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Development of a Synthetic Method for Multifunctionalized Pyrroles Using Isocyanide Dichloride as a Key Intermediate

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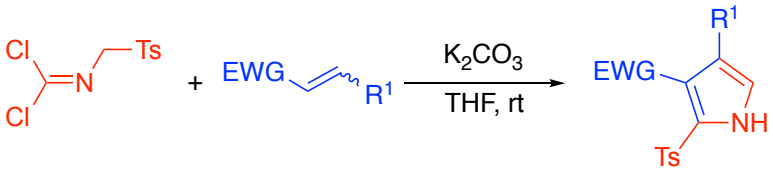


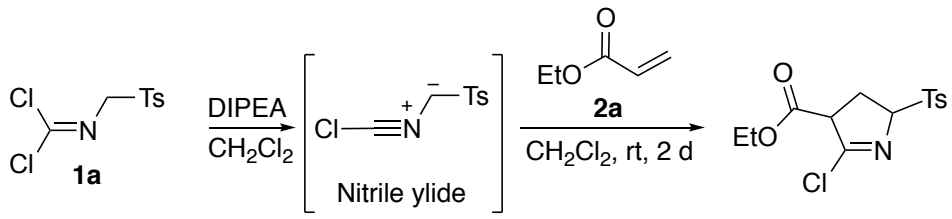
Abstract

Multifunctionalized pyrrole derivatives were synthesized using a highly efficient method based on the Michael addition of carbanions generated *in situ* from isocyanide dichloride to α,β-unsaturated carbonyl compounds. The reactions proceeded smoothly to afford the pyrrole derivatives in good to high yields. A wide range of Michael acceptors, such as α,β-unsaturated carbonyl compounds and nitroolefin, were successfully applied to this reaction.

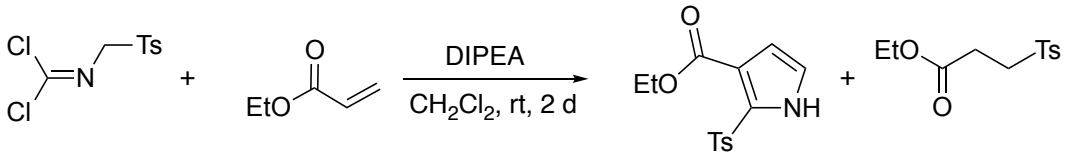
Multifunctionalized pyrroles are important building blocks in organic synthesis as well as in pharmaceuticals, natural products, and functional materials.[1,2] Many different approaches to the synthesis of pyrrole derivatives have been reported, including transition-metal-catalyzed synthetic methods.[3] However, these methods have relied mainly on precisely designed substrates that are not readily available.[4,5] Thus, the direct assembly of pyrroles from basic chemicals remains an important research objective.[6] To accomplish this objective, isocyanide dihalides and α,β-unsaturated carbonyl compounds were used for the synthesis of oligosubstituted pyrroles. Isocyanide dihalides are readily formed by addition of chlorine or bromine to isocyanides.[7] A one-pot synthetic method was developed for formation of multifunctional

dihydrooxazole and oxazole derivatives using isocyanide dichloride.[8] To extend this work to the synthesis of multifunctionalized heterocycles using versatile starting materials, α,β-unsaturated carbonyl compounds such as ethyl acrylate were examined. The atom-economic nature of the reaction makes cycloaddition to these substrates an ideal route to oligosubstituted pyrroles without the need for transition metal catalysts.[9] This report describes the highly efficient formation of multifunctional pyrrole derivatives by reaction of isocyanide dichloride with α,β-unsaturated carbonyl compounds, including an unexpected rearrangement reaction.

Initially isocyanide dichloride **1a**,[10] which is easily prepared from the corresponding 4-toluenesulfonylmethylisocyanide (TsMIC) with SO_2Cl_2, was examined to determine its ability to participate in 1,3-dipolar cycloaddition with an ethyl acrylate (**2a**) upon treatment of diisopropylethylamine (DIPEA) to afford the 3,4-dihydropyrrole derivative (Eq. 1).[11,12,13] After several attempts, the results showed that the 3,4-dihydropyrrole derivative was not obtained; instead, pyrrole **3aa**[14] was obtained in 30% yield along with tosylpropionate **4** in 14% yield (Eq. 2). These unexpected results lead to the development of the synthetic method for pyrrole derivatives.



(1)

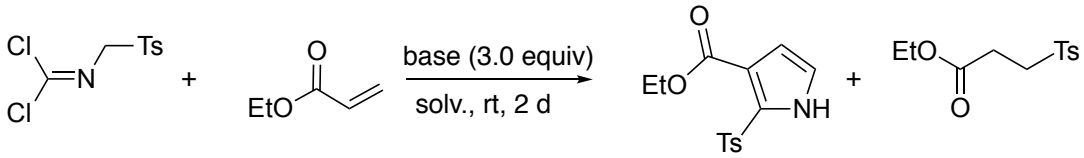


(2)

Bases other than DIPEA were evaluated for their ability to generate enolates during Michael addition in CH_2Cl_2 (entries 2–7). The use of Et_3N resulted in formation of the desired **3aa** in 53% yield along with side-product **4** in 22% yield (entry 2). Interestingly, use of DBU as a base produced **4** in 72% yield without any of the desired **3aa** (entry 3). Formation of **4** could be suppressed when 1.0 equiv of **2a** was used in the presence of

Et_3N (entry 4). A significant increase in yield of **3aa** (to 92%) was observed when K_2CO_3 was used as a base (entry 5). Other bases, such as Na_2CO_3, and Cs_2CO_3, were not effective in this reaction (entries 6 and 7). The use of K_2CO_3, dichloroethane, THF, and acetonitrile as solvents was also examined and the results indicated that THF was the optimal solvent to produce **3aa** in high yield (entries 8–10).

Table 1. Optimized reaction conditions.



1a **2a** (1.0 equiv) **3aa** **4**

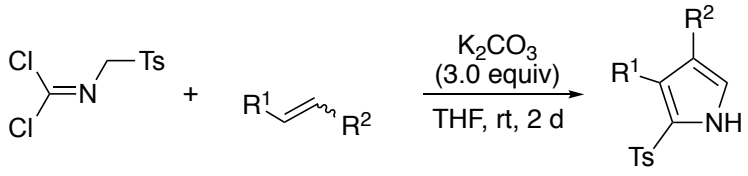
Entry	Base	Solvent	Yield of **3aa** (%)	Yield of **4** (%)
1[a]	DIPEA	CH_2Cl_2	30	14
2[a]	Et_3N	CH_2Cl_2	53	22
3[a]	DBU	CH_2Cl_2	-	72
4	Et_3N	CH_2Cl_2	32	-
5	K_2CO_3	CH_2Cl_2	92	-
6	Na_2CO_3	CH_2Cl_2	15	-
7	Cs_2CO_3	CH_2Cl_2	56	-
8	K_2CO_3	dichloroethane	90	-
9	K_2CO_3	THF	97	-
10	K_2CO_3	MeCN	87	-

[a] 3.0 equiv of **2a** used.

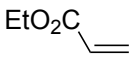
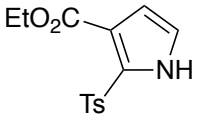
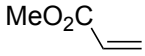
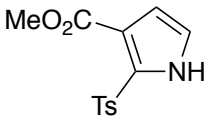
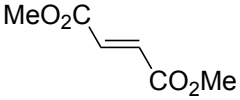
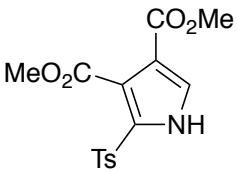
The reactivity of isocyanide dichloride **1a** with various Michael acceptors was examined in the presence of K_2CO_3 (Table 2); the results are shown in Table 2. For these experiments, optimal amounts of isocyanide dichloride **1a** (1.0 equiv) and Michael acceptors **2a–i** (1.0 equiv) were used in the presence of 3.0 equiv K_2CO_3. The results demonstrate that these conditions allowed the reaction to proceed using a wide variety

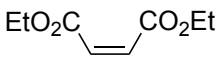
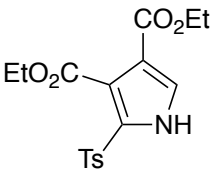
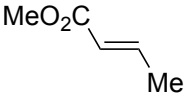
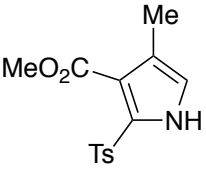
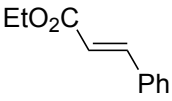
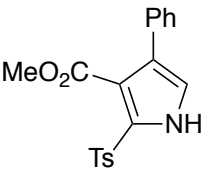
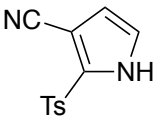
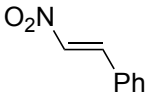
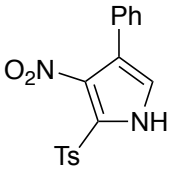
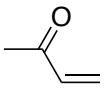
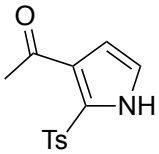
of Michael acceptors and that most reactions were complete within 2 days. Methyl acrylate (**2b**) was also a suitable substrate for this reaction and afforded **3ab** in 81% yield (entry 2). Both the *cis* and *trans* isomers, such as fumarate **2c** and malate **2d**, possessed similar reactivity (entries 3 and 4). Methyl crotonate (**2e**) and ethyl cinnamate (**2f**) showed lower reactivity than the others, resulting in only 32% yield of **3ae** and a trace amount of **3af** (entries 5 and 6). The other Michael acceptors, such as acrylonitrile (**2g**), nitrostyrene (**2h**), and methyl vinyl ketone (**2i**), were also applicable to this reaction, affording the products in good yields (entries 7–9).

Table 2. Results of the synthesis of pyrroles using various Michael acceptors.



1a **2** (1.0 equiv) **3**

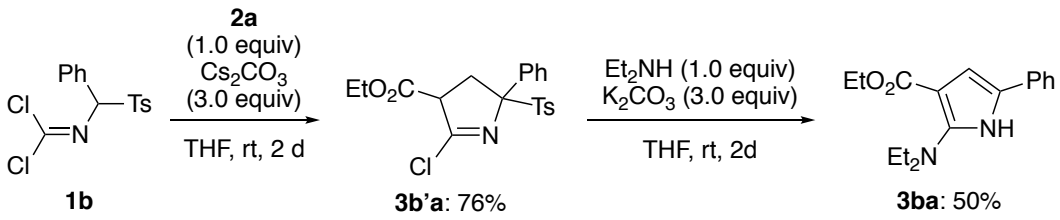
Entry[a]	**2**	**3**; Yield (%)
1	 **2a**	 **3aa**; 97%
2	 **2b**	 **3ab**; 81%
3	 **2c**	 **3ac**; 83%

4	 **2d**	 **3ad**; 61%
5	 **2e**	 **3ae**; 32%
6	 **2f**	 **3af**; trace
7	 **2g**	 **3ag**; 64%
8	 **2h**	 **3ah**; 43%
9	 **2i**	 **3ai**; 69%

[a] Reaction was conducted using 1.0 equiv of Michael acceptor **2** and 3.0 equiv K_2CO_3.

The α-substituted isocyanide dichloride **1b** was also investigated. Reaction of **1b** with

2a in the presence of Cs_2CO_3 as a base gave the corresponding imino chloride **3b'a** in 76% yield. Iminochloride **3b'a** was converted easily to 2-aminopyrrole **3ba** through an addition-elimination reaction (Eq. 3). Furthermore, reaction of **1b** with dimethyl fumarate (**2c**) proceeded to afford the tetrasubstituted pyrrole **3bc** in moderate yield (Eq. 4).



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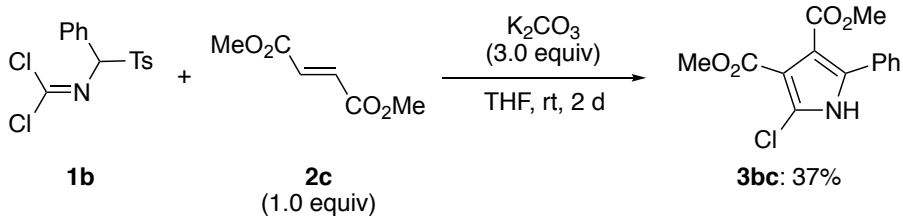
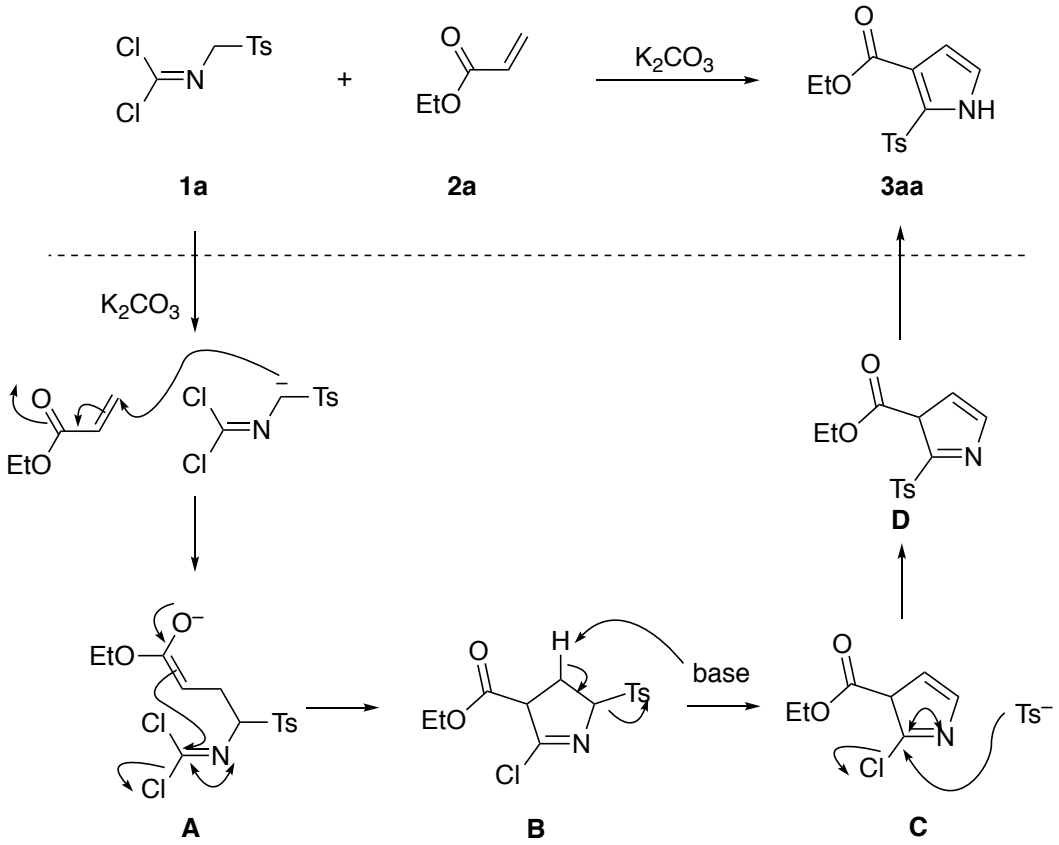


(4)

To determine the reaction mechanism, a series of controlled experiments were conducted. To confirm the generation of nitrile ylide from the isocyanide dichloride **1a** under basic conditions, ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$. Treatment of isocyanide dichloride **1a** with 3.0 equiv K_2CO_3 did not induce a chemical shift of the methylene hydrogen atom (at 4.71 ppm). The same behavior was observed with ^{13}C NMR, in which the signal for the imino carbon (at 145.6 ppm) did not shift. Thus, the nitrile ylide was not generated from isocyanide dichloride **1a**. In addition, the Michael addition of the tosylate group proceeded to afford the tosylpropionate **4** (Table 1, entries 1–3). Based on these results, the mechanism for this reaction is proposed in Scheme 1. The carbanion generated from **1a** under basic conditions attacks the β-position of **2a** to afford the enolate **A**, which undergoes nucleophilic addition-elimination to an imino dichloride to afford intermediate **B**. Then, the tosylate group is removed from **B** under basic conditions and the remaining tosylate attacks the imino chloride moiety to afford **D**. Finally, isomerization proceeds to give **3aa**. In reaction of **1b** with **2c** (Eq. 4), aromatization proceeds more quickly than addition of

tosylate to imino chloride intermediate.

Scheme 1. Proposed reaction mechanism



In conclusion, an efficient method for the synthesis of multifunctionalized pyrrole derivatives utilizing isocyanide dichloride was developed. The key to the success of the reaction was the Michael addition of a carbanion generated from isocyanide dichloride to the α,β-unsaturated carbonyl compound, followed by nucleophilic addition-elimination to the iminodichloride. The reactions proceeded smoothly to afford the pyrrole derivatives in good to high yields. A wide range of Michael acceptors were applied successfully to this reaction.

Experimental Section

General: ^{1}H NMR spectra were recorded on a 400 MHz NMR spectrometer. Chemical shifts δ are reported in ppm using TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J) and integration. ^{13}C NMR spectra were recorded on 100 MHz NMR spectrometer. The chemical shifts were determined in the δ-scale relative to $CDCl_3$ (δ = 77.0 ppm). The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. HRMS (DART and ESI) was measured with and TOF mass spectrometers. All melting points were measured using a micro melting point apparatus. Dehydrated solvents were purchased for the reactions and used without further desiccation. Compound **1a** was prepared according to the literature.[10]

General procedure

(Phenyl(tosyl)methyl)carbonimidic dichloride (1b)

To a solution of 1-((isocyano(phenyl)methyl)sulfonyl)-4-methylbenzene (0.30 mmol) in $CHCl_3$ (1.0 mL), SO_2Cl_2 (3.0 mmol) in $CHCl_3$ (3.0 mL) was added dropwise at –45 ℃. The reaction mixture was stirred for 10 min at –45 ℃, then allowed to warm to room temperature. After removing the solvents, **1b** was obtained and was used without further purification.[8]

To a suspension of the **1a** (0.30 mmol) and K_2CO_3 (0.9 mmol) in THF (3.0 mL), Michael acceptor **2** (0.30 mmol) was added at room temperature, then the whole was stirred at room temperature for 2 days. To the reaction mixture, water (2.0 mL) was added and separated. The aqueous layer was extracted with $CHCl_3$ (5 mL x 3) and the combined organic layers were washed with brine, and dried over Na_2SO_4. Concentration and the subsequent purification by silica gel flash column chromatography gave the corresponding pyrrole derivatives **3**.

Ethyl 2-tosyl-1*H*-pyrrole-3-carboxylate (3aa)[14]

Silica gel column chromatography (hexane/ethyl acetate = 3/1) gave **3aa** (86 mg, 97% yield) as a white solid of mp = 94–96 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.25 (t, J = 6.8 Hz, 3H), 2.40 (s, 3H), 4.22 (t, J = 6.8 Hz, 2H), 6.74 (d, J = 2.8 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H). 9.83 (brs, 1H).

^{13}C NMR ($CDCl_3$): 14.2, 21.7, 60.6, 114.5, 118.7, 120.6, 128.1, 129.4, 130.3, 137.6, 144.5, 161.8. IR (KBr): 3240, 1710, 1470, 1310, 1210, 1160, 1040 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{14}H_{16}NO_4S$ $[M+H]^+$: 294.0800. Found: 294.0809.

Methyl 2-tosyl-1*H*-pyrrole-3-carboxylate (3ab)

Silica gel column chromatography (hexane/ ethyl acetate = 3/1) gave **3ab** (68 mg, 81% yield) as a white solid of mp = 137–139 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.34 (s, 3H), 3.68 (s, 3H), 6.67 (t, *J* = 2.8 Hz, 1H), 6.85 (d, *J* = 2.8 Ha, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H), 9.93 (brs, 1H). ^{13}C NMR ($CDCl_3$): 21.7, 51.6, 114.5, 118.2, 120.8, 128.2, 129.4, 130.4, 137.5, 144.6, 162.3. IR (KBr): 3230, 1700, 1470, 1310, 1210, 1150, 1030 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{13}H_{14}NO_4S$ $[M+H]^+$: 280.0644. Found: 280.0651.

Dimethyl 2-tosyl-1*H*-pyrrole-3,4-dicarboxylate (3ac)

Silica gel column chromatography (hexane/ ethyl acetate = 2/1) gave **3ac** (84 mg, 83% yield) as a white solid of mp = 87–90 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.36 (s, 3H), 3.72 (s, 3H), 3.87 (s, 3H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.39 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 9.80 (brs, 1H). ^{13}C NMR ($CDCl_3$): 21.6, 51.8, 51.9, 116.6, 121.7, 126.9, 127.6, 128.6, 129.9, 137.4, 145.0, 162.3, 164.2. IR (KBr): 3150, 1710, 1590, 1450, 1380, 1290, 1220, 1150, 1080, 1070 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{15}H_{16}NO_6S$ $[M+H]^+$: 338.0698. Found: 338.0699.

Diethyl 2-tosyl-1*H*-pyrrole-3,4-dicarboxylate (3ad)

Silica gel column chromatography (hexane/ ethyl acetate = 2/1) gave **3ad** (67 mg, 61% yield) as a white solid of mp = 154–157 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.20 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 6.8 Hz, 3H), 2.31 (s, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.35 (t, *J* = 6.8 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.38 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 10.5 (brs, 1H). ^{13}C NMR ($CDCl_3$): 13.9, 14.1, 21.6, 60.7, 62.1, 116.8, 122.2, 126.9, 127.6, 128.1, 129.9, 137.6, 144.9, 162.3, 163.9. IR (KBr): 3130, 1720, 1590, 1510, 1440, 1380, 1280, 1210, 1160 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{20}NO_6S$ $[M+H]^+$: 366.1011. Found: 366.1005.

Methyl 4-methyl-2-tosyl-1*H*-pyrrole-3-carboxylate (3ae)

Silica gel column chromatography (hexane/ ethyl acetate = 3/1) gave **3ae** (29 mg, 32% yield) as an amorphous. ^{1}H NMR ($CDCl_3$): 2.14 (s, 3H), 2.34 (s, 3H), 3.61 (s, 3H), 6.68 (d, *J* = 2.8 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 9.75 (brs, 1H). ^{13}C NMR ($CDCl_3$): 12.0, 21.6, 51.2, 116.7, 120.2, 125.5, 127.9, 129.3, 130.2, 138.1, 144.2, 163.2. IR (KBr): 3150, 1710, 1590, 1450, 1380, 1290, 1220, 1150, 1080, 1070 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{14}H_{16}NO_4S$ $[M+H]^+$: 294.0800. Found: 294.0803.

2-Tosyl-1*H*-pyrrole-3-carbonitrile (3ag)

Silica gel column chromatography (hexane/ ethyl acetate = 3/1) gave **3ag** (47 mg, 64% yield) as a white solid of mp = 165–168 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.41 (s, 3H), 6.57 (t, *J* = 2.8 Hz, 1H), 6.92 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 8.4 Hz, 2H), 9.90 (brs, 1H). ^{13}C NMR ($CDCl_3$): 21.7, 97.5, 113.2, 115.6, 122.5, 127.5, 130.3, 134.5, 137.0, 145.6. IR (KBr): 3270, 2230, 1750, 1640, 1590, 1470, 1380, 1310, 1230, 1150, 1090, 1040 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{12}H_{11}N_2O_2S$ $[M+H]^+$: 247.0541. Found: 247.0538.

3-Nitro-4-phenyl-2-tosyl-1*H*-pyrrole (3ah)

Silica gel column chromatography (hexane/ ethyl acetate = 4/1) gave **3ah** (45 mg, 43% yield) as a white solid of mp = 165–167 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.37 (s, 3H), 6.87 (d, *J* = 3.2 Hz, 1H), 7.19 (s, 1H), 7.22–7.30 (m, 6H), 7.91 (d, *J* = 8.0 Hz, 2H), 10.3 (brs, 1H). ^{13}C NMR ($CDCl_3$): 21.7, 119.8, 124.7, 127.6, 128.2, 128.3, 128.9, 129.1, 129.8, 130.5, 136.0, 145.6. IR (KBr): 3260, 1650, 1510, 1450, 1370, 1350, 1320, 1230, 1170, 1140, 1080 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{15}N_2O_4S$ $[M+H]^+$: 343.0753. Found: 343.0751.

1-(2-Tosyl-1*H*-pyrrol-3-yl)ethan-1-one (3ai)

Silica gel column chromatography (ethyl acetate = 2/1) gave **3ai** (54 mg, 69% yield) as a white solid of mp = 143–145 °C (hexane/ ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.31 (s, 3H), 2.31 (s, 3H), 6.56 (t, *J* = 2.8 Hz, 1H), 6.89 (t, *J* = 2.8 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H), 10.5 (brs, 1H). ^{13}C NMR ($CDCl_3$): 21.6, 28.3, 113.7, 121.2, 126.2, 128.4, 129.2, 137.3, 144.4, 192.3. IR (KBr): 3150, 1660, 1600, 1470, 1410, 1370, 1320, 1320, 1220, 1180, 1150, 1090 cm^{-1}. HRMS–DART (*m/z*): Calcd for

$C_{13}H_{14}NO_3S$ $[M+H]^+$: 264.0694. Found: 264.0699.

Ethyl 5-chloro-2-phenyl-2-tosyl-3,4-dihydro-2*H*-pyrrole-4-carboxylate (3b'a)

Silica gel column chromatography (hexane/ethyl acetate = 4/1) gave **3b'a** (308 mg, 76% yield, 1.0 mmol scale) as a white solid of mp = 77–79 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 0.80 (t, J = 7.2 Hz, 3H), 2.27 (s, 3H), 3.14 (dd, J = 2.0, 17.6 Hz, 1H), 3.53–3.64 (m, 2H), 3.73 (m, 1H), 4.40 (dd, J = 2.0, 17.6 Hz, 1H), 7.01 (d, J = 8.0 Hz, 2H), 7.09–7.19 (m, 5H), 7.43 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): 13.4, 21.6, 47.3, 47.9, 61.3, 102.5, 127.6, 128.5, 128.9, 129.2, 130.3, 131.2, 132.6, 145.0, 169.6, 170.5. IR (KBr): 2990, 1730, 1630, 1600, 1510, 1490, 1450, 1370, 1340, 1300, 1200, 1150, 1100, 1090 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{20}H_{21}NO_4SCl$ $[M+H]^+$: 406.0871 . Found: 406.0879.

Ethyl 2-(diethylamino)-5-phenyl-1*H*-pyrrole-3-carboxylate (3ba)

To a solution of **3b'a** (0.3 mmol) in THF (3.0 mL), diethylamine (0.3 mmol) was added dropwise and the whole was stirred at room temperature for 2 days. Water (2.0 mL) was added to the reaction mixture and aqueous layer was extracted with $CHCl_3$ (5 mL x 3). Combined organic layers were washed with brine and dried over Na_2SO_4. Concentration and the residue was purified by silica gel column chromatography (hexane/diethyl ether = 2/1) gave **3ba** (43 mg, 50% yield) as an amorphous. ^{1}H NMR ($CDCl_3$): 1.04 (t, J = 7.2 Hz, 6H), 1.19 (t, J = 7.2 Hz, 3H), 3.02 (q, J = 7.2 Hz, 4H), 4.14 (q, J = 7.2 Hz, 2H), 5.87 (d, J = 2.8 Hz, 1H), 7.21–7.51 (m, 5H), 7.96 (brs, 1H). ^{13}C NMR ($CDCl_3$): 12.4, 14.3, 46.6, 59.1, 95.3, 111.2, 127.3, 127.5, 128.0, 128.7, 131.1, 132.4, 140.2, 165.1. IR (KBr): 3300, 2980, 1680, 1590, 1530, 1490, 1450, 1380, 1270, 1240, 1150, 1100 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{23}N_2O_2$ $[M+H]^+$: 287.1760. Found: 287.1768.

Dimethyl 2-chloro-5-phenyl-1*H*-pyrrole-3,4-dicarboxylate (3bc)

Silica gel column chromatography (hexane/ethyl acetate = 5/1) gave **3bc** (33 mg, 37% yield) as a white solid of mp = 104–107 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 3.70 (s, 3H), 3.76 (s, 3H), 7.19–7.37 (m, 5H), 9.11 (brs, 1h). ^{13}C NMR ($CDCl_3$): 51.8, 52.2, 112.5, 114.2, 120.3, 127.5, 128.7, 129.8, 132.5, 163.3, 165.6. IR (KBr): 3190, 2950, 1690, 1510, 1490, 1460, 1410, 1340, 1290, 1220, 1130, 1080 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{14}H_{13}NO_4Cl$ $[M+H]^+$: 294.0533. Found: 294.0536.

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Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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