Journal of Organometallic Chemistry 693 (2008) 3897–3901

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Practical one-pot sequential procedure for the preparation of *N*-arylated 3,4-disubstituted pyrroles from alkenes

Rui Zhu, Lixin Xing, Yantao Liu, Fangkun Deng, Xinyan Wang *, Yuefei Hu *

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, PR China

ARTICLE INFO

Article history:
Received 2 September 2008
Received in revised form 18 September 2008
Accepted 25 September 2008
Available online 4 October 2008

Keywords:
Alkenes
Arylations
Copper
Coupling
Pyrroles

ABSTRACT

By using ^{t}BuONa and Cs_2CO_3 as a mixed base, van Leusen pyrrole synthesis and copper-catalyzed *N*-arylation of pyrrole proceeded sequentially in a single flask to give *N*-arylated 3,4-disubstituted pyrroles smoothly. Thus, a series of desired *N*-arylated pyrroles were prepared directly from the electron-deficient alkenes.

1. Introduction

N-Arylated substituted pyrroles have been found very important applications in pharmaceutical researches [1–13]. Paal-Knorr pyrrole synthesis offered a classic route for their preparation, but with limitation by using pre-formed 1,4-diketones [8–13]. Recently, many alternative synthetic methods have been developed for this purpose. Prominent among them are those one-pot sequential procedures [14–19], by which the *N*-arylated substituted pyrroles were prepared directly from simple, readily available and easily varied substrates. They also can be considered to fall under the banner of "green chemistry" because only a single reaction solvent, work-up procedure, and purification step was required.

In our recent project on chemical biology, a variety of *N*-arylated 3,4-disubstituted pyrroles (**1**) were designed as synthetic intermediates. For a rapid access to structural diversity, a two-step route was designed including a van Leusen pyrrole synthesis [20] starting from alkenes (**2**) followed by an *N*-arylation (Scheme 1). In comparison with the other methods, Ullmann-type coupling of pyrroles (**3**) and arylhalides (**4**) was chosen for the *N*-arylation step because it represents a most straightforward and inexpensive approach [21]. Although many highly efficient ligand-mediated Ullmann-type couplings have been developed recently under mild conditions [22–31], we found that Buchwald's procedure [31] was the most suitable for the preparation of substituted pyrroles. Thus, a highly practical one-pot sequential procedure for the preparation of *N*-arylated 3,4-disubstituted pyrroles (**1**) starting from alkenes (**2**) was established as shown in Scheme 1.

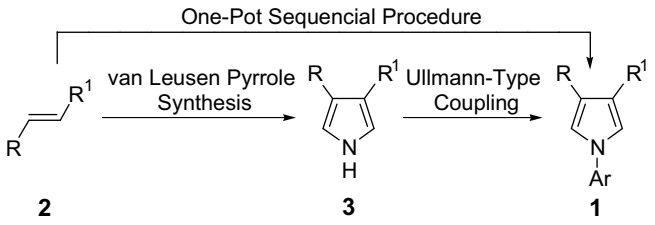
2. Results and discussion

It is well-known that van Leusen pyrrole synthesis is one of the most convenient methods for the preparation of 3,4-disubstituted pyrroles (**3**) by reaction of an electron-deficient alkene (**2**) and TosMIC (toluenesulphonylmethyl isocyanide) in the presence of a base. Although the desired pyrrole products usually were obtained in moderate yields, the method featured with readily available starting materials. For example, the mixture of ethyl 3-phenylacrylate (**2a**) and TosMIC in THF was treated with ^{t}BuONa at −30 °C for 10 min to give ethyl 4-phenylpyrrole-3-carboxylate (**3a**) in 56% yield [32]. Subsequently, **3a** underwent a copper-catalyzed *N*-arylation of iodobenzene (**4a**) to give ethyl 1,4-diphenylpyrrole-3-carboxylate (**1a**) under the conditions in Scheme 2. We interestingly found that the electron-withdrawing substituents on C3 and C4 of pyrroles facilitated the reaction time very much. For example, the *N*-arylation of pyrrole was finished around 23 h [31], while **1a** was produced in 80% yield within 8 h.

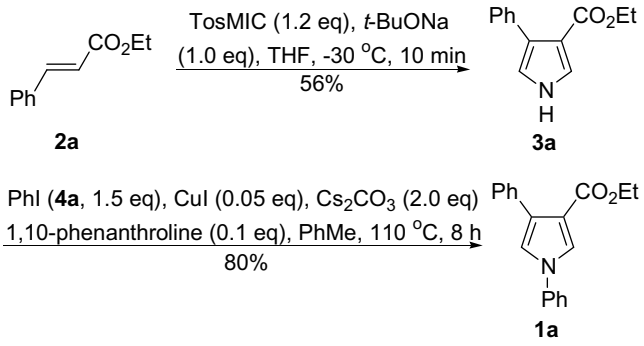
Since both steps were base-promoted reactions and van Leusen pyrrole synthesis proceeded very fast at −30 °C, we were encouraged to combine those two-steps into a one-pot sequential procedure without separation of the intermediate **3a**. Thus, the mixture of **2a**, TosMIC, PhI (**4a**), CuI, 1,10-phenanthroline in toluene was

* Corresponding authors. Tel.: +86 10 62795380; fax: +86 10 62771149.
E-mail address: yfh@mail.tsinghua.edu.cn (Y. Hu).

0022-328X/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2008.09.051



Scheme 1.



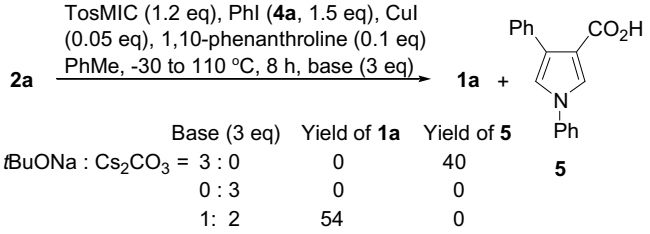
Scheme 2.

treated with 3.0 equiv. of ^{t}BuONa at −30 °C for 10 min and then the resultant mixture was refluxed until the intermediate **3a** was completely exhausted (monitored by TLC). Unfortunately, instead of the expected product **1a**, 1,4-diphenylpyrrole-3-carboxylic acid (**5**) was obtained in 40% yield, that must result from the fact that the ester group of **3a** was unstable to ^{t}BuONa in the *N*-arylation step (110 °C) (Scheme 3). To overcome this problem, we tried to use Cs_2CO_3 as a base, but **1a** was not obtained at all because Cs_2CO_3 is not strong enough to generate a carbanion of TosMIC. Finally, when 1:2 mixture of ^{t}BuONa and Cs_2CO_3 was used, **1a** was obtained as a single product and its total yield gained 10% more than that in two-step route. In this procedure, ^{t}BuONa served as a base for van Leusen pyrrole synthesis and Cs_2CO_3 for the *N*-arylation, respectively.

To optimize conditions, a brief screen for Cu resources and ligands was made by using **2a** as a substrate. As shown in Table 1, CuI (entry 1) and *N,N*'-dimethyl-ethyldiamine (entry 7) proved to be the best catalyst and ligand, respectively.

According to those experimental results, the optimized conditions for the one-pot sequential preparation of **1a** from **2a** were established as shown in Scheme 4 [33].

To generalize this novel procedure, the reactions of iodobenzene (**4a**) with different electron-deficient alkenes (**2a–j**) were tested under the optimized conditions. As shown in Table 2, all acrylate derivatives (**2a–d**) gave the corresponding *N*-arylpyrroles **1a–d** in satisfactory yields (entries 1–4). However, when chalcone



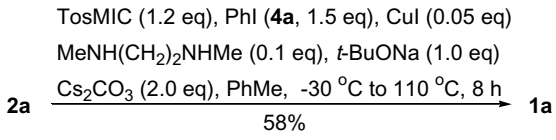
Scheme 3.

Table 1
A brief screen on Cu resources and ligands[a,b,c].

2a → (Copper and Ligand) → 1a

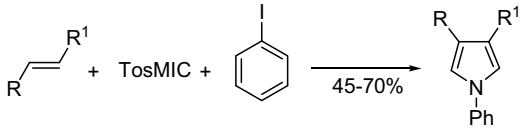
Entry	Cu source	Time (h)	Yield[d] (%)	Entry	Ligand	Time (h)	Yield[d] (%)
1	CuI	8	54	6	1,10-Phenanthroline	8	54
2	CuBr	8	50	7	$MeNH(CH_2)_2NHMe$	8	58
3	$Cu(OAc)_2$	10	30	8	$Me_2N(CH_2)_2NH_2$	24	Trace
4	CuO	10	24	9	Proline	24	20
5	Cu powder	8	20	10	2,2-Bipyridine	24	24

[a] The reaction proceeded with **2a** (3.0 mmol), TosMIC (3.6 mmol), **4a** (4.5 mmol), ^{t}BuONa (3 mmol), Cs_2CO_3 (6.0 mmol), copper (0.15 mmol), ligand (0.3 mmol) in toluene.
[b] 1,10-Phenanthroline was used as a ligand in entries 1–5.
[c] CuI was used in entries 6–10.
[d] Isolated yields were obtained.



Scheme 4.

Table 2
Preparation of **1a–j** from **2a–j** and **4a**[a,b,c].



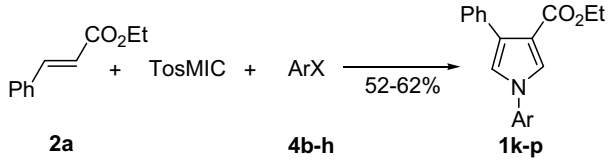
Entry	2 and 1 R	2 and 1 R^1	Time (h)	Yield of 1 (%)	Entry	2 and 1 R	2 and 1 R^1	Time (h)	Yield of 1 (%)
1(**a**)	Ph	CO_2Et	8	58	6(**f**)	Ph	COMe	10	50
2(**b**)	$PhCH_2$	CO_2Et	8	56	7(**g**)	Ph	CN	8	70
3(**c**)	CO_2Et	CO_2Et	6	52	8(**h**)	2-BrPh	COPh	8	66
4(**d**)	Me	CO_2Me	8	45	9(**i**)	4-MePh	COPh	8	68
5(**e**)	Ph	COPh	8	68	10(**j**)	4-NO_2Ph	COPh	7	62

[a] The conditions in Scheme 4 were used.
[b] Toluene was the solvent for entries 1–4 and DMF for entries 5–10.
[c] Isolated yields were obtained.

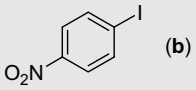
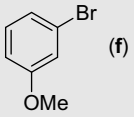
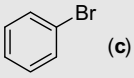
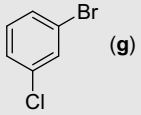
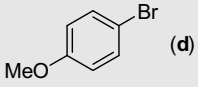
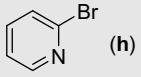
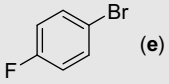
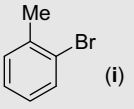
(**2e**) was used as a substrate, the intermediate 4-phenyl-3-benzoylpyrrole (**3e**) [34] was isolated instead of the expected *N*-arylated product 1,4-diphenyl-3-benzoylpyrrole (**1e**). The control experiments proved that this problem was caused by the fact that **3e** had a very bad solubility in toluene. The solution is to simply replace toluene with DMF, by which **1e** was obtained in 68% yield (entry 5). Under the similar conditions, the all other chalcone derivatives **2f–j** were converted into the corresponding **1f–j** smoothly (entries 6–10).

Then, the reactions of ethyl 3-phenylacrylate (**2a**) with different phenylhalides (**4b–i**) were tested under similar conditions (Table 3). Since bromobenzene (**4c**) gave a very close result with that of iodobenzene (**4a**) when prolonged reaction time was used (entry 2), the inexpensive phenylbromides (**4c–j**) were well employed for our purpose. It was clearly observed that a pyridine ring had

Table 3
Preparation of **1k–p** from **2a** and **4b–h**[a,b].



2a **4b-h** **1k-p**

Entry	Ar-X (**4**)	Time (h)	Yield of **1** (%)	Entry	Ar-X (**4**)	Time (h)	Yield of **1** (%)
1	 (**b**)	5	61 (**k**)	5	 (**f**)	24	56 (**n**)
2	 (**c**)	24	55 (**a**)	6	 (**g**)	24	58 (**o**)
3	 (**d**)	24	52 (**l**)	7	 (**h**)	5	62 (**p**)
4	 (**e**)	24	56 (**m**)	8	 (**i**)	24	0 (**q**)

[a] The conditions in Scheme 4 were used.
[b] Isolated yields was obtained.

much more reactivity than benzene rings. 2-Bromopyridine (**4h**) gave the product **1p** in the best yield in the shortest reaction time (entry 7). Like most reported results that 2-substitutents had hindered effects [22–31], the *N*-arylation of 1-bromo-2-methybenzene (**4i**) failed under our conditions (entry 8).

In conclusion, a highly practical one-pot sequential procedure for the preparation of *N*-arylated 3,4-disubstituted pyrroles was developed, which in fact proceeded through a van Leusen pyrrole synthesis followed by a ligand-mediated copper-catalyzed *N*-arylation of pyrroles. Although both reactions are promoted by bases, they could not share a common base because significantly different strengths of bases were required for each of them. When the mixture of *t*-BuONa and Cs_2CO_3 was used in the procedure, each step proceeded sequentially with extremely high orderliness and efficiency. By using the novel procedure, one work-up procedure was saved and total yields of the products were increased significantly. Thus, a series of *N*-arylated 3,4-disubstituted pyrroles were prepared directly from the electron-deficient alkenes. It can be expected that any alkenes suitable for van Leusen pyrrole synthesis can be converted into the corresponding *N*-arylated 3,4-disubstituted pyrroles conveniently by our procedure.

3. Experimental

All melting points were determined on a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer. The ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 300 spectrometer in $CDCl_3$ with TMS as internal reference. The *J* values are given in Hz. MS were recorded on a VG-ZAB-MS spectrometer with 70 eV. Elementary analysis data were obtained on a Perkin–Elmer-241C apparatus.

3.1. A typical procedure for one-pot sequential preparation of 1,4-diphenylpyrrole-3-carboxylic acid ethyl ester (*1a*)

To a stirred mixture of ethyl 3-phenylacrylate (**2a**, 530 mg, 3 mmol), TosMIC (700 mg, 3.6 mmol), PhI (**4a**, 920 mg, 4.5 mmol), CuI (29 mg, 0.15 mmol), $(MeNHCH_2)_2$ (26.5 mg, 0.3 mmol) and Cs_2CO_3 (1.95 g, 6 mmol) in toluene (30 mL) was treated with *t*-BuONa (300 mg, 3.15 mmol) at −25 °C under nitrogen. Ten minutes later, the system was heated to reflux for 8 h (monitored by TLC). Then the resultant mixture was cooled to room temperature and H_2O was added respectively. After it filtered through a pad of Celite (eluted by CH_2Cl_2), the organic layer was separated and washed with H_2O, brine and dried over Na_2SO_4. Removal of the solvent yielded the crude product, which was purified by chromatography (PE:EtOAc:DCM = 10:1:1) to give pure product **1a** (510 mg, 58%) as colorless crystals.

The similar procedure was used in the preparation of **1b–p**. DMF was used as a reaction solvent in the **1e-j** in Table 1.

3.1.1. 1,4-Diphenylpyrrole-3-carboxylic acid ethyl ester (*1a*)

M.p. 68–70 °C (EtOAc-PE). IR: ν 3141, 3049, 1672, 1601 cm^{-1}. ^1H NMR: δ 7.77 (d, J = 2.7 Hz, 1H), 7.58–7.28 (m, 10H), 7.07 (d, J = 2.7 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 164.1, 139.1, 134.1, 129.5, 129.0, 128.1, 127.5, 126.6, 126.5, 125.6, 120.3, 119.3, 115.1, 59.4, 14.1. MS *m/z* (%): 291 (M^+, 100). Anal. Calc. for $C_{19}H_{17}NO_2$ (291.34): C, 78.33; H, 5.88; N, 4.81. Found: C, 78.03; H, 5.78; N, 4.85%.

*3.1.2. 1-Phenyl-4-benzylpyrrole-3-carboxylic acid ethyl ester (**1b**)*

M.p. 60–61 °C (EtOAc-PE). IR: *v* 3135, 3054, 2976, 1694, 1599 cm^{-1}. ^1H NMR: δ 7.69 (d, *J* = 2.0 Hz, 1H), 7.42–7.19 (m, 10H), 6.61 (d, *J* = 2.1 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.15 (s, 2H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR: δ 164.8, 141.1, 139.6, 129.5, 128.8, 128.2, 127.0, 126.4, 125.7, 125.0, 120.5, 119.5, 116.0, 59.4, 32.4, 14.4. MS *m/z* (%): 305 (M^+, 36.6), 259 (100). Anal. Calc. for $C_{20}H_{19}NO_2$ (305.37): C, 78.66; H, 6.27; N, 4.59. Found: C, 78.77; H, 6.19; N, 4.58%.

*3.1.3. 1-Phenylpyrrole-3,4-dicarboxylic acid diethyl ester (**1c**)*

M.p. 46–48 °C (EtOAc-PE) (lit. [34] 48 °C). ^1H NMR: δ 7.60 (s, 2 H), 7.48–7.42 (m, 5H), 4.33 (q, *J* = 7.2 Hz, 4H), 1.37 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR: δ 163.1, 138.7, 129.7, 127.4, 125.7, 120.8, 117.6, 60.1, 14.1.

*3.1.4. 1-Phenyl-4-methylpyrrole-3-carboxylic acid methyl ester (**1d**) [35]*

Colorless oil. ^1H NMR: δ 7.64 (d, *J* = 2.4 Hz, 1H), 7.42–7.27 (m, 5H), 6.82 (d, *J* = 2.4 Hz, 1H), 3.82 (s, 3H), 2.33 (s, 3H). ^{13}C NMR: δ 165.0, 139.2, 129.2, 126.0, 124.3, 122.6, 119.8, 118.5, 115.9, 50.2, 11.3.

*3.1.5. 1,4-Diphenyl-3-benzoylpyrrole (**1e**)*

M.p. 118–120 °C (EtOAc-PE). IR: *v* 3270, 3116, 1644, 1630, 1596 cm^{-1}. ^1H NMR: δ 7.85 (d, *J* = 7.3 Hz, 2H), 7.47–7.17 (m, 15H). ^{13}C NMR: δ 191.1, 139.5, 139.3, 134.1, 131.7, 129.7, 129.4, 128.7, 128.6, 127.9, 127.1, 126.9, 126.5, 123.5, 120.7, 119.9. MS *m/z* (%): 323 (M^+, 100), 246 (65.8), 77 (80). Anal. Calc. for $C_{23}H_{17}NO$ (323.39): C, 85.42; H, 5.30; N, 4.33. Found: C, 85.31; H, 5.28; N, 4.37%.

*3.1.6. 1,4-Diphenyl-3-acetylpyrrole (**1f**)*

Light yellow oil. IR: *v* 3128, 2923, 1716, 1655, 1598 cm^{-1}. ^1H NMR: δ 7.69 (d, *J* = 1.5 Hz, 1H), 7.50–7.34 (m, 10H), 7.05 (d, *J* = 1.5 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR: δ 193.6, 139.2, 134.4, 129.6, 129.1, 127.7, 127.6, 126.8, 126.7, 125.6, 124.9, 120.6, 120.3, 28.5. MS *m/z* (%): 261 (M^+, 67.8), 247 (18.9), 246 (100), 77 (45.5). Anal. Calc. for $C_{18}H_{15}NO$ (261.32): C, 82.73; H, 5.79; N, 5.36. Found: C, 82.70; H, 5.89; N, 5.33%.

*3.1.7. 1,4-Diphenyl-3-cyanopyrrole (**1g**)*

M.p. 87–88 °C (EtOAc-PE). IR: *v* 3142, 3127, 3051, 2221, 1598 cm^{-1}. ^1H NMR: δ 7.68 (d, *J* = 3.8 Hz, 2H), 7.58–7.24 (m, 10H). ^{13}C NMR: δ 138.6, 132.1, 129.7, 128.6, 128.1, 127.5, 127.4, 127.2, 126.2, 120.7, 117.7, 116.2, 93.3. MS *m/z* (%): 244 (M^+, 100). Anal. Calc. for $C_{17}H_{12}N_2$ (244.29): C, 83.58; H, 4.95; N, 11.47. Found: C, 83.65; H, 4.89; N, 11.40%.

*3.1.8. 1-Phenyl-4-(2-bromophenyl)-3-benzoylpyrrole (**1h**)*

M.p. 142–143 °C (EtOAc-PE). IR: *v* 3127, 3066, 1640, 1594 cm^{-1}. ^1H NMR: δ 7.84 (d, *J* = 6.9 Hz, 2H), 7.53–7.47 (m, 7 H), 7.42–7.23 (m, 5H), 7.20–7.06 (m, 2H). ^{13}C NMR: δ 190.7, 139.3, 139.2, 135.7, 132.5, 131.7, 131.6, 129.7, 129.3, 128.3, 127.9, 126.9, 126.9, 125.8, 124.9, 120.8, 120.7. MS *m/z* (%): 402 (0.1), 400 (M^+, 0.1), 323 (26.7), 322 (100), 77 (15.5). Anal. Calc. for $C_{23}H_{16}BrNO$ (402.28): C, 68.67; H, 4.01; N, 3.48. Found: C, 68.77; H, 4.06; N, 3.49%.

*3.1.9. 1-Phenyl-4-(4-methylphenyl)-3-benzoylpyrrole (**1i**)*

M.p. 135–137 °C (EtOAc-PE). IR: *v* 3118, 3063, 2917, 1627, 1597 cm^{-1}. ^1H NMR: δ 7.86 (d, *J* = 2.4 Hz, 2H), 7.47–7.33 (m, 11H), 7.13-7.10 (m, 3 H), 2.33 (s, 3H). ^{13}C NMR: δ 191.0, 139.6, 139.3, 136.0, 131.6, 131.1, 129.7, 129.4, 128.6, 128.4, 127.9, 127.1, 126.8, 123.4, 120.6, 119.6, 21.0. MS *m/z* (%): 337 (M^+, 100), 260 (48.5), 77 (30.1). Anal. Calc. for $C_{24}H_{19}NO$ (337.41): C, 85.43; H, 5.68; N, 4.15. Found: C, 85.33; H, 5.71; N, 4.13%.

*3.1.10. 1-Phenyl-4-(4-nitrophenyl)-3-benzoylpyrrole (**1j**)*

M.p. 162–164 °C (EtOAc-PE). IR: *v* 3137, 3073, 1638, 1595 cm^{-1}. ^1H NMR: δ 8.12 (d, *J* = 7.5 Hz, 2H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.60–7.30 (m, 12H). ^{13}C NMR: δ 190.7, 146.1, 141.2, 139.2, 138.9, 132.2, 129.9, 129.3, 129.0, 128.3, 128.2, 127.5, 126.4, 123.3, 121.3, 120.9. MS *m/z* (%): 368 (M^+, 87.4), 292 (50.6), 77 (100). Anal. Calc. for $C_{23}H_{16}N_2O_3$ (368.38): C, 74.99; H, 4.38; N, 7.60. Found: C, 74.89; H, 4.34; N, 7.55%.

*3.1.11. 1-(4-Nitrophenyl)-4-phenylpyrrole-3-carboxylic acid ethyl ester (**1k**)*

M.p. 176–178 °C (EtOAc-PE). IR: *v* 3132, 3082, 2988, 1675 cm^{-1}. ^1H NMR: δ 8.36–8.33 (m, 2H), 7.86 (d, *J* = 2.8 Hz, 1H), 7.61–7.38 (m, 7H), 7.15 (d, *J* = 2.4 Hz, 1H), 4.24 (q, *J* = 6.9 Hz, 2H), 1.27 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR: δ 163.8, 145.6, 143.9, 133.4, 129.7, 129.1, 127.8, 127.1, 125.6, 125.4, 120.0, 119.0, 117.3, 60.0, 14.2. MS *m/z* (%): 336 (M^+, 100), 291 (51.9). Anal. Calc. for $C_{19}H_{16}N_2O_4$ (336.34): C, 67.85; H, 4.79; N, 8.33. Found: C, 67.88; H, 4.72; N, 8.36%.

*3.1.12. 1-(4-Methoxyphenyl)-4-phenylpyrrole-3-carboxylic acid ethyl ester (**1l**)*

M.p. 100–101 °C (EtOAc-PE). IR: *v* 3139, 3055, 1707 cm^{-1}. ^1H NMR: δ 7.68 (m, 1H), 7.52 (m, 2H), 7.37–7.32 (m, 5H), 6.99–6.96 (m, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR: δ 164.4, 158.4, 134.3, 132.9, 129, 2 127.9, 127.6, 126.5, 126.1, 122.2, 120.0, 114.8, 114.7, 59.5, 55.4, 14.2. MS *m/z* (%): 321 (M^+, 100), 276 (49.4). Anal. Calc. for $C_{20}H_{19}NO_3$ (321.37): C, 74.75; H, 5.96; N, 4.36. Found: C, 74.84; H, 6.00; N, 4.32%.

*3.1.13. 1-(4-Fluorophenyl)-4-phenylpyrrole-3-carboxylic acid ethyl ester (**1m**)*

M.p. 104–106 °C (EtOAc-PE). IR: *v* 3078, 2980, 1710 cm^{-1}. ^1H NMR: δ 7.69 (d, *J* = 2.4 Hz, 1H), 7.53–7.51 (m, 2H), 7.42–7.29 (m, 5H), 7.15–7.14 (m, 2H), 6.99 (d, *J* = 2.7 Hz, 1H), 4.25 (q, *J* = 3.6 Hz, 2H), 1.25 (t, *J* = 3.6 Hz, 3H). ^{13}C NMR: δ 164.3, 162.8, 159.6, 134.1, 129.2, 128.4, 127.7, 126.7, 126.1, 122.6, 122.5, 119.8, 116.7, 116.4, 115.5, 59.7, 14.2. MS *m/z* (%): 309 (M^+, 100), 264 (76.5). Anal. Calc. for $C_{19}H_{16}FNO_2$ (309.33): C, 73.77; H, 5.21; N, 4.53. Found: C, 73.66; H, 5.18; N, 4.50%.

*3.1.14. 1-(3-Methoxyphenyl)-4-phenylpyrrole-3-carboxylic acid ethyl ester (**1n**)*

M.p. 77–78 °C (EtOAc-PE). IR: *v* 3153, 2975, 1679 cm^{-1}. ^1H NMR: δ 7.73 (d, *J* = 2.4 Hz, 1H), 7.53 (s, 1H), 7.51 (s, 1H), 7.38-7.23 (m, 4H), 7.01–6.79 (m, 4H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR: δ 164.2, 160.5, 140.4, 134.1, 130.4, 129.1, 128.1, 127.5, 126.5, 125.7, 119.5, 115.2, 112.7, 112.0, 106.7, 59.5, 55.2, 14.1;MS *m/z* (%): 321 (M^+, 100), 276 (46.7). Anal. Calc. for $C_{20}H_{19}NO_3$ (321.37): C, 74.75; H, 5.96; N, 4.36. Found: C, 74.79; H, 5.91; N, 4.33%.

*3.1.15. 1-(3-Chlorophenyl)-4-phenylpyrrole-3-carboxylic acid ethyl ester (**1o**)*

M.p. 99–101 °C (EtOAc-PE). IR: *v* 3144, 3074, 2978, 1686 cm^{-1}. ^1H NMR: δ 7.75 (d, *J* = 3.0 Hz, 1H), 7.51–7.32 (m, 9H), 7.05 (d, *J* = 3.0 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR: δ 146.1, 140.4, 135.4, 133.9, 130.7, 129.2, 128.8, 127.7, 126.8, 125.6, 120.8, 119.3, 118.6, 116.0, 59.7, 14.2. MS *m/z* (%): 325 (M^+, 100), 280 (54.3). Anal Calcd for $C_{19}H_{16}ClNO_2$ (325.79): C, 70.05; H, 4.95; N, 4.30. Found: C, 70.09; H, 4.89; N, 4.34%.

*3.1.16. 1-(Pyridin-2-yl)-4-phenylpyrrole-3-carboxylic acid ethyl ester (**1p**)*

M.p. 38–39 °C (EtOAc-PE). IR: *v* 3163, 3094, 2972, 1708, 1595 cm^{-1}. ^1H NMR: δ 8.47 (d, *J* = 0.7 Hz, 1H), 8.21 (d, *J* = 2.4 Hz,

1H), 7.83–7.78 (m, 1H), 7.57–7.51 (m, 3H), 7.41–7.26 (m, 5H), 4.24 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 164.1, 149.9, 148.6, 138.6, 134.0, 129.1, 128.4, 127.5, 126.6, 124.4, 121.2, 117.8, 116.0, 111.4, 59.6, 14.1. MS m/z (%): 292 (M^+, 100), 247 (95.1). Anal. Calc. for $C_{18}H_{16}N_2O_2$ (292.33): C, 73.95; H, 5.52; N, 9.58. Found: C, 73.89; H, 5.58; N, 9.61%.

*3.1.17. 1,4-Diphenylpyrrole-3-carboxylic acid (**5**)*

M.p. 214–216 °C (EtOAc-PE). IR: ν 3144, 3057, 2627, 1680, 1654 cm^{-1}. ^{1}H NMR (DMSO-d$_6$): δ 11.99 (br. 1H), 7.89 (d, J = 1.5 Hz, 1H), 7.61–7.15 (m, 11H). ^{13}C NMR (DMSO-d_6): δ 165.7, 139.3, 134.8, 130.3, 129.5, 128.2, 127.9, 127.1, 126.8, 126.4, 120.5, 115.9. MS m/z (%): 265 (2.1), 264 (18.7), 263 (M^+, 100). Anal. Calc. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.49; H, 4.94; N, 5.28%.

Acknowledgments

This work was supported by NNSF of China (20672066, 30600779).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2008.09.051.

References

[1] R. Di Santo, A. Tafi, R. Costi, M. Botta, M. Artico, F. Corelli, M. Forte, F. Caporuscio, L. Angiolella, A.T. Palamara, J. Med. Chem. 48 (2005) 5140.
[2] T. Purkarthofer, K. Gruber, M.H. Fechter, H. Griengl, Tetrahedron 61 (2005) 7661.
[3] S. Jiang, H. Lu, S. Liu, Q. Zhao, Y. He, A.K. Debnath, Antimicrob. Agents Chemother. 48 (2004) 4349.
[4] A. Tafi, R. Costi, M. Botta, R. Di Santo, F. Corelli, S. Massa, A. Ciacci, F. Manetti, M. Artico, J. Med. Chem. 45 (2002) 2720.
[5] S. Yu, J. Saenz, J.K. Srirangam, J. Org. Chem. 67 (2002) 1699.
[6] A. Tafi, J. Anastassopoulou, T. Theophanides, M. Botta, F. Corelli, S. Massa, M. Artico, R. Costi, R. Di Santo, R. Ragno, J. Med. Chem. 39 (1996) 1227.
[7] H. Jendralla, E. Baader, W. Bartmann, G. Beck, A. Bergmann, E. Granzer, B. Von Kerekjarto, K. Kesseler, R. Krause, W. Schubert, G. Wess, J. Med. Chem. 33 (1990) 61.
[8] M.M. Mc Gee, S. Gemma, S. Butini, A. Ramunno, D.M. Zisterer, C. Fattorusso, B. Catalanotti, G. Kukreja, I. Fiorini, C. Pisano, C. Cucco, E. Novellino, V. Nacci, D.C. Williams, G. Campiani, J. Med. Chem. 48 (2005) 4367.
[9] M. Paillet-Loilier, F. Fabis, A. Lepailleur, R. Bureau, S. Butt-Gueulle, F. Dauphin, C. Delarue, H. Vaudry, S. Rault, Bioorg. Med. Chem. Lett. 15 (2005) 3753.
[10] G. Sbardella, A. Mai, M. Artico, R. Loddo, M.G. Setzu, P. La Colla, Bioorg. Med. Chem. Lett. 14 (2004) 1537.
[11] M.L. Testa, L. Lamartina, F. Mingoia, Tetrahedron 60 (2004) 5873.
[12] N.J. Kevin, J.L. Duffy, B.A. Kirk, K.T. Chapman, W.A. Schleif, D.B. Olsen, M. Stahlhut, C.A. Rutkowski, L.C. Kuo, L.X. Jin, J.H. Lin, E.A. Emini, J.R. Tata, Bioorg. Med. Chem. Lett. 13 (2003) 4027.
[13] P.R. Bovy, D.B. Reitz, J.T. Collins, T.S. Chamberlain, G.M. Olins, V.M. Corpus, E.G. McMahon, M.A. Palomo, J.P. Koepke, G.J. Smits, D.E. McGraw, J.F. Gaw, J. Med. Chem. 36 (1993) 101.
[14] C.V. Galliford, K.A. Scheidt, J. Org. Chem. 72 (2007) 1811.
[15] A.E. Mattson, A.R. Bharadwaj, A.M. Zuhl, K.A. Scheidt, J. Org. Chem. 71 (2006) 5715.
[16] R. Dhawan, B.A. Arndtsen, J. Am. Chem. Soc. 126 (2004) 468.
[17] D. Tejedor, D. Gonzalez-Cruz, F. Garcia-Tellado, J.J. Marrero-Tellado, M.L. Rodriguez, J. Am. Chem. Soc. 126 (2004) 8390.
[18] A.R. Bharadwaj, K.A. Scheidt, Org. Lett. 6 (2004) 2465.
[19] H. Nakano, T. Ishibashi, T. Sawada, Tetrahedron Lett. 44 (2003) 4175.
[20] D. van Leusen, A.M. van Leusen, Org. React. 57 (2003) 419.
[21] S.V. Ley, A.W. Thomas, Angew. Chem. Int. Ed. 42 (2003) 5400.
[22] R. Zhu, L. Xing, X. Wang, C. Cheng, D. Su, Y. Hu, Adv. Synth. Catal. 350 (2008) 1253.
[23] J. Mao, J. Guo, H. Song, S. Ji, Tetrahedron 64 (2008) 1383.
[24] H. Ma, X. Jiang, J. Org. Chem. 72 (2007) 8943.
[25] M. Taillefer, N. Xia, A. Ouali, Angew. Chem. Int. Edu. 46 (2007) 934.
[26] L. Zhu, L. Cheng, Y. Zhang, R. Xie, J. You, J. Org. Chem. 72 (2007) 2737.
[27] J.C. Antilla, J.M. Baskin, T.E. Barder, S.L. Buchwald, J. Org. Chem. 69 (2004) 5578.
[28] H.J. Cristau, P.P. Cellier, J.F. Spindler, M. Taillefer, Chem. Eur. J. 10 (2004) 5607.
[29] D. Jiang, H. Fu, Y. Jiang, Y. Zhao, J. Org. Chem. 72 (2004) 672.
[30] D. Ma, Q. Cai, Synlett (2004) 128.
[31] A. Klapars, J.C. Antilla, X. Huang, S.L. Buchwald, J. Am. Chem. Soc. 123 (2001) 7727.
[32] S. Massa, R. Di Santo, A. Mai, M. Botta, M. Artico, S. Panico, G. Simonetti, Farmaco 45 (1990) 833.
[33] E.C. Kornfeld, R.G. Jones, J. Org. Chem. 19 (1954) 1671.
[34] H.P. Dijkstra, R. ten Have, A.M. van Leusen, J. Org. Chem. 63 (1998) 5332.
[35] C.M. Yang, W.V. Murray, L.J. Wilson, Tetrahedron Lett. 44 (2003) 1783.