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Synthesis of Polysubstituted 2-Piperidinones via a Michael Addition/Nitro-Mannich/Lactamization Cascade

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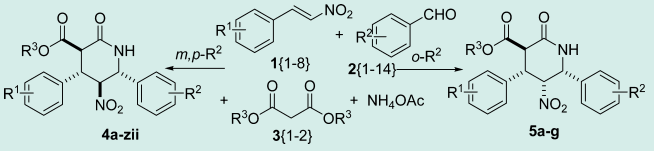
Supporting Information

ABSTRACT: An efficient and practical method has been developed for the diversity-oriented synthesis of polysubstituted 2-piperidinones via four-component reaction between substituted nitrostyrenes, aromatic aldehydes, ammonium acetate, and dialkyl malonates for the generation of a wide range of structurally interesting and pharmacologically significant compounds. It is worth mentioning that in the course of this reaction, the formation of products was highly stereoselective. Two differently stereochemical classes of polysubstituted 2-piperidinones depended on the substitutent position of aromatic aldehyde.



KEYWORDS: *multicomponent reaction, polysubstituted piperidines, substituted nitrostyrenes, stereoselectivity, dialkyl malonates*

INTRODUCTION

The piperidine ring is a key structural unit for numerous natural products, synthetic pharmaceuticals, and a wide variety of biologically active compounds.[1] The novel polysubstituted piperidine derivatives have been a rich source of candidates with potential pharmaceutical applications that have encouraged the design and synthesis of new analogs with increased pharmacological activity. Thus, to meet the need of modern drug discovery, the synthetic methodology of polysubstituted piperidines is developed continually to address the many challenges associated with the design of new pharmaceutical agents. Although, there are several methods for the preparation of the polysubstituted piperidine derivatives,[2] most current procedures either require advanced starting materials or involve multistep. The development of efficient methods for the synthesis of polysubstituted piperidine derivatives still requires attention.

Over the past decades, multicomponent reactions as an efficient synthetic strategy have drawn considerable attention, because complex products are formed in a one-pot reaction and diversity can be simply attained by relatively simple starting materials.[3] To the best of our knowledge, there are only a few multicomponent reactions for the construction of structurally and stereochemically diverse polysubstituted piperidine derivatives.[4] Obviously, the development of simple and environmentally multicomponent reactions for efficient preparation of polysubstituted piperidines is therefore a significant challenge.

Recently, the atom and step economic synthesis of these heterocyclic compounds by condensation reactions employing nitroalkenes as a useful building block for the formation of carbon−carbon bond have drawn attention.[5] It is known that Michael addition of activated methylenes to nitroolefins is an efficient synthetic tool for the construction of nitrogen-containing ketoesters.[6] Transformation of the corresponding adducts could yield a variety of useful synthetic intermediates, we envisioned the Michael addition of activated methylenes to nitroolefins, the nitro-Mannich reaction and an intramolecular lactamization in a single operation. As a part of our continuous interest directed toward the development of new methodologies using nitrostyrenes as essential building blocks for the synthesis of polysubstituted piperidines, we report the results of our recent efforts devoted to efficient one-pot, multicomponent reactions from substituted nitrostyrenes **1** (Figure 1), aromatic aldehydes **2** (Figure 2), dialkyl malonates **3** (Figure 3), and ammonium acetate for the direct formation of substituted piperidine ring.

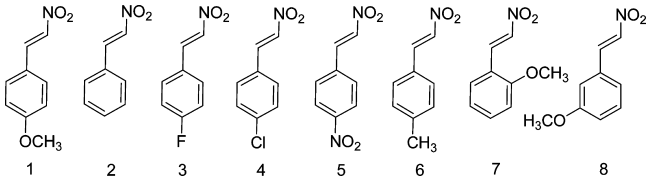


Figure 1. Diversity of substituted nitrostyrenes **1**{*1*−*8*}.

RESULTS AND DISCUSSION

Our initial test reaction was run without any catalyst or promoter in methanol at room temperature for 48 h, but no reaction occurred (Table 1, entry 1). It is known that weak bases can promote the Michael-type reaction, but K_2CO_3 only afforded a trace amount. The use of a stronger base was required. In fact, two equivalents of NaOH in methanol appears

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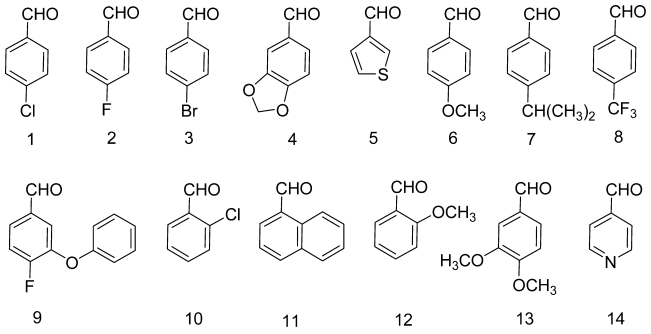


Figure 2. Diversity of aromatic aldehydes **2**{*1*−*14*}.

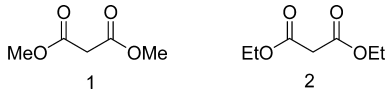
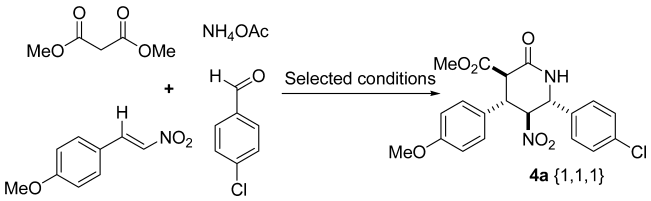


Figure 3. Diversity of dialkyl malonates **3**{*1*−*2*}.

Table 1. Optimization of Promoters, Solvents, and Temperature in the Synthesis of 4a{*1,1,1*}[a]



entry	additive (mol %)	solvent	*T* (°C)	time (h)	yield (%)[b]
1	0	MeOH	rt	48	0
2	K_2CO_3 (50%)	MeOH	rt−85	45 min/40 h	trace
3	NaOH (50%)	MeOH	rt−85	45 min/40 h	10
4	NaOH (50%)	MeOH	0−85	45 min/40 h	15
5	NaOH (100%)	MeOH	0−85	45 min/40 h	21
6	NaOH (150%)	MeOH	0−85	45 min/40 h	32
7	NaOH (200%)	MeOH	0−85	45 min/40 h	67
8	NaOH (250%)	MeOH	0−85	45 min/40 h	67
9	NaOH (200%)	MeOH	0−85	45 min/48 h	67
10	piperidine (200%)	MeOH	0−85	45 min/40 h	15
11	NaOMe (200%)	MeOH	0−85	45 min/40 h	62
12	NaOH (200%)	EtOH	0−85	45 min/40 h	63
13	NaOH (200%)	THF	0−85	45 min/40 h	trace
14	NaOH (200%)	CH_3CN	0−85	45 min/40 h	trace

[a]Reaction condition: 1-nitro-2-(*p*-methoxyphenyl)ethene/dimethyl malonate/*p*-chlorobenzaldehyde/ammonia acetate =1/1/1/1.5 (mol). [b]isolated yields.

to be optimal (Table 1, entry 7) when the reactants were initially mixed at 0 °C for 45 min before heating at reflux for 40 h. Our studies have revealed that 1-nitro-2-(p-methoxyphenyl)-ethene{*1*} readily affords polymer at higher temperatures in the presence of strong base. To prevent polymerization of the starting nitrostyrene, we needed to begin the reaction at 0 °C for a short period and then heat the reaction to reflux in methanol. The desired product from the reaction contains two acidic centers thus requiring a second equivalent of strong base to maximize the yield. The use of NaOMe is similarly effective as NaOH (Table 1, entry 11). Nonprotic solvents and tertiary amine bases are ineffective for this transformation (Table 1, entries 10, 13, and 14).

To determine the scope of the designed protocol, a number of commercially available aldehydes **2**{*1*−*14*} and substituted nitrostyrenes **1**{*1*−*8*} generated from aromatic aldehydes and nitromethane were condensed with dialkyl malonates **3**{*1*−*2*}, and ammonium acetate under optimized reaction condition, and the results are summarized in Table 2. As shown in Table 2, both electron-deficient and electron-rich aromatic aldehydes were applicable to the reaction, affording the products in moderate to good yields.

The structures of all compounds were elucidated with the aid of ^{1}H and ^{13}C NMR. A couple of enantiomers were obtained in each case, and the other diastereomer could not be detected in the reaction products. Surprised by the significant difference between these results, the desired products have been divided into two groups, depending on the substitution pattern of aromatic aldehydes. The first group comprises meta- or para-substituted aromatic ring of aromatic aldehydes, 4-pyrdinyl and 3-thiophenyl (**4a**{*1,1,1*}−**4zii**{*8,1,1*}, Table 2), the second includes ortho-substituted aromatic ring of aromatic aldehydes and 2-naphthenyl (**5a**{*2,10,1*}−**5g**{*5,10,1*}, Table 2).

While meta- or para- substituted aromatic groups, 3-thiophenyl and 4-pyrdinyl located at C(4) and C(6), compounds **4a**{*1,1,1*}−**4zii**{*8,1,1*} possessed the same pattern of splitting appears in the ^{1}H NMR spectra of all trans isomers with small deviations,[7] even when some signals are overlapped. The structure of **4a**{*1,1,1*} was shown in Figure 4. X-ray crystallographic analysis determined that product **4a**{*1,1,1*} possesses trans-oriented four continuous substituents at C(3), C(4), C(5), and C(6). On the basis of spectroscopic evidence the structure of compound **4a**{*1,1,1*}−**4zii**{*8,1,1*} was identified as methyl (±)-trans- 4,6-bis(aryl)-5-nitro-2-oxopiperidine-3-carboxylate.[8] The 3,4-trans-4,5-trans-5,6-trans configuration seemed to be thermodynamically favorable because all substituents on the piperidine core could exist as equatorial.

However, when ortho-substituted aromatic aldehydes and 2-naphthene carbaldehyde were used in the title reaction to yield products **5a**{*2,10,1*}−**5g**{*5,10,1*}, very interesting results were obtained. As shown in Figure 5, the relative configuration of the product was determined by X-ray analysis of **5f**{*7,12,1*}. On the basis of spectroscopic evidence the structure of compound **5a**{*2,10,1*}−**5g**{*5,10,1*} were identified as alkyl (±)-*trans*(C3/C4)-*cis*(C4/C5/C6)-4,6-diaryl-5-nitro-2-oxopiperidine-3-carboxylate.

It is known that a nitro group is an electron-withdrawing substituent, in the presence of strong bases, a proton on the α carbon adjacent to the NO_2 substituent (Figure 6, **A** and **B**) is abstract to a resonance-stabilized N-oxide oxime (Figure 6, **C**). Reprotonation can occur on the α carbon (Figure 6, **C**) returning to the nitro form (Figure 6, **A** and **B**). In this way, base catalyzes an equilibrium between isomeric nitro and N-oxide oxime form of a nitropiperidinone. Thus, under a long reaction time, while meta- or para- substituted aromatic groups, 3-thiophenyl and 4-pyrdinyl located at C(4) and C(6), a proton attacks α carbon (Figure 6, **D**) from the cis face of the 4,6-diaryl groups giving a thermodynamic stabilized product (Figure 6, **A**). While ortho-substituted aromatic group located at C(4) and C(6), a proton attacks α carbon with difficulties (Figure 6, **D**) from the cis face of the 4,6- diaryl groups with a big steric hindrance, so a proton attacks α carbon selectively without a steric hindrance (Figure 6, **D**) from the trans face of the 4,6-diaryl groups giving a cis (NO_2/diaryl) product (Figure 6, **C**).

The reaction mechanism shown in Scheme 1 is proposed. First, the Michael addition of malonate to the substituted

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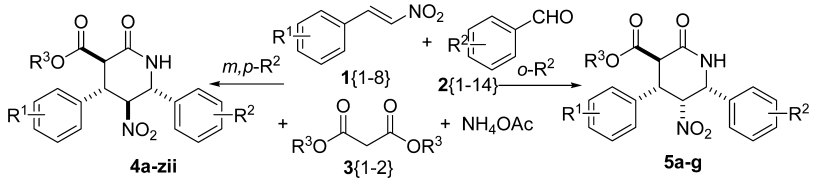
Table 2. Preparation of the Alkyl 5-Nitro-2-oxo-4,6-diarylpiperidine-3-carboxylates[a]



entry	R^1	R^2	R^3	product	yield (%)[b]
1	*p*-CH_3O	*p*-Cl	CH_3	**4a**{*1,1,1*}	67
2	H	*p*-F	CH_3	**4b**{*2,2,1*}	72
3	H	*p*-Cl	CH_3	**4c**{*2,1,1*}	76
4	H	*p*-Br	CH_3	**4d**{*2,3,1*}	74
5	H	*3,4*-OCH_2CH_2O	CH_3	**4e**{*2,4,1*}	63
6	H	3-thiophenyl	CH_3	**4f**{*2,5,1*}	67
7	*p*-F	*p*-CH_3O	CH_3	**4g**{*3,6,1*}	60
8	*p*-F	*p*-Cl	CH_3	**4h**{*3,1,1*}	66
9	*p*-Cl	*p*-CH_3O	CH_3	**4i**{*4,6,1*}	73
10	*p*-O_2N	*p*-Cl	CH_3	**4j**{*5,1,1*}	48
11	H	*p*-^{i}Pr	CH_3	**4k**{*2,7,1*}	62
12	*p*-F	*p*-CF_3	CH_3	**4l**{*3,8,1*}	57
13	*p*-CH_3	*p*-Cl	CH_3	**4m**{*6,1,1*}	50
14	*p*-CH_3O	*3,4*-$(CH_3O)_2$	CH_3	**4n**{*1,13,1*}	54
15	*p*-CH_3O	3-PhO-4-F	CH_3	**4o**{*1,9,1*}	53
16	*p*-CH_3O	*p*-Br	CH_3	**4p**{*1,3,1*}	63
17	*p*-CH_3O	*3,4*-OCH_2CH_2O	CH_3	**4q**{*1,4,1*}	56
18	*p*-CH_3O	3-thiophenyl	CH_3	**4r**{*1,5,1*}	62
19	*p*-F	*3,4*-OCH_2CH_2O	CH_3	**4s**{*3,4,1*}	66
20	*p*-F	*p*-Br	CH_3	**4t**{*3,3,1*}	64
21	*p*-F	3-thiophenyl	CH_3	**4u**{*3,5,1*}	58
22	H	*p*-Br	C_2H_5	**4v**{*2,3,2*}	72
23	H	*p*-Cl	C_2H_5	**4w**{*2,1,2*}	74
24	*p*-F	*p*-Br	C_2H_5	**4x**{*3,3,2*}	63
25	*p*-CH_3O	4-pyridinyl	CH_3	**4y**{*1,14,1*}	49
26	*p*-O_2N	*p*-CH_3O	CH_3	**4zi**{*5,6,1*}	54
27	*m*-CH_3O	*p*-Cl	CH_3	**4zii**{*8,1,1*}	63
28	H	*o*-Cl	CH_3	**5a**{*2,10,1*}	68
29	H	2-naphthenyl	CH_3	**5b**{*2,11,1*}	58
30	*p*-F	2-naphthenyl	CH_3	**5c**{*3,11,1*}	55
31	*p*-CH_3O	*o*-Cl	CH_3	**5d**{*1,10,1*}	60
32	*p*-F	*o*-Cl	CH_3	**5e**{*3,10,1*}	60
33	*o*-CH_3O	*o*-CH_3O	CH_3	**5f**{*7,12,1*}	57
34	*p*-O_2N	*o*-Cl	CH_3	**5g**{*5,10,1*}	54

[a]Reaction condition: substituted nitrostyrene/aromatic aldehyde/dialkyl malonate/ammonia acetate =1/1/1/1 (mol), 200 mol % NaOH, 0 °C, 45 min, 85 °C, 40 h, solvent: MeOH for **4a**−**u**, **4y**−**zii**, and 5**a**−**g**; EtOH for **4v**−**x**. [b]Isolated yields.

nitrostyrene formed 2-(1-aryl-2-nitroethyl)malonate, which is followed by nitro-Mannich nucleophilic addition in intermediate arylimine to form 2-(3-amino-2-nitro-1,3-diaryl propyl)-malonate. Finally, intramolecular lactamization in 2-(3-amino-

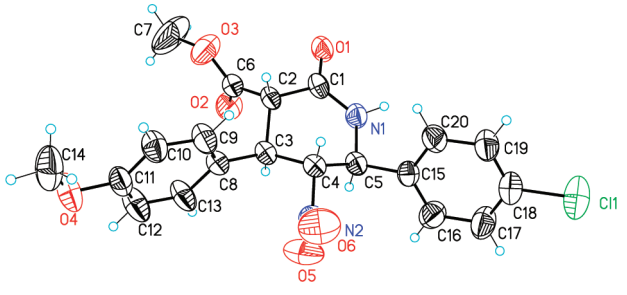


Figure 4. Molecular structure of 2-piperidinone **4a**{*1,1,1*}.

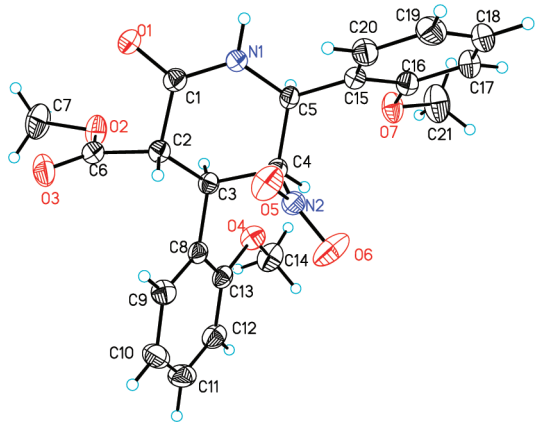


Figure 5. Molecular structure of 2-piperidinone **5f**{*7,12,1*}.

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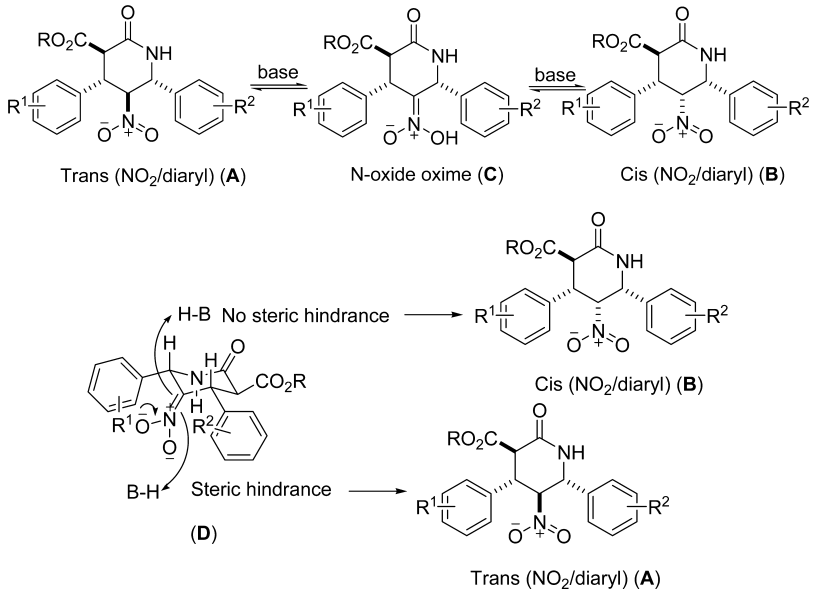
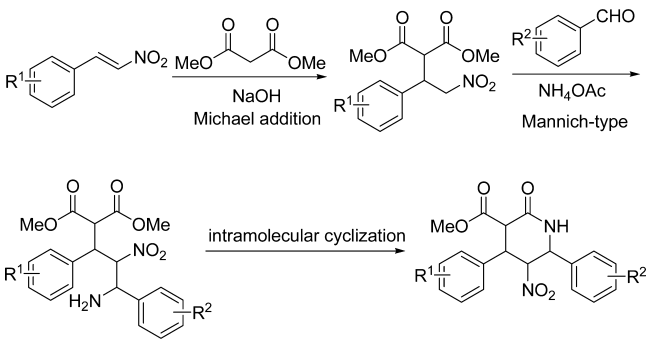


Figure 6. Proposed mechanistic pathways to rationalize the stereochemistry.

Scheme 1. Possible Mechanism for the Formation of Products 4a{*1,1,1*}−4zii{*8,1,1*} and 5a{*2,10,1*}−5g{*5,10,1*}



2-nitro-1,3-diarylpropyl)malonate gave the cyclic amide with elimination of alcohol.

CONCLUSION

In summary, we have described a versatile and efficient synthetic method in which a multicomponent reaction is used under mild reaction conditions to produce a broad range of functionalized alkyl (±)-*trans*-4,6-diaryl-5-nitro-2-oxopiperidine-3-carboxylates and alkyl (±)-*trans*(C3/C4)-*cis*(C4/C5/C6)-4,6-diaryl-5-nitro-2-oxopiperidine-3-carboxylates and in moderate to good yields, which are useful as versatile synthetic intermediates and potentially as biologically active compounds. Their stereochemical classes of polysusbtituted 2-piperidinones depended on the substitutent position of starting material aromatic aldehydes. Particularly valuable features of this method included operational simplicity, mild conditions, and commercially available materials. We expect that the resulting biologically intriguing structures 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 a ZAB-HS mass spectrometer with 70 eV. X-ray crystallographic analysis was performed with a Smart-1000 CCD diffractometer. The elemental analyses were performed in a Perkin-Elmer 240C instrument. 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 Alkyl 5-Nitro-2-oxo-4,6-diarylpiperidine-3-carboxylates. The appropriate dialkyl malonate (2 mmol), appropriate 2-aryl-1-nitroethene (2 mmol),and sodium hydroxide (160 mg, 4 mmol) were dissolved in 15 mL of methanol or ethanol at 0 °C, and the resultant mixture was stirred at 0 °C (ice−water bath) for 45 min, then the resultant mixture was stirred sequentially from 0 °C to room temperature. To the resultant solution appropriate aromatic aldehyde (2 mmol) and ammonium acetate (230 mg, 3 mmol) were added at room temperature. The reaction mixture was stirred under reflux for 40 h, and the completion of reaction was confirmed by TLC (EtOAc/methanol 10:1). Subsequently, the precipitated product was filtered off and the solid washed with methanol and diethyl ether two times to give a product **4a**{*1,1,1*}−**4zii**{*8,1,1*} or **5a**{*2,10,1*}−**5g**{*5,10,1*}. The filtrate was purified by flash chromatography (silica gel, EtOAc/CH_2Cl_2, 10/1) to give other product **4a**{*1,1,1*}−**4zii**{*8,1,1*} or **5a**{*2,10,1*}−**5g**{*5,10,1*}. The merged crude product was purified ulteriorly by crystallization from hot ethanol-ethyl acetate or ethyl acetate-dichloromethane to yield pure **4a**{*1,1,1*}−**4zii**{*8,1,1*} or **5a**{*2,10,1*}−**5g**{*5,10,1*}. The air-dried product showed a single spot on TLC and was pure enough for all analytical purposes.

*Methyl 6-(4-Chlorophenyl)-4-(4-methoxyphenyl)-5-nitro-2-oxopiperidine-3-carboxylate (**4a**{1,1,1}):* White solid; mp 222−223 °C (MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.31 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.06

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(d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.08 (s, 1H), 5.05 (d, J = 9.6 Hz, 1H), 4.82 (dd, J = 9.6 and 10.8 Hz, 1H), 4.10 (dd, J = 10.8 and 12.0 Hz, 1H), 3.75 (d, J = 12.0 Hz, 1H), 3.70 (s, 3H), 3.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.97, 166.00, 159.90, 136.14, 134.00, 129.82(2C), 128.54(2C), 128.27(2C), 126.06, 114.76(2C), 91.86, 59.77, 55.22, 54.36, 52.98, 46.08; IR (KBr, cm^{-1}) 3178, 3068, 2948, 1727, 1683, 1555, 1517, 1347, 1256, 1186, 1014, 827; MS(EI) (m/z) 418.09 [$(M - 1)^+$] (68%); Anal. Calcd for $C_{20}H_{19}ClN_2O_6$ (%) C 57.35, H 4.57, N 6.69; found C 57.48, H 4.40, N 6.78.

*Methyl 6-(2-Chlorophenyl)-4-(4-methoxyphenyl)-5-nitro-2-oxopiperidine-3-carboxylate (**5d**{1,10,1}):* White solid; mp 257−258 °C (MeOH/CH_2Cl_2); ^{1}H NMR (DMSO-d_6, 600 MHz) δ (ppm) 8.68 (s, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.36−7.40 (m, 2H), 7.32 (d, J = 7.2 Hz, 1H), 7.21 (d, J = 7.8 Hz, 2H), 6.92 (d, J = 7.8 Hz, 2H), 5.77 (d, J = 4.2 Hz, 1H), 5.35 (dd, J = 4.2 and 4.2 Hz, 1H), 4.56 (dd, J = 11.4 and 4.2 Hz, 1H), 4.30 (d, J = 13.2 Hz, 1H), 3.72 (s, 3H), 3.55 (s, 3H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ (ppm) 169.43, 166.56, 159.06, 133.11, 131.48, 130.34, 129.47, 128.36, 128.15, 127.59, 127.40, 114.45, 87.30, 55.00, 53.89, 52.29, 48.20, 41.30; IR (KBr, cm^{-1}): 3192, 3074, 2951, 1750, 1683, 1552, 1514, 1379, 1255, 1030, 837; MS(EI) (m/z) 417.07 [$(M - 1)^+$] (100%); Anal. Calcd for $C_{20}H_{19}ClN_2O_5$ (%) C 57.35, H 4.57, N 6.69; Found C 57.44, H 4.62, N 6.52.

■ 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.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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(8) See Supporting Information.