A base-induced ring-opening process of 2-substituted-1,3,4-oxadiazoles for the generation of nitriles at room temperature

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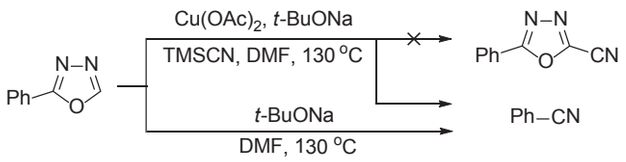
A novel base-catalysed 1,3,4-oxadiazole fragmentation for the synthesis of nitriles at room temperature has been developed. This reaction is performed under transition-metal-free conditions, and provides a new ring cleavage reaction of 1,3,4-oxadiazoles in organic synthesis.

Keywords: 2-substituted-1,3,4-oxadiazole, heterocycle, ring cleavage, nitrile

Ring cleavage reactions of the 1,3,4-oxadiazoles can lead to new aliphatic nitrogen-containing compounds or to other ring systems. However, few reports mention the ring-cleavage of 2-substituted-1,3,4-oxadiazoles. We now describe a novel base-catalysed 1,3,4-oxadiazole fragmentation for the formation of nitriles at room temperature.

The significance of the present chemistry is two-fold: (1) It is the first example of a direct transformation of 2-substituted-1,3,4-oxadiazoles to nitriles, which are useful in organic synthesis.[1–4] Although, there are many methods for the preparation of nitriles from simpler substrates compared to 2-substituted-1,3,4-oxadiazoles, such as aryl halides,[5,6] carboxylic acids[7,8] and methyl arenes,[9–11] the newly developed protocol provide an alternative route for the cyanation in which the cyano-group could be formed *via* a ring cleavage process of heterocycles.[12] (2) The research not only reveals a new ring cleavage route for 2-subsitituted-1,3,4-oxadiazoles, but also offers mechanistic insights into this reaction, which may suggest new ring-opening processes of other heteroarenes.

As a part of our interest in cyanation,[13] we attempted to synthesise 5-phenyl-1,3,4-oxadiazole-2-carbonitrile through the copper-catalysed C–H activation of 2-phenyl-1,3,4-oxadiazole. However, the reaction failed to provide the desired product, and instead yielded benzonitrile as the final product. Moreover, benzonitrile was also obtained in the absence of copper (Scheme 1). The surprising finding prompted us to investigate the reaction in more detail in order to possibly optimise the reaction conditions and to understand the mechanism of the reaction.



Scheme 1

Further investigations indicated the reaction could be completed even at room temperature in DMF using *t*-BuONa as the base (Table 1, entry 1). Water proved to have a negative effect on the process (entries 2–4). After screening different solvents and bases, the results indicated the necessity of both a strong base and a polar aprotic solvent. No desired product was detected in the absence of either of them. The combination of DMF and *t*-BuONa provided the best results (entry 1). The amount of *t*-BuONa was also optimised, and 1.0 equiv. *t*-BuONa proved to be the best selection for the reaction (entry 12).

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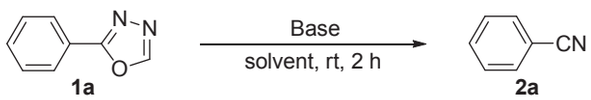
With the optimised conditions in hand, a series of 2-aryl-1,3,4-oxadizoles were chosen to establish the scope and generality of the method (Table 2). Both electron-rich and electron-defect 2-aryl-1,3,4-oxadizoles gave good to excellent yields. It should be noted that a poor yield of **2d** was observed even after longer reaction time, presumably due to the poor solubility of 4-(1,3,4-oxadiazol-2-yl)phenol **1d** in DMF. Alternatively, the hydroxyl group enhance the electronic density on the 1,3,4-oxadizole ring by conjugative effects, which may inhibit the ring-opening process.

In order to examine the possibility for large-scale operation, we also scaled up the reaction to 10 mmol, and the reaction proceeded well with 93% yield of **2c** just by prolonging the reaction time to 12 h. The outcome was also satisfactory (**2i**, **2j**) when sterically hindered substrates were employed. Heteroaryl nitriles such as **2m** and **2n**, could be produced from corresponding 2-aryl-1,3,4-oxadiazoles. To our delight, the scope of the protocol could be extended to the preparation of the benzyl nitrile (**2o**) and the alkyl nitrile (**2p**). To further highlight the potential of this chemistry, aromatic nitrile **4**, a crucial intermediate to L692,429 **5**, a non-peptidyl growth hormone secretagogue[21] and losartan potassium **6**, an angiotensin II receptor antagonist,[22] was synthesised from **1j** and **3** through a one-pot reaction involving a Suzuki coupling and cyanation reaction (Scheme 2).

Table 1 Optimisation of the reaction conditions[a]

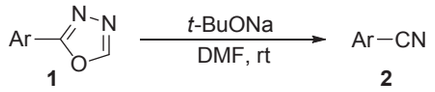


1a **2a**

Entry	Base	Solvent	Yield/%[b]
1	*t*-BuONa	DMF	99, 81[c]
2	*t*-BuONa	H_2O	NR
3	*t*-BuONa	DMF/H_2O (v/v=1/1)	NR
4	*t*-BuONa	DMF/H_2O (v/v=2/1)	4
3	*t*-BuONa	EtOAc	NR
4	*t*-BuONa	MeCN	NR
5	*t*-BuONa	Diglyme	NR
6	*t*-BuONa	DMSO	84
7	*t*-BuONa	DMAc	92
8	NaOH	DMF	21
9	K_2CO_3	DMF	NR
10	K_3PO_4	DMF	NR
11	NEt_3	DMF	NR
12	*t*-BuONa	DMF	99[d], 36[e], 3[f]

[a]Reaction condition: **1a** 0.5 mmol, base 1.0 mmol, solvent 1 mL, room temperature, 2 h. [b]GC yields. [c]The reaction time is 1 h. [d]1.0 equiv. *t*-BuONa was used. [e]0.50 equiv. *t*-BuONa was used. [f]0.25 equiv. *t*-BuONa was used. NR, No reaction.

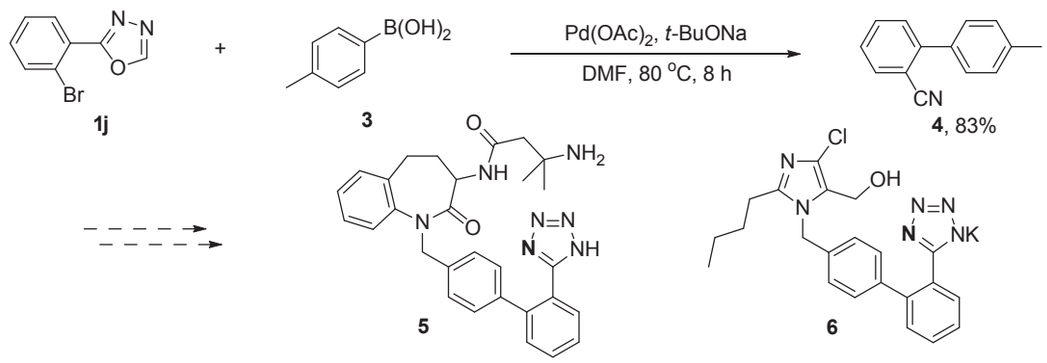
Table 2 The synthesis of nitriles from 2-substituted-1,3,4-oxadiazole[a]



1 **2**

Entry	Ar	1	Time/h	a	Yield/%[b]	M.p./°C	Lit. m.p./°C
1	Ph	**1a**	4	**2a**	90	Oil	Oil[14]
2	3-$CH_3C_6H_4$	**1b**	4	**2b**	95	Oil	Oil[15]
3	4-$MeOC_6H_4$	**1c**	4	**2c**	97, 93[c]	56–58	61–62[14]
4	4-HOC_6H_4	**1d**	24	**2d**	45[d]	110–112	110–113[14]
5	4-$F_3CC_6H_4$	**1e**	8	**2e**	89	36–38	39–41[15]
6	4-ClC_6H_4	**1f**	4	**2f**	98	92–94	90–93[15]
7	4-$O_2NC_6H_4$	**1g**	4	**2g**	94	145–147	148–150[14]
8	4-FC_6H_4	**1h**	8	**2h**	84	32–34	32–34[15]
9	2-$O_2NC_6H_4$	**1i**	4	**2i**	95	108–110	107–109[16]
10	2-BrC_6H_4	**1j**	4	**2j**	88	192–194	194–195[17]
11	2-Naphthyl	**1k**	8	**2k**	84	64–66	63–68[14]
12	3,4,5-Trimethylphenyl	**1l**	8	**2l**	99	92–94	91–94[18]
13	3-Pyridyl	**1m**	8	**2m**	93	48–50	50–51[19]
14	2-Pyridyl	**1n**	8	**2n**	91	Oil	26–28[20]
15	Benzyl	**1o**	4	**2o**	87	Oil	Oil[18]
16	2-Phenylethyl	**1p**	4	**2p**	92	Oil	Oil[18]

[a]Reaction condition: **1** 0.5 mmol, *t*-BuONa 0.5 mmol, DMF 1 mL, room temperature. [b] Isolated yields. [c] Reaction condition: **1c** 10.0 mmol, *t*-BuONa 10.0 mmol, DMF 10 mL, room temperature, 12 h. [d]The reaction was performed in DMSO.



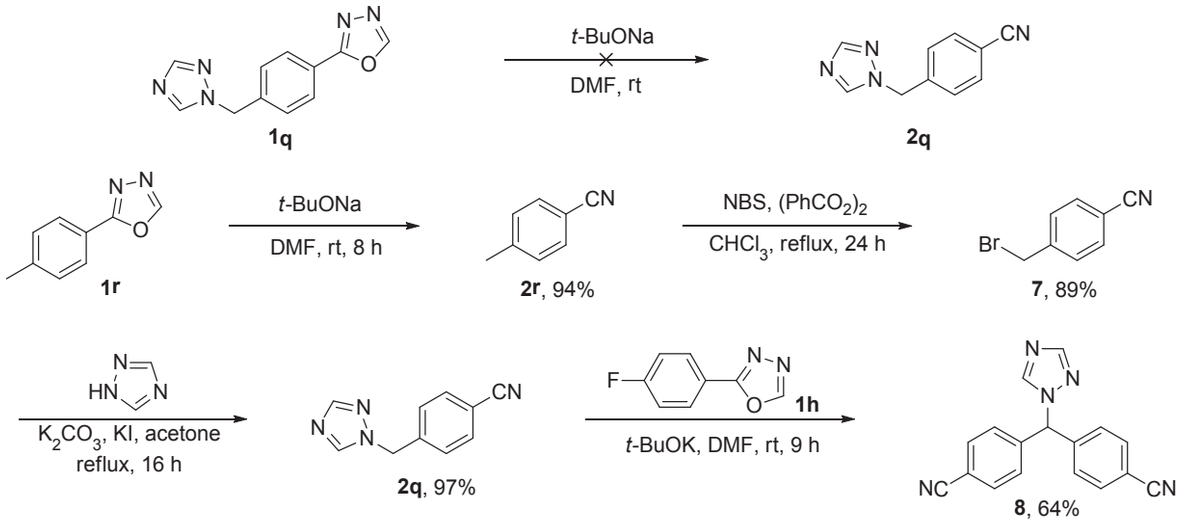
Scheme 2

The synthesis of letrozole **8**, which is an oral non-steroidal aromatase inhibitor for the treatment of hormonally-responsive breast cancer after surgery,[23] was also achieved with our present transformation as the key step (Scheme 3). Initially, we intended to prepare **2q** by the cyanation of **1q** under basic conditions, but the reaction failed to provide the desired product. Alternatively, the formation of **2q** could be realised using **1r** as the starting material *via* cyanation, bromination and electrophilic substitution. In the last step, **2q** was reacted with **1h** under optimised conditions to afford letrozole **8** in a one-pot cyanation and nucleophilic substitution (Scheme 3).

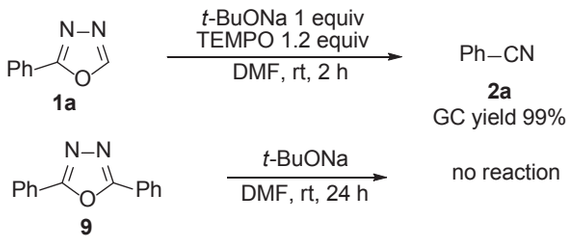
In order to study the mechanism, several control experiments were carried out. First, the cyanation of **1a** gave benzonitrile **2a** in DMSO (Table 1, entry 6), showing that the cyano-group originated from the 1,3,4-oxadiazole ring, and benzonitrile **2a** aroseby 1,3,4-oxadiazole fragmentation. Second, the reaction proceeded smoothly in the presence of 1.2 equiv. of TEMPO (Scheme 4). Moreover, the reaction was not sensitive to moisture and oxygen, because the reaction could took place under air atmosphere in DMF which was used directly without drying. It could be concluded that the transformation do not proceed through a radical intermediate.[24–26] Subsequently, 2,5-diphenyl-1,3,4-oxadiazole **9** was employed in the protocol, but no reaction occurred indicating that the hydrogen on 5 position of 1,3,4-oxadiazole ring may be necessary for the ring-opening process.[12]

The role of the DMF in the reaction can be explained since the solvation of the sodium ion in DMF enhances the basicity of *t*-BuONa. This has a positive effect on the formation of a carbanion intermediate. Based on these results above, a proposed mechanism for the reaction was illustrated in Scheme 5. A corresponding carbanion intermediate is formed by removal of a proton from the 5 position of the 2-substituted-1,3,4-oxadiazole with strong base. This is followed by a ring-opening transformation to yield the nitrile.

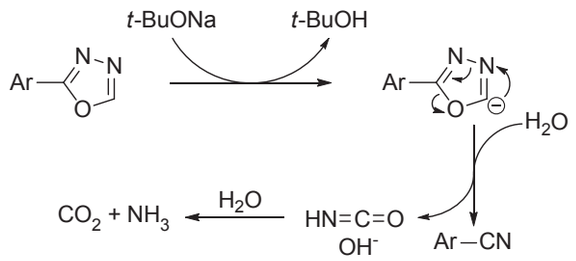
In conclusion, we have discovered and optimised a novel, methodology for the synthesis of nitriles from 2-substituted-1,3,4-oxadiazoles *via* a base-induced ring-opening process at room temperature under transition-metal-free conditions. Although 2-substituted-1,3,4-oxadiazoles compared to other starting materials of cyanation have no advantage from synthetic point of view, the transformation offers another approach to cyanation in which nitriles can be formed by a heterocyclic ring cleavage process. In addition, it is an efficient protocol for the fragmentation of 1,3,4-oxadiazole ring, due to its mild conditions, high yields and simple work-up procedures, offering potential for applications in organic synthesis.



Scheme 3



Scheme 4



Scheme 5

Experimental

2-Subsituted-1,3,4-oxadiazoles were prepared from corresponding carboxylic acids according to previous literature[27,28] (see Electronic Supplementary Information, ESI). All other chemical reagents were obtained from commercial suppliers and used without further purification. All the products were known compounds, which were identified by appropriate technique such as ^{1}H NMR, and ^{13}H NMR and compared with previously reported data. Analytical TLC was performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm), and the plates were visualised by exposure to UV light. Mass spectra were taken on a Finnigan TSQ Quantum-MS instrument in the electrospray ionisation mode. ^{1}H NMR and ^{13}C NMR spectra were recorded on an Avance 500 Bruker spectrometer operating at 500 MHz and 125 MHz in $CDCl_3$ or DMSO-d_6, respectively. Chemical shifts were reported in ppm. GC analyses are performed on an Agilent 7890A instrument (Column: Agilent 19091J-413: 30 m × 320 µm × 0.25 µm, carrier gas: H2, FID detection. GC/MS data were obtained by using a Saturn2000 GC/MS series. HP 5890 GC was equipped with a CPSTIL-8CB mass selective detector.

Synthesis of nitriles from 2-substituted-1,3,4-oxadiazoles; general procedure

A mixture of 2-substituted-1,3,4-oxadiazole (0.5 mmol), *t*-BuONa (0.5 mmol) and DMF or DMSO (1 mL) was stirred at room temperature for an appropriate time. When the reaction completed, EtOAc (5 mL) and petroleum ether (5 mL) were added, and the mixture was washed by water (3 × 10 mL) to remove DMF or DMSO. The organic layer was collected and filtered through a bed of silica gel layered over Celite. The volatiles were removed under reduced pressure to afford the final product. In a few cases, further column chromatography on silica gel was needed to afford the pure desired product.

4'-Methylbiphenyl-2-carbonitrile **(4):** A mixture of **1j** (0.5 mmol), **3** (0.6 mmol), $Pd(OAc)_2$ (0.01 mmol), *t*-BuONa (1.0 mmol) and DMF (1 mL) was stirred at 80 °C for 8 h. When the reaction completed, EtOAc (5 mL) and petroleum ether (5 mL) were added, and the mixture was washed by water (3 × 10 mL) to remove DMF. The organic layer was collected and filtered through a bed of silica gel layered over Celite. The volatiles were removed under reduced pressure, and further column chromatography on silica gel was needed to afford the pure desired product **4** (83%), white solid, m.p. 46–48 °C (lit.[19] 49–50 °C).

Letrozole **(8):** **2r** was prepared by the general procedure for the synthesis of nitriles from 2-substituted-1,3,4-oxadiazoles in 94% yield, colourless oil, m.p. < 30 °C (lit.[15] 26–28 °C).

A mixture of *p*-toluonitrile **2r** (5 mmol), *N*-bromosuccinimide (5 mmol) and benzoyl peroxide (10 mg) was refluxed in chloroform (15 mL) for 24 h. The completion of reaction was detected by TLC. The solvent was evaporated under reduced pressure and then ethyl acetate and H_2O was added. The organic layer was extracted and washed 3 times with brine. After evaporation of ethyl acetate, compound **7** was obtained as a white solid (yield 89%), m.p. 112–114 °C (lit.[29] 113–115 °C). The product was used for the next step without any further purification.

A mixture of methyl 4-(bromomethyl)benzoate **7** (3 mmol), 1*H*-1,2,4-triazole (4.5 mmol), K_2CO_3 (4.5 mmol), KI (0.15 mmol) and acetone (10 mL) was stirred under reflux for 16 h. Then, water (20 mL) was added to the mixture. The product was extracted with ethyl acetate (3 × 5 mL). The organic phase was dried over Na_2SO_4, and the solvent was evaporated under vacuum affording the product **2q** (methyl 4-((1*H*-1,2,4-triazol-1-yl)methyl)benzoate, 97%), white solid, m.p. 78–80 °C, (lit.[30] 77–79 °C).

At –5 °C and under argon atmosphere, *t*-BuOK (3 mmol) was suspended in anhydrous DMF (2.5 mL) with vigorous stirring. Over a period of 1 h, **2q** (0.75 mmol) dissolved in 1 mL DMF was added

dropwise to the reaction mixture, followed by dropwise addition of 2-(4-fluorophenyl)-1,3,4-oxadiazole **1h** (1.09 mmol) in 0.5 mL DMF over 30 min. After 7.5 h, the mixture was quenched with 3 M HCl until acidic (pH < 5), neutralised with $NaHCO_3$, diluted with 50 mL water and then extracted with 3 × 15 mL EtOAc. The organic fraction was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to yield the pure compounds **8** (Letrozole, 64%), white solid, m.p. 180–182 °C, (lit.[31] 181–183 °C).

Electronic Supplementary Information

The ESI is available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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