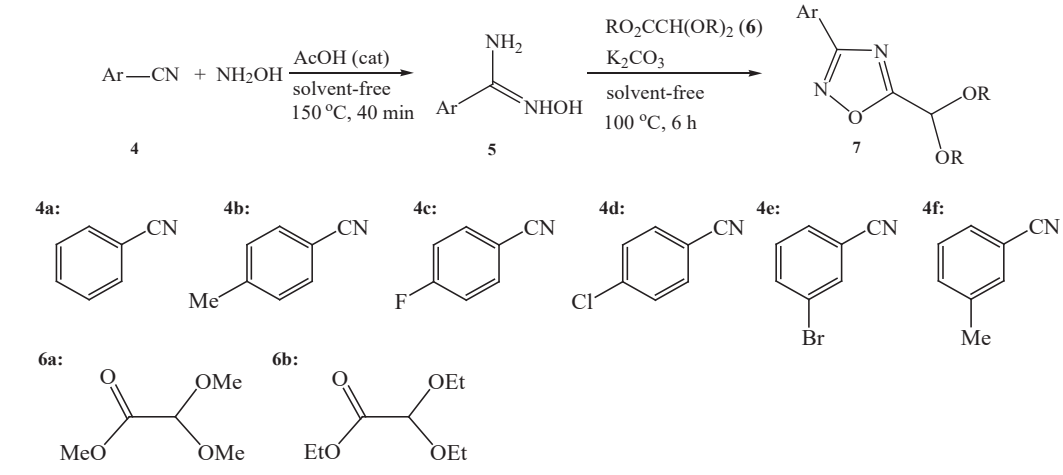
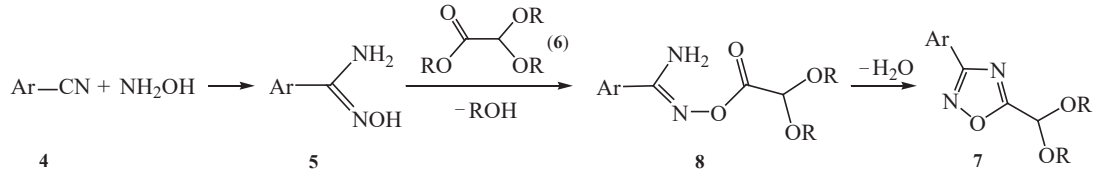


Scheme 1 One-pot synthesis of 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles **7**.



Scheme 2 Suggested reaction mechanism.

at 15.0 and 62.7 ppm for the two ethoxy groups. The signal of C-atom of the acetal moiety was observed at 94.4 ppm, as well as two characteristic resonances at 167.5 and 175.2 ppm for the two C-atoms of the oxadiazole ring, along with other four distinct resonances for the 4-chlorophenyl substituent in agreement with the proposed structure.

A suggested mechanism for the formation of the 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles **7** is provided in Scheme 2. It is reasonable to assume that first, arylnitrile **4** and hydroxylamine are converted *in situ* to amidoxime **5**. Next, amidoxime is condensed with the ester **6** to form the *O*-acylamidoxime intermediate **8**. Then, this intermediate may undergo an intramolecular condensation-cyclisation to produce 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles **7**.

In conclusion, we have developed an efficient one-pot reaction for the preparation of 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles of potential synthetic and pharmacological interest. The simplicity of the starting materials, one-pot as well as solvent-free conditions and excellent yields of the products are the main advantages of this method. Hydrolysis of the obtained 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles gives 3-aryl-1,2,4-oxadiazole-5-carbaldehydes.[31] In view of extensive use of heteroaromatic aldehydes as synthetic intermediates and target compounds, the 3-aryl-5-(dialkoxymethyl)-1,2,4-oxadiazoles prepared in the present study may find useful applications in synthetic organic chemistry.

Experimental

All the chemicals were obtained from Merck (Germany), and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on an Agilent Technologies (HP) 5973 mass spectrometer operating at an ionisation potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured with Bruker DRX-400 Avance (at 400.1 and 100.6 MHz) instrument using $CDCl_3$ solvent with TMS as an internal standard. Chromatography columns were prepared from Merck silica gel 60 mesh.

Synthesis of compounds **7a–l***; general procedure*

A mixture of the appropriate nitrile (**4**, 2 mmol), hydroxylamine 50% (0.132 g, 2 mmol), and a catalytic amount of AcOH was stirred at 150 ºC for 40 min. After nearly complete conversion to the corresponding amidoxime, as was indicated by TLC monitoring, the appropriate 2,2-dialkoxyacetate (**6**, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) were added to the reaction mixture which was stirred at 100 ºC for further 6 h. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature and the residue was purified by column chromatography using *n*-hexane-EtOAc (6:1) as eluent. The solvent was removed, and the product was obtained.

5-(Dimethoxymethyl)-3-phenyl-1,2,4-oxadiazole (**7a**): Colourless oil; yield: 0.409 g (93%); IR (KBr) (ν_{max}/cm^{-1}): 1575, 1529, 1473, 1446, 1341, 1285, 1195, 1119, 1067 (C – O), 984, 904, 787, 724, 693; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.54 (s, 6H, 2 × OCH_3), 5.73 (s, 1H, CH), 7.46–7.56 (m, 3H, 3 × CH), 8.14 (dd, J = 7.6, 1.2 Hz, 2H, 2 × CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 54.4, 96.6, 126.8, 128.2, 129.4, 132.0, 168.9, 174.9; EI-MS: *m/z* (%) = 220 ([M]$^+$, 34), 190 (42), 161 (20), 118 (12), 75 (100), 51 (6). Anal. calcd for $C_{11}H_{12}N_2O_3$ (220.23): C, 59.99; H, 5.49; N, 12.72; found: C, 60.19; H, 5.57; N, 12.49%.

5-(Diethoxymethyl)-3-phenyl-1,2,4-oxadiazole (**7b**): Colourless oil; yield: 0.456 g (92%); IR (KBr) (ν_{max}/cm^{-1}): 1575, 1528, 1476, 1445, 1334, 1284, 1118, 1061 (C–O), 909, 723, 694; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 6H, 2 × CH_2CH_3), 3.78 and 3.83 (2 × dq, ^{2}J = 9.6, ^{3}J = 7.2 Hz, 4H, 2 × OCH_2CH_3), 5.83 (s, 1H, CH), 7.52–7.46 (m, 3H, 3 × CH), 8.14 (dd, J = 7.6, 1.6 Hz, 2H, 2 × CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.0, 62.6, 94.5, 126.4, 127.6, 128.8, 131.4, 175.0, 168.2; EI-MS: *m/z* (%) = 249 ([M + H]$^+$, 31), 218 (4), 204 (65), 175 (15), 147 (12), 132 (4), 119 (38), 103 (100), 75 (19); Anal. calcd for $C_{13}H_{16}N_2O_3$ (248.28): C, 62.89; H, 6.50; N, 11.28; found: C, 62.74; H, 6.64; N, 11.14%.

5-(Dimethoxymethyl)-3-(4-methylphenyl)-1,2,4-oxadiazole (**7c**): Colourless oil; yield: 0.449 g (96%); IR (KBr) (ν_{max}/cm^{-1}): 1592, 1540,

1479, 1415, 1340, 1253, 1200, 1113, 1066 (C–O), 985, 916, 889, 867, 825, 706, 669; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.44 (s, 3H, CH_3), 3.55 (s, 6H, 2 × OCH_3), 5.73 (s, 1H, CH), 7.31 (d, *J* = 8.4 Hz, 2H, 2 × CH), 8.03 (d, *J* = 8.4 Hz, 2H, 2 × CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.6, 53.9, 96.1, 123.4, 127.6, 129.6, 141.8, 168.4, 174.2; EI-MS: *m/z* (%) = 234 ([M]$^+$, 36), 203 (22), 175 (19), 132 (28), 116 (9), 91 (17), 75 (100), 51 (5); Anal. calcd for $C_{12}H_{14}N_2O_3$ (234.25): C, 61.53; H, 6.02; N, 11.96; found: C, 61.57; H, 6.09; N, 11.86%.

5-(Diethoxymethyl)-3-(4-methylphenyl)-1,2,4-oxadiazole (**7d**): Colourless oil; yield: 0.503 g (96%); IR (KBr) (ν_{max}/cm^{-1}): 1595, 1479, 1334, 1283, 1117, 1062, 910, 821, 748; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.2 Hz, 6H, 2 × CH_2CH_3), 2.42 (s, 3H, CH_3), 3.78 and 3.82 (2 × dq, ^2J = 9.6, ^3J = 7.2 Hz, 4H, 2 × OCH_2CH_3), 5.80 (s, 1H, CH), 7.29 (d, *J* = 8.4 Hz, 2H, 2 × CH), 8.02 (d, *J* = 8.4 Hz, 2H, 2 × CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.0, 21.6, 62.6, 94.5, 123.5, 127.5, 129.5, 141.7, 168.3, 174.8; EI-MS: *m/z* (%) = 263 ([M + H]$^+$, 60), 218 (43), 189 (18), 161 (13), 133 (43), 118 (13), 103 (100), 91 (16), 75 (34), 65 (7); Anal. calcd for $C_{14}H_{18}N_2O_3$ (262.31): C, 64.11; H, 6.92; N, 10.68; found: C, 64.30; H, 7.07; N, 10.49%.

5-(Dimethoxymethyl)3-(4-fluorophenyl)-1,2,4-oxadiazole (**7e**): Pale yellow oil; yield: 0.433 g (91%); IR (KBr) (ν_{max}/cm^{-1}): 1605, 1507, 1479, 1417, 1336, 1286, 1232, 1196, 1158, 1119, 1069 (C–O), 985, 906, 844, 755, 685; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.51 (s, 6H, 2 × OCH_3), 5.70 (s, 1H, CH), 7.15 (dd, $^3J_{FH}$ = 8.8, $^3J_{HH}$ = 8.8 Hz, 2H, 2 × CH), 8.10 (dd, $^3J_{HH}$ = 8.8, $^4J_{FH}$ = 5.6 Hz, 2H, 2 × CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 53.8, 96.0, 116.1 (d, $^2J_{FC}$ = 22.0 Hz), 122.5 (d, $^4J_{FC}$ = 3.3 Hz), 129.8 (d, $^3J_{FC}$ = 8.8 Hz), 164.7 (d, $^1J_{FC}$ = 250.3 Hz), 167.5, 174.5; EI-MS: *m/z* (%) = 238 ([M]$^+$, 27), 207 (36), 179 (23), 151 (10), 136 (25), 121 (13), 109 (10), 95 (13), 75 (100), 57 (9); Anal. calcd for $C_{11}H_{11}FN_2O_3$ (238.22): C, 55.46; H, 4.65; N, 11.76; found: C, 55.38; H, 4.72; N, 11.64%.

5-(Diethoxymethyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (**7f**): Colourless oil; yield: 0.490 g (92%); IR (KBr) (ν_{max}/cm^{-1}): 1606, 1480, 1416, 1333, 1284, 1229, 1118, 1062, 913, 847, 755; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.2 Hz, 6H, 2 × CH_2CH_3), 3.78 and 3.81 (2 × dq, ^2J = 9.6, ^3J = 7.2 Hz, 4H, 2 × OCH_2CH_3), 5.81 (s, 1H, CH), 7.17 (dd, $^3J_{FH}$ = 8.8, $^3J_{HH}$ = 8.8 Hz, 2H, 2 × CH), 8.13 (dd, $^3J_{HH}$ = 8.8, $^4J_{FH}$ = 5.6 Hz, 2H, 2 × CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.0, 62.6, 94.4, 116.0 (d, $^2J_{FC}$ = 21.9 Hz), 122.6 (d, $^4J_{FC}$ = 3.3 Hz), 129.8 (d, $^3J_{FC}$ = 8.8 Hz), 164.7 (d, $^1J_{FC}$ = 250.3 Hz), 167.7, 175.1; EI-MS: *m/z* (%) = 266 ([M]$^+$, 14), 222 (59), 199 (19), 193 (33), 137 (100), 122 (32), 103 (91), 95 (25), 86 (20), 75 (73); Anal. calcd for $C_{13}H_{15}FN_2O_3$ (266.27): C, 58.64; H, 5.68; N, 10.52; found: C, 58.62; H, 5.76; N, 10.44%.

3-(4-Chlorophenyl)-5-(dimethoxymethyl)-1,2,4-oxadiazole (**7g**): White solid; yield: 0.483 g (95%); m.p. 78–79 °C; IR (KBr) (ν_{max}/cm^{-1}): 1591, 1565, 1466, 1408, 1337, 1199, 1112, 1069 (C–O), 1010, 986, 899, 867, 834, 744, 701, 663; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.52 (s, 6H, 2 × OCH_3), 5.71 (s, 1H, CH), 7.45 (d, *J* = 8.8 Hz, 2H, 2 × CH), 8.05 (d, *J* = 8.8 Hz, 2H, 2 × CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 53.9, 96.0, 124.7, 128.9, 129.2, 137.6, 167.5, 174.6; EI-MS: *m/z* (%) = 256 ([M]$^+$ ^{37}Cl, 7), 254 ([M]$^+$ ^{35}Cl, 20), 223 (24), 195 (11), 152 (16), 137 (9), 102 (9), 75 (100), 50 (5); Anal. calcd for $C_{11}H_{11}ClN_2O_3$ (254.67): C, 51.88; H, 4.35; N, 11.00; found: C, 51.87; H, 4.36; N, 10.98%.

3-(4-Chlorophenyl)-5-(diethoxymethyl)-1,2,4-oxadiazole (**7h**): Colourless oil; yield: 0.542 g (96%); IR (KBr) (ν_{max}/cm^{-1}): 1596, 1472, 1407, 1331, 1117, 1062 (C–O), 1015, 911, 837, 741, 700; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.2 Hz, 6H, 2 × CH_2CH_3), 3.77 and 3.81 (2 × dq, ^2J = 10.4, ^3J = 7.2 Hz, 4H, 2 × OCH_2CH_3), 5.82 (s, 1H, CH), 7.46 (d, *J* = 8.4 Hz, 2H, 2 × CH), 8.06 (d, *J* = 8.4 Hz, 2H, 2 × CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.0, 62.7, 94.4, 124.9, 128.9, 129.2, 137.5, 167.5, 175.2; EI-MS: *m/z* (%) = 284 ([M]$^+$ ^{37}Cl, 10), 282 ([M]$^+$ ^{35}Cl, 29), 238 (67), 209 (65), 181 (22), 153 (100), 138 (40), 111 (29), 103 (51), 75 (57); Anal. calcd for $C_{13}H_{15}ClN_2O_3$ (282.73): C, 55.23; H, 5.35; N, 9.91; found: C, 55.41; H, 5.39; N, 9.79%.

3-(3-Bromophenyl)-5-(dimethoxymethyl)-1,2,4-oxadiazole (**7i**): Pale yellow oil; yield: 0.544 g (91%); IR (KBr) (ν_{max}/cm^{-1}): 1564, 1518, 1452, 1402, 1332, 1195, 1114, 1067, 985, 905, 797, 740, 681; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.55 (s, 6H, 2 × OCH_3), 5.73 (s, 1H, CH), 7.38 (t, *J* = 8.0 Hz, 1H, CH), 7.66 (ddd, *J* = 8.0, 1.6, 1.2 Hz, 1H, CH), 8.08 (ddd, *J* = 8.0, 1.6, 1.2 Hz, 1H, CH), 8.32 (t, *J* = 1.6 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 53.9, 96.0, 123.0, 126.1, 128.2, 130.4, 130.6, 134.4, 167.3, 174.7; EI-MS: *m/z* (%) = 300 ([M]$^+$ ^{81}Br, 20), 298 ([M]$^+$ ^{79}Br, 20), 269 (28), 241 (7), 239 (8), 198 (5), 196 (5), 157 (5), 155 (5) 102 (9), 75 (100), 50 (7); Anal. calcd for $C_{11}H_{11}BrN_2O_3$ (299.12): C, 44.17; H, 3.71; N, 9.37; found: C, 44.05; H, 3.63; N, 9.25%.

3-(3-Bromophenyl)-5-(diethoxymethyl)-1,2,4-oxadiazole (**7j**): Pale yellow oil; yield: 0.589 g (90%); IR (KBr) (ν_{max}/cm^{-1}): 1561, 1466, 1408, 1309, 1268, 1188, 1075, 997, 893, 812, 784, 673; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.2 Hz, 6H, 2 × CH_2CH_3), 3.78 and 3.82 (2 × dq, ^2J = 9.6, ^3J = 7.2 Hz, 4H, 2 × OCH_2CH_3), 5.83 (s, 1H, CH), 7.36 (t, *J* = 8.0 Hz, 1H, CH), 7.64 (ddd, *J* = 8.0, 1.6, 1.2 Hz, 1H, CH), 8.06 (ddd, *J* = 8.0, 1.6, 1.2 Hz, 1H, CH), 8.29 (t, *J* = 1.6 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.0, 62.7, 94.4, 122.9, 126.1, 128.3, 130.4, 130.6, 134.3, 167.2, 175.4; EI-MS: *m/z* (%) = 328 ([M]$^+$ ^{81}Br, 13), 326 ([M]$^+$ ^{79}Br, 13), 284 (82), 255 (49), 253 (46), 225 (16), 199 (93), 184 (31), 183 (82), 182 (31), 159 (17), 157 (17), 118 (23), 102 (100), 75 (84), 50 (27); Anal. calcd for $C_{13}H_{15}BrN_2O_3$ (327.18): C, 47.72; H, 4.62; N, 8.56; found: C, 47.58; H, 4.43; N, 8.40%.

5-(Dimethoxymethyl)-3-(3-methylphenyl)-1,2,4-oxadiazole (**7k**): Colourless oil; yield: 0.435 g (93%); IR (KBr) (ν_{max}/cm^{-1}): 1580, 1520, 1460, 1335, 1284, 1197, 1118, 1070 (C–O), 984, 907, 848, 799, 742, 688; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 3.54 (s, 6H, 2 × OCH_3), 5.73 (s, 1H, CH), 7.33 (d, *J* = 7.6 Hz, 1H, CH), 7.38 (t, *J* = 7.6 Hz, 1H, CH), 7.94 (d, *J* = 7.6 Hz, 1H, CH), 7.97 (s, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.3, 53.9, 96.0, 124.7, 126.1, 128.2, 128.8, 132.2, 138.7, 168.4, 174.3; EI-MS: *m/z* (%) = 234 ([M]$^+$, 45), 203 (36), 175 (27), 147 (9), 132 (27), 116 (10), 91 (24), 75 (100), 51 (6); Anal. calcd for $C_{12}H_{14}N_2O_3$ (234.25): C, 61.53; H, 6.02; N, 11.96; found: C, 61.37; H, 5.95; N, 11.88%.

5-(Diethoxymethyl)-3-(3-methylphenyl)-1,2,4-oxadiazole (**7l**): Colourless oil; yield: 0.493 g (94%); IR (KBr) (ν_{max}/cm^{-1}): 1581, 1457, 1333, 1285, 1210, 1118, 1064, 914, 790, 686; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.2 Hz, 6H, 2 × CH_2CH_3), 2.42 (s, 3H, CH_3), 3.78 and 3.81 (2 × dq, ^2J = 9.6, ^3J = 7.2 Hz, 4H, 2 × OCH_2CH_3), 5.82 (s, 1H, CH), 7.32 (d, *J* = 7.6 Hz, 1H, CH), 7.37 (t, *J* = 7.6 Hz, 1H, CH), 7.92 (d, *J* = 7.6 Hz, 1H, CH), 7.95 (s, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.0, 21.3, 62.6, 94.5, 124.7, 126.2, 128.2, 128.7, 132.1, 138.6, 168.4, 174.9; EI-MS: *m/z* (%) = 262 ([M]$^+$, 35), 218 (74), 189 (55), 161 (28), 133 (100), 118 (54), 103 (88), 91 (68), 86 (20), 75 (80), 65 (29); Anal. calcd for $C_{14}H_{18}N_2O_3$ (262.31): C, 64.11; H, 6.92; N, 10.68; found: C, 64.15; H, 7.04; N, 10.49%.

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