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PAPER

Inverse electron-demand 1,3-dipolar cycloaddition of nitrile oxide with common nitriles leading to 3-functionalized 1,2,4-oxadiazoles†

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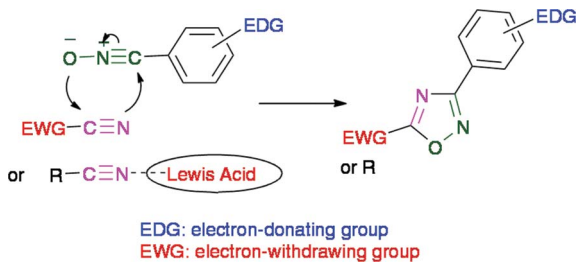
A carbamoyl-substituted nitrile oxide was generated upon treatment of easily available 2-methyl-4-nitro-3-isoxazolin-5(2*H*)-one with THF (not dried); the reaction proceeded efficiently even in the absence of any special reagents and reaction conditions. The nitrile oxide caused 1,3-dipolar cycloaddition with common aliphatic nitriles or electron-rich aromatic nitriles to afford 3-functionalized 1,2,4-oxadiazoles, which are expected to serve as precursors for the preparation of a variety of functional materials by the chemical transformation of the carbamoyl group. While conventional preparative methods for 1,2,4-oxadiazoles involve the cycloaddition of an electron-rich nitrile oxide with an electron-deficient nitrile or a nitrile activated by a Lewis acid, our method employs the complementary combination of an electron-rich nitrile and an electron-deficient nitrile oxide- the inverse electron-demand 1,3-cycloaddition. The DFT calculations using B3LYP 6-31G* supported the abovementioned inverse reactivity, and also suggested the presence of an accelerating effect by the carbamoyl group as a result of hydrogen bond formation with a dipolarophilic nitrile.

Introduction

Nitrile oxides, one of the most popular classes of 1,3-dipoles, have served as useful synthetic tools for the synthesis of five-membered heterocyclic compounds. Indeed, 2-isoxazolines (or isoxazoles) can be readily prepared by the cycloaddition of a nitrile oxide with alkenes (or alkynes), and their ring-opened products are used as precursors for a variety of functional materials.[1] Furthermore, a nitrile is also usable as a dipolarophile for cycloaddition with a nitrile oxide to construct a 1,2,4-oxadiazole framework directly, which is advantageous compared to other synthetic approaches that require more extensive synthetic manipulations.[2]

Numerous 1,2,4-oxadiazole derivatives have been synthesized over the last century; one of the typical methods involves the cycloaddition of nitrile oxides with nitriles to form two bonds in a single step (Scheme 1).[2] Although the reaction has been recognized to be useful for synthesizing versatile 1,2,4-oxadiazoles, the limited scope of substituents at the 3- and 5-positions is a serious problem for the reaction; since the nitrile oxides used in this method are restricted to benzonitrile oxide or its derivatives, the substituent at the 3-position of the produced oxadiazole is necessarily an aromatic group.[2] Furthermore, the electron density of dipolarophilic nitriles should decrease for the cycloaddition with electron-rich benzonitrile oxides. In most cases, nitriles having an electron-withdrawing group are employed[3,4] except in special cases in which electron-rich nitriles bearing an enamino group[5] or a heteroatom substituent are used.[6] For the cycloaddition of a nitrile oxide with common aliphatic nitriles, the activation of the nitrile by a metal[7] or a Lewis acid[8] is required. Although there are few reports of cycloadditions using aliphatic nitriles in the absence of an activator, it is clear that nitriles should be used as the solvent and severe reaction conditions are necessary.[9] Hence, there are no reports on the construction of a 1,2,4-oxadiazole framework by the cycloaddition of a nitrile oxide with a highly reduced amount of a common nitrile (not as a solvent) under mild conditions. Moreover, the abovementioned limitations prevent the direct syntheses of functionalized oxadiazoles, although pharmaceutical and agrochemical demand for them are increasing considerably.



Scheme 1 A typical method for the synthesis of 1,2,4-oxadiazoles.

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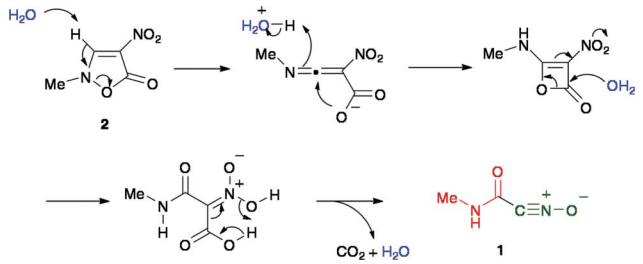
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of new compounds **3e**, **3g**, and **3i–k** are available. See DOI: 10.1039/c1ob05682d

We recently reported a new method for generating the carbamoyl-substituted nitrile oxide **1** from easily available 2-methyl-4-nitroisoxazolin-5(2*H*)-one (**2**)[10–13] through treatment with water (Scheme 2).[14] The nitrile oxide undergoes cycloaddition with alkenes or alkynes to afford the corresponding functionalized isoxazoles or isoxazolines in good to high yields. On the basis of these experimental findings, we hypothesized that the nitrile oxide bearing an electron-withdrawing group would undergo inverse electron-demand 1,3-dipolar cycloaddition with electron-rich aliphatic nitriles; 3-carbamoyl-5-alkyl-1,2,4-oxadiazoles **3** would be directly synthesized in a single step, which promises the construction of functionalized 1,2,4-oxadiazoles because the carbamoyl group can be transformed to other functional groups.



Scheme 2 A plausible mechanism for the generation of nitrile oxide **1**.

Results and discussion

When an aqueous solution of 2-methyl-4-nitroisoxazolin-5(2*H*)-one (**2**) was stirred at 30 °C for one day, furoxan **4** was isolated in 80% yield,[14] which indicated the generation of nitrile oxide **1** even in the absence of any special reagents or conditions. In the present reaction, water serves as a base to induce ring-opening reaction, and the following anomalous hydration/dehydration sequence leads to nitrile oxide **1** (Scheme 2). For the cycloaddition of **1** with unsaturated hydrocarbons, a mixed solvent system (acetonitrile/water, v/v = 3/1) was employed to make the reaction system homogeneous, although the use of just water was enough for the generation of **1**. During a survey of reaction conditions, a trace amount of oxadiazole **3a** was detected in a reaction mixture (reaction temperature, 80 °C). The formation of **3a** provides crucial evidence for the cycloaddition of nitrile oxide **1** with acetonitrile **5a**, which proceeded under relatively mild conditions without any activation by a Lewis acid. Hence, we hypothesized that the diminished electron density of nitrile oxide **1** as a result of the presence of a carbamoyl group would promote cycloaddition with non-activated common nitriles.

In order to convince this hypothesis, theoretical studies using DFT calculations (B3LYP 6-31G*) were performed for two conventional synthetic methods in addition to our approach. Namely, we calculated the HOMO and LUMO energies for three reactant combinations: A) 2,4,6-trimethylbenzonitrile oxide and malononitrile;[4] B) benzonitrile oxide and acetonitrile coordinated with boron trifluoride;[8] and C) *N*-unsubstituted carbamoyl nitrile oxide **1′** and acetonitrile **5a**, in which **1′** was employed as a simplified model compound (Fig. 1). In combinations A and B, the energy difference between the HOMO of the nitrile oxides and the LUMO of the nitriles is smaller than that between the LUMO of the nitrile oxides and the HOMO of the nitriles. These calculations

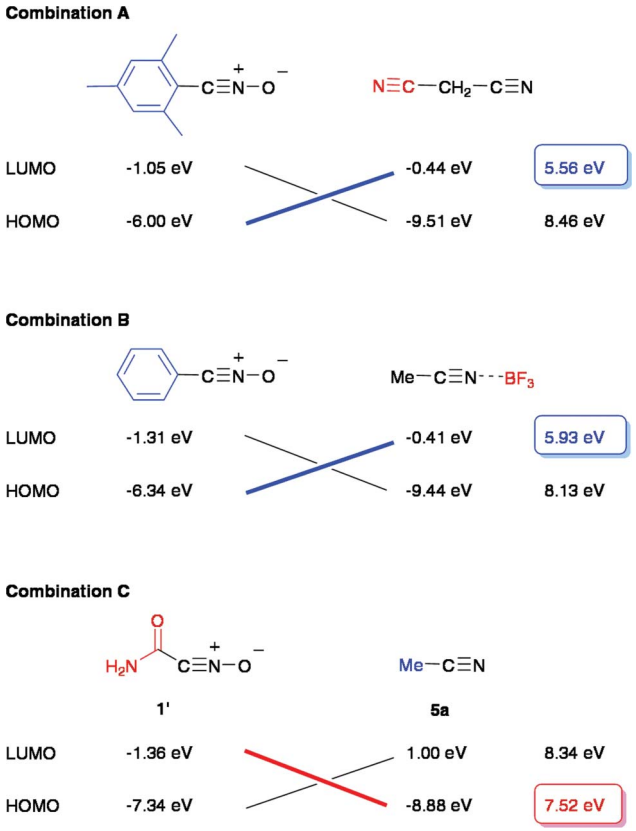
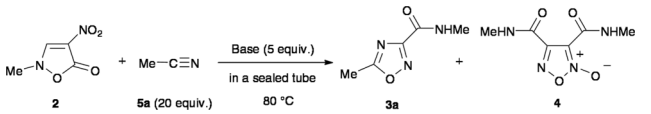


Fig. 1 Calculated energy correlations between nitrile oxides and nitriles.

are in good agreement with the fact that both reactions proceed very smoothly. In contrast, the reaction we proposed (combination C) showed the opposite tendency; the energy difference between the LUMO of the nitrile oxide and the HOMO of the nitrile is smaller than that between the HOMO of the nitrile oxide and the LUMO of the nitrile. This result encourages us to study in detail the cycloaddition reaction of nitrile oxide **1** with common aliphatic nitriles.

While nitroisoxazolone **2** could be recovered even after refluxing in an acetonitrile solution (Table 1, run 1), heating in a sealed tube was effective in promoting cycloaddition. Indeed, 14% of oxadiazole **3a**[10] was formed when a mixture of **2** and 20 equivalents of acetonitrile **5a** was heated in a sealed tube (a screw-capped test tube) at 80 °C (run 2). Notably, the 1,3-dipolar cycloaddition of the nitrile oxide with a small excess of the nitrile proceeded under mild conditions even in the absence of a Lewis acid. This result prompted us to survey oxygen-containing compounds that could serve as a base to induce the ring-opening reaction although a catalytic amount of water is still necessary as a trigger for the decarboxylation and the dehydration leading to nitrile oxide **1** (Scheme 2). When water was used as a base, the generation of **1** was accelerated; however, a considerable amount of furoxan **4** was formed (run 3). Bulky *tert*-butyl alcohol suppressed this side reaction to afford **3a** in improved yields (runs 4 and 5). While less basic phenol derivatives were usable as a base (runs 6 and 7), ethyl acetate, diethyl ether, and 1,4-dioxane did not show efficacy (runs 8–10). In contrast, more basic THF served as a good generator of nitrile oxide **1**, increasing the yield of **3a** up to 81% when the reaction mixture was heated for two days (runs 11 and 12). Thus,

Table 1 Study on bases for the reaction of isoxazolone **2** and 20 equiv. of acetonitrile **5a** in a sealed tube



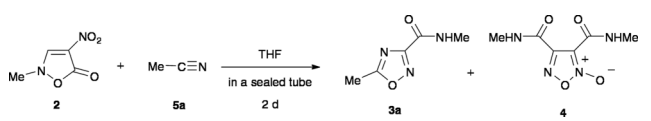
Run	Base	Time/d	Yield/% 3a[a]	Yield/% 4[a]	Recovery/% 2
1[b]	—	1	0	0	100
2	—	1	14	0	86
3	H_2O	1	31	34	0[c]
4	*t*-BuOH	1	56	10	29
5	*t*-BuOH	2	71	15	0
6	PhOH	1	51	43	0
7	*p*-$NO_2C_6H_4OH$	1	31	21	0[c]
8	AcOEt	1	1	0	99
9	Et_2O	1	12	7	54
10	1,4-Dioxane	1	0	0	100
11	THF	1	62	17	21
12	THF	2	81	19	0

[a] Based on **2**. [b] Isoxazolone **2** was heated in acetonitrile under reflux without using a sealed tube. [c] A complex mixture was formed.

among the oxygen-containing compounds, THF was found to be the most suitable; THF possesses appropriate basicity and polarity in addition to its hygroscopic property, which would be favorable for the formation of nitrile oxide **1** from nitroisoxazolone **2** with a catalytic amount of water as shown in Scheme 2.

We next turned our attention to the evaluation of reaction temperature and the molar ratio of acetonitrile **5a** and THF. An efficient cycloaddition was achieved at 80 °C, while the reaction did not substantially proceed at 50 °C (Table 2, runs 1 and 2). When the amount of acetonitrile (**5a**) was decreased from 20 to 5 equivalents, the dimerization of **1** proceeded considerably to afford furoxan **4** (run 3). The use of a large amount of THF with 5 equivalents of **5a** resulted in the formation of a complicated reaction mixture concomitant with decreased yields of both **3a** and **4** (run 4). These results showed that 20 equivalents of **5a** were necessary to suppress the undesired dimerization and side-reactions. Alternations in the equivalents of THF showed that a decreased amount depressed the reaction rate (run 5), which is an evidence that THF surely

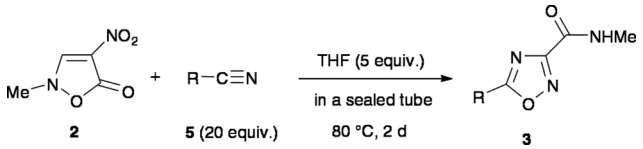
Table 2 Study on the molar ratios of acetonitrile **5a** and THF



Run	MeCN 5a/equiv.	THF/equiv.	Temp./°C	Yield/% 3a[a]	Yield/% 4[a]	Recovery/% 2
1	20	5	80	81	19	0
2	20	5	50	5	0	95
3	5	5	80	48	52	0
4	5	50	80	18	25	8
5	20	2	80	21	11	68
6	20	50	80	76	24	0

[a] Based on **2**.

Table 3 Cycloaddition of nitrile oxide **1** with nitriles **5**



Run	*R*		Yield/%
1	Me	**a**	81
2	Et	**b**	73
3	*i*-Pr	**c**	89
4	*t*-Bu	**d**	83
5	Ph	**e**	84
6	*p*-MeC_6H_4	**f**	86
7	*p*-$MeOC_6H_4$	**g**	92
8[a]	*p*-$NO_2C_6H_4$	**h**	23
9[a]	*p*-$NO_2C_6H_4$	**h**	56
10[b]	*p*-ClC_6H_4	**i**	52
11	*p*-ClC_6H_4	**i**	60
12	3-Pyridyl	**j**	63
13	4-Pyridyl	**k**	45

[a] 50 equivalents of THF were used. [b] Carried out at 100 °C.

participate in the generation of nitrile oxide **1**. On the other hand, a large excess (50 equiv. THF) afforded **3a** and **4** (run 6) in yields similar to those for the reaction carried out under the conditions of run 1. This indicates that the dilution of a reaction mixture with THF is possible, if necessary.

The present cycloaddition was carried out by using nitriles **5b–k** under the reaction conditions optimized for acetonitrile (**5a**). The common aliphatic nitriles **5b–d** reacted smoothly with nitrile oxide **1** generated from isoxazolone **2** to afford the corresponding oxadiazoles **3b–d**[10] in good yields (Table 3, runs 2–4). Electron-rich benzonitriles **5e–g** were also usable as substrates leading to the formation of oxadiazoles **3e–g** in high yields (runs 5–7). In this regard, the current reaction is a complementary method to conventional cycloadditions using combinations of electron-rich nitrile oxides and electron-deficient nitriles.

p-Nitrobenzonitrile (**5h**), which is a solid at the reaction temperature, showed less reactivity; this can be attributed to the heterogeneity of the reaction mixture as well as the electron-deficiency of the nitrile (run 8). The disadvantageous insolubility was overcome by using 50 equivalents of THF to homogenize the reaction mixture, which resulted in an increase in the yield of **3h**[10] to 56% (run 9). The same problem was also observed for the reaction involving *p*-chlorobenzonitrile (**5i**). The problem was similarly solved by conducting the reaction homogeneously using a large amount of THF (run 10) or heating at a temperature (100 °C) higher than the melting point of **5i** (90–93 °C) (run 11). The cycloaddition was also applicable to electron-deficient cyanopyridines **5j** and **5k** affording pyridyloxadiazoles **3j** and **3k**, respectively, in moderate yields (runs 12 and 13).

The carbamoyl group of the nitrile oxide plays an important role not only as an electron-withdrawing group but also as an accelerator in the cycloaddition by forming a hydrogen bond with a dipolarophilic nitrile. Indeed, it is known that the cycloaddition of benzonitrile oxide is significantly accelerated when a nitrile has an amino[4,15] or a hydroxy[16] group near the reaction site, which can form a hydrogen bond with the nitrile oxide (Fig. 2A and

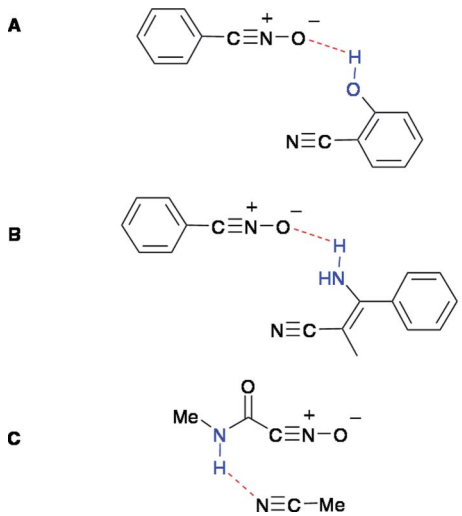


Fig. 2 Hydrogen bond attracting a nitrile oxide and a nitrile.

2B). Referring to these experimental results, we reasoned that the carbamoyl group exerts a template-effect as well as activates the nitrile through hydrogen bonding as shown in Fig. 2C.

In order to probe the effect of the hydrogen bond, DFT calculations were performed for transition states **6** and **7**, in which only the orientation of the carbamoyl group is different (Fig. 3). The interatomic distance between the two nitrogen atoms of N–H···N in transition state **6** was calculated to be 2.94 Å, which indicates the existence of a hydrogen bond. In addition, transition state **6** was found to be more stable than **7** in 4.4 kcal/mol. This result strongly supports the possibility of the activation of the nitrile by the formation of a hydrogen bond with the carbamoyl group of nitrile oxide **1**, which facilitates the inverse electron-demand cycloaddition. The cycloaddition of a nitrile oxide bearing an ester substituent with a nitrile to produce an oxadiazole has not been reported, which might be attributed to the absence of activation by hydrogen bonding.

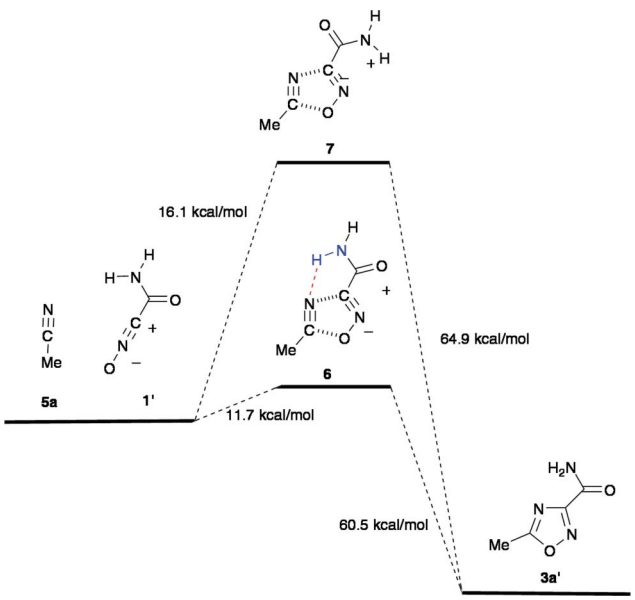


Fig. 3 Activation energies for two kinds of transition states **6** and **7**.

Conclusions

5-Substituted 3-carbamoyl-1,2,4-oxadiazoles **3** were prepared in a single step by the 1,3-dipolar cycloaddition of nitrile oxide **1** with common nitriles **5**; the reaction proceeded under mild conditions even in the absence of a Lewis acid. Furthermore, theoretical studies using DFT calculations well support the inverse electron-demand 1,3-dipolar cycloaddition and also suggest that the carbamoyl group of nitrile oxide **1** activates the dipolarophilic nitrile by hydrogen bonding.

This reaction enables the direct synthesis of 3-functionalized 5-alkyl-1,2,4-oxadiazoles **3**, which are not available by conventional 1,3-dipolar cycloadditions of nitrile oxides with nitriles without using an activator or severe conditions. Among functionalized 1,2,4-oxadiazoles, carbamoyl-substituted ones have attracted much attention because of their biological activity (such as anti-fibrotic-,[17] dermal anti-scarring-,[17] and antibacterial activities[18]), and utility for diabetes,[19] obesity,[19] pesticides,[20] building blocks for pseudopeptides,[21] and nucleobase analogues.[22] Furthermore, the carbamoyl group also serves as a precursor of other functional groups.[23] Thus, the present reaction will be useful for constructing a library for the research of new biologically active compounds.

Experimental

General

The melting points were determined on a Yanaco micro-melting-points apparatus, and were uncorrected. All the reagents and solvents were commercially available and used as received. The ^{1}H NMR spectra were measured on a Bruker DPX-400 at 400 MHz with TMS as an internal standard. The ^{13}C NMR spectra were measured on a Bruker DPX-400 at 100 MHz, and assignments of ^{13}C NMR spectra were performed by DEPT experiments. The IR spectra were recorded on a Horiba FT-200 IR spectrometer. The mass spectra were recorded on a JEOL JMS-AX505HA a mass spectrometer. The high resolution mass spectra were measured on a JEOL JMS-DX303HF. The elemental microanalyses were performed using a Yanaco MT-3 CHN corder.

2-Methyl-4-nitro-3-isoxazolin-5(2*H*)-one (2)[14]. Nitroisoxazolone **2** was easily prepared from commercially available ethyl nitroacetate through three steps with simple experimental manipulations; 1) the condensation of nitroacetate with orthoformate, 2) the condensation with hydroxylamine, and 3) the *N*-methylation with dimethyl sulfate (Details are given in the ESI†).

Cycloaddition of nitrile oxide with dipolarophiles

General procedure. In a screw capped test tube (ϕ = 10 mm, H = 90 mm), a mixture of nitroisoxazolone **2** (144 mg, 1.0 mmol), nitrile (20 mmol), and THF (0.41 mL, 5.0 mmol) was heated at 80 °C for 2 d. After removal of the solvent under reduced pressure, the residue was subjected to column chromatography on silica gel or recrystallization to isolate cycloadduct **3**. The structures of oxadiazoles **3a–d**, **3f** and **3h** were confirmed by comparing the spectral data with those of authentic samples prepared by an alternative method.[10]

3-(*N*-Methylcarbamoyl)-5-phenyl-1,2,4-oxadiazole (3e). Recrystallized from benzene. Colorless needles. Mp 132–133 °C. IR (Nujol) 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.09 (d, J = 5.0 Hz, 3H), 7.0–7.2 (br, 1H), 7.56 (dd, J = 7.5, 7.5 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 8.17 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6 (CH_3), 122.4 (C), 127.5 (CH), 128.4 (CH), 132.6 (CH), 156.2 (C), 163.0 (C), 175.9 (C); MS (EI) 203 (M^+, 100), 202 (75), 192 (90). HRMS Calcd. for $C_{10}H_9N_3O_2$: 203.0695, Found: 203.0689. Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68%. Found: C, 59.12; H, 4.50; N, 20.60%.

5-(4-Methoxyphenyl)-3-(*N*-methylcarbamoyl)-1,2,4-oxadiazole (3g). Recrystallized from benzene. Colorless needles. Mp 148–149 °C. IR (Nujol) 1674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.08 (d, J = 5.0 Hz, 3H), 3.91 (s, 3H), 7.03 (d, J = 8.7 Hz, 2H), 7.0–7.2 (br, 1H), 8.11 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4 (CH_3), 55.6 (CH_3), 114.7 (CH), 115.8 (C), 125.9 (C), 130.3 (CH), 157.3 (C), 163.7 (C), 176.6 (C); MS (EI) 233 (M^+, 100). HRMS Calcd. for $C_{11}H_{11}N_3O_3$: 233.0800, Found: 233.0797. Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02%. Found: C, 56.61; H, 4.85; N, 18.04%.

5-(4-Chlorophenyl)-3-(*N*-methylcarbamoyl)-1,2,4-oxadiazole (3i). Recrystallized from benzene. Colorless needles. Mp 175–177 °C. IR (Nujol) 1674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.09 (d, J = 5.2 Hz, 3H), 7.11 (br s, 1H), 7.55 (d, J = 8.8 Hz, 2H), 8.12 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5 (CH_3), 121.7 (C), 129.6 (CH), 129.7 (CH), 140.1 (C), 156.9 (C), 163.9 (C), 175.9 (C); MS (EI) 237 (M^+, 100), 239 (M^++2, 33). HRMS Calcd. for $C_{10}H_8N_3O_2Cl$: 237.0305, Found: 237.0304. Anal. Calcd for $C_{10}H_8N_3O_2Cl$: C, 50.54; H, 3.39; N, 17.68%. Found: C, 50.91; H, 3.05; N, 17.97%.

3-(*N*-Methylcarbamoyl)-5-(3-pyridyl)-1,2,4-oxadiazole (3j). Recrystallized from $CHCl_3$. Orange needles. Mp 188–190 °C. IR (Nujol) 1674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.11 (d, J = 5.1 Hz, 3H), 7.0–7.2 (br, 1H), 7.54 (dd, J = 7.9, 5.0 Hz, 1H), 8.47 (ddd, J = 7.9, 1.8, 1.6 Hz, 1H), 8.88 (dd, J = 5.0, 1.6 Hz, 1H), 9.42 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5 (CH_3), 119.9 (C), 124.0 (CH), 135.5 (CH), 149.2 (CH), 153.9 (CH), 156.7 (C), 164.0 (C), 174.8 (C); MS (EI) 204 (M^+, 30), 203 (100). HRMS Calcd. for $C_9H_8N_4O_2$: 204.0647, Found: 204.0629. Anal. Calcd for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44%. Found: C, 52.89; H, 3.94; N, 27.31%.

3-(*N*-Methylcarbamoyl)-5-(4-pyridyl)-1,2,4-oxadiazole (3k). Recrystallized from benzene. Orange granules. Mp 195–196 °C. IR (Nujol) 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.11 (d, J = 5.0 Hz, 3H), 7.0–7.2 (br, 1H), 8.03 (d, J = 4.5 Hz, 2H), 8.12 (d, J = 4.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7 (CH_3), 123.5 (CH), 132.3 (C), 153.4 (CH), 158.7 (C), 166.4 (C), 177.1 (C); MS (EI) 204 (M^+, 51), 203 (100). HRMS Calcd. for $C_9H_8N_4O_2$: 204.0647, Found: 204.0633. Anal. Calcd for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44%. Found: C, 52.71; H, 3.95; N, 27.22%.

Acknowledgements

We are grateful to Prof. Satoshi Minakata, Osaka University, Japan for his kind assistance.

Notes and references

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