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PII: S0040-4020(17)30331-9

DOI: 10.1016/j.tet.2017.03.074

Reference: TET 28580

To appear in: *Tetrahedron*

Received Date: 8 February 2017

Revised Date: 20 March 2017

Accepted Date: 21 March 2017

Please cite this article as: Zhao D, Zhu Y, Guo S, Chen W, Zhang G, Yu Y, A three-component one-pot synthesis of penta-substituted pyrroles via ring opening of α-nitroepoxides, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.03.074.

Graphical Abstract

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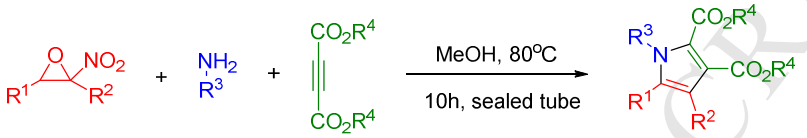
Zhejiang Province Key Laboratory of Anti-Cancer Drug Research, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, P. R. China



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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

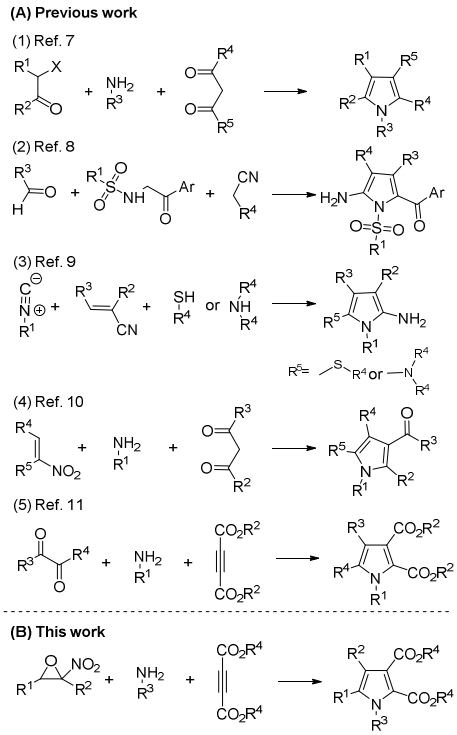
Keywords:
penta-substituted pyrroles
α-nitroepoxides
primary amines
dialkyl acetylenedicarboxylates
one-pot synthesis

ABSTRACT

A novel and facile one-pot reaction has been developed to synthesize a variety of penta-substituted pyrroles from α-nitroepoxides, primary amines and dialkyl acetylenedicarboxylates under the conditions without catalyst. Furthermore, the controlled experiments has been performed and a possible mechanism has also been proposed.

1. Introduction

Pyrrole is one of the most important simple heterocycles, and many substituted or functionalized pyrrole derivatives are widely used in different fields.[1] In pharmaceutical field, pyrrole ring as an important structural unit widely exists in natural and unnatural products showing different bioactivities, such as antibiotics,[2] anti-HIV agents,[3] anti-inflammatory agents,[4] immunosuppressive and anticancer agents.[5] So the synthesis of various polysubstituted pyrroles is improtant, and a variety of synthetic strategies have been developed,[6] such as the Hantzsch method or modified Hantzsch methodologies using α-haloketones, ammonia or primary amines and β-dicarbonyl compounds as substrates (Scheme 1-A, Eq. 1),[7] the reaction of aldehydes, N-(substituted sulfonamido) acetophenones and α-activated nitriles (Scheme 1-A, Eq. 2),[8] the synthesis method using isonitriles as the source of the heterocyclic nitrogen (Scheme 1-A, Eq. 3),[9] the reaction of nitroalkenes, amines and 1,3-dicarbonyl compounds (Scheme 1-A, Eq. 4),[10] the reaction of glyoxals or α-diketones, primary amines and dialkyl acetylenedicarboxylates which needs other additives (Scheme 1-A, Eq. 5).[11] Although these strategies have been developed, the synthesis of penta-substituted pyrroles from readily available starting materials under simple conditions remains in demand. So, we develop a facile one-pot method to provide penta-substituted pyrroles via α-nitroepoxides, primary amines and dialkyl acetylenedicarboxylates (Scheme 1-B).

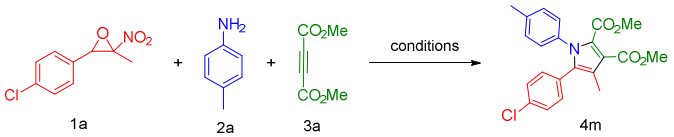


Scheme 1. Previous and New Synthesis of Polysubstituted pyrrole Derivatives

2. Results and discussion

* Corresponding author. Tel./fax: +86-571-8820-8450, +86-571-8820-8452; e-mail addresses: guolinzhang@zju.edu.cn (G. Zhang), yyu@zju.edu.cn (Y. Yu).

Table 1. Optimization of Reaction Conditions [a]



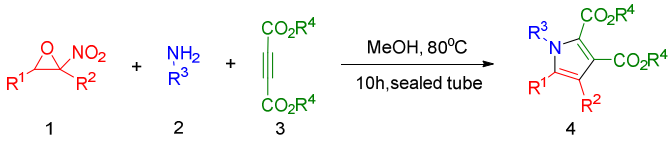
Entry	Base (equiv.)	Solvent	T(°C)	1a:2a:3a (equiv.)	Conversion[c] (%)
1	K_2CO_3 (1)	MeOH	80	1:1:1.05	25
2	Et_3N (1)	MeOH	80	1:1:1.05	33
3	DIEA (1)	MeOH	80	1:1:1.05	45
4	-	MeOH	80	1:1:1.05	92(90)[d]
5	-	EtOH	80	1:1:1.05	78
6	-	n-propanol	80	1:1:1.05	23
7	-	n-butyl alcohol	80	1:1:1.05	trace
8	-	t-butanol	80	1:1:1.05	12
9	-	CH_2Cl_2	80	1:1:1.05	n.r.
10	-	CH_3CN	80	1:1:1.05	n.r.
11	-	DMF	80	1:1:1.05	n.r.
12	-	MeOH	RT	1:1:1.05	11
13	-	MeOH	50	1:1:1.05	12
14[b]	-	MeOH	Reflux	1:1:1.05	69
15	-	MeOH	100	1:1:1.05	40
16	-	MeOH	80	1:1:1	90(88)[d]
17	-	MeOH	80	1:1.05:1	83
18	-	MeOH	80	1:1.1:1.1	79

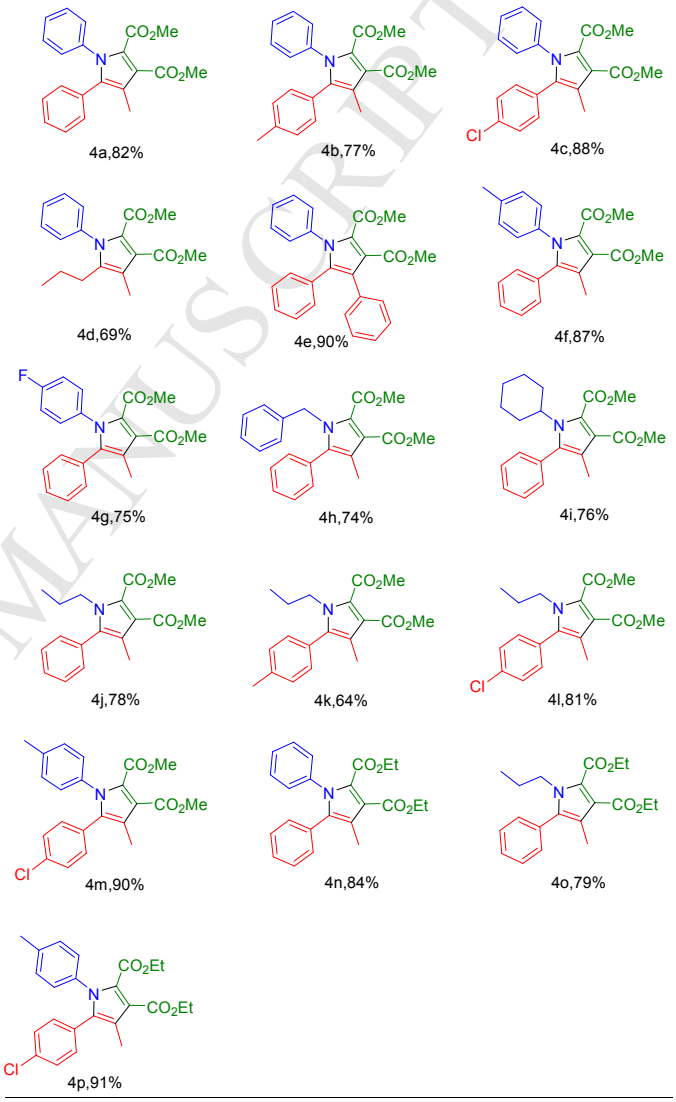
[a]Reaction conditions: 3-(4-chlorophenyl)-2-methyl-2-nitrooxirane (0.5 mmol, 1.0 equiv.), *p*-toluidine and dimethyl acetylenedicarboxylate, base, 3 mL of solvent, 10 h, in sealed tube. [b]Reaction was performed in reflux device. [c]Determined by high-performance liquid chromatography, based on the disappearance of the starting 3-(4-chlorophenyl)-2-methyl-2-nitrooxirane. [d]Isolated yields.

Initially, 3-(4-chlorophenyl)-2-methyl-2-nitrooxirane **1a**, *p*-toluidine **2a** and dimethyl acetylenedicarboxylate **3a** were selected as reagents to optimize the reaction conditions. Firstly, screening of bases (Table 1, entries 1–4) revealed that the good conversion occurred under the conditions without any additive (Table 1, entry 4). Then, the optimization of solvent demonstrated that MeOH (Table 1, entry 4) was superior to other aprotic and protic solvents (Table 1, entries 5–11). In addition, when the reaction was conducted at different temperatures, the conversion decreased in different degrees (Table 1, entries 12–15). Furthermore, when changing the ratio of reaction substrates, the conversion of the reaction slightly decreased (Table 1, entries 16–18). On the basis of the initial study, the optimal reaction conditions was obtained, that is, 3-(4-chlorophenyl)-2-methyl-2-nitrooxirane **1a**, *p*-toluidine **2a** and dimethyl acetylenedicarboxylate **3a** were conducted in sealed tube at 80°C for 10 h with MeOH as solvent (Table 1, entry 4).

Subsequently, the scope of the reaction was studied using a set of α-nitroepoxides **1**, primary amines **2** and dialkyl acetylenedicarboxylates **3** under the optimized reaction conditions. The α-nitroepoxides were prepared through the straightforward epoxidation of nitroalkenes, which could be readily obtained by standard nitroaldol/Henry reaction.[12] The results were shown in Table 2. On the whole, the desired products of all reactions were obtained in the yield of 64% ~ 91%.

Table 2. Scope of the Reaction of α-Nitroepoxides, Primary amines and Dialkyl acetylenedicarboxylates Under Optimal Conditions [a]



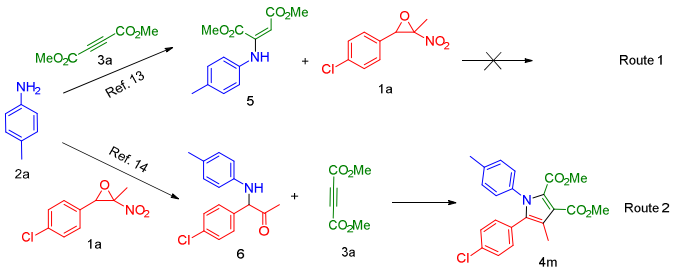


[a]Reaction conditions: all reactions were conducted under the conditions from Table 1, entry 4. Isolated yields.

No matter aryl or alkyl substitution at R^1 and R^2 positions of nitroepoxides **1** could give the corresponding products in good yields (**4a**-**4e**), especially, the yield of **4e** with phenyl at the R^1 and R^2 positions was 90%. Moreover, both aliphatic amines and aromatic amines were reactive (**4a**, **4f**-**4j**), and aromatic amines afforded the desired products in a higher yield than aliphatic amines (**4a** compared to **4j**, **4b** compared to **4k**, **4c** compared to **4l**). Furthermore, the yields of reactions using diethyl acetylenedicarboxylate or dimethyl acetylenedicarboxylate were basically the same and just had slightly difference (**4n** compared to **4a**, **4o** compared to **4j**, **4p** compared to **4m**). In our experiments, the highest yield was obtained, when 3-(4-

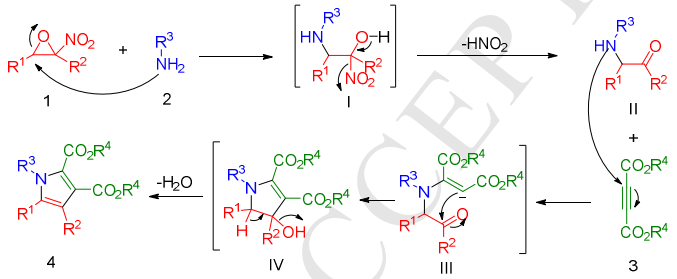
chlorophenyl)-2-methyl-2-nitrooxirane, *p*-toluidine and diethyl acetylenedicarboxylate were used as the reagents (**4p**).

In order to study the proposed mechanism of this reaction, the controlled experiments were performed (Scheme 2). Firstly, the possible intermediates **5** and **6** were obtained by separately treating 3-(4-chlorophenyl)-2-methyl-2-nitrooxirane **1a** and dimethyl acetylenedicarboxylate **3a** with *p*-toluidine **2a**.[13,14] Then, intermediate **5** and 3-(4-chlorophenyl)-2-methyl-2-nitrooxirane **1a** reacted under the optimal reaction conditions above (Route 1), meanwhile, intermediate **6** and dimethyl acetylenedicarboxylate **3a** reacted under the same conditions (Route 2). The result was that only the Route 2 proceeded effectively to give the desired product **4m**.



Scheme 2. Controlled Experiments

Based on the results presented above, a possible reaction mechanism is proposed as shown in Scheme 3. In the case of amine **2**, the nitroepoxide **1** is attacked by the lone-pair electrons on the nitrogen of amine **2** and undergoes a ring opening to give the intermediate **I**. The intermediate **I** affords the intermediate **II** driven by the excellent leaving ability of nitro.[15] Then, the lone-pair electrons on the nitrogen of intermediate **II** continues to attack dialkyl acetylenedicarboxylates **3** orderly forming the intermediate **III** and **IV**. Subsequently, intermediate **IV** transforms into final product **4** by eliminating one molecule of H_2O.



Scheme 3. Proposed Mechanism

3. Conclusion

In conclusion, we have developed a novel, one-pot three-component strategy to synthesize penta-substituted pyrroles from α-nitroepoxides, primary amines and dialkyl acetylenedicarboxylates. This reaction was finished in good yields via a ring opening, an intermolecular nucleophilic attack and an intramolecular condensation. Due to the advantage of operational simplicity and no need for any additives, this reaction would be a practical strategy for pharmaceutical building blocks. The structures of the penta-substituted pyrroles **4** were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.

4. Experimental section

4.1 General

All solvents were purified according to standard methods prior to use. Melting points were recorded on a BÜCHI B-540 melting point apparatus. NMR spectra were recorded for ^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz. For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard (δ=0) and data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t= triplet, q=quartet, m=multiplet), and coupling constant(s) in Hertz. For ^{13}C NMR, TMS (δ=0) or DMSO (δ=40.45) was used as internal standard and spectra were obtained with complete proton decoupling. LC-MS and HRMS data was obtained using Agilent Technologies 6224 TOF LC/MS. The starting material α-nitroepoxides were prepared according to literature methods.[11] The starting material primary amines and dialkyl acetylenedicarboxylates were commercially available. The intermediates **5** and **6** were prepared according to literature methods.[12, 13]

4.2 *General procedure for the synthesis of penta-substituted pyrroles 4*

A mixture of α-nitroepoxide **1** (0.5 mmol, 1.0 equiv.) and primary amine **2** (0.5 mmol, 1.0 equiv.) in MeOH (3 mL) was stirred at 80°C oil bath. After 3 min, dialkyl acetylenedicarboxylate **3** (0.525 mmol, 1.05 equiv.) was added dropwise. The mixture was unceasingly stirred in sealed tube at 80°C oil bath for 10h (TLC monitoring). After completion, the solvent MeOH was evaporated in vacuo and the residue was treated with column chromatography (silica gel, 5–8% EtOAc/hexane) to give pure penta-substituted pyrroles **4a-4p**.

*4.2.1 Dimethyl 4-methyl-1,5-diphenyl-1H-pyrrole-2,3-dicarboxylate **(4a)***. Pale yellow solid; yield: 82% (0.1431g); mp: 134.3~134.7°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 3H), 7.22 – 7.19 (m, 3H), 7.11 – 7.09 (m, 2H), 7.04 (m, 2H), 3.90 (s, 3H), 3.67 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.98, 161.72, 137.99, 135.89, 130.73, 130.60, 128.44, 128.11, 127.96, 127.67, 125.86, 119.55, 118.46, 52.01, 51.73, 10.66. HRMS (ESI): m/z calcd for $C_{21}H_{20}NO_4$ $[M+H]^+$: 350.1387, found: 350.1387.

*4.2.2 Dimethyl 4-methyl-1-phenyl-5-(p-tolyl)-1H-pyrrole-2,3-dicarboxylate **(4b)***. Pale yellow solid; yield: 77% (0.1398g); mp: 149.7~150.3°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 3H), 7.12 – 7.09 (m, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.94 – 6.91 (m, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 2.27 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.08, 161.70, 138.10, 137.47, 136.06, 130.55, 128.71, 128.42, 128.14, 128.07, 127.57, 125.53, 119.67, 118.27, 51.97, 51.73, 21.19, 10.67. HRMS (ESI): m/z calcd for $C_{22}H_{22}NO_4$ $[M+H]^+$: 364.1543, found: 364.1549.

*4.2.3 Dimethyl 5-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyrrole-2,3-dicarboxylate **(4c)***. Pale yellow solid; yield: 88% (0.1685g); mp: 156.8~157.6°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 3H), 7.20 – 7.17 (m, 2H), 7.10 – 7.07 (m, 2H), 6.98 – 6.95 (m, 2H), 3.89 (s, 3H), 3.67 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.77, 161.63, 137.72, 134.44, 133.82, 131.92, 129.07, 128.64, 128.36, 128.33, 128.05, 126.34, 119.45, 118.80, 52.09, 51.77, 10.66. HRMS (ESI): m/z calcd for $C_{21}H_{19}ClNO_4$ $[M+H]^+$: 384.0997, found: 384.0999.

*4.2.4 Dimethyl 4-methyl-1-phenyl-5-propyl-1H-pyrrole-2,3-dicarboxylate **(4d)***. Yellow liquid; yield: 69% (0.1087g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 3H), 7.22 – 7.19 (m, 2H), 3.87 (s, 3H), 3.60 (s, 3H), 2.31 (t, 2H), 2.15 (s, 3H), 1.33 – 1.25 (m, 2H), 0.75 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz,

$CDCl_3$) δ 166.70, 161.05, 138.16, 136.82, 128.80, 128.67, 128.02, 122.98, 120.89, 116.55, 51.87, 51.66, 26.35, 22.68, 13.79, 9.96. HRMS (ESI): m/z calcd for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1543, found: 316.1543.

4.2.5 Dimethyl 1,4,5-triphenyl-1H-pyrrole-2,3-dicarboxylate ***(4e)***. Yellow solid; yield: 90% (0.1850g); mp: 162.1~162.9°C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 3H), 7.20 – 7.15 (m, 7H), 7.12 – 7.08 (m, 1H), 7.07 – 7.03 (m, 2H), 6.92 – 6.89 (m, 2H), 3.80 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.77, 160.49, 138.04, 137.10, 133.26, 131.13, 130.14, 129.85, 128.50, 128.42, 128.37, 128.00, 127.83, 127.79, 126.76, 123.04, 122.86, 122.49, 52.33, 51.91. HRMS (ESI): m/z calcd for $C_{26}H_{22}NO_4$ $[M+H]^+$: 412.1543, found: 412.1545.

4.2.6 Dimethyl 4-methyl-5-phenyl-1-(p-tolyl)-1H-pyrrole-2,3-dicarboxylate ***(4f)***. Pale yellow solid; yield: 87% (0.1580g); mp: 132.7~133.2°C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.20 (m, 3H), 7.06 – 7.03 (m, 4H), 6.98 (m, 2H), 3.89 (s, 3H), 3.68 (s, 3H), 2.29 (s, 3H), 2.18 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 166.03, 161.82, 137.98, 135.89, 135.33, 130.74, 130.70, 129.10, 127.94, 127.77, 127.59, 125.90, 119.31, 118.34, 52.03, 51.71, 21.13, 10.69. HRMS (ESI): m/z calcd for $C_{22}H_{22}NO_4$ $[M+H]^+$: 364.1543, found: 364.1548.

4.2.7 Dimethyl 1-(4-fluorophenyl)-4-methyl-5-phenyl-1H-pyrrole-2,3-dicarboxylate ***(4g)***. White solid; yield: 75% (0.1377g); mp: 135.5~136.0°C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.21 (m, 3H), 7.10 – 7.07 (m, 2H), 7.04 – 7.02 (m, 2H), 6.96 – 6.91 (m, 2H), 3.90 (s, 3H), 3.69 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.06, 162.94, 161.47, 160.96, 136.34, 133.99, 133.96, 130.71, 130.32, 129.94, 129.87, 128.12, 127.88, 125.28, 120.29, 118.46, 115.55, 115.37, 52.08, 51.90, 10.61. HRMS (ESI): m/z calcd for $C_{21}H_{19}FNO_4$ $[M+H]^+$: 368.1293, found: 368.1294.

4.2.8 Dimethyl 1-benzyl-4-methyl-5-phenyl-1H-pyrrole-2,3-dicarboxylate ***(4h)***. Colorless liquid; yield: 74% (0.1344g); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 3H), 7.22 – 7.16 (m, 5H), 6.80 (d, *J* = 6.8 Hz, 2H), 5.33 (s, 2H), 3.88 (s, 3H), 3.72 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.57, 161.66, 138.10, 137.14, 130.75, 130.58, 128.61, 128.54, 128.43, 127.12, 126.04, 122.51, 121.58, 118.28, 51.85, 49.30, 10.39. HRMS (ESI): m/z calcd for $C_{22}H_{22}NO_4$ $[M+H]^+$: 364.1543, found: 364.1543.

4.2.9 Dimethyl 1-cyclohexyl-4-methyl-5-phenyl-1H-pyrrole-2,3-dicarboxylate ***(4i)***. White solid; yield: 76% (0.1350g); mp: 124.0~126.5°C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 3H), 7.26 – 7.23 (m, 2H), 3.98 -3.91 (m, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 1.97 (s, 3H), 1.86 – 1.82 (m, 4H), 1.72 (d, *J* = 12.8 Hz, 2H), 1.53 (d, *J* = 10.4 Hz, 1H), 1.11 – 1.04 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.89, 164.14, 134.76, 132.04, 131.12, 128.47, 128.42, 125.31, 118.07, 117.58, 59.06, 52.49, 51.43, 32.71, 26.23, 25.02, 10.70. HRMS (ESI): m/z calcd for $C_{21}H_{26}NO_4$ $[M+H]^+$: 356.1856, found: 356.1857.

4.2.10 Dimethyl 4-methyl-5-phenyl-1-propyl-1H-pyrrole-2,3-dicarboxylate ***(4j)***. Colorless liquid; yield: 78% (0.1229g); ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 3H), 7.28 – 7.25 (m, 2H), 4.02 (dd, *J* = 8.4, 6.7 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 1.98 (s, 3H), 1.55 – 1.47 (m, 2H), 0.67 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.83, 161.79, 136.68, 131.07, 130.74, 128.58, 128.51, 121.64, 121.23, 117.80, 51.84, 51.82, 47.53, 24.78, 10.94, 10.21. HRMS (ESI): m/z calcd for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1543, found: 316.1548.

4.2.11 Dimethyl 4-methyl-1-propyl-5-(p-tolyl)-1H-pyrrole-2,3-dicarboxylate ***(4k)***. Colorless liquid; yield: 64% (0.1053g); ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.24 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.03 – 3.99 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.41 (s, 3H), 1.97 (s, 3H), 1.55 – 1.47 (m, 2H), 0.68 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.91, 161.78, 138.39, 136.82, 130.58, 129.29, 128.03, 121.41, 121.27, 117.70, 51.79, 47.50, 24.79, 21.34, 10.95, 10.22. HRMS (ESI): m/z calcd for $C_{19}H_{24}NO_4$ $[M+H]^+$: 330.1700, found: 330.1703.

4.2.12 Dimethyl 5-(4-chlorophenyl)-4-methyl-1-propyl-1H-pyrrole-2,3-dicarboxylate ***(4l)***. Pale yellow solid; yield: 81% (0.1414g); mp: 66.7~67.4°C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.22 – 7.19 (m, 2H), 4.02 – 3.98 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 1.97 (s, 3H), 1.54 – 1.46 (m, 2H), 0.68 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ166.60, 161.74, 135.16, 134.72, 132.05, 129.51, 128.95, 122.20, 121.14, 118.12, 51.92, 51.84, 47.54, 24.79, 10.93, 10.19. HRMS (ESI): m/z calcd for $C_{18}H_{21}ClNO_4$ $[M+H]^+$: 350.1154, found: 350.1156.

4.2.13 Dimethyl 5-(4-chlorophenyl)-4-methyl-1-(p-tolyl)-1H-pyrrole-2,3-dicarboxylate ***(4m)***. White solid; yield: 90% (0.1787g); mp: 132.4~133.0°C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 7.98 – 6.95 (m, 4H), 3.88 (s, 3H), 3.68 (s, 3H), 2.31 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.88, 161.75, 138.30, 135.03, 134.48, 133.71, 131.93, 129.32, 129.14, 128.33, 127.72, 126.30, 119.22, 118.65, 52.16, 51.81, 21.19, 10.71. HRMS (ESI): m/z calcd for $C_{22}H_{21}ClNO_4$ $[M+H]^+$: 398.1154, found: 398.1159.

4.2.14 Diethyl 4-methyl-1,5-diphenyl-1H-pyrrole-2,3-dicarboxylate ***(4n)***. Pale yellow solid; yield: 84% (0.1584g); mp: 99.8~100.6°C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 3H), 7.22 – 7.19 (m, 3H), 7.12 – 7.09 (m, 2H), 7.05-7.02 (m, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.19 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.61, 161.22, 138.12, 135.65, 130.73, 130.65, 128.42, 128.19, 128.08, 127.96, 127.62, 125.91, 119.71, 118.31, 60.97, 60.63, 14.32, 13.84, 10.65. HRMS (ESI): m/z calcd for $C_{23}H_{24}NO_4$ $[M+H]^+$: 378.1700, found: 378.1701.

4.2.15 Diethyl 4-methyl-5-phenyl-1-propyl-1H-pyrrole-2,3-dicarboxylate ***(4o)***. Pale yellow liquid; yield: 79% (0.1356g); ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 3H), 7.27 – 7.24 (m, 2H), 4.32 (dq, *J* = 12.0, 7.1 Hz, 4H), 4.03 – 3.99 (m, 2H), 1.97 (s, 3H), 1.56 – 1.48 (m, 2H), 1.35 (dt, *J* = 12.7, 7.1 Hz, 6H), 0.68 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.52, 161.29, 136.53, 131.16, 130.75, 128.56, 128.46, 121.60, 121.50, 117.51, 60.70, 60.69, 47.52, 24.82, 14.35, 14.15, 10.99, 10.16. HRMS (ESI): m/z calcd for $C_{20}H_{26}NO_4$ $[M+H]^+$: 344.1856, found: 344.1856.

4.2.16 Diethyl 5-(4-chlorophenyl)-4-methyl-1-(p-tolyl)-1H-pyrrole-2,3-dicarboxylate ***(4p)***. White solid; yield: 91% (0.1934g); mp: 128.7~129.4°C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.17 (m, 2H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.98 – 6.95 (m, 4H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 2.17 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.45, 161.22, 138.23, 135.18, 134.26, 133.64, 131.93, 129.25, 128.30, 127.81, 126.41, 119.39, 118.51, 61.05, 60.62, 21.17, 14.31, 13.86, 10.66. HRMS (ESI): m/z calcd for $C_{24}H_{25}ClNO_4$ $[M+H]^+$: 426.1467, found: 426.1467.

Acknowledgements

This project was supported from Zhejiang Provincial Natural Science Foundation of China (LY16H300001) to G. Zhang, National Natural Science Foundation of China (No. 81273356 and 81473074), National Science & Technology Major Projects for "Major New Drugs Innovation and Development" of China

(2014ZX09304002-007) and Osteoporosis & Breast Cancer Research Center, USA to Y. Yu, National Natural Science Foundation of China (No. 81402778) to W. Chen.

Supplementary data

Supplementary data (Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all products.) associated with this article can be found in online version at http://dx.doi.org/

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13. Synthesis of intermediate **5**: A mixture of dimethyl acetylenedicarboxylate **3a** (1.0 mmol, 1.0 eq.) and *p*-toluidine **2a** (1.0 mmol, 1.0 eq.) in MeOH (2 mL) was stirred in an oven-dried sealed tube at 80 °C for 6 h (TLC indicated that the reaction was complete). After cooling to room temperature, the reaction was concentrated and then purified through silica gel column chromatography to afford the intermediate **5**. See: Liu, J.; Wei, W.; Zhao, T. *J. Org. Chem.* **2016**, *81*, 9326.
14. Synthesis of intermediate **6**: A mixture of 3-(4-chlorophenyl)-2-methyl-2- nitrooxirane **1a** (1.0 mmol), p-toluidine **2a** (1.5 mmol, 1.5 eq.) was stirred in n-propanol (10.0 mL) at 25°C for 0.5 h. After the completeness of the reaction, the mixture was diluted with water and extracted three times with $CHCl_3$ (3 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (DCM/MeOH) on silica gel to afford intermediate **6**. See: Guo, X.; Chen, W.; Chen, B. *Org. Lett.* **2015**, *17*, 1157.
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