Synthesis of Tetrasubstituted NH Pyrroles and Polysubstituted Furans via an Addition and Cyclization Strategy

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Abstract: The $FeCl_3$-catalyzed addition and cyclization of enamino esters with nitroolefins provides a straightforward and general method for the synthesis of tetrasubstituted NH pyrroles. This novel method tolerates a wide range of functionality, and allows for rapid elaboration of the nitroolefins into a variety of substituted pyrroles in good yields. Further, an efficient KOAc-promoted addition and cyclization protocol toward substituted furans has been described as well.

Key words: tetrasubstituted NH pyrroles, polysubstituted furans, addition, cyclization

Pyrroles have a privileged role in organic chemistry. Highly substituted pyrroles are one of the important classes of structural unit frequently found in many natural products[1] and pharmaceuticals.[2] Furthermore, many of the substituted pyrroles have been widely used in material science[3] and supramolecular chemistry.[4] As a consequence, polysubstituted pyrroles have received considerable attention over the years and various methods for their preparation have been developed.[5]

In the past several years, transition-metal-catalyzed cyclizations[6] and multicomponent coupling reactions[7] for the preparation of substituted pyrroles have been reported.[8] Transition metals, such as palladium,[9] copper,[10] gold,[11] silver,[12] and ruthenium[13] were shown to be active catalysts in pyrrole ring formation. However, iron-catalyzed cyclization reactions[14] for the construction of pyrrole rings has rarely been reported. Recently, iron salts have been extensively investigated as alternative and promising catalysts for many organic transformations due to their low price and environmentally friendly character.[15] In connection with our recent work on the synthesis of multisubstituted pyrroles, we wish to report herein an $FeCl_3$-catalyzed polysubstituted NH pyrrole ring formation reaction.

Recently, we have developed an addition and cyclization reaction of enamino esters to nonhalogenated nitroolefins for the synthesis of fully substituted pyrroles.[16] Although this metal-free method showed good functional group tolerance, it was not suitable for the synthesis of NH pyrroles. Due to the importance of the NH pyrroles in organic chemistry,[17] our efforts were directed in exploring efficient methods for the synthesis of substituted NH pyrroles by using readily available enamino esters and nitroolefins as the starting materials.

The study began with the addition and cyclization reaction of enamino ester **2a** with nitroolefin **1a** in MeOH in the absence of catalyst. The desired NH pyrrole **3a** (see Figure 1 for the X-ray structure) was observed in low yield (Table 1, entry 1). Although glycol proved to be the most effective solvent, the NH pyrrole **3a** was only obtained in moderate yield (Table 1, entry 3). Thus, various potential catalysts, such as CuI, $FeCl_3$, $FeCl_2$, PTSA, I_2, Ph_3P, were screened in order to improve the efficiency of the transformation (Table 1, entries 5–10). To our delight, $FeCl_3$ was shown to be an active catalyst in the reaction, and the desired NH pyrrole **3a** was obtained in 80% yield (Table 1, entry 6). $FeCl_2$ and PTSA were less effective (Table 1, entries 7, 8).

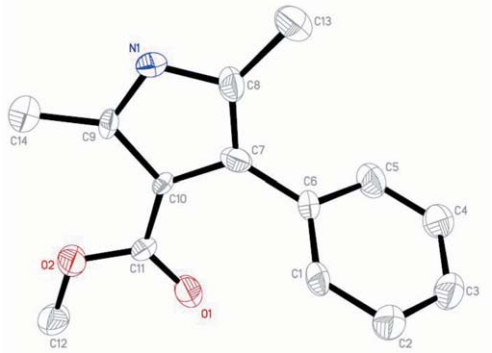

Figure 1 X-ray structure of **3a**

With the optimized conditions in hand, we have explored the substrates scope. The $FeCl_3$-catalyzed addition and cyclization reaction of enamino ester **2a** with nitroolefins **1a–j** are summarized in Table 2. These transformations displayed high functional group tolerance. Various nitroolefins with methyl, methoxy, amino, chloro, and fluoro groups on the arene rings proceeded smoothly to give the corresponding pyrroles **3a–h** in good yields (Table 2, entries 1–8). In general, the reaction was insensitive to the electronic effects of the aromatic substituents on the nitroolefins. A lower yield was observed for the addition and cyclization of enamino ester **2a** with (*Z*)-2-(2-nitroprop-1-enyl)furan (**1i**) due to the partial decomposition of the nitroolefin **1i** in the presence of the $FeCl_3$ catalyst

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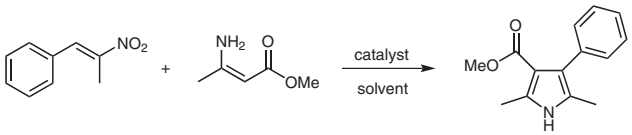
Table 1 Addition and Cyclization of Enamino Ester to Nitroolefin for Synthesis of NH Pyrrole[a]



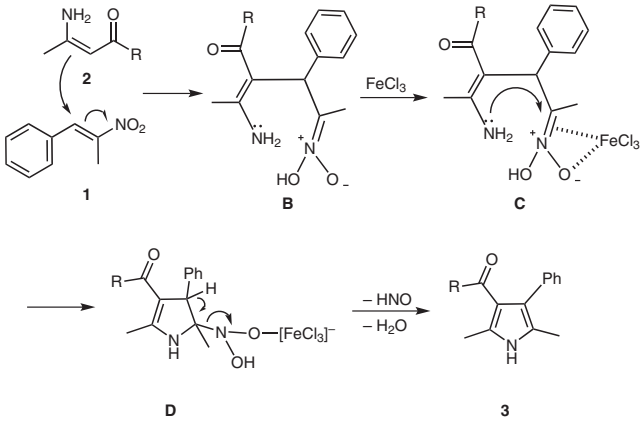
1a 2a 3a

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	–	MeOH	5	50
2	–	DMSO	5	n.r.[b]
3	–	glycol	5	63
4	–	MeCN	5	n.r.[b]
5	CuI	glycol	15	50[c]
6	$FeCl_3$	glycol	4	80[d]
7	$FeCl_2$	glycol	5	72[e]
8	PTSA	glycol	8	60[f]
9	I_2	glycol	15	63[g]
10	Ph_3P	glycol	15	55[h]

[a] Reaction conditions: **1a** (0.5 mmol) and **2a** (0.75 mmol) in solvent (3 mL) at 100 °C.
[b] n.r.: no reaction.
[c] CuI (10 mol%).
[d] $FeCl_3$ (10 mol%).
[e] $FeCl_2$ (10 mol%).
[f] PTSA (20 mol%).
[g] I_2 (20 mol%).
[h] Ph_3P (20 mol%).

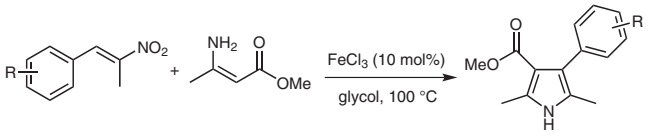
(Table 2, entry 9). Similarly, 5*H*-pyrrole **3j** was obtained in moderate yield (Table 2, entry 10). In addition, the substrate derived from 3-oxo-*N*-phenylbutanamide underwent the desired reaction to give the corresponding product **3k** in good yield (Table 2, entry 11). We have also extended the reaction scope to (*Z*)-4-aminopent-3-en-2-one. The desired pyrrole product **3l** was obtained under the conditions albeit in low yields (Table 2, entry 12).

The plausible mechanism for the reaction is shown in Scheme 1. Enamines **2** and nitroolefin **1** undergo Michael reaction to form an intermediate **B**.[14a] Then $FeCl_3$ interacts with intermediate **B** to generate an electron-deficient complex **C**,[15a,c] which undergoes intramolecular electrophilic cyclization and elimination reaction to gave the desired NH pyrrole **3**.[14a]



Scheme 1 Proposed mechanism for the reaction

Table 2 $FeCl_3$-Catalyzed Addition and Cyclization of Enamino Ester **2a** to Nitroolefins **1**[a]



1a–j 2a 3a–j

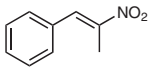
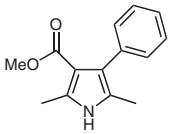
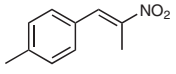
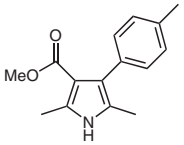
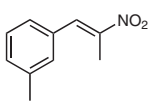
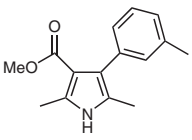
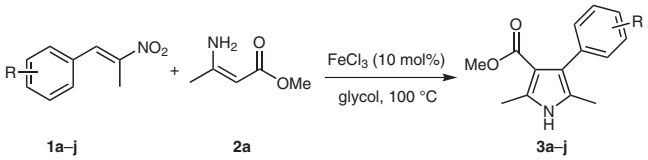
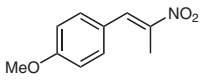
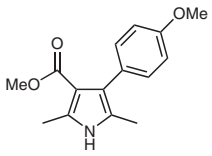
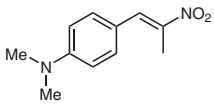
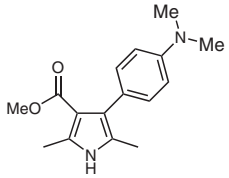
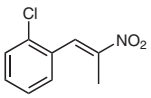
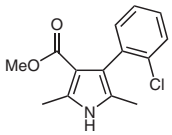
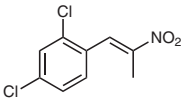
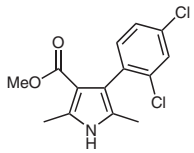
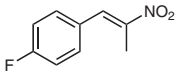
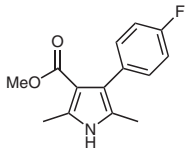
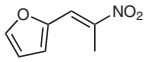
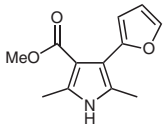
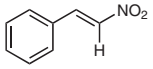
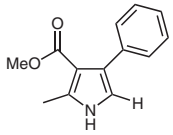
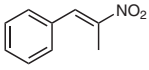
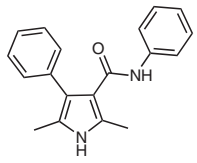
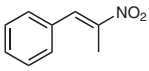
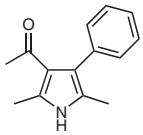
Entry	1		Pyrrole		Time (h)	Yield (%)
1	**1a**		**3a**		4	80
2	**1b**		**3b**		6	79
3	**1c**		**3c**		6	75

Table 2 $FeCl_3$-Catalyzed Addition and Cyclization of Enamino Ester **2a** to Nitroolefins **1**[a] (continued)



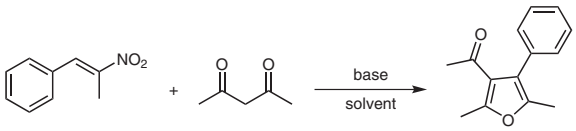
1a–j 2a 3a–j

Entry	1		Pyrrole		Time (h)	Yield (%)
4	**1d**		**3d**		8	74
5	**1e**		**3e**		10	53
6	**1f**		**3f**		10	60
7	**1g**		**3g**		10	65
8	**1h**		**3h**		6	77
9	**1i**		**3i**		8	37
10	**1j**		**3j**		5	42
11	**1a**		**3k**		4	70[b]
12	**1a**		**3l**		4	30[c]

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), and $FeCl_3$ (10 mol%) in glycol (3 mL) at 100 °C.
[b] Compound **1a** (0.5 mmol), (*Z*)-3-amino-*N*-phenylbut-2-enamide (0.75 mmol), and $FeCl_3$ (10 mol%) in glycol (3 mL) at 100 °C.
[c] Compound **1a** (0.5 mmol) and (*Z*)-4-aminopent-3-en-2-one (0.75 mmol) in glycol–H_2O (2:1, 3 mL) at 140 °C.

Although a number of methods have been developed for the construction of furan rings,[18,19] a facile and general synthetic method still remains an attractive goal. Following the success of substituted pyrroles construction, our attention was turned to furan ring formation by the same strategy. Upon screening various bases, catalysts, solvents, and temperature, it was found that the combination of the nitroolefin **1a** with pentane-2,4-dione (**2b**) or β-keto ester **2c** in the presence of KOAc in MeCN at 120 °C gave the best result (Table 3). This facile and efficient method shows a promising approach to substituted furans.

Table 3 Addition and Cyclization Reaction for the Synthesis of Substituted Furan[a]



1a 2b 4a

Entry	Base	Solvent	Time (h)	Yield (%)
1	–	glycol	7	n.r.[b]
2	KOAc	glycol	7	44[b]
3	KOAc	glycol	7	60
4	KOAc	THF	7	64
5	KOAc	DMSO	7	43
6	KOAc	H_2O	7	49
7	**KOAc**	**MeCN**	**6**	**75**
8	NaOAc	MeCN	6	29
9	K_3PO_4	MeCN	6	26
10	Et_3N	MeCN	6	46

[a] Reaction conditions: **1a** (0.45 mmol) and **2b** (0.3 mmol), base (0.6 mmol), in solvent (2 mL) at 120 °C.
[b] $FeCl_3$ (10 mol%) was used; n.r. = no reaction.

Under the optimized conditions, the scope of the KOAc-promoted addition and cyclization reaction was investigated (Table 4). This general method tolerates a wide range of functionality, and allows for rapid elaboration of the nitroolefins into a variety of substituted furans in good yields. For the electronic effects of the transformation, the electron-rich nitroolefins showed better reactivity and gave slightly higher yields than electron-deficient ones (Table 4, entries 3–16). Further, 4-furanyl substituted furans were achieved when 2-(2-nitroprop-1-enyl)furan (**1i**) was used as the substrate (Table 4, entries 17, 18).

In summary, we have developed a general protocol for $FeCl_3$-catalyzed addition and cyclization of enamino ester and nitroolefins for the construction of tetrasubstituted NH pyrroles. This attractive addition and cyclization strategy is also suitable for substituted furans formation in the presence of KOAc. These general protocols employ readily available starting materials and tolerate a wide range of functionality. Thus, a straightforward approach to substituted NH pyrroles and furans has been developed.

Column chromatography was carried out on silica gel. ^{1}H NMR spectra were recorded on 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$. Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification. The nitroolefins **1** were prepared according to the literature.[20]

Tetrasubstituted NH Pyrroles 3; General Procedure

A vial (25 mL) was charged with nitroolefin **1** (0.5 mmol), methyl (*Z*)-3-aminobut-2-enoate (**2a**; 86 mg, 0.75 mmol), and glycol (3 mL) and the mixture was stirred at 100 °C. After completion of the reaction (detected by TLC, eluent: hexane–EtOAc, 8:1), the reaction mixture was cooled to r.t. EtOAc (30 mL) was added to the mixture and then washed with brine (2 × 30 mL). The organic layer was concentrated in vacuo. The residue was purified by chromatography on silica gel with hexane–EtOAc–Et_3N (50:5:0.1) as the eluent to afford **3** (Table 2).

Methyl 2,5-Dimethyl-4-phenyl-1*H*-pyrrole-3-carboxylate (3a)

Yield: 92.3 mg (80%); yellow solid; mp 165–166 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 7.34–7.30 (m, 2 H), 7.25–7.21 (m, 3 H), 3.61 (s, 3 H), 2.45 (s, 3 H), 2.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 139.4, 137.5, 133.6, 130.7, 129.2, 127.0, 125.7, 113.3, 53.7, 17.0, 14.5.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}NO_2$ + Na (M + Na$^+$): 252.0995; found: 252.0996.

Methyl 2,5-Dimethyl-4-*p*-tolyl-1*H*-pyrrole-3-carboxylate (3b)

Yield: 96.6 mg (79%); yellow solid; mp 164–165 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.13 (s, 4), 3.62 (s, 3 H), 2.46 (s, 3 H), 2.34 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 135.3, 133.9, 132.9, 130.1, 128.1, 123.5, 122.3, 110.1, 50.4, 21.2, 13.7, 11.1.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{17}NO_2$ + Na (M + Na$^+$): 266.1151; found: 266.1153.

Methyl 2,5-Dimethyl-4-*m*-tolyl-1*H*-pyrrole-3-carboxylate (3c)

Yield: 92.2 mg (75%); yellow solid; mp 118–120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H), 7.24–7.19 (t, *J* = 8.0 Hz, 1 H), 7.05–7.03 (m, 3 H), 3.62 (s, 3 H), 2.45 (s, 3 H), 2.34 (s, 3 H), 2.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 137.0, 136.2, 134.4, 131.2, 127.7, 127.5, 126.9, 123.9, 122.6, 110.3, 50.7, 21.8, 13.9, 11.5.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{17}NO_2$ + Na (M + Na$^+$): 266.1151; found: 266.1154.

Methyl 4-(4-Methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (3d)

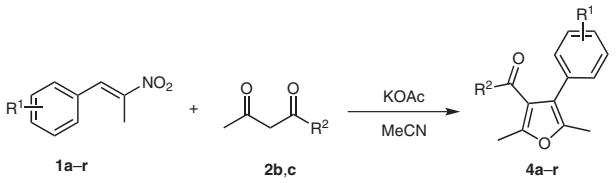
Yield: 96.4 mg (74%); yellow solid; mp 143–145 °C.

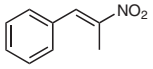
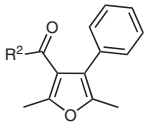
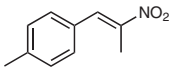
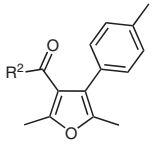
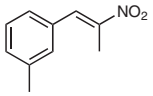
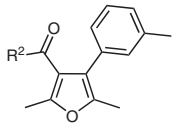
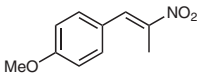
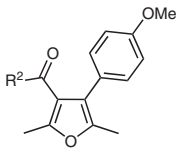
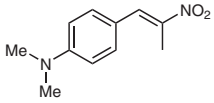
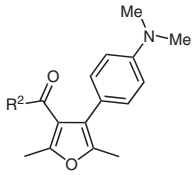
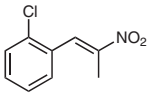
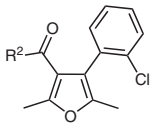
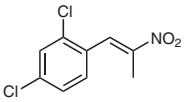
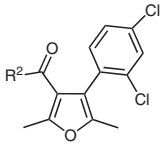
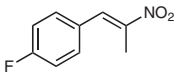
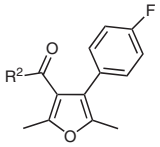
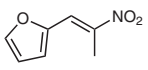
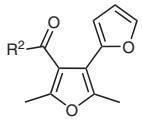
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1 H), 7.17–7.14 (d, *J* = 8.4 Hz, 2 H), 6.88–6.86 (d, *J* = 8.8 Hz, 2 H), 3.79 (s, 3 H), 3.62 (s, 3 H), 2.44 (s, 3 H), 2.04 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 161.0, 137.3, 134.6, 131.7, 126.9, 125.2, 116.2, 113.3, 58.5, 53.7, 17.1, 14.4.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{17}NO_3$ + Na (M + Na$^+$): 282.1101; found: 282.1099.

Table 4 Synthesis of Polysubstituted Furans by KOAc-Promoted Addition and Cyclization Reaction of **2b**,**c** with Nitroolefins **1**[a]



Entry	**1**		Furan **4**	R^2	Time (h)	Yield (%)
1	**1a**			**4a** Me	5	75
2				**4b** OEt	7	74[b]
3	**1b**			**4c** Me	6	75
4				**4d** OEt	7	70[b]
5	**1c**			**4e** Me	6	74
6				**4f** OEt	7	70[b]
7	**1d**			**4g** Me	5	75
8				**4h** OEt	7	68[b]
9	**1e**			**4i** Me	5	58
10				**4j** OEt	24	58[b]
11	**1f**			**4k** Me	6	67
12				**4l** OEt	7	64[b]
13	**1g**			**4m** Me	6	60
14				**4n** OEt	7	56[b]
15	**1h**			**4o** Me	5	66
16				**4p** OEt	7	67[b]
17	**1i**			**4q** Me	5	45
18				**4r** OEt	11	61[b]

[a] Reaction conditions: **1** (0.45 mmol), **2b** (0.3 mmol), and KOAc (0.6 mmol) in MeCN (2 mL) at 120 °C.
[b] Compound **1** (0.3 mmol) and **2c** (0.6 mmol).

Methyl 4-[4-(Dimethylamino)phenyl]-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (3e)
Yield: 71.5 mg (53%); brown solid; mp 175–176 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H), 7.14–7.12 (d, *J* = 7.6 Hz, 2 H), 6.75–6.73 (d, *J* = 8.4 Hz, 2 H), 3.63 (s, 3 H), 2.94 (s, 6 H), 2.44 (s, 3 H), 2.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 149.1, 134.1, 131.2, 124.6, 123.6, 122.5, 112.3, 110.3, 50.7, 41.0, 14.1, 11.5.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{20}N_2O_2$ + Na (M + Na^+): 295.1417; found: 295.1415.

Methyl 4-(2-Chlorophenyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (3f)
Yield: 78.9 mg (60%); yellow solid; mp 155–156 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 7.39–7.37 (m, 1 H), 7.24–7.17 (m, 3 H), 3.56 (s, 3 H), 2.48 (s, 3 H), 1.98 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 135.7, 135.0, 134.2, 132.5, 129.1, 128.0, 126.2, 124.4, 119.8, 111.0, 50.8, 13.9, 11.4.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{14}ClNO_2$ + Na (M + Na^+): 286.0605; found: 286.0602.

Methyl 4-(2,4-Dichlorophenyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (3g)
Yield: 96 mg (65%); yellow solid; mp 185–186 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.24 (s, 1 H), 7.54 (s, 1 H), 7.34–7.32 (m, 2 H), 7.19–7.18 (m, 2 H), 3.43 (s, 3 H), 2.38 (s, 3 H), 1.90 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.9, 134.9, 134.8, 133.7, 131.4, 128.1, 126.4, 124.3, 117.2, 109.6, 50.1, 13.1, 10.8.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{13}Cl_2NO_2$ + Na (M + Na^+): 320.0216; found: 320.0207.

Methyl 4-(4-Fluorophenyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (3h)
Yield: 94.5 mg (77%); white solid; mp 187–189 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.16 (s, 1 H), 7.15 (s, 2 H), 7.09–7.08 (m, 2 H), 3.47 (s, 3 H), 2.38 (s, 3 H), 1.99 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.2, 161.7 (d, $J_{C,F}$ = 240.9 Hz), 133.8, 132.5, 131.9 (d, $J_{C,F}$ = 7.8 Hz), 123.7, 120.2, 114.0 (d, $J_{C,F}$ = 20.5 Hz), 108.9, 49.9, 13.3, 10.9.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{14}FNO_2$ + Na (M + Na^+): 270.0901; found: 270.0905.

Methyl 4-(Furan-2-yl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (3i)
Yield: 41.1 mg (37%); white solid; mp 125–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1 H), 7.39 (s, 1 H), 6.39 (s, 1 H), 6.31 (s, 1 H), 3.69 (s, 3 H), 2.41 (s, 3 H), 2.17 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 149.3, 140.9, 134.3, 126.2, 111.8, 110.4, 110.1, 107.8, 50.7, 13.5, 11.7.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{13}NO_3$ + Na (M + Na^+): 242.0788; found: 242.0793.

Methyl 2-Methyl-4-phenyl-1*H*-pyrrole-3-carboxylate (3j)
Yield: 45.2 mg (42%); brown solid; mp 126–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (s, 1 H), 7.39–7.22 (m, 5 H), 6.50 (s, 1 H), 3.68 (s, 3 H), 2.49 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 136.3, 135.7, 129.1, 127.6, 127.0, 126.2, 115.6, 109.4, 50.5, 13.9.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{13}NO_2$ + Na (M + Na^+): 238.0838; found: 238.0838.

2,5-Dimethyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (3k)
Yield: 100.1 mg (70%); yellow solid; mp 178–180 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (s, 1 H), 7.46–7.43 (m, 2 H), 7.39–7.34 (m, 3 H), 7.18–7.14 (m, 2 H), 7.08–7.07 (m, 3 H), 6.97–6.93 (m, 1 H), 2.54 (s, 3 H), 2.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4, 138.3, 135.3, 133.5, 130.9, 128.8, 128.7, 127.3, 123.6, 123.2, 119.2, 119.1, 113.2, 13.3, 10.9.

1-(2,5-Dimethyl-4-phenyl-1*H*-pyrrol-3-yl)ethanone (3l)
Yield: 32.2 mg (30%); brown solid; mp 118–120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (s, 1 H), 7.39–7.36 (m, 2 H), 7.32–7.24 (m, 3 H), 2.51 (s, 3 H), 2.08 (s, 3 H), 1.92 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 136.7, 133.6, 130.4, 128.1, 126.5, 123.5, 122.1, 121.2, 30.6, 14.1, 10.9.

Substituted Furans 4; General Procedure
A 25 mL round-bottomed flask was charged with nitroolefin **1** (0.45 mmol; 0.3 mmol for **2c**), KOAc (59 mg, 0.6 mmol), pentane-2,4-dione (**2b**; 30 mg, 0.3 mmol) or ethyl acetoacetate (**2c**; 78 mg, 0.6 mmol), and MeCN (2 mL), and the reaction mixture was stirred at 120 °C. After completion of the reaction (detected by TLC, eluent: hexane–EtOAc, 20:1), the mixture was cooled to r.t. The reaction mixture was diluted with EtOAc (15 mL) and then washed with H_2O (2 × 10 mL). The organic layer was concentrated in vacuo and the residue was purified by chromatography on silica gel with hexane–EtOAc (60:1) as the eluent to afford **4** (Table 4).

1-(2,5-Dimethyl-4-phenylfuran-3-yl)ethanone (4a)
Yield: 48.4 mg (75%); orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.34 (m, 3 H), 7.26–7.24 (d, *J* = 6.0 Hz, 2 H), 2.54 (s, 3 H), 2.17 (s, 3 H), 1.94 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.1, 156.1, 146.9, 133.7, 129.8, 128.4, 127.3, 122.9, 120.8, 30.7, 14.2, 11.6.

Ethyl 2,5-Dimethyl-4-phenylfuran-3-carboxylate (4b)
Yield: 54.5 mg (74%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5 H), 4.16–4.10 (m, 2 H), 2.59 (s, 3 H), 2.21 (s, 3 H), 1.13–1.09 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 157.4, 147.1, 133.2, 129.9, 127.6, 126.7, 121.3, 113.4, 59.7, 14.0, 13.9, 11.7.

1-(2,5-Dimethyl-4-*p*-tolylfuran-3-yl)ethanone (4c)
Yield: 51.5 mg (75%); yellow solid; mp 54–56 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.20 (m, 2 H), 7.14–7.12 (m, 2 H), 2.53 (s, 3 H), 2.39 (s, 3 H), 2.16 (s, 3 H), 1.94 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3, 156.0, 146.8, 136.9, 130.6, 129.7, 129.1, 122.9, 120.6, 30.7, 21.2, 14.2, 11.6.

Ethyl 2,5-Dimethyl-4-*p*-tolylfuran-3-carboxylate (4d)
Yield: 54.2 mg (70%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.14 (m, 4 H), 4.17–4.12 (m, 2 H), 2.57 (s, 3 H), 2.38 (s, 3 H), 2.20 (s, 3 H) 1.17–1.12 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 157.2, 146.9, 136.3, 130.1, 129.8, 128.3, 121.2, 113.4, 59.7, 21.2, 14.1, 13.9, 11.7.

1-(2,5-Dimethyl-4-*m*-tolylfuran-3-yl)ethanone (4e)
Yield: 50.3 mg (74%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.27 (t, *J* = 7.6 Hz, 1 H), 7.16–7.15 (d, *J* = 7.2 Hz, 1 H), 7.05–7.03 (m, 2 H), 2.53 (s, 3 H), 2.38 (s, 3 H), 2.17 (s, 3 H), 1.93 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3, 156.0, 146.8, 137.9, 133.6, 130.5, 128.3, 128.0, 126.9, 122.9, 120.8, 30.7, 21.4, 14.2, 11.6.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{16}O_2$ + Na (M + Na^+): 251.1043; found: 251.1049.

Ethyl 2,5-Dimethyl-4-*m*-tolylfuran-3-carboxylate (4f)
Yield: 53.9 mg (70%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 1 H), 7.13–7.06 (m, 3 H), 4.17–4.11 (m, 2 H), 2.59 (s, 3 H), 2.38 (s, 3 H), 2.21 (s, 3 H), 1.14–1.10 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 157.3, 146.9, 136.9, 133.1, 130.7, 127.5, 127.0, 121.3, 113.5, 59.6, 21.4, 14.0, 13.9, 11.7.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}O_3$ + Na (M + Na^+): 281.1148; found: 281.1151.

1-[4-(4-Methoxyphenyl)-2,5-dimethylfuran-3-yl]ethanone (4g)
Yield: 55.1 mg (75%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.15 (d, *J* = 9.2 Hz, 2 H), 6.96–6.93 (d, *J* = 8.8 Hz, 2 H), 3.85 (s, 3 H), 2.53 (s, 3 H), 2.15 (s, 3 H), 1.95 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.2, 158.8, 156.0, 146.8, 130.9, 125.7, 122.9, 120.2, 113.8, 55.1, 30.7, 14.2, 11.5.

Ethyl 4-(4-Methoxyphenyl)-2,5-dimethylfuran-3-carboxylate (4h)
Yield: 56.3 mg (68%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.18 (d, *J* = 8.8 Hz, 2 H), 6.93–6.90 (d, *J* = 8.8 Hz, 2 H), 4.16–4.14 (m, 2 H), 3.84 (s, 3 H), 2.58 (s, 3 H), 2.19 (s, 3 H), 1.17–1.13 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4, 158.4, 157.3, 146.9, 131.1, 125.4, 120.9, 113.5, 113.0, 59.7, 55.2, 14.1, 11.7.

1-{4-[4-(Dimethylamino)phenyl]-2,5-dimethylfuran-3-yl}ethanone (4i)
Yield: 45 mg (58%); yellow solid; mp 85–87 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.08 (d, *J* = 8.8 Hz, 2 H), 6.76–6.74 (d, *J* = 8.8 Hz, 2 H), 2.98 (s, 6 H), 2.52 (s, 3 H), 2.16 (s, 3 H), 1.96 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 155.8, 149.6, 146.6, 130.5, 123.1, 121.0, 120.7, 112.2, 40.4, 30.7, 14.2, 11.6.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{19}NO_2$ + Na (M + Na^+): 280.1308; found: 280.1307.

Ethyl 4-[4-(Dimethylamino)phenyl]-2,5-dimethylfuran-3-carboxylate (4j)
Yield: 49.9 mg (58%); yellow solid; mp 47–48 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.15 (d, *J* = 8.8 Hz, 2 H), 6.78–6.75 (d, *J* = 9.2 Hz, 2 H), 4.19–4.16 (m, 2 H), 2.98 (s, 6 H), 2.58 (s, 3 H), 2.23 (s, 3 H), 1.21–1.17 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 157.0, 149.4, 146.7, 130.7, 121.2, 120.9, 113.5, 111.8, 59.7, 40.6, 14.2, 11.8.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{22}NO_3$ (M + H^+): 288.1594; found (M + H^+): 288.1593.

1-[4-(2-Chlorophenyl)-2,5-dimethylfuran-3-yl]ethanone (4k)
Yield: 49.5 mg (67%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.45 (m, 1 H), 7.32–7.25 (m, 3 H), 2.56 (s, 3 H), 2.08 (s, 3 H), 1.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.1, 156.6, 147.5, 134.7, 132.8, 131.9, 129.6, 129.2, 126.8, 122.6, 117.9, 29.8, 14.5, 11.6.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{13}ClO_2$ + Na (M + Na^+): 271.0496; found: 271.0500.

Ethyl 4-(2-Chlorophenyl)-2,5-dimethylfuran-3-carboxylate (4l)
Yield: 53.5 mg (64%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 1 H), 7.27–7.21 (m, 3 H), 4.12–3.99 (m, 2 H), 2.59 (s, 3 H), 2.12 (s, 3 H), 1.02–0.98 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 157.4, 147.4, 134.7, 132.7, 131.7, 128.9, 128.5, 126.1, 118.6, 113.9, 59.6, 13.9, 13.6, 11.7.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}ClO_3$ + Na (M + Na^+): 301.0602; found: 301.0597.

1-[4-(2,4-Dichlorophenyl)-2,5-dimethylfuran-3-yl]ethanone (4m)
Yield: 51.1 mg (60%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (s, 1 H), 7.31–7.28 (m, 1 H), 7.19–7.18 (m, 1 H), 2.56 (s, 3 H), 2.08 (s, 3 H), 1.97 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.6, 156.8, 147.7, 135.4, 134.3, 132.6, 131.4, 129.5, 127.2, 122.5, 117.0, 29.9, 14.5, 11.6.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{12}Cl_2O_2$ + Na (M + Na^+): 305.0107; found: 305.0108.

Ethyl 4-(2,4-Dichlorophenyl)-2,5-dimethylfuran-3-carboxylate (4n)
Yield: 52.5 mg (56%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.45 (s, 1 H), 7.27–7.25 (m, 1 H), 7.17–7.15 (m, 1 H) 4.12–4.06 (m, 2 H), 2.59 (s, 3 H), 2.12 (s, 3 H), 1.09–1.05 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 157.6, 147.7, 135.5, 133.6, 132.5, 131.4, 128.9, 126.5, 117.7, 113.8, 59.8, 13.9, 13.8, 11.7.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{14}Cl_2O_3$ +Na (M + Na^+): 335.0212; found: 335.0214.

1-[4-(4-Fluorophenyl)-2,5-dimethylfuran-3-yl]ethanone (4o)
Yield: 46.2 mg (66%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.20 (m, 2 H), 7.12–7.08 (m, 2 H), 2.54 (s, 3 H), 2.15 (s, 3 H), 1.96 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.6, 163.3 (d, $J_{C,F}$ = 245.4 Hz), 156.3, 147.1, 131.5 (d, $J_{C,F}$ = 8.2 Hz), 129.6, 122.8, 119.7, 115.5 (d, $J_{C,F}$ = 21.4 Hz), 30.7, 14.3, 11.5.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{13}FO_2$ + Na (M + Na^+): 225.0792; found: 225.0791.

Ethyl 4-(4-Fluorophenyl)-2,5-dimethylfuran-3-carboxylate (4p)
Yield: 52.4 mg (67%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.19 (m, 2 H), 7.07–7.03 (m, 2 H), 4.14–4.10 (m, 2 H), 2.57 (s, 3 H), 2.18 (s, 3 H), 1.14–1.10 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 163.1 (d, $J_{C,F}$ = 244.1 Hz), 157.5, 147.1, 131.6 (d, $J_{C,F}$ = 8.2 Hz), 129.1, 120.3, 114.6 (d, $J_{C,F}$ = 21.4 Hz), 113.3, 59.7, 14.1, 13.9, 11.6.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}FO_3$ + Na (M + Na^+): 285.0897; found: 285.0902.

1-[4-(Furan-2-yl)-2,5-dimethylfuran-3-yl]ethanone (4q)
Yield: 27.4 mg (45%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (s, 1 H), 6.48 (s, 1 H), 6.35 (s, 1 H), 2.52 (s, 3 H), 2.26 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.6, 156.5, 149.4, 146.1, 142.3, 121.9, 111.2, 111.0, 109.6, 29.6, 14.2, 11.9.

HRMS (ESI): *m/z* calcd for $C_{12}H_{12}O_3$ + Na (M + Na^+): 227.0679; found: 227.0687.

Ethyl 4-(Furan-2-yl)-2,5-dimethylfuran-3-carboxylate (4r)
Yield: 42.9 mg (61%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.46 (s, 1 H), 6.49–6.45 (m, 2 H), 4.25–4.23 (m, 2 H), 2.54 (s, 3 H), 2.35 (s, 3 H), 1.27–1.24 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 157.5, 149.1, 146.6, 141.5, 112.9, 111.8, 110.6, 108.9, 59.9, 14.1, 13.9, 12.5.

HRMS (ESI): *m/z* calcd for $C_{13}H_{14}O_4$ + Na (M + Na^+): 257.0784; found: 257.0795.

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