#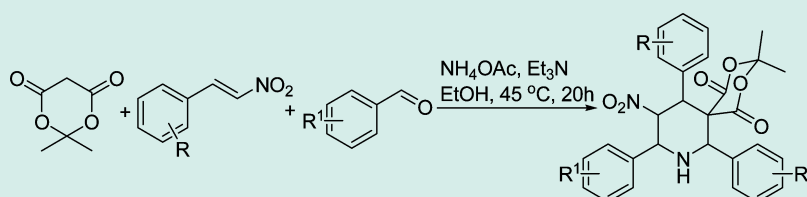 One-Pot Multicomponent Synthesis of Highly Functionalized Piperidines from Substituted β-Nitrostyrenes, Meldrum's Acid, Aromatic Aldehydes, and Ammonium Acetate

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S *Supporting Information*

ABSTRACT: An efficient and straightforward synthetic protocol has been developed for the diversity-oriented synthesis of highly functionalized piperidines containing a Meldrum's acid moiety via pseudo five-component reaction between aromatic aldehydes, ammonium acetate, substituted β-nitrostyrenes and Meldrum's acid for the generation of a wide range of structurally interesting and pharmacologically significant compounds.

KEYWORDS: *multicomponent reaction, polysubstituted piperidine, aromatic aldehyde, Meldrum's acid, substituted nitrostyrene*

INTRODUCTION

Functionalized piperidines have valuable medicinal chemistry properties.[1] For example, the alkaloids SS20846A and Palinavir have been reported to be highly potent inhibitors in the treatment of the immunodeficiency virus (HIV).[2] In clinic, Concerta was used to treat attention deficit hyperactivity disorder,[3] Risperdal was used for treatment of schizophrenia,[4] and Aricept for Alzheimer's disease.[5] Some investigations also reported that substituted piperidine derivatives find applications as anticancer, antihistaminic, bactericidal, CNS stimulant and depressant, herbicidal, insecticidal, and fungicidal agents.[6] The studies showed that some 3-nitro piperidine derivatives have potent farnesyltransferase (FTase) inhibitory (Figure 1).[7] Given their immense pharmaceutical usefulness, the development of efficient syntheses of these bioactive functionalized piperidines has thus attracted many organic and medicinal chemists for decades. Traditionally, there were several methods for the preparation of the polysubstituted piperidine derivatives,[8] such as hetero aza-Diels–Alder reaction,[9] aza-[3 + 3]-

cycloaddition reaction,[10] alkylation, and reduction of oxazolo-piperidones.[11] More recently, a straightforward protocol to access new, highly functionalized piperidine derivatives was developed from easily available allylic alcohols and propargylic amines via ruthenium catalysis.[12] Similarly, other developed approaches included an iridium-catalyzed enantioselective hydrogenation, diphenylprolinol silyl ether mediated Michael reaction and aziridinium ring expansion.[13] D'hoogue and De Kimpe also reported the ring expansion of azetidines to piperidines.[14] In 2003, Hong and co-workers reported a [6 + 3] cycloaddition of azomethine ylides with fulvenes, in which fulvenes served as 6π components, thus leading to the synthesis of racemic piperidine derivatives.[15] More recently, Wang and co-workers also reported similar results, which the CuI/KF-BiphamPhos-catalyzed synthesized highly substituted piperidines via the above reaction.[16] Additionally, promoted by iodide anion the rhodium complex dimer, [Cp*RhCl₂]₂, catalyzed efficiently the transfer hydrogenation of various quaternary pyridinium salts under mild conditions, affording poly substituted piperidines.[17]

Multicomponent reactions received increasing attention because they addressed both diversity and complexity from simple and readily available substrates. Some new multicomponent reactions have been investigated extensively for the synthesis of substituted piperidines. For example, the five-component reaction between β-ketoesters, aromatic aldehydes, and anilines afforded a straightforward synthesis of highly
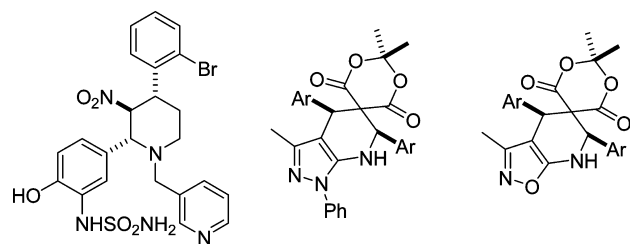

Figure 1. 3-Nitro piperidine FTase inhibitor and spiro{[1,3]-dioxanopiperidine}-4,6-dione derivatives.

functionalized piperidine derivatives.[18] An NHC (N-hetero-cyclic carbenes)-catalyzed azalactone ring-opening and piperidine ring-closing cascade with α,β-unsaturated aldehydes (enals) in a one-pot operation gave multifunctionalized piperidines in excellent yields under mild conditions.[19] Despite these advances, the development of novel and efficient methodologies for the preparation of multisubstituted piperidines, such as the FTase inhibitor in Figure 1, using readily available starting materials under mild conditions is still highly desirable.

Meldrum's acid derivatives are known for their wide range of biological activities. Among them, spirocyclic compounds containing a Meldrum's acid moiety are very useful building blocks for the total synthesis of natural products and are also significant intermediates for the construction of complex heterocycles for medicinal research.[20,21] Recently some investigations indicated that spiro Meldrum's acid derivatives serve as precursors to exotic amino acids, which are often used to enhance biological activities of peptides, peptidomimetics and proteins.[20] In view of the biological significance, there has been extensive attention toward the development of synthetic routes for the synthesis of compounds containing Meldrum's acid moiety (Figure 1).[20−23]

Recently, we reported a very straightforward one-pot multicomponent synthesis of poly substituted 2-piperidinones using β-nitrostyrenes as essential building blocks with aromatic aldehydes, dialkyl malonates, and ammonium acetate.[8,24] As a part of our continuous interest directed toward the development of new methodologies using nitrostyrenes as essential building blocks for the synthesis of multisubstituted piperidines, we report the results of our recent efforts devoted to efficient five-component reaction between substituted β-nitrostyrenes **1** (Figure 2), Meldrum's acid **2** (Figure 3), aromatic aldehydes **3**
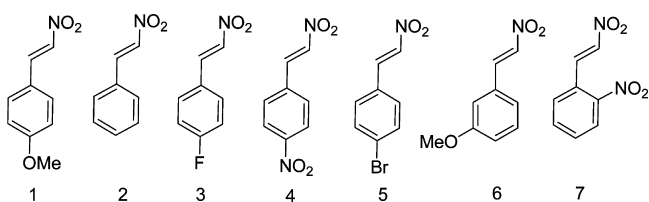

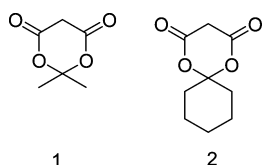**Figure 2.** Diversity of substituted nitrostyrenes **1**{*1−7*}.

Figure 3. Diversity of Meldrum's acid **2**{*1−2*}.

(Figure 4), and ammonium acetate for the direct formation of highly functionalized piperidines containing a Meldrum's acid moiety. They can be transformed easily to 2,4,6-triaryl-3-aminopiperidins under mild conditions using reported methods.[25]

■ RESULTS AND DISCUSSION

The Michael addition of Meldrum's acid and substituted β-nitrostyrenes, nitro-Mannich and intermolecular Mannich reaction cascade with in situ formed acyclic imines by a base catalyst afforded highly functionalized piperidines. The general
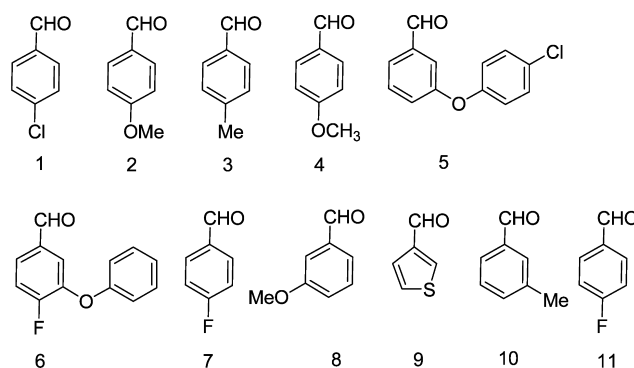

Figure 4. Diversity of aromatic aldehydes **3**{*1−11*}.

procedure was first optimized with different bases, solvents and temperature for this purpose. Herein, β-nitro-p-methoxystyrene (**1a**), Meldrum's acid (**2**), p-chlorobenzaldehyde (**3a**), and ammonium acetate were chosen as a set of model substrates for the synthesis of a representative piperidine **4a** (Table 1). First,

Table 1. Optimization of Reaction Conditions in the Synthesis of 4a{1,1,1}

entry	1a/2/3a (mol)/base/solvent/T (°C)/t (h)	yield (%) of 4a[a]
1	1/1/3/piperidine (1 equiv)/EtOH/rt/20	47
2	1/1/3/piperidine (1 equiv)/EtOH/0/20	44
3	1/1/3/piperidine (1 equiv)/EtOH/45/20	53
4	1/1/3/piperidine (1 equiv)/EtOH/65/20	34
5	1/1/3/piperidine (1 equiv)/EtOH/45/25	53
6	1/1/3/piperidine (1 equiv)/DMF/45/20	trace
7	1/1/3/piperidine (1 equiv)/THF/45/20	45
8	1/1/3/piperidine (1 equiv)/MeCN/45/20	43
9	1/1/3/NaOH (1 equiv)/EtOH/rt/20	42
10	1/1/3/Et$_3$N (1 equiv)/EtOH/45/20	68
11	1/1/3/Li$_2$CO$_3$ (1 equiv)/EtOH/45/20	65
12	1/1/3/Na$_2$CO$_3$(1eq)/EtOH/45/20	70
13	1/1/3/Et$_3$N(0.5eq)/EtOH/45/20	56
14	1/1/3/Et$_3$N (1.5 equiv)/EtOH/45/20	70
15	1/1/3/Et$_3$N (2 equiv)/EtOH/45/20	75
16	1/1/3/Et$_3$N (2.5 equiv)/EtOH/45/20	73
17	1/1/3/Et$_3$N (2 equiv)/EtOH/55/16	65
18	1/1/2/Et$_3$N (2 equiv)/EtOH/45/20	60
19	1/1/4/Et$_3$N (2 equiv)/EtOH/45/20	75

[a]Isolated yield.

we initiated our investigations by optimization of the temperature and solvent using piperidine as a base because our previous results showed that piperidine was the better basic promoter for such Michael addition and aza-Mannich reaction. It was found that the best reaction temperature for the synthesis of piperidine **4a** was 45 °C (Table 1, entry 3). Screening of the solvent effect revealed that all the reactions proceeded to give the desired product **4a** in 43−53% yields,

Table 2. Preparation of Highly Functionalized Piperidines
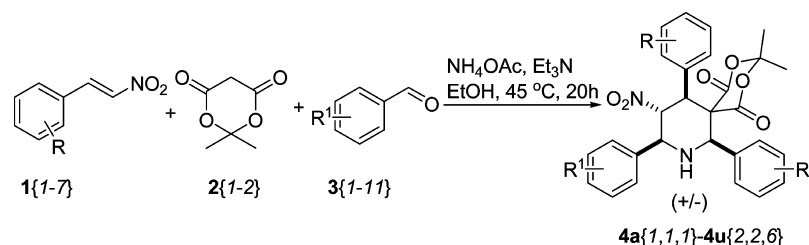
entry	R	R^1	product	yield (%)^a
1	*p*-MeO	*p*-Cl	**4a**{*1,1,1*}	75
2	*p*-MeO	*p*-MeO	**4b**{*1,1,2*}	68
3	*p*-MeO	*p*-Me	**4c**{*1,1,3*}	66
4	*p*-MeO	*p*-Br	**4d**{*1,1,4*}	71
5	*p*-MeO	*m*-(4-ClPh)O	**4e**{*1,1,5*}	56
6	*p*-MeO	3-PhO-4-F	**4f**{*1,1,6*}	55
7	H	*p*-F	**4g**{*2,1,7*}	56
8	H	*p*-Me	**4h**{*2,1,3*}	68
9	H	*m*-MeO	**4i**{*2,1,8*}	53
10	*p*-F	*p*-Me	**4j**{*3,1,3*}	63
11	*p*-F	3-thiophenyl	**4k**{*3,1,9*}	53
12	*p*-O$_2$N	*p*-MeO	**4l**{*4,1,2*}	60
13	*p*-O$_2$N	*p*-Br	**4m**{*4,1,4*}	65
14	*p*-Br	*p*-MeO	**4n**{*5,1,2*}	58
15	*p*-Br	*p*-Br	**4o**{*5,1,4*}	59
16	*m*-MeO	*m*-Me	**4p**{*6,1,10*}	67
17	*o*-O$_2$N	3-thiophenyl	**4q**{*7,1,9*}	62
18	*o*-O$_2$N	*p*-Cl	**4r**{*7,1,1*}	71
19	*p*-MeO	*p*-F$_3$C	**4s**{*1,1,11*}	70
20^b	*p*-MeO	*p*-Br	**4t**{*1,2,4*}	73
21^b	H	3-PhO-*4-F*	**4u**{*2,2,6*}	71

^{a}Isolated yield. ^{b}1,5-Dioxa-2,3-dioxospiro[5,5]undecane was used.

except DMF, with 1 equivalent piperidine at 45 °C for ∼20 h (entries 3 and 5−8). Ethanol proved to be a promising solvent, affording product **4a** with 53% yield (entry 3). Next, we surveyed a range of bases for optimization and found that Et$_3$N was the best among piperidine, NaOH, Na$_2$CO$_3$ and Li$_2$CO$_3$. The optimum amount of Et$_3$N for the reaction was found to be 1.5 to 2 equivalents. When the amount of Et$_3$N was decreased from 1.5 to 0.5 equiv, the yield of the piperidine **4a** reduced (Table 1, entry 13), but the use of 2.5 equiv Et$_3$N did not affect the yield (Table 1, entry 16). When two equiv 4-chlorobenzaldehyde (**2a**) was used, a 60% yield of **4a** was obtained (Table 1, entry 18). Excessive 4-chlorobenzaldehyde (**2a**) could not further improve the reaction (Table 1, entry 19). Thus, the most suitable reaction conditions for the model reaction were established (entry 15).

With these reaction conditions identified, our attention turned to examination of the scope of the multicomponent reaction. To determine the scope of the designed protocol, a number of commercially available aldehydes **3**{*1−11*} and substituted nitrostyrenes **1**{*1−7*} generated from aromatic aldehydes and nitromethane were condensed with Meldrum's acid **2**{*1−2*}, and ammonium acetate under optimized reaction condition, and the results were summarized in Table 2. As shown in Table 2, aldehydes were found to afford the expected product. Aliphatic aldehydes were incompatible with this multicomponent reaction, whereas *p*-chlorobenzaldehyde and *p*-bromobenzaldehyde proved to be good substrates. Two

different Meldrum's acids also were useful for the multi-component reaction.

The structure of **4a**{*1,1,1*} and **4b**{*1,1,2*} were shown in Figures 5 and 6. X-ray crystallographic analysis determined that product **4a**{*1,1,1*} and **4b**{*1,1,2*} possess trans-oriented three contiguous substituents at C(2), C(3), and C(4), but cis-oriented three aromatic rings. On the basis of spectroscopic evidence the structure of compound **4a**{*1,1,1*}-**4u**{*2,2,6*} was identified as 8-aza-7,9,11-triaryl-3,3-dimethyl-10-nitro-2,4-dioxaspiro[5,5]nondecane-1,5-dione or 2-aza-1,3,5-triaryl-4-nitro-8,15-dioxadispiro[5,2,5^9,2^6]hexadecane-7,16-dione. The 2,3-trans-3,4-trans-4,6-cis configuration seemed to be thermo-dynamically favorable because all substituents at C(2), C(3), C(4), and C(6) on the piperidine core could exist as equatorial. Moreover, for the product **4a**{*1,1,1*} and **4b**{*1,1,2*}, an intermolecular hydrogen bond was observed on the basis of their X-ray crystallographic data. See Supporting Information for the bond length of the intermolecular hydrogen bond of the product **4a**{*1,1,1*} and **4b**{*1,1,2*}. Additionally, the existence of the intermolecular hydrogen bond was further confirmed by the proton-NMR of the NH proton. In CDCl$_3$, the NH proton, hydrogen bonded with the carbonyl moiety, resonates at 2.62−2.87 ppm as a triplet peak, whereas in DMSO-d_6, it resonates low field, at 3.86 ppm. And the splitting signals of the NH proton were observed, not as a common broad single peak, this was because the intermolecular hydrogen bond and two bulky aryls of C2 and C6 caused difficulties of exchanging the NH proton with deuterated solvents.
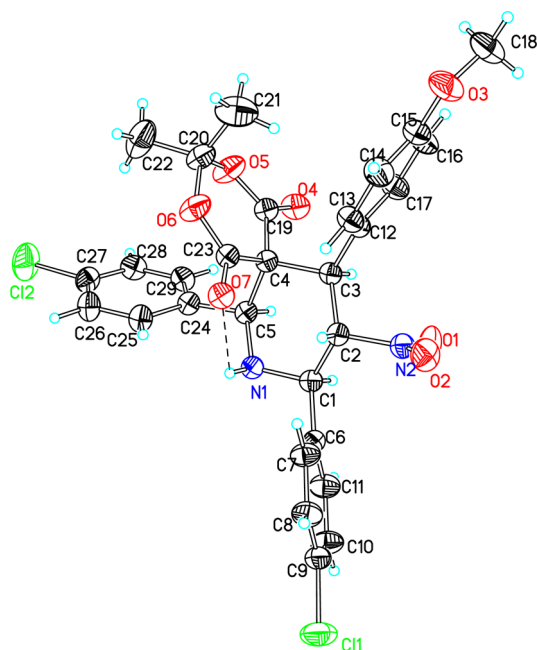
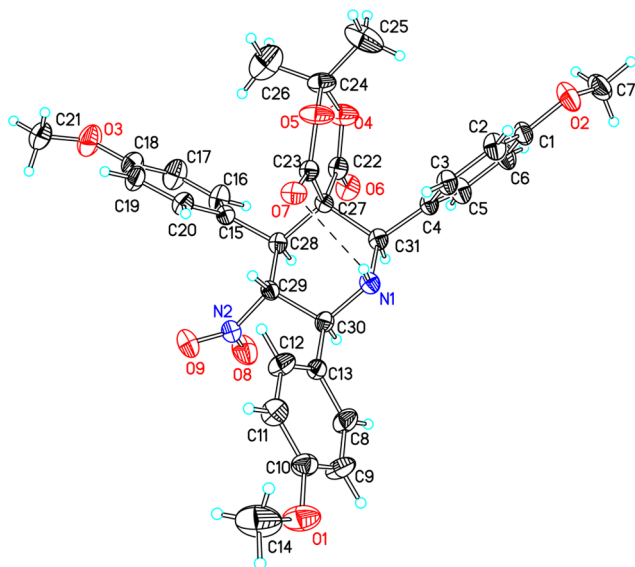**Figure 5.** Molecular structure of 2,4,6-triarylpiperidine **4a**{*1,1,1*}.

Figure 6. Molecular structure of 2,4,6-triarylpiperidine **4b**{*1,1,2*}.

The reaction mechanism shown in Scheme 1 was proposed. First, under basic conditions, the Michael addition of Meldrum's acid to the substituted nitrostyrene formed 2-(1-aryl-2-nitroethyl) Meldrum's acid, which was followed by nitro-Mannich nucleophilic addition on the intermediate arylimine generated from aromatic aldehydes and ammonium acetate to form 2-(3-amino-2-nitro-1,3-diaryl propyl) Meldrum's acid. Then, another equivalent of aromatic aldehyde and amine reacted to generate the corresponding imine. Finally, intramolecular nitro-Mannich nucleophilic addition in 2-(3-aylideneamino-2-nitro-1,3-diarylpropyl) Meldrum's acid gave the cyclic amine.

We tested four-component reaction of *o*-methoxybenzaldehyde, Meldrum's acid, 1-methoxy-4-(2-nitrovinyl)benzene, and ammonium acetate in the above same conditions. (*E/Z*)-5-(3-(2-Methoxybenzylideneamino)-3-(2-methoxyphenyl)-1-(4-me-

thoxyphenyl)-2-nitropropyl)-2,2-dimethyl-1,3-dioxane-4,6-dione {*1,1,12*} was only obtained in 66% (Scheme 2). The (E)-structure of compound {*1,1,12*} was determined by X-ray crystallographic analysis (Figure 7). Thus the final intramolecular nitro-Mannich reaction deeded to afford the cyclic compound **4** did not occur. This result indicates the steric hindrance caused by the ortho-substituted aromatic group on the imine carbon is problematic for the intramolecular attack by the anion of the substituted Meldrums acid moiety. Therefore, the four-component reaction from substituted nitrostyrenes, ortho-substituted aromatic aldehydes with a steric hindrance, Meldrum's acid, and ammonium acetate will not likely form the desirable products. Additionally, aromatic ketones were used in the title reaction as a substitute of aromatic aldehydes, the desirable multisubstituted piperidines were not obtained under the above conditions.

■ CONCLUSION

In summary, we have demonstrated an efficient, one-pot method for the expeditious synthesis of highly functionalized piperidines via a one-pot, five-component reaction from aromatic aldehydes, ammonium acetate, substituted *β*-nitrostyrenes and Meldrum's acid which involves sequential Michael addition, nitro-Mannich reaction, the formation of acyclic imines and intermolecular nitro-Mannich reaction. This protocol, combining construction and modification of the piperidine skeleton, increases the structural diversity of final products from readily available starting materials. We expect that the resulting structurally intriguing compounds will have broad applications in our related biomedical program.

■ EXPERIMENTAL PROCEDURES

General. All melting points were determined in a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded in a Nicolet FT-IR 5DX spectrometer. The ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded in a Bruker AV-600 spectrometer with TMS as internal reference in CDCl$_3$ or DMSO-d_6 solutions. The *J* values are given in hertz. Only discrete or characteristic signals for the ^{1}H NMR are reported. The MS spectra were obtained on an Agilent 1200−6460 QQQ mass spectrometer. High-resolution ESI mass spectra were obtained on a UHR-TOF maXis (ESI) mass spectrometer. X-ray crystallographic analysis was performed with a SMART APEX-II diffractometer. Flash chromatography was performed on silica gel (230−400 mesh) eluting with ethyl acetate−hexanes mixture. All reactions were monitored by thin layer chromatography (TLC). All reagents and solvents were purchased from commercial sources and purified commonly before used.

General Procedure for Preparation of 2,4,6-Triarylpiperidines. The appropriate Meldrum's acid **2**{*1−2*}(3.0 mmol), appropriate 2-aryl-1-nitroethene **1**{*1−7*}(3 mmol), and triethylamine (606 mg, 6.0 mmol) were dissolved in 15 mL of ethanol at room temperature, and the resultant mixture was stirred at the same reaction temperature for 3 h. To the resultant solution appropriate aromatic aldehyde **3**{*1−11*} (9.0 mmol) and ammonium acetate (346 mg, 4.5 mmol) were added at room temperature. The reaction mixture was stirred under 45 °C for ~20 h, and the completion of reaction was confirmed by TLC (Hexanes/EtOAc, 5:1). Subsequently, the solvent was removed by reduced pressure, the residues was added with water (10 mL) and was extracted with dichloro-

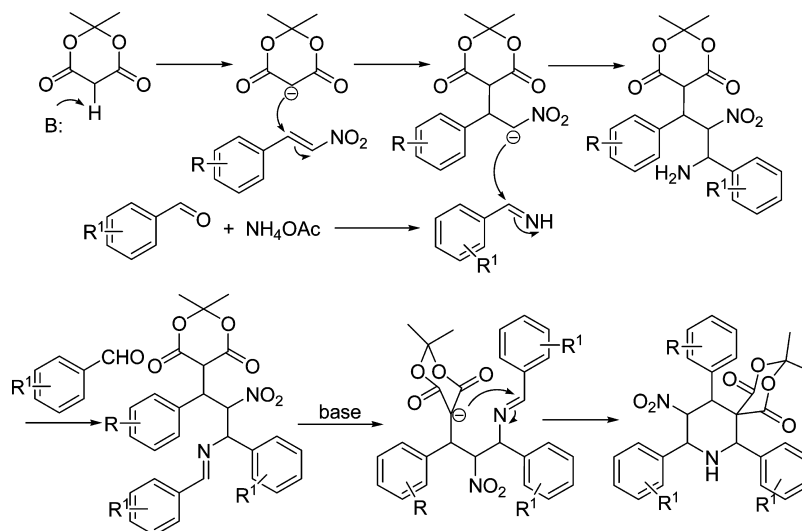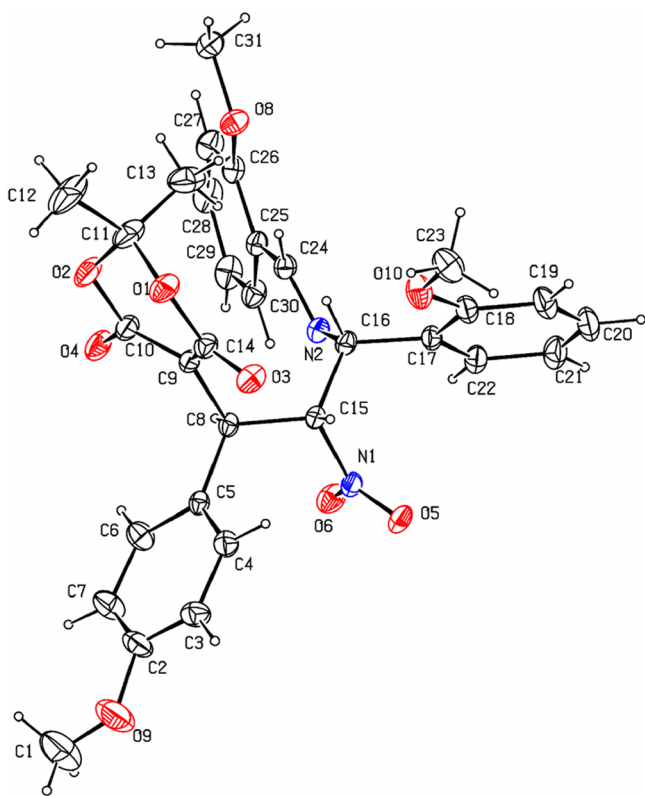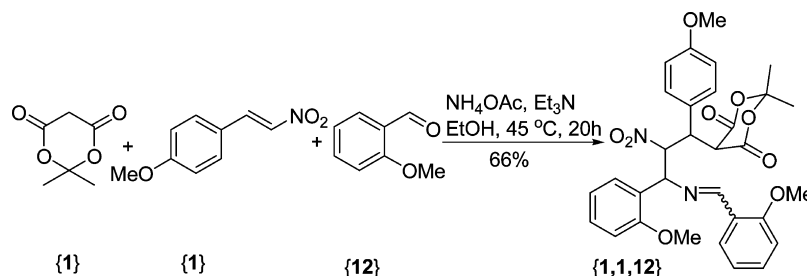**Scheme 1. Possible Mechanism for the Formation of Products 4a{1,1,1}-4u{2,2,6}**

Scheme 2. One-Pot Reaction of Meldrum's Acid, 1-Methoxy-4-(2-nitrovinyl)benzene, o-Methoxybenzaldehyde, and Ammonium acetate

Figure 7. Molecular structure of compound {1,1,12}.

methane (10 mL × 2). The organic phase was washed with water (10 mL) and brine (5 mL), and dried over anhydrate sodium sulfate. After removal of dichloromethane, the crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 1/10) to give the desired product **4a**{1,1,1}-**4u**{2,2,6}. The air-dried product showed a single spot on TLC and was pure enough for all analytical purposes.

8-Aza-7,9-di(p-chlorophenyl)-11-(p-methoxyphenyl)-3,3-dimethyl-10-nitro-2,4-dioxa-1,5-dioxo spiro[5,5]undecane (4a). mp: 202.3−202.4 °C (EtOAc/PE). ^{1}H NMR (CDCl$_3$, 600 MHz) δ (ppm): 7.49 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.22 (bs, 2H), 7.19 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 6.01 (dd, J = 11.4 and 10.2 Hz, 1H), 4.84 (d, J = 10.2 Hz, 1H), 4.53 (t, J = 9.0 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 3.73 (s, 3H), 2.71 (t, J = 9.0 Hz, 1H), 0.77 (s, 3H), 0.59 (s, 3H). ^{13}C NMR (CDCl$_3$, 150 MHz) δ (ppm): 165.49, 164.10, 159.26, 134.61, 134.32, 134.21, 133.09, 128.46, 128.21, 127.89, 127.57, 124.30, 113.67, 105.80, 87.26, 67.27, 63.28, 61.06, 54.21, 49.42, 28.10, 26.80. IR (KBr, cm^{-1}): 3335, 3039, 2963, 1760, 1720, 1563, 1509, 1480, 1378, 1291, 1099, 831, 784. HRESIMS calcd for C$_{29}$H$_{26}$Cl$_2$N$_2$O$_7$ (M + H)$^+$ 585.1117; found 585.1179.

8-Aza-7,9,11-tri(p-methoxyphenyl)-3,3-dimethyl-10-nitro-2,4-dioxa-1,5-dioxospiro[5,5]undecane (4b). mp: 194.2−194.9 °C (EtOAc/PE). ^{1}H NMR (CDCl$_3$, 600 MHz) δ (ppm): 7.47 (d, J = 7.8 Hz, 2H), 7.23 (bs, 2H), 7.16 (d, J = 7.8 Hz, 2H), 6.93 (d, J = 7.8 Hz, 2H), 6.84 (d, J = 7.8 Hz, 2H), 6.82 (d, J = 7.8 Hz, 2H), 6.03 (t, J = 10.8 Hz, 1H), 4.83 (d, J = 10.2 Hz, 1H), 4.51 (d, J = 10.2 Hz, 1H), 4.48 (t, J = 10.8 Hz,

1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 2.76 (t, J = 9.6 Hz, 1H), 0.74 (s, 3H), 0.61 (s, 3H). ^{13}C NMR (CDCl$_3$, 150 MHz) δ (ppm): 166.90, 165.45, 160.11, 160.04, 129.37, 128.47, 127.37, 125.80, 114.75, 114.50, 114.28, 106.50, 88.52, 68.48, 64.43, 62.28, 55.36, 55.30, 50.53, 29.16, 27.79. IR (KBr, cm^{-1}): 3130, 3045, 2954, 1756, 1716, 1581, 1549, 1515, 1301, 1257, 1031, 832, 784. HRESIMS calcd for $C_{31}H_{32}N_2O_9$ (M + H)$^+$ 577.2108; found 577.2175.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional experimental details, general information, and ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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