An efficient method for the one-pot tandem synthesis of 3,5-disubstituted-1,2,4-oxadiazoles from benzyl halides

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The first example of a one-pot tandem approach for the synthesis of 3,5-disubstituted-1,2,4-oxadiazole derivatives from benzyl halides and amidoxime is reported. Derivatives of 3,5-disubstituted 1,2,4-oxadiazole were obtained in excellent yields under mild conditions using DMSO in the absence of an additional oxidant. Benzyl bromides bearing a range of substituents proved to be suitable substrates for this method which provides a very efficient and convenient application of the Kornblum oxidation.

Keywords: 3,5-disubstituted-1,2,4-oxadiazoles, benzyl halides, Kornblum oxidation, one-pot tandem reaction

The unique biological activity and remarkable chemical structure of heterocyclic compounds containing the 1,2,4-oxadiazole scaffold, has received considerable attention (Fig. 1).[1] 1,2,4-Oxadiazole derivatives possess different pharmacological activities including antitumor, antibacterial, analgesic, anti-inflammatory, anticancer, monoamine oxidase inhibition, tyrosine kinase inhibition, muscarinic agonism, and histamine H_3 antagonism.[2-10] The 1,2,4-oxadiazole ring system is also widely reported as a β amyloid-imaging probe that plays an important role in Alzheimer's drug discovery,[11] and peptide building blocks.[12] This scaffold appears in several drugs and drug leads such as the metabotropic glutamate subtype 5 (mGlu 5) receptor,[13] and S1P1 agonist.[14] Consequently a new synthetic route to 3,5 di-substituted 1,2,4-oxadiazoles, involving a rapid, mild, efficient, and one-pot method is desirable.

O-Acylation of an amidoxime by an activated carbonyl compounds in the first step followed by a second step of cyclodehydration, is a standard method for the synthesis of 1,2,4-oxadiazole.[15] There are many reports an improving the chemical yields, conditions, and reaction time of this method.[16] However, these methods suffer from the disadvantages such as extended reaction times, low yields, and harsh conditions. To overcome the drawbacks, different activated carbonyl compounds have been used for the *O*-acylation step including esters, acid chlorides, anhydrides and aldehydes.[17-20]

However, to our knowledge there are no reports on the use of aryl halides as starting materials in the synthesis of 1,2,4-oxadiazole synthesis in a one-pot manner. Therefore, we have evaluated the feasibility of synthesising 1,2,4-oxadiazoles from amidoximes and commercially available benzyl halides under mild conditions.

Results and discussion

As a part of our efforts to develop new route for the synthesis of biologically active heterocyclic compounds from readily available building blocks,[21,22] we describe a novel and straightforward approach for the preparation of 3,5-disubstituted 1,2,4-oxadiazoles which involves an *in situ* oxidation–cyclocondensation sequence starting from benzyl bromides (Scheme 1).

The selective oxidation of the benzylic positions of arenes to the carbonyl compounds is an important step in the synthesis of bioactive compounds.[23] Several methods have been developed to carry out the conversion of halides to the corresponding aldehydes, such as the Kornblum reaction (DMSO/$NaHCO_3$).[24] The mechanism of the conventional Kornblum oxidation involves an alkoxy sulfonium ion, which in the presence of a base such as K_2CO_3, undergoes elimination to form the desired aldehyde.

In the first step a series of benzyl bromides, under mild Kornblum oxidation conditions, were reacted with DMSO in the presence of K_2CO_3 as basic catalyst both under microwave irradiation and conventional heating. The striking observation was that the reaction under heating at 110 °C was considerably accelerated as compared to that under classical conditions using microwaves irradiation.

Thus, under modified Kornblum oxidation conditions, benzyl bromide substrates **1** in DMSO in the presence of K_2CO_3 at 110 °C were converted into the corresponding aldehydes in excellent yields. Subsequently the aldehydes were prepared *in situ* without further purification, and condensed with different amidoximes at 110 °C to form the corresponding 3,5-disubstituted 1,2,4-oxadiazole derivatives **3a–h** in acceptable yields of 73–82%.Treatment of the benzylic substrate **1** with DMSO leads to an alkoxy sulfonium ion **4** which in the presence of K_2CO_3 undergo elimination of dimethyl sulfide (DMS) to form the corresponding aldehyde **5**.[25,26] Next, the resulting aldehyde condenses with the amine and a further molecule of DMSO may add to this to form a sulfoxonium salt. In the third step this loses the former aldehyde proton and dimethylsulfide to form an amide. Next the hydroxyl group of the oxime adds to the carbonyl group of the amide. Finally loss of water gives the

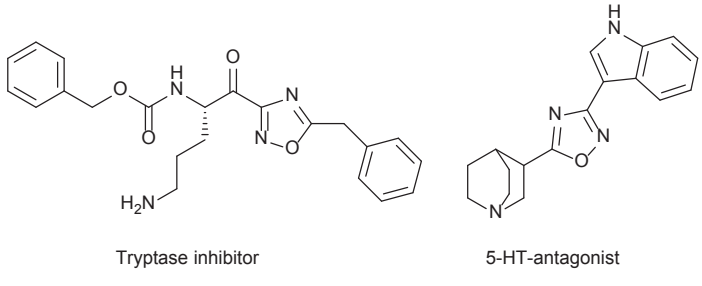
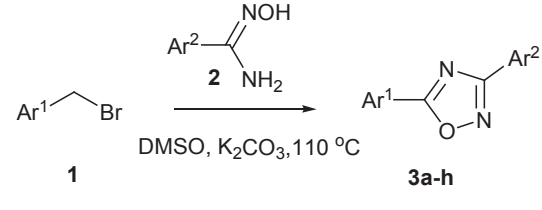


Fig. 1 Two examples of biologically active 1,2,4-oxadiazoles.



Scheme 1 Synthesis of 3,5-disubstituted-1,2,4-oxadiazole derivatives.

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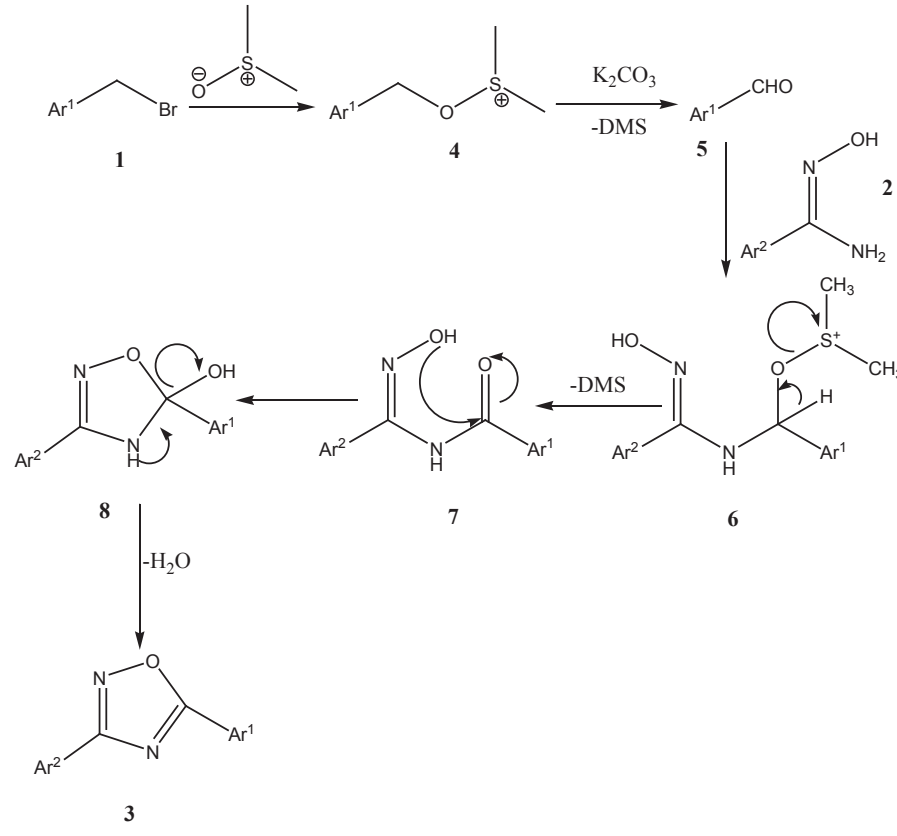

Scheme 2 The proposed mechanism.

Table 1 Synthesis of 3,5-disubstituted-1,2,4-oxadiazole derivatives **3a–h**

Entry	Ar^1	Ar^2	Yield/%[a]	Melting point/°C (lit.)
1	Ph	Ph	80	106–108(109–110) [27]
2	4-CH_3–C_6H_4	4-CH_3–C_6H_4	77	134–135(135–136) [28]
3	4-Cl–C_6H_4	Ph	75	120–121(118–119) [29]
4	2-Cl–C_6H_4	3-NO_2–C_6H_4	73	153–154(156–157) [30]
5	4-CH_3–C_6H_4	4-Cl–C_6H_4	82	135–137(138–140) [31]
6	4-Cl–C_6H_4	4-Cl–C_6H_4	78	180–182(183–185) [32]
7	2,4-$Cl_2C_6H_3$	4-CH_3–C_6H_4	80	143–144(145–146) [33]
8	4-Br–C_6H_4	4-F–C_6H_4	76	175–176(177–179) [34]

[a]Isolated yield after recrystallisation.

N=C of the 3,5-disubstituted 1,2,4-oxadiazoles **3a–h** in good yields (Scheme 2).

In this method, the starting materials were completely converted to the corresponding products within 6–8 h. All the products were characterised by melting point determination and confirmed by ^{1}H and ^{13}C NMR spectral data (Table 1).

In conclusion, we have shown that 3,5-disubstituted-1,2,4-oxadiazole derivatives can be simply synthesised thorough an *in situ* oxidation–cyclodehydration sequence starting from benzyl halides and different amidoximes. The reaction was accomplished in the presence of DMSO and K_2CO_3 at 110 °C, without using additional reagents or catalysts. Some of the principal synthetic benefits of this method are the mild conditions, easy experimental installation, easy isolation of the products, and the high yields. The simplicity of this procedure makes it an interesting alternative to other approaches.

Experimental

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectrum was recorded on Bruker FT-500, using TMS as an internal standard. The elemental analysis was performed with an Elementar Analysen system GmbH VarioEL CHNS mode. All reagents and solvents were purchased from Aldrich and Merck, and used without any purification.

Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles derivatives **3a–h***; general procedure*

A mixture of benzyl bromide **1** (1 mmol) and K_2CO_3 (1.5 mmol) in dimethyl sulfoxide (DMSO) (1 mL) was stirred for 4 h at 110 °C. Then, benzamidoxime **2** (1 mmol) were added to the reaction mixture and stirring was continued at 110 °C for 4 h. The reaction mixture was cooled to room temperature and H_2O (3 mL) was added. The precipitate was filtered, washed with H_2O (2 mL) and dried. The crude products were purified by column chromatography using diethyl ether/ethyl acetate (5:1) as an eluent to give pure 3,5-diphenyl-1,2,4-oxadiazole **3a–h**.

3,5-Diphenyl-1,2,4-oxadiazole (**3a**): Colourless crystals; m.p 106–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 7.48–7.57 (m, 5H), 7.60 (t, *J* = 7.1 Hz, 1H), 8.20 (d, *J* = 7.5 Hz, 2H), 8.28 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 125.1, 126.4, 127.4, 128.2, 128.6, 129.7, 131.3, 132.8, 168.9, 175.5.

3,5-Di-p-*tolyl-1,2,4-oxadiazole* (**3b**): Colourless crystals; m.p 134–135 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 2.35 (s, 3H), 2.40 (s, 3H), 7.24 (d, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.7 Hz, 2H), 8.05 (d, *J* = 7.7 Hz, 2H), 8.16 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.5, 21.6, 122.2, 126.3, 127.1, 128.4, 129.4, 129.6, 141.2, 143.2, 168.7, 175.5.

5-(4-Chlorophenyl)-3-phenyl-1,2,4-oxadiazole (**3c**): Colourless crystals; m.p 120–121 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 7.33–7.51 (m, 5H), 8.22 (d, *J* = 7.7 Hz, 2H), 8.38 (d, *J* = 7.4, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 121.3, 125.7, 126.4, 129.8, 129.9, 130.4, 131.1, 138.1, 165.5, 171.3.

5-(2-Chlorophenyl)-3-(3-nitrophenyl)-1,2,4-oxadiazole (**3d**): Yellow solid; m.p 153–154 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 7.59 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 8.18 (d, *J* = 7.4 Hz, 1H), 8.32–8.80 (m, 2H), 8.86 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 121.5, 123.5, 124.1, 126.3, 127.9, 129.8, 130.4, 131.8, 132.3, 132.5, 133.7, 150.2, 167.3, 175.2.

*3-(*p*-Methylphenyl)-5-(*p*-chlorophenyl)-1,2,4-oxadiazole* (**3e**): Yellow solid; m.p 135–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 2.33 (s, 3H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 7.7 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H), 8.08 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 121.7. 123.1, 125.4, 128.8, 129.3, 135.4, 142.2, 164.2, 176.5.

*3,5-Bis(*p*-chlorophenyl)-1,2,4-oxadiazole* (**3f**): White solid; m.p 180–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 7.51 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 7.8 Hz, 2H), 8.01 (d, *J* = 8.1 Hz, 2H), 8.24 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 121.2, 123.7, 124.6, 126.2, 128.3, 129.8, 134.3, 136.9, 165.4, 171.3.

*3-(2,4-Dichlorophenyl)-5-(*p*-methylphenyl)-1,2,4-oxadiazole* (**3g**): Yellow solid; m.p 143–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 3.22 (s, 3H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 7.3, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 23.3. 118.1, 122.7, 125.4, 128.2, 130.8, 131.9, 132.4, 135.2, 141.3, 165.9, 171.3.

*3-(*p*-Bromophenyl)-5-(*p*-flourophenyl)-1,2,4-oxadiazole* (**3h**): White solid; m.p 175–176 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 7.15 (d, *J* = 8 Hz, 2H), 7.29 (s, 1H), 7.32–7.44 (m, 3H), 8.24 d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 114.2, 117.4, 119.2, 124.8, 126.1, 130.9, 133.7, 164.3, 168.1, 175.6.

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