Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

PAPER

Cascade nitrosation and addition-elimination of nitroacetanilides for highly efficient synthesis of 1,4,2,5-dioxadiazine derivatives†

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A domino nitrosation and addition-elimination of nitroacetanilides with $NaNO_2$ and H_2SO_4 has been developed to synthesize a variety of 1,4,2,5-dioxadiazine-3,6-dicarboxamides in excellent yields. The substrates can be extended to aryl nitromethyl ketones. The cascade reaction mechanism was proposed and the conjugated aryl moiety is considerated to help stablizing the *aci*-nitroso species, the key intermediates in the cascade reaction. The methodology is practical and efficient because it avoids the purification of the intermediates. The nitroacetanilides were prepared from nitroacetic acid and various anilines employing DCC/DMAP as coupling reagents, and this protocol also possesses advantages like easy handling and high yields.

Introduction

Scientists have never stopped persuing maximum efficiency during their research. Cascade reactions, being able to proceed two or more consecutive steps of reactions without purification of the intermediates, have received increasing interest of the chemical community.[1]

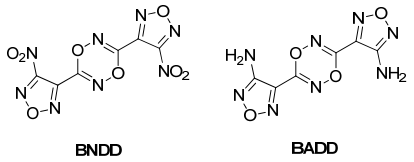
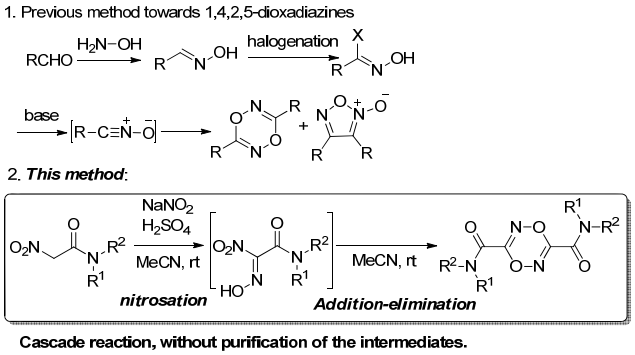


Fig. 1 Explosives BNDD and BADD.

1,4,2,5-Dioxadiazine is the key structure of effective explosives BNDD [3,6-bis(4-nitro-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazene)] and BADD [3,6-bis(4-amino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazene)][2] (Fig. 1), and it can be incorporated into chelating and bridging ligands.[3] Since the first synthesis of 1,4,2,5-dioxadiazenes,[4] almost 120 years passed away. However, little progress has been made to synthetic methods of 1,4,2,5-dioxadiazenes. Most of the reported 1,4,2,5-dioxadiazenes were synthesized still via the traditional approach, dimerization of nitrile oxides.[2-5] The nitrile oxides were obtained from halogenated oximes, which were prepared from the corresponding oximes, generated from aldehydes and hydroxylamine hydrochloride (Scheme 1). Therefore, this method suffers from drawbacks such as tedious steps, poor yields, and poor chemoselectivity in the dimerization step. Therefore, a novel protocol involving high efficiency in both yield and reaction steps is still required.

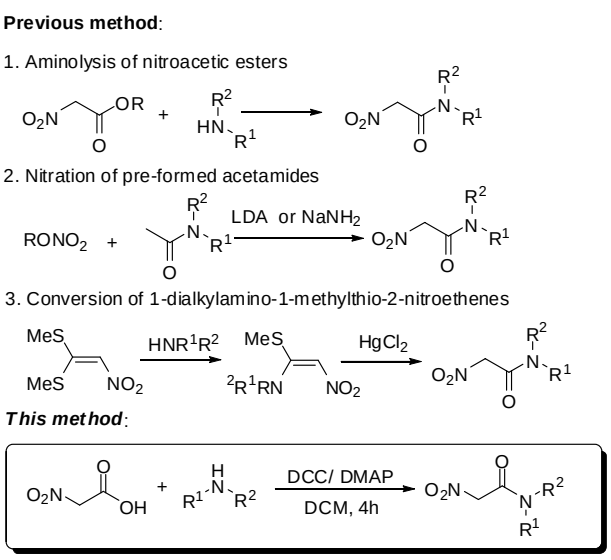
Though with rare report, the elimination of nitrous acid from nitrooximes can generate 1,4,2,5-dioxadiazines.[2, 6] Recently, Harayama and co-workers revealed the nitrosation of cyanoacetanilides and further use of their products *aci*-nitrosocyanoacetanilides to synthesize quinoxalinone-*N*-oxides.[7] We hypothesized that nitrosation of nitroacetamides should be also achievable, and envisioned that two equivalents of generated *aci*-nitrosonitroacetanilides will undergo intermolecular addition-elimination to afford 1,4,2,5-dioxadiazine-3,6-dicarboxamides by loss of two equivalents of nitrous acid.



Scheme 1 Synthesis of 1,4,2,5-dioxadiazenes.

In regard of the synthesis of nitroacetamides, there is no universal method available. The aminolysis of nitroacetic esters is a traditional method to produce the corresponding amides. The method is very limited because harsh reaction conditions are needed and the high acidity of the hydrogen atom on the 2-position carbon in nitroacetic esters would lead to the salt formation with amines.[8] Another approach upon nitration of pre-formed acetamides suffers from unkind requests of moisture sensitive base (LDA[9] or $NaNH_2$[10]), low temperature (-25 °C), and toxic and explosive reagent ($RONO_2$), so its application is also rare. The method of conversion of 1-amino-1-methylthio-2-nitroethenes to 2-nitroacetamides is really special among those

amide bond formation protocols; however, highly functionalized precursor 1,2-bismethylthio-2-nitroethane and poisonous Hg(II) dichloride are indispensable, so this approach is hardly a general one (Scheme 2).[11] Mioskowski and Charette accomplished the esterification of nitroacetic acid with various alcohols in the presence of DCC (*N*,*N*'-dicyclohexylcarbodiimide).[12] Thus, we assumed that the method can be extended to condense nitroacetic acid and amines for the synthesis of nitroacetamides.[13]



Scheme 2 Synthesis of nitroacetamides.

Herein, we first reported an easily accessible protocol to prepare nitroacetanilides, and then the use of the afforded nitroacetanilides to develop a highly efficient method to synthesize 1,4,2,5-dioxadiazine-3,6-dicarboxamides via the cascade nitrosation and intermolecular addition-elimination. Although the explosives BNDD and BADD are important 1,4,2,5-dioxadiazine derivatives, they are not our target molecules due to their explosive property.

Results and discussion

Synthesis of nitroacetanilides via coupling of nitroacetic acid and anilines

We first examined condensation of nitroacetic acid and *N*-phenylbenzylamine (**1a**) using a variety of coupling reagents (Table 1). DCC was first employed in the reaction with a small amount of DMAP (4-dimethylaminopyridine, 0.5 equivalent to DCC) as an additive, affording *N*-benzyl-2-nitro-*N*-phenylacetamide (**2a**) in 43% yield (Table 1, entry 1). Changing the additive to HOBt (1-hydroxybenzotriazole) did not improve the yield (Table 1, entry 2). Though has similar function in coupling with DCC, EDC [*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide] did not show any coupling performance in the reaction, even with HOBt as the additive (Table 1, entries 3 and 4). Uronium/aminium salts HBTU [*O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate] was also applied but no **2a** was generated (Table 1, entry 5). Then the loading molar ratio of the acid and DCC was further optimized (Table 1, entries 6–12). Increasing the loading amount of the acid to 2.0 equivalents and coupling reagent to 1.5 equivalents, almost quantitive the amide was obtained (Table 1, entry 8). However, considering that the byproduct DCU (1,3-dicyclohexylurea) was a little difficult to be entirely removed, we tried to decrease the excessive loading of DCC while maintaining the perfect yield. Decreasing the loading amount of DCC to 1.2 equivalents lead to a dropped yield of 51 % (Table 1, entry 9), and the yield raised to 84% while increasing nitroacetic acid to 2.2 equivalents, but dropped to 54% when nitroacetic acid was increased to 2.5 equivalents (Table 1, entry 11). Thus, we needed to increase the loading amount of DCC. However, the yield was 85% while loaded 1.4 equivalents of DCC (Table 1, entry 11), not as good as that of using 1.5 equivalents. Therefore, 2.0 equivalents of nitroacetic acid and 1.5 equivalents of DCC were the optimal loading amounts for the reaction.

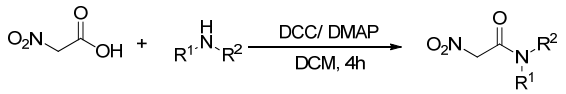
Table 1 Optimization of coupling reagents.[a]

1a **2a**

Entry	Reagents	Amine:Acid:Reagent:Additive (equiv.)	Yield (%)[b]
1	DCC/DMAP	1.0:1.2:1.2:0.06	43
2	DCC/HOBt	1.0:1.2:1.2:1.2	33
3	EDC/DMAP	1.0:1.2:1.2:0.06	0
4	EDC/HOBt	1.0:1.2:1.2:1.2	Trace
5	HBTU/TEA[c]	1.0:1.2:1.2:2.4	0
6	DCC/DMAP	1.0:1.5:1.2:0.06	55
7	DCC/DMAP	1.0:1.5:1.5:0.07	66
8	**DCC/DMAP**	**1.0:2.0:1.5:0.07**	**99**
9	DCC/DMAP	1.0:2.0:1.2:0.06	51
10	DCC/DMAP	1.0:2.2:1.2:0.06	84
11	DCC/DMAP	1.0:2.5:1.2:0.06	54
12	DCC/DMAP	1.0:2.2:1.4:0.07	85

[a] The reactions were performed on 2 mmol scale in 10 mL of dichloromethane. [b] Isolated yield after column chromatography on silica gel. [c] The reaction was conducted in CH_3CN.

Table 2 Scope and limitation of the coupling reaction of nitroacetic acid and amines with DCC/DMAP.



1 **2**

Entry	R^1	R^2	Product	Yield (%) [a,b]
1	Bn	Ph	**2a**	99
2	H	Ph	**2b**	70
3	Me	Ph	**2c**	96
4	*n*-Pr	Ph	**2d**	99
5	*i*-Pr	Ph	**2e**	83
6	4-ClBn	Ph	**2f**	85
7	Ph	Ph	**2g**	70
8	Bn	2-$CH_3C_6H_4$	**2h**	75
9	Bn	3-$CH_3C_6H_4$	**2i**	96
10	Bn	4-$CH_3C_6H_4$	**2j**	90
11	Bn	4-BrC_6H_4	**2k**	79
12	Bn	4-IC_6H_4	**2l**	64
13	Bn	Bn	**2m**	0

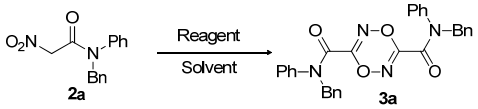
[a] The reactions were performed on 2 mmol scale in 10 mL of solvent. Amine:Acid:DCC (equiv.) = 1.0:2.0:1.5. [b] Isolated yield after column chromatography on silica gel.

With the optimized set of reaction conditions, we next investigated the scope and limitation of the coupling reaction with respect to different amines (Table 2). All alkyl aryl amines worked well in the reaction whether anilines with electron-withdrawing or electron-donating aromatic substituents (Table 2, entries 1–12). Unfortunately, dibenzylamine, a dialkyl amine, failed in the coupling reaction (Table 2, entry 13). As a result, a dozen of 2-nitroacetanilides was synthesized in moderate to perfect yields.

Cascade nitrosation and intermolecular addition-elimination of nitroacetamides

N-Benzyl-nitroacetanilide (**2a**) was selected as model substrate for the cascade nitrosation and intermolecular addition-elimination towards 1,4,2,5-dioxadiazine-3,6-dicarboxamide (**3a**). Surprisingly, the victory was won at the first battle. The target molecule **3a** was obtained in a perfect yield using sodium nitrite as the nitrosation reagent in the presence of H_2SO_4 (Table 3, entry 1). During the reaction, an intermediate *aci*-nitrosonitroacetanilide was observed and able to be isolated. Other solvents, including protic solvent MeOH, protic and acidic solvent AcOH, chlorinated solvent DCM and chloroform, and strong polar aprotic solvent DMF, seemed to be totally ineffective for the reaction (Table 2, entries 1–12).

Table 3 Optimization of solvent and reagent for the cascade reaction[a].

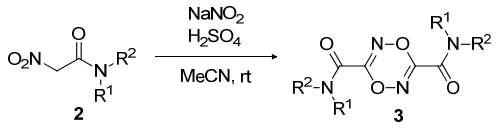


Entry	Reagent	Solvent	Time (h)	Yield (%)[b]
1	**$NaNO_2/H_2SO_4$**	**CH_3CN**	**120**	**99**
2	$NaNO_2/H_2SO_4$	MeOH	>120	No Rxn[c]
3	$NaNO_2/H_2SO_4$	$CHCl_3$	>120	No Rxn[c]
4	$NaNO_2/H_2SO_4$	CH_2Cl_2	>120	No Rxn[c]
5	$NaNO_2/H_2SO_4$	AcOH	>120	No Rxn[c]
6	$NaNO_2/H_2SO_4$	DMF	>120	No Rxn[c]

[a] The reactions were performed on 80 mg scale of **2a** in 4 mL of solvent. [b] Isolated yield after column chromatography on silica gel. [c] No Rxn = No reaction occurred.

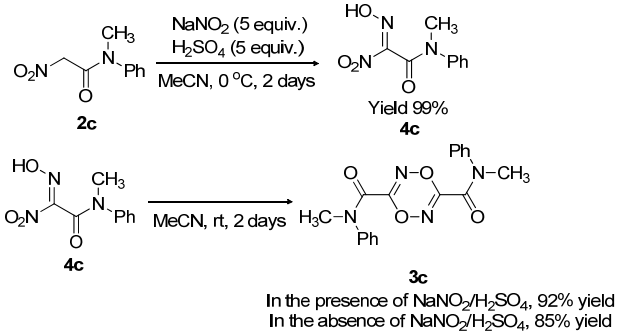
All the nitroacetanilides (**2a**–**2l**) were investigated under the optimized reaction conditions, and all reactions proceeded smoothly, although different reaction times were required for complete consumption the substrates in each of cases (Table 4). Nitroacetanilides **2a,c-f** with different *N*-alkyl groups were successfully converted into 1,4,2,5-dioxadiazine-3,6-dicarboxamides **3a,c-f** in good to excellent yields (72–99%) (Table 4, entries 1, 3–6). However, the reaction of secondary aniline **2b** produced **3b** in only 35% yield (Table 4, entry 2), presumably because the active *N*-H in the amide would result in the formation of its enolate, which reduces electrophilicity of the C=N bond in the oxime, affecting the cyclization. *N*,*N*-Diphenyl-nitroacetamide (**2g**) with two phenyl groups on the nitrogen gave rise to N^3,N^3,N^6,N^6-tetraphenyl-1,4,2,5-dioxadiazine-3,6-dicarboxamide (**3g**) in 83% yield (Table 4, entry 7). *N*-Benzyl-nitroacetanilides **2h-j** with substituted electron-donating methyl group on different positions of the *N*-phenyl group were attempted under the optimized reaction conditions, and all of the reactions gave rise to the corresponding 1,4,2,5-dioxadiazine-3,6-dicarboxamides **3h-j** in good to excellent yields (83%–99%) (Table 4, entries 8–10). Finally, *N*-benzyl-nitroacetanilides **2k-l** with substituted electron-withdrawing halogenated groups on the *para*-position of the *N*-phenyl group furnished the desired 1,4,2,5-dioxadiazine-3,6-dicarboxamides **3k-l** as well (Table 4, entries 11–12).

Table 4 Transformation of nitroacetanilides to 1,4,2,5-dioxadiazines via the cascade reaction.

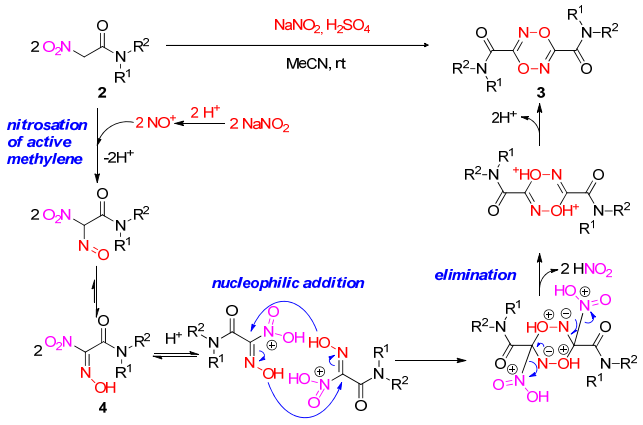


Entry	R^1	R^2	Product	Time (h)	Yield (%)[a,b]
1	Ph	Bn	**3a**	120	99
2	Ph	H	**3b**	48	35
3	Ph	Me	**3c**	120	92
4	Ph	*n*-Pr	**3d**	100	97
5	Ph	*i*-Pr	**3e**	48	72
6	Ph	4-ClBn	**3f**	72	85
7	Ph	Ph	**3g**	24	83
8	2-$CH_3C_6H_4$	Bn	**3h**	120	83
9	3-$CH_3C_6H_4$	Bn	**3i**	61	97
10	4-$CH_3C_6H_4$	Bn	**3j**	120	99
11	4-BrC_6H_4	Bn	**3k**	24	80
12	4-IC_6H_4	Bn	**3l**	72	87

[a] The reactions were performed on 80 mg scale of **2** in 4 mL of solvent. [b] Isolated yield after column chromatography on silica gel.



Scheme 3 Transformation of *aci*-nitrosonitroacetanilide (**4c**) to 1,4,2,5-dioxadiazine-3,6-dicarboxamide (**3c**)

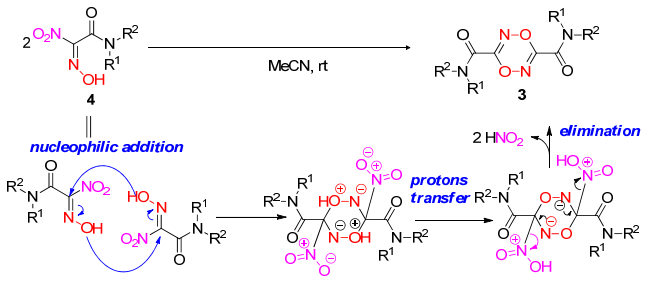


Scheme 4. Plausible mechanism for the cascade reaction.

To gain mechanistic insight into the cascade reaction, we isolated one of the *aci*-nitrosonitroacetanilide intermediates (**4c**) and investigated the reactivity of it. Intermolecular addition-elimination of **4c** proceeded smoothly to give rise to **3c** in 92% yield under the same conditions that generated **4c** (Scheme 3).

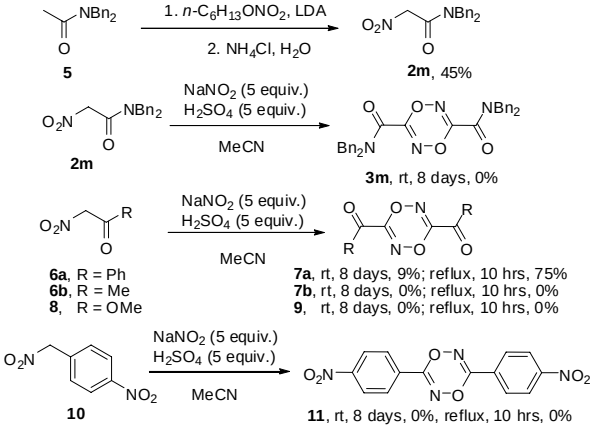
After taking these results into consideration, a plausible mechanism for the cascade reaction is proposed (Scheme 4). Initially, the active methylene of **2** reacts with a nitrosyl cation to generate *aci*-nitroso species **4** after isomerization. Subsequently, the nitro group is protonated under the acidic conditions, and the hydroxy group in *aci*-nitroso species **4** undergoes a nucleophilic addition to the electron-deficient imine group in another molecule of **4**. To be noted, the nucleophilic additions might take place simultaneous or asynchronous. After the elimination of two molecules of nitrous acid and the deprotonation of the oxonium in the six-membered ring, 1,4,2,5-dioxadiazines are generated. The cyclization can occur smoothly at room temperature because the imine group shows strong eletrophilicity due to attachment with two electron-withdrawing groups, nitro and amide groups.

To be surprised, when the intermediate *aci*-nitrosonitroacetanilide **4c** was stirred in MeCN in the absence of $NaNO_2/H_2SO_4$ at room temperature, the desired product **2c** was obtained as well, though in slightly lower yield than that in the presence of $NaNO_2/H_2SO_4$ (Scheme 3). This fact indicates that the cyclization can occur without the participation of the acid. Thus, we presented an alternative plausible mechanism for the transformation of *aci*-nitrosonitroacetanilides to 1,4,2,5-dioxadiazine-3,6-dicarboxamides in the absence of $NaNO_2/H_2SO_4$. Firstly, the hydroxy group in *aci*-nitroso species **4** undergoes a nucleophilic addition to the electron-deficient imine group in another molecule of **4**. Then the protons transfer from the six-membered ring to the nitro groups, and two molecules of nitrous acid are eliminated, furnishing 1,4,2,5-dioxadiazines (Scheme 5). To be noted, this mechanism can be involved in the cascade reaction since the conversion of **4c** to **3c** occurred in similar yields during the same time whether in the presence or absence of an acid. On the other hand, the rate determined step should be irrelevant with the acid-participated steps.



Scheme 5 Plausible mechanism for the transformation of *aci*-nitrosonitroacetanilides to 1,4,2,5-dioxadiazine-3,6-dicarboxamides in the absence of $NaNO_2/H_2SO_4$.

To extend the application and the substrate scope of the developed cascade reaction, we tested other nitromethylene-compounds (Scheme 6). First, *N*,*N*-dibenzyl-nitroactamide (**2m**), an *N*,*N*-dialkyl substituted nitroactamide, was prepared by nitration of *N*,*N*-dibenzylacetamide (**5**)[9] and subjected to optimized reaction conditions. However, no desired product was generated. Nitroacetophenone (**6a**) and nitroacetone (**6b**) were synthesized from nitromethane and the corresponding *N*-acylimidazoles and subjected to the cascade reaction. 2-Nitroacetophone (**6a**) successfully gave rise to the corresponding 3,6-dibenzoyl-1,4,2,5-dioxadiazine (**7a**) in only 9% yield at roomtermperature for 8 days. However, the yield was improved to 75% when the reaction was performed under refluxing conditions for 10 hours. Whereas, nitroacetone (**6b**) failed to produce the expected 3,6-diacetyl-1,4,2,5-dioxadiazine (**7b**). The above experimental results indicates that all substrates with conjugated aryl moieties generated the desired 1,4,2,5-dioxadiazine derivatives. On the contrary, no reaction occurred for all the substrates without conjugated aryl moieties. In addition, it is noteworthy that for the reactions succeeded to produce 1,4,2,5-dioxadiazine derivatives, *aci*-nitroso species were observed on the TLC monitoring. Therefore, we proposed that the conjugated aryl moiety may have a great impact to stablize the *aci*-nitroso species, the intermediates for the reaction, making the reaction to proceed successfully. Furthermore, methyl nitroacetate (8) and 1-nitro-4-(nitromethyl)benzene (**10**) were attempted as well, but failed to produce the desired products, possibly the methylene in **10** is not active enough to proceed the nitrosation step, which is a necessary step for the reaction.



Scheme 6. Extension of the substrate scope

Conclusion

In summary, we first developed an effective and practical method to synthesize nitroacetanilides by coupling nitroacetic acid and anilines with DCC/DMAP as coupling reagents. Then we used nitroacetanilides to exploit a cascade nitrosation and intermolecular addition-elimination for accessing 1,4,2,5-dioxadiazine-3,6-dicarboxamides with $NaNO_2/H_2SO_4$. The latter reaction is broad in scope with respect to nitroacetanilides, with up to 99% yields. The substrates can be extended to aryl nitromethyl ketones. The cascade reaction mechanism was proposed and the conjugated aryl moiety is considerated to help stablizing the *aci*-nitroso species, the key intermediates in the cascade reaction.

Experimental section

General information

Melting points (m.p.) were determined on a Yanaco MP-500 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR

spectra were recorded on a Brucker 400 NMR spectrometer at 400 MHz and 100 MHz, respectively, in $CDCl_3$ with TMS as the internal standard and chemical shifts were reported in ppm. IR spectra were taken on a Nicolet AVATAR 330 FT-IR spectrometer in dichloromethane (DCM). HRMS spectra were performed on a Brucker LC/MSD TOF mass spectrometer. Reagents used were obtained from commercial suppliers and used without purification. Column chromatography was carried out with silica gel (200–300 mesh) with petroleum ether (PE, 60 °C–90 °C) and ethyl acetate (EA) as the eluent. All reactions were followed by thin-layer chromatography (TLC) where practical, using silica gel 60 F_{254} fluorescent treated silica gel plates, which were visualised under UV light (250 nm).

General procedure for the preparation of nitroacetanilides 2 using DCC/DMAP as coupling reagents

To a suspension of nitroacetic acid (315 mg, 3 mmol) in CH_2Cl_2 (5 mL) was added a solution of an amine **1** (2 mmol), DCC (825 mg, 3 mmol) and DMAP (25 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The resulting solution was stirred for 4 h. During this period a white solid DCU was precipitated and subsequently filtrated. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel column chromatography to give the pure product **2**.

***N*-Benzyl-2-nitro-*N*-phenylacetamide (2a)**. 267 mg, 99 % yield. Colorless crystals, m.p. 117–118 °C. R_f = 0.39 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 – 7.37 (m, 3H, ArH), 7.28 – 7.26 (m, 3H, ArH), 7.21 – 7.18 (m, 2H, ArH), 7.03 – 7.00 (m, 2H, ArH), 4.96 (s, 2H, CH_2NO_2), 4.93 (s, 2H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.7 (C=O), 139.6 (C), 135.8 (C), 130.2 (CH), 129.4 (CH), 129.0 (CH), 128.6 (CH), 128.2 (CH), 127.9 (CH), 77.1 (CH_2NO_2), 53.6 (NCH_2). IR (DCM) ν (cm^{-1}): 1681 (C=O), 1562 (NO_2), 1375 (NO_2). HRMS (ESI) calcd. for $C_{15}H_{15}N_2O_3$ $[M+H]^+$ *m/z* 271.1077, found 271.1081.

2-Nitro-*N*-phenylacetamide (2b). 115 mg, 64 % yield. Colorless crystals, m.p. 149–151 °C, lit[14]. m.p. 136–138 °C. R_f = 0.15 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v).^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.57(s, 1H, NH), 7.57 (d, J = 7.7 Hz, 1H, ArH), 7.35 (t, J = 7.7 Hz, 1H, ArH), 7.12 (t, J = 7.7 Hz, 1H, ArH), 5.54 (s, 2H, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.8 (C=O), 129.0 (CH), 137.9 (C), 124.3 (CH), 119.4 (CH), 79.3 (CH_2NO_2).

***N*-Methyl-2-nitro-*N*-phenylacetamide (2c)**. 186 mg, 96 % yield. Colorless crystals, m.p. 63–65 °C. R_f = 0.43 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 – 7.42 (m, 3H, ArH), 7.26 (d, J = 7.6 Hz, 2H, ArH), 4.99 (s, 2H, CH_2), 3.36 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.7 (C=O), 141.4 (C), 130.5 (CH), 129.2 (CH), 127.0 (CH), 76.9 (CH_2), 37.8 (CH_3). IR (DCM) ν (cm^{-1}): 1661 (C=O), 1595 (NO_2), 1356 (NO_2). HRMS (ESI) calcd. for $C_9H_{10}N_2NaO_3$ $[M+Na]^+$ *m/z* 217.0584, found 217.0588.

2-Nitro-*N*-phenyl-*N*-propylacetamide (2d). 115 mg, 52 % yield. Colorless crystals, m.p. 64–65 °C. R_f = 0.39 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 – 7.42 (m, 3H, ArH), 7.23 (d, J = 6.9 Hz, 2H, ArH), 4.94 (s, 2H, CH_2NO_2), 3.73 (t, J = 7.6 Hz, 2H, NCH_2), 1.58 (sixtet, J = 7.6 Hz, 2H, CH_2CH_3), 0.93 (d, J = 7.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.4 (C=O), 140.0 (C), 130.4 (CH), 129.3 (CH), 128.0 (CH), 77.2 (CH_2NO_2), 51.5 (NCH_2), 20.6 (NCH_2CH_2), 11.1 (CH_3). IR (DCM) ν (cm^{-1}): 1681 (C=O), 1557 (NO_2), 1373 (NO_2). HRMS (ESI) calcd. for $C_{11}H_{15}N_2O_3$ $[M+H]^+$ *m/z* 223.1077, found 223.1081.

***N*-Isopropyl-2-nitro-*N*-phenylacetamide (2e)**. 185 mg, 83 % yield. Colorless crystals, m.p. 90–91 °C. R_f = 0.31 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 – 7.47 (m, 3H, ArH), 7.20 – 7.18 (m, 2H, ArH), 4.98 (hept, J = 6.8 Hz, 1H, CH), 4.83 (s, 2H, CH_2), 1.12 (d, J = 6.8 Hz, 6H, CH_3×2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.2 (C=O), 136.1 (C), 130.0 (CH), 129.9 (CH), 129.6 (CH), 77.7 (CH_2NO_2), 47.6 (CH), 20.6 (CH_3). IR (DCM) ν (cm^{-1}): 1673 (C=O), 1560 (NO_2), 1379 (NO_2). HRMS (ESI) calcd. for $C_{11}H_{15}N_2O_3$ $[M+H]^+$ *m/z* 223.1077, found 223.1084.

***N*-(4-Chlorobenzyl)-2-nitro-*N*-phenylacetamide (2f)**. 258 mg, 85 % yield. Colorless crystals, m.p. 95–96 °C. R_f = 0.42 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 – 7.39 (m, 3H, ArH), 7.26 (d, J = 8.0 Hz, 2H, ArH), 7.14 (d, J = 8.0 Hz, 2H, ArH), 7.04 – 7.00 (m, 2H, ArH), 4.96 (s, 2H, CH_2NO_2), 4.89 (s, 2H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.8 (C=O), 139.4 (C), 134.3 (C), 133.9 (C), 130.4 (CH), 130.4 (CH), 129.5 (CH), 128.8 (CH), 128.1 (CH), 77.0 (CH_2NO_2), 53.0 (NCH_2). IR (DCM) ν (cm^{-1}): 1681 (C=O), 1557 (NO_2), 1373 (NO_2). HRMS (ESI) calcd. for $C_{15}H_{14}ClN_2O_3$ $[M+H]^+$ *m/z* 305.0687, found 305.0690.

2-Nitro-*N*,*N*-diphenylacetamide (2g). 107 mg, 42 % yield. Colorless crystals, m.p. 155–156 °C. R_f = 0.39 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 – 7.23 (m, 10H, ArH), 5.14 (s, 2H, CH_2NO_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.6 (C=O), 141.1 (C), 140.4 (C), 130.5 (CH), 129.3 (CH), 129.1 (CH), 128.4 (CH), 127.0 (CH), 125.7 (CH), 77.7 (CH_2NO_2). IR (DCM) ν (cm^{-1}): 1682 (C=O), 1559 (NO_2), 1364 (NO_2). HRMS (ESI) calcd. for $C_{14}H_{13}N_2O_3$ $[M+H]^+$ *m/z* 257.0921, found 257.0924.

***N*-Benzyl-2-nitro-*N*-(*o*-tolyl)acetamide (2h)**. 213 mg, 75 % yield. Colorless crystals, m.p. 71–74 °C. R_f = 0.52 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 – 7.25 (m, 4H, ArH), 7.20 – 7.12 (m, 3H, ArH), 6.78 (d, J = 7.8 Hz, 1H, ArH), 5.27 (d, J = 13.9 Hz, 1H, 1H in CH_2NO_2), 4.89 (d, J = 13.7 Hz, 1H in NCH_2), 4.75 (d, J = 13.7 Hz, 1H in NCH_2), 4.41 (d, J = 13.9 Hz, 1H, 1H in CH_2NO_2), 2.12 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.0 (C=O), 137.9 (C), 135.9 (C), 135.6 (C), 132.0 (CH), 129.7 (CH), 129.5 (CH), 129.2 (CH), 128.5 (CH), 128.0 (CH), 127.6 (CH), 77.1 (CH_2NO_2), 52.7 (NCH_2), 17.2 (CH_3). IR (DCM) ν (cm^{-1}): 1680 (C=O), 1562 (NO_2), 1375 (NO_2). HRMS (ESI) calcd. for $C_{16}H_{17}N_2O_3$ $[M+H]^+$ *m/z* 285.1234, found 285.1238.

***N*-Benzyl-2-nitro-*N*-(*m*-tolyl)acetamide (2i)**. 273 mg, 96 % yield. Colorless crystals, m.p. 90–91 °C. R_f = 0.46 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 – 7.27 (m, 3H, ArH), 7.25 (d, J = 7.1 Hz, 1H, ArH), 7.22 – 7.17 (m, 3H, ArH), 6.84 (s, 1H, ArH), 6.77 (d, J = 7.6 Hz, 2H, ArH), 4.97 (s, 2H, CH_2NO_2), 4.91 (s, 2H, NCH_2), 2.32 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.7 (C=O), 140.6 (C), 139.6 (C), 135.9 (C), 130.1 (CH), 129.9 (CH), 129.0 (CH), 128.5 (CH), 128.5 (CH), 127.9 (CH), 125.1 (CH), 77.1 (CH_2NO_2), 53.6 (NCH_2), 21.2 (CH_3). IR (DCM) ν (cm^{-1}): 1681 (C=O), 1562 (NO_2), 1374 (NO_2). HRMS (ESI) calcd. for

$C_{16}H_{17}N_2O_3$ $[M+H]^+$ *m/z* 285.1234, found 285.1237.

***N*-Benzyl-2-nitro-*N*-(*p*-tolyl)acetamide (2j)**. 256 mg, 90 % yield. Colorless crystals, m.p. 96–97 °C. R_f= 0.46 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 – 7.26 (m, 3H, ArH), 7.21 – 7.18 (m, 2H, ArH), 7.16 (d, *J* = 8.0 Hz, 1H, ArH), 6.88 (d, *J* = 8.0 Hz, 2H, ArH), 4.96 (s, 2H, CH_2NO_2), 4.90 (s, 2H, NCH_2), 2.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.9 (C=O), 139.5 (C), 136.9 (C), 135.9 (C), 130.8 (CH), 129.0 (CH), 128.5 (CH), 127.9 (CH), 77.1 (CH_2NO_2), 53.6 (NCH_2), 23.7 (CH_3). IR (DCM) *v* (cm^{-1}): 1675 (C=O), 1559 (NO_2), 1374 (NO_2). HRMS (ESI) calcd. for $C_{16}H_{17}N_2O_3$ $[M+H]^+$ *m/z* 285.1234, found 285.1237.

***N*-Benzyl-*N*-(4-bromophenyl)-2-nitroacetamide (2k)**. 274 mg, 79 % yield. Colorless crystals, m.p. 114–115 °C. R_f= 0.46 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (d, *J* = 8.6 Hz, 2H, ArH), 7.31 – 7.27 (m, 3H, ArH), 7.20 – 7.16 (m, 2H, ArH), 6.89 (d, *J* = 8.6 Hz, 2H, ArH), 4.96 (s, 2H, CH_2NO_2), 4.90 (s, 2H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.5 (C=O), 138.5 (C), 135.4 (C), 133.5 (CH), 129.9 (CH), 129.0 (CH), 128.7 (CH), 128.1 (CH), 123.6 (C), 76.9 (CH_2NO_2), 53.6 (NCH_2). IR (DCM) *v* (cm^{-1}): 1681 (C=O), 1557 (NO_2), 1372 (NO_2). HRMS (ESI) calcd. for $C_{15}H_{14}BrN_2O_3$ $[M+H]^+$ *m/z* 349.0182, found 349.0186.

***N*-Benzyl-*N*-(4-iodophenyl)-2-nitroacetamide (2l)**. 253 mg, 64 % yield. Colorless crystals, m.p. 124–125 °C. R_f= 0.43 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 8.5 Hz, 2H, ArH), 7.30 – 7.27 (m, 3H, ArH), 7.19 – 7.17 (m, 2H, ArH), 6.75 (d, *J* = 8.5 Hz, 2H, ArH), 4.96 (s, 2H, CH_2NO_2), 4.90 (s, 2H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.4 (C=O), 139.5 (CH), 139.2 (C), 135.5 (C), 130.1 (CH), 129.0 (CH), 128.7 (CH), 128.1 (CH), 95.2 (C), 76.9 (CH_2NO_2), 53.6 (NCH_2). IR (DCM) *v* (cm^{-1}): 1681 (C=O), 1557 (NO_2), 1374 (NO_2). HRMS (ESI) calcd. for $C_{15}H_{14}IN_2O_3$ $[M+H]^+$ *m/z* 397.0044, found 397.0049.

Preparation of 2-(hydroxyimino)-*N*-methyl-2-nitro-*N*-phenylacetamide (4c)

To a mixture of *N*-methyl-2-nitro-*N*-phenylacetamide (**2c)** (80 mg, 0.412 mmol) and sodium nitrite (142 mg, 2.06 mmol) in MeCN (4.0 mL) was added sulfuric acid (206 mg, 2.06 mmol) at 0 °C. The mixture was stirred for 2 days (the reaction was monitored by TLC until consumption of **2c**), and water (5 mL) was added, following by addition dichloromethane (5 mL). The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography to afford the pure product **4c**.

2-(Hydroxyimino)-*N*-methyl-2-nitro-*N*-phenylacetamide (4c). 91 mg, 99 % yield. Colorless crystals, m.p. 94–95 °C. R_f= 0.35 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.96 (s, 1H, OH), 7.49 – 7.38 (m, 3H, ArH), 7.29 – 7.27 (m, 2H, ArH), 3.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 156.1 (C=O), 154.3 (C=N), 140.0 (C), 129.6 (CH), 129.1 (CH), 126.0 (CH), 35.9 (CH_3). IR (DCM) *v* (cm^{-1}): 1633 (C=O), 1590 (C=N), 1549 (NO_2), 1338 (NO_2). HRMS (ESI) calcd. for $C_9H_{10}N_3O_4$ $[M+H]^+$ *m/z* 224.0666, found 224.0671.

General procedure for the cascade nitrosation and addition-elimination of nitroacetanilides

To a mixture of nitroacetamide **2** (80 mg) and sodium nitrite (5 equiv. of **2**) in MeCN (4.0 mL) was added sulfuric acid (5 equiv. of **2**) at 0 °C. The mixture was stirred at rt for 24–120 h, then water (5 mL) was added, following by addition dichloromethane (5 mL). The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography to afford the pure product **3**.

***N*^{3},*N*^{6}-Dibenzyl-*N*^{3},*N*^{6}-diphenyl-1,4,2,5-dioxadiazine-3,6-dicarboxamide (3a)**. 73.5 mg, 99 % yield. Colorless crystals, m.p. 154–156 °C. R_f = 0.54 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 – 7.29 (m, 10H, ArH), 7.24 – 7.19 (m, 8H, ArH), 7.06 – 7.03 (m, 2H, ArH), 5.09 (s, 2H, NCH_2), 5.07 (s, 2H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.3 (C=O), 155.6 (C=O), 151.3 (C=N), 140.4 (C), 139.3 (C), 135.5 (C), 135.5 (C), 129.4 (CH), 129.2 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.9 (CH), 127.8 (CH), 127.1 (CH), 111.4 (C=N), 53.9 (NCH_2), 53.6 (NCH_2). IR (DCM) *v* (cm^{-1}): 1659 (C=O), 1619 (O-C=N). HRMS (ESI) calcd. for $C_{30}H_{25}N_4O_4$ $[M+H]^+$ *m/z* 505.1870, found 505.1868.

***N*^{3},*N*^{6}-Diphenyl-1,4,2,5-dioxadiazine-3,6-dicarboxamide (3b)**. 25 mg, 35 % yield. Colorless crystals, m.p. 185–186 °C. R_f= 0.41 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.30 (s, 1H, NH), 11.06 (s, 1H, NH), 7.75 (d, *J* = 7.8 Hz, 2H, ArH), 7.61 (d, *J* = 7.7 Hz, 2H, ArH), 7.42 – 7.37 (m, 4H, ArH), 7.21 – 7.16 (m, 2H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.5 (C=O), 151.6 (C=O), 151.3 (C=N), 137.4 (C), 137.3 (C), 129.1 (CH), 128.9 (CH), 125.1 (CH), 125.0 (CH), 120.7 (CH), 119.8 (CH), 110.4 (C=N). IR (DCM) *v* (cm^{-1}): 1666 (C=O), 1633 (O-C=N). HRMS (ESI) calcd. for $C_{16}H_{13}N_4O_4$ $[M+H]^+$ *m/z* 325.0931, found 325.0943.

***N*^{3},*N*^{6}-Dimethyl-*N*^{3},*N*^{6}-diphenyl-1,4,2,5-dioxadiazine-3,6-dicarboxamide (3c)**. 67 mg, 92 % yield. Colorless crystals, m.p. 129–130 °C. R_f= 0.43 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 – 7.26 (m, 10H, ArH), 3.50 (s, 3H, CH_3), 3.46 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.2 (C=O), 155.3 (C=O), 151.4 (C=N), 142.1 (C), 140.8 (C), 129.6 (CH), 129.3 (CH), 128.4 (CH), 128.3 (CH), 126.9 (CH), 126.1 (CH), 111.2 (C=N), 37.8 (CH_3), 37.5 (CH_3). IR (DCM) *v* (cm^{-1}): 1666 (C=O), 1617 (O-C=N). HRMS (ESI) calcd. for $C_{18}H_{17}N_4O_4$ $[M+H]^+$ *m/z* 353.1244, found 353.1245.

***N*^{3},*N*^{6}-Diphenyl-*N*^{3},*N*^{6}-dipropyl-1,4,2,5-dioxadiazine-3,6-dicarboxamide (3d)**. 71.3 mg, 97 % yield. Colorless oil. R_f = 0.64 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 – 7.26 (m, 10H, ArH), 3.89 – 3.81 (m, 4H, NCH_2×2), 1.73 – 1.61 (m, 4H, CH_2CH_3×2), 0.99 (t, *J* = 7.5 Hz, 3H, CH_3), 0.97 (t, *J* = 7.5 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.1 (C=O), 155.2 (C=O), 151.7 (C=N), 140.7 (C), 139.3 (C), 129.5 (CH), 129.2 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.2 (CH), 111.5 (C=N), 51.7 (NCH_2), 51.6 (NCH_2), 20.6 (CH_2CH_3), 20.5 (CH_2CH_3), 11.1 (CH_3), 11.1 (CH_3). IR (DCM) *v* (cm^{-1}): 1660 (C=O), 1615 (O-C=N). HRMS (ESI) calcd. for $C_{22}H_{25}N_4O_4$ $[M+H]^+$ *m/z* 409.1870, found 409.1867.

***N*^{3},*N*^{6}-Diisopropyl-*N*^{3},*N*^{6}-diphenyl-1,4,2,5-dioxadiazine-3,6-dicarboxamide (3e)**. 53 mg, 72 % yield. Colorless crystals, m.p. 169–170 °C. R_f= 0.46 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 – 7.39 (m, 2H, ArH), 7.34 – 7.32 (m, 6H, ArH), 7.23 – 7.21 (m, 2H, ArH), 5.02

(hept, 1H, CH), 4.90 (hept, 1H, CH), 1.22 (d, J = 6.8 Hz, 6H, CH_3×2), 1.21 (d, J = 6.8 Hz, 6H, CH_3×2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.8 (C=O), 155.2 (C=O), 151.5 (C=N), 136.7 (C), 135.6 (C), 130.2 (CH), 129.7 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.6 (CH), 111.8 (C=N), 48.8 (CH), 48.3 (CH), 20.5 (CH_3), 20.5 (CH_3). IR (DCM) ν (cm^{-1}): 1659 (C=O), 1618 (O-C=N). HRMS (ESI) calcd. for $C_{22}H_{25}N_4O_4$ $[M+H]^+$ *m/z* 409.1870, found 409.1877.

N^3,N^6-Bis(4-chlorobenzyl)-N^3,N^6-diphenyl-1,4,2,5-dioxadiazine-3,6-dicarboxamide (3f). 64 mg, 85 % yield. Colorless crystals, m.p. 181–183 °C. R_f = 0.60 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 – 7.17 (m, 16H, ArH), 7.06 – 7.03 (m, 2H, ArH), 5.04 (s, 2H, NCH_2), 5.02 (s, 2H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.3 (C=O), 155.7 (C=O), 151.2 (C=N), 140.2 (C), 139.0 (C), 134.0 (CH), 133.9 (C), 133.8 (C), 130.1 (CH), 129.7 (CH), 129.6 (CH), 129.3 (CH), 128.9 (CH), 128.8 (CH), 128.8 (C), 128.7 (C), 127.9 (CH), 127.0 (CH), 111.2 (C=N), 53.3 (NCH_2), 53.0 (NCH_2). IR (DCM) ν (cm^{-1}): 1660 (C=O), 1621 (O-C=N). HRMS (ESI) calcd. for $C_{30}H_{22}Cl_2N_4NaO_4$ $[M+Na]^+$ *m/z* 595.0910, found 595.0920.

N^3,N^3,N^6,N^6-Tetraphenyl-1,4,2,5-dioxadiazine-3,6-dicarboxamide (3g). 62 mg, 83 % yield. Colorless crystals, m.p. 187–188 °C. R_f = 0.54 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 – 7.27 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.3 (C=O), 155.3 (C=O), 152.1 (C=N), 141.1 (C), 140.0 (C), 129.6 (CH), 129.3 (CH), 128.5 (CH), 128.1 (CH), 127.6 (CH), 126.1 (CH), 111.6 (C=N). IR (DCM) ν (cm^{-1}): 1667 (C=O), 1615 (O-C=N). HRMS (ESI) calcd. for $C_{28}H_{21}N_4O_4$ $[M+H]^+$ *m/z* 477.1557, found 477.1567.

N^3,N^6-Dibenzyl-N^3,N^6-di(*o*-tolyl)-1,4,2,5-dioxadiazine-3,6-dicarboxamide (3h). 62 mg, 83 % yield. Colorless crystals, m.p. 229–231 °C. R_f = 0.66 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 – 7.29 (m, 10H, ArH), 7.24 – 7.05 (m, 5H, ArH), 7.03 – 6.85 (m, 2H, ArH), 6.73 – 6.54 (m, 1H, ArH), 5.87 – 5.19 (m, 2H, NCH_2), 4.62 – 4.17 (m, 2H, NCH_2), 2.54 – 2.08 (m, 6H, CH_3×2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.8 (C=O), 156.1 (C=O), 150.6 (C=N), 136.1 (C), 135.9 (C), 135.4 (C), 135.2 (C), 131.4 (C), 131.3 (C), 131.2 (C), 131.2 (C), 130.4 (CH), 129.9 (CH), 129.8 (CH), 129.7 (CH), 129.6 (CH), 129.5 (CH), 129.4 (CH), 129.3 (CH), 129.0 (CH), 129.0 (CH), 128.9 (CH), 128.9 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 128.0 (CH), 127.9 (CH), 126.7 (CH), 126.5 (CH), 126.3 (CH), 126.2 (CH), 123.9 (CH), 105.0 (C=N), 53.5 (NCH_2), 52.8 (NCH_2), 52.5 (NCH_2), 52.3 (NCH_2), 18.0 (CH_3) 17.8 (CH_3), 17.7 (CH_3), 17.6 (CH_3). IR (DCM) ν (cm^{-1}): 1650 (C=O), 1618 (O-C=N). HRMS (ESI) calcd. for $C_{32}H_{28}N_4NaO_4$ $[M+Na]^+$ *m/z* 555.2003, found 555.2008.

N^3,N^6-Dibenzyl-N^3,N^6-di(*m*-tolyl)-1,4,2,5-dioxadiazine-3,6-dicarboxamide (3i). 73 mg, 97 % yield. Colorless crystals, m.p. 132–134 °C. R_f = 0.60 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 – 7.27 (m, 8H, ArH), 7.12 – 6.97 (m, 6H, ArH), 6.89 – 6.80 (m, 2H, ArH), 5.07 (s, 2H, NCH_2), 5.06 (s, 2H, NCH_2), 2.23 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.2 (C=O), 155.6 (C=O), 151.3 (C=N), 140.4 (C), 139.5 (C), 139.4 (C), 139.2 (C), 135.7 (C), 135.6 (C), 129.4 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 125.0 (CH), 124.1 (CH), 111.5 (C=N), 53.9 (NCH_2), 53.6 (NCH_2), 21.2 (CH_3), 21.1 (CH_3). IR (DCM) ν (cm^{-1}): 1658 (C=O), 1617 (O-C=N). HRMS (ESI) calcd. for $C_{32}H_{29}N_4O_4$ $[M+H]^+$ *m/z* 533.2183, found 533.2194.

N^3,N^6-Dibenzyl-N^3,N^6-di(*p*-tolyl)-1,4,2,5-dioxadiazine-3,6-dicarboxamide (3j). 73.5 mg, 99 % yield. Colorless crystals, m.p. 124–126 °C. R_f = 0.60 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 – 7.27 (m, 10H, ArH), 7.06 (d, J = 8.1 Hz, 2H, ArH), 7.00 (d, J = 8.1 Hz, 2H, ArH), 6.96 (d, J = 8.1 Hz, 2H, ArH), 6.91 (d, J = 8.1 Hz, 2H, ArH), 5.05 (s, 2H, NCH_2), 5.03 (s, 2H, NCH_2), 2.27 (s, 3H, CH_3), 2.25 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.3 (C=O), 155.6 (C=O), 151.4 (C=N), 138.6 (C), 138.4 (C), 137.9 (C), 136.7 (C), 135.7 (C), 135.6 (C), 130.0 (CH), 129.7 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.7 (CH), 126.9 (CH), 111.5 (C=N), 53.9 (NCH_2), 53.6 (NCH_2), 21.0 (CH_3). IR (DCM) ν (cm^{-1}): 1658 (C=O), 1618 (O-C=N). HRMS (ESI) calcd. for $C_{32}H_{29}N_4O_4$ $[M+H]^+$ *m/z* 533.2183, found 533.2191.

N^3,N^6-Dibenzyl-N^3,N^6-bis(4-bromophenyl)-1,4,2,5-dioxadiazine-3,6-dicarboxamide (3k). 61 mg, 80 % yield. Colorless crystals, m.p. 143–145 °C. R_f = 0.60 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 – 7.24 (m, 14H, ArH), 7.07 (d, J = 8.3 Hz, 2H, ArH), 6.94 (d, J = 8.3 Hz, 2H, ArH), 5.05 (s, 2H, NCH_2), 5.02 (s, 2H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.1 (C=O), 155.4 (C=O), 151.1 (C=N), 139.3 (C), 138.1 (C), 135.1 (C), 135.1 (C), 132.7 (CH), 132.4 (CH), 129.7 (CH), 128.9 (CH), 128.8 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 122.8 (CH), 122.7 (CH), 111.1 (C=N), 53.8 (NCH_2), 53.5 (NCH_2). IR (DCM) ν (cm^{-1}): 1660 (C=O), 1620 (O-C=N). HRMS (ESI) calcd. for $C_{30}H_{23}Br_2N_4O_4$ $[M+H]^+$ *m/z* 661.0081, found 661.0086.

N^3,N^6-Dibenzyl-N^3,N^6-bis(4-iodophenyl)-1,4,2,5-dioxadiazine-3,6-dicarboxamide (3l). 66 mg, 87 % yield. Colorless crystals, m.p. 169–171 °C. R_f = 0.57 (silica gel plate, ethyl acetate–petroleum ether 1/3, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, J = 8.3 Hz, 2H, ArH), 7.50 (d, J = 8.3 Hz, 2H, ArH), 7.37 – 7.24 (m, 10H, ArH), 6.92 (d, J = 8.3 Hz, 2H, ArH), 6.79 (d, J = 8.3 Hz, 2H, ArH), 5.04 (s, 2H, NCH_2), 5.02 (s, 2H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.0 (C=O), 155.3 (C=O), 151.1 (C=N), 140.1 (C), 138.9 (C), 138.7 (CH), 138.4 (CH), 135.1 (C), 135.1 (C), 129.8 (CH), 129.0 (CH), 128.8 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 111.1 (C=N), 94.4 (C), 94.2 (C), 53.8 (NCH_2), 53.5 (NCH_2). IR (DCM) ν (cm^{-1}): 1655 (C=O), 1618 (O-C=N). HRMS (ESI) calcd. for $C_{30}H_{23}I_2N_4O_4$ $[M+H]^+$ *m/z* 756.9803, found 756.9812.

3,6-Dibenzoyl-1,4,2,5-dioxadiazine (7a) 220 mg (1 mmol scale), 75 % yield. Colorless, crystals, m.p. 87–88 °C. R_f = 0.57 (silica gel plate, ethyl acetate–petroleum ether 1/3, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (dd, J = 8.8, 1.6 Hz, 2H, ArH), 7.86 (dd, J = 8.8, 1.2 Hz, 2H, ArH), 7.74 – 7.67 (m, 2H, ArH), 7.58 – 7.51 (m, 4H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 181.8 (C=O), 180.4 (C=O), 154.3 (C=N), 135.4 (CH), 135.3 (CH), 133.9 (C), 133.8 (C), 130.5 (CH), 129.6 (CH), 129.2 (CH), 129.0 (CH), 111.6 (C=N). IR (DCM) ν (cm^{-1}): 1682 (C=O), 1666 (C=O), 1611 (O-C=N), 1597 (O-C=N). HRMS (ESI) calcd. for

$C_{16}H_{11}N_2O_4$ $[M+H]^+$ *m/z* 295.0713, found 295.0719.

Preparation of *N,N*-dibenzyl-nitroactamide (2m)

To a solution of diisopropylamine (875 mg, 6 mmol) in THF (10 mL) was added butyllithium (2.73 mL, 1.6 M in THF, 6 mmol) at -25 °C under nitrogen atmosphere. A solution of *N,N*-dibenzyl-actamide (**5**) (1.2 g, 5 mmol) in THF (5 mL) was slowly added via a syringe. After 30 min, the reaction mixture was allowed to warm to 0 °C, *n*-$C_6H_{13}ONO_2$ (883 mg, 6 mmol) was added and the resulting mixture was stirred for 2 hours. The reaction was quenched with aqueous NH_4Cl solution, following by extraction with DCM. The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography to afford the pure product **2m**.

***N,N*-Dibenzyl-nitroacetamide (2m)**. 639 mg, 45 % yield. Colorless crystals, m.p. 94–96 °C. R_f= 0.40 (silica gel plate, ethyl acetate–petroleum ether 1/3, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 – 7.30 (m, 6H, ArH), 7.25 (d, *J* = 7.2 Hz, 2H, ArH), 7.14 (d, *J* = 7.2 Hz, 2H, ArH), 5.29 (s, 2H, CH_2NO_2), 4.67 (s, 2H, NCH_2), 4.37 (s, 2H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.7 (C=O), 135.7 (C), 134.6 (C), 129.4 (CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 126.2 (CH), 77.0 (CH_2NO_2), 50.0 (NCH_2), 49.4 (NCH_2). IR (DCM) *v* (cm^{-1}): 1684 (C=O), 1551 (NO_2), 1370 (NO_2). HRMS (ESI) calcd. for $C_{16}H_{17}N_2O_3$ $[M+H]^+$ *m/z* 285.1234, found 285.1235.

Preparation of nitromethyl compounds (6, 8, and 10)

Nitromethyl ketones **6**,[15,16] methyl nitroacetate (**8**),[17] and 1-nitro-4-(nitromethyl)benzene (**10**)[18] were prepared following the literature procedures.

2-Nitro-1-phenylethanone (6a). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 7.6 Hz, 2H, ArH), 7.69 (t, *J* = 7.5 Hz, 1H, ArH), 7.55 (dd, *J* = 7.6, 7.5 Hz, 2H, ArH), 5.90 (s, 2H, CH_2NO_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 185.6 (C=O), 135.1 (C), 133.4 (CH), 129.3 (CH), 128.2 (CH), 81.2 (CH_2NO_2).

Nitroacetone (6b). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.31 (s, 2H, CH_2NO_2), 2.33 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 193.8 (C=O), 83.7 (CH_2NO_2), 27.4 (CH_3).

Methyl 2-nitroacetate (8). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.19 (s, 2H, CH_2NO_2), 3.88 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.2 (C=O), 76.1 (CH_2NO_2), 53.6 (OCH_3).

1-Nitro-4-(nitromethyl)benzene (10). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 8.7 Hz, 2H, ArH), 7.59 (d, *J* = 8.7 Hz, 2H, ArH), 5.53 (s, 2H, CH_2NO_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 139.5 (C), 129.9 (C), 129.2 (CH), 124.1 (CH), 72.6 (CH_2NO_2).

Acknowledgment

This work was supported in part by The National Basic Research Program of China (No. 2013CB328905) and the National Natrual Science Foundation of China (Nos. 21172017 and 20092013). Mr. Zhanhui Yang is thanked for his generous experimental support.

Notes and references

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† Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **2, 3, 6, 7a, 8,** and **10.** See DOI: 10.1039/b000000x/

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