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Highly efficient Cu-catalyzed oxidative coupling of tertiary amines and siloxyfurans

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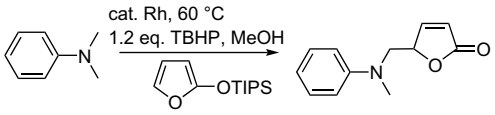
ABSTRACT

A mild, selective, and efficient protocol for the synthesis of γ-aminoalkyl butenolides via the oxidative coupling between tertiary amines and siloxyfurans catalyzed by simple copper salts was developed. Compared with the reported method, our method employs copper catalyst instead of the expensive rhodium catalyst. Besides TBHP, both O_2 and H_2O_2 can also be utilized as oxidant to effect the coupling.

1. Introduction

One of the challenges synthetic organic chemists facing in the 21th century is the development of mild, selective, and efficient C–C bond formation reactions via CH-activation mode.[1–5] The CH-activation of tertiary amines, an important class of organic compounds, has attracted a lot of attentions lately[6–9] because the iminium ion generated in situ could participate in a plethora of different transformations.[10] Inspired by earlier seminar work by Murahashi on the Ru-catalyzed α-cyanation of tertiary amines via CH-activation,[8] Li et al. recently developed a series of elegant C–C bond formation reactions (referred by Li as cross-dehydrogenative couplings) between tertiary amines and a variety of nucleophiles such as nitro alkanes,[9e,i] terminal alkynes,[9a] indoles,[9d] malonates,[9c] malononitriles,[9c] 2-naphthol,[9f] and phenylboronic acids[9j] as well as Morita–Baylis–Hillman (MBH) adducts[9f] employing copper salt as catalyst and anhydrous TBHP as the oxidant. Even more impressive is that they were able to develop an enantioselective coupling between terminal alkynes and the sp^3 C–H bonds adjacent to nitrogen in tetrahydroisoquinolines.[9b] This method could provide rapid access to several biologically important chiral tetrahydroisoquinoline alkanoids.

In 2006, Doyle reported an efficient oxidative Mannich reaction between tertiary amines and siloxyfurans using TBHP as oxidant catalyzed by $Rh_2(cap)_4$, allowing a fast and expedient route for the synthesis of γ-aminoalkyl butenolides (Eq. 1). Similar to the cross-dehydrogenative coupling reactions, an iminium species was proposed as the reaction intermediate and this raise the possibility that the same transformation could be catalyzed by copper salts as well. If this assumption turns out to be true, the synthetic utility of this reaction would be greatly enhanced since the price of copper is significantly lower than rhodium, especially when the reaction is run on large scale. Herein, we report that the oxidative coupling between tertiary amines and siloxyfurans can be efficiently catalyzed by simple copper salts using either TBHP or O_2 as the oxidant.



(1)

2. Results and discussion

We began our study by examining different copper salts as the catalysts using *N*,*N*-dimethyl aniline (**1**) and siloxyfuran **2** as the coupling partners and the results are shown in Table 1. We were glad to discover that running the reaction in methanol in the presence of 5% CuCl at 55 °C for 3 h led to the formation of the desired γ-aminoalkyl butenolide in 69% yield (Table 1, entry 1). Out of the various copper salts tried, CuBr was found to be the best, affording the desired product in 78% yield while other copper salts such as $CuBr_2$, $CuCl_2$, CuI, $Cu(OAc)_2$, and CuO were less effective (Table 1, entries 2–7). Replacing the solvent methanol with ethanol resulted in a sizable decrease in terms of product yield (entry 8). Though the use of 1.2 equiv of anhydrous TBHP proved to be sufficient, it is discovered that 1 equiv excess of **1** is needed in order to obtain high product yield. Control experiment also showed that no desired butenolide was formed in the absence of copper catalyst (entry 9). As a result, we decided to set running the reaction at 55 °C in the presence of 5% CuBr as the standard reaction condition.

Under the standard condition, various amines were coupled with different siloxylfurans and the results are listed in Table 2. In all cases, the desired products were formed in moderate to good yields. It should be noted that besides *N*,*N*-dimethyl anilines,

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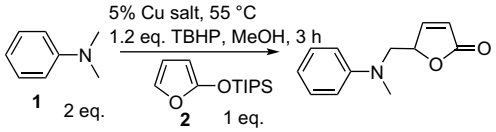
Table 1
Optimization of reaction conditions



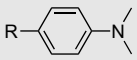
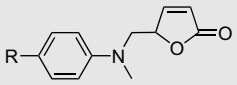
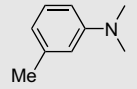
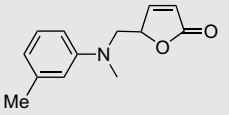
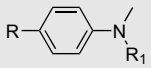
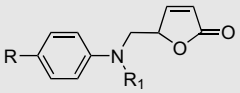
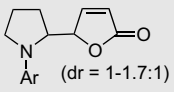
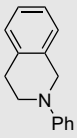
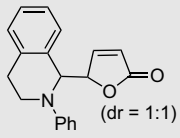
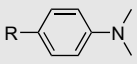
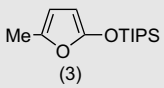
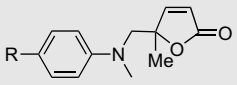
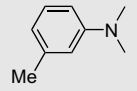
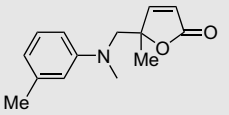
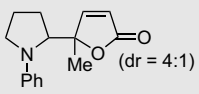
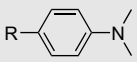
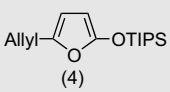
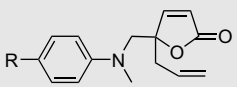
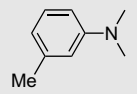
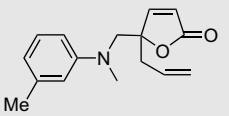
Entry	Catalyst	Yield[a] (%)
1	CuCl	69
2	CuBr	78
3	$CuBr_2$	75
4	$CuCl_2$	70
5	$CuCl_2$	52
6	$Cu(OAc)_2$	67
7	CuO	6
8	CuBr[b]	55
9	None	None

[a] All yields are isolated yields.
[b] Ethanol was used instead of MeOH.

N,*N*-methyl alkyl anilines could also participate in the reaction satisfactorily, and the coupling only occurred at the methyl substituent selectively (Table 2, entry 3). Cyclic amines such as pyrrolidines and tetrahydroisoquinolines could also be effectively coupled. Unlike other amines, it only requires 1 equiv of *N*-phenyl tetrahydroisoquinoline for its efficient coupling with **2** to take place, furnishing the desired butenolide in 73% yield. The coupling reaction also took place when T-HYDRO (70% ^{t}BuOOH in H_2O) was used in place of anhydrous TBHP, though the yields are lower by 5–12%. Other siloxylfurans such as 5-methyl and 5-allyl substituted siloxyfurans **3** and **4** could also couple with anilines and pyrrolidine derivatives satisfactorily (Table 2, entries 6–10).

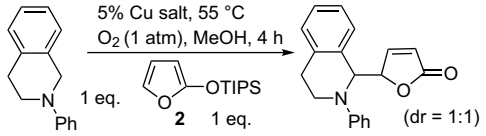
As satisfactory as the above procedure is, the desire to use a cleaner oxidant prompted us to investigate the possibility of using O_2 as the oxidant. Since the side product derived from O_2 is water, its use would enhance the synthetic value of this transformation even further. Much to our delight, we found *N*-phenyl tetrahydro isoquinoline could couple efficiently with siloxyfuran **2** in the presence of 5% CuBr under a balloon of O_2 (1 atm) at 55 °C and the desired coupling product was isolated in 60% yield after 4 h. Further

Table 2
The oxidative coupling of tertiary amines and siloxyfurans catalyzed by CuBr using TBHP as oxidant

Entry	Amine	2-Siloxyfuran	Product		Yield[a,b] (%)
1		2		R=H R=Me R=Br R=Ph R=HCO	78 70 (64) 66 60 40
2		2			74
3		2		R=H, R1=Et R=Me, R1=Et R=Me, R1=^{n}Bu	68 67 55
4		2		Ar=Ph Ar=*p*-MePh Ar=*p*-MeOPh	72 (60) 53 50
5		2			73 (68)[c]
6				R=H R=Me	70 75
7		3			64
8		3			60
9				R=H R=Me	68 70
10		4			60

[a] All yields are isolated yields.
[b] The yields in parenthesis are those obtained with T-HYDRO.
[c] Only 1 equiv of *N*-phenyl tetrahydroisoquinoline is used.

Table 3
Optimization of reaction conditions



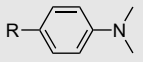
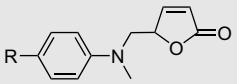
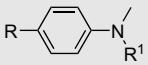
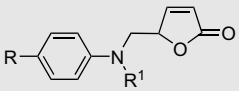
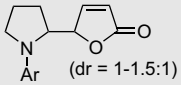
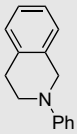
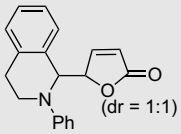
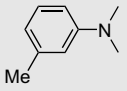
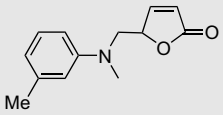
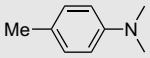
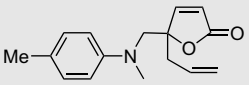
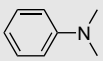
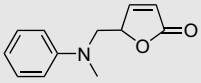
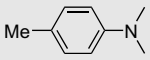
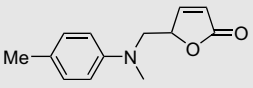
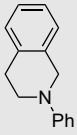
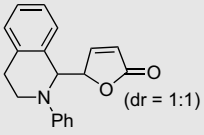
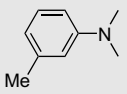
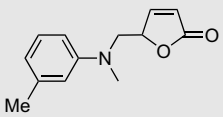
Entry	Catalyst	Yield[a] (%)
1	CuBr	60
2	$CuBr_2$	82
3	$CuCl_2$	70
4	CuCl	57
5	CuI	55[b]
6	$Cu(OAc)_2$	45
7	CuO	20

[a] All yields are isolated yields.
[b] Reaction run for 20 h.

test revealed $CuBr_2$ to be a superior catalyst, whereas other catalysts are less efficient (Table 3). On the other hand, switching to the use of air resulted in a much more sluggish and messier reaction.

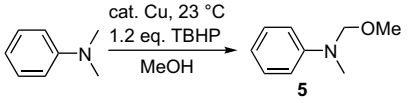
Using $CuBr_2$ as the catalyst, various substituted anilines and pyrrolidines could couple with siloxyfurans **2**–**4** and the results are summarized in Table 4 (entries 1–6). Compared to the reaction using TBHP as the oxidant, the yields are generally lower and, despite its earlier success, *N*,*N*-dimethyl aniline was found to be unsuitable for the reaction when O_2 was used as the oxidant. We also briefly examined the coupling reaction using another green oxidant H_2O_2 (30% in water). The coupling also took place satisfactorily and the yields are comparable to those obtained with O_2 (Table 4, entries 7–10). With H_2O_2, *N*,*N*-dimethyl aniline was found to be a viable substrate (Table 4, entry 7). In order to probe the possible reaction mechanism, *N*,*N*-dimethyl aniline was subjected to the standard reaction condition using methanol as the solvent in the absence of siloxyfuran **2**. NMR analysis of the crude product indicated the formation of compound **5** in about 50% yield. Switching the solvent methanol to CH_2Cl_2 gave the compound **6** instead. These results are consistent with the ones reported by Doyle when

Table 4
Cu-Catalyzed oxidative coupling of tertiary amines with siloxyfurans using O_2 or H_2O_2 as oxidant

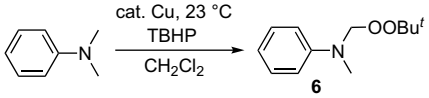
Entry	Amine	2-Siloxyfuran	Product		Yield[a] (%)
1[b]		2		R=H R=Me	<15 68
2[b]		2		R=Me R1=Et R=Me R1=^{n}Bu	55 40
3[b]		2		Ar=Ph Ar=*p*-MeOPh	65 62
4[b]		2			82
5[b]		3			60
6[b]		4			58
7[c]		2			50
8[c]		2			65
9[c]		2			64
10[c]		2			58

[a] All yields are isolated yields.
[b] O_2 was used as the oxidant.
[c] H_2O_2 was used as the oxidant.

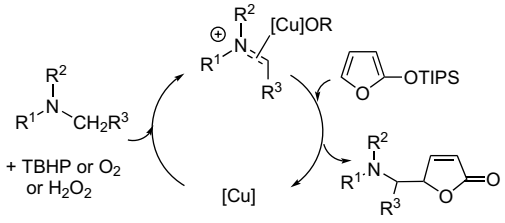
rhodium was used as the catalyst. It also gave support to the notion that an iminium ion intermediate was generated in situ. Preliminary mechanistic study also indicated that all three reactions proceeded smoothly in the presence of 2 equiv of BHT, a free radical inhibitor. This result strongly suggests that reaction may not involve a radical process. In accord with others,[9] a tentative mechanism is proposed in Scheme 1. It is thought that an iminium species is first generated by copper catalysis and the copper-coordinated iminium ion is then trapped by the siloxyfuran to form the γ-aminoalkyl butenolide.



(2)



(3)



Scheme 1.

3. Conclusion

In summary, we have developed a mild, selective, and efficient oxidative coupling protocol for the coupling of tertiary amines and siloxyfurans to synthesize γ-aminoalkyl butenolides using simple copper salts as catalyst. The reaction could be run using TBHP, O_2, or H_2O_2 as the oxidant though the best yields are achieved with anhydrous TBHP. Our results are comparable to those reported and the use of a relatively cheap copper catalyst in place of expensive rhodium catalyst could be beneficial for large scale preparations. Further investigations are currently underway to develop new transformations as well as to gain more insight into the reaction mechanism.

4. Experimental

4.1. General information

All solvents and reagents were purchased from the suppliers and used without further purification. Yields reported are for isolated yields unless otherwise stated. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ at room temperature on a Varian INOVA-400 spectrometer. The chemical-shift scale is based on internal TMS. MS spectra were performed on an Agilent 1100 series mass spectrometer. HRMS analyses were performed on a Shimadzu QP-2000 mass spectrometer. IR spectra were recorded by Thermo Electron Nicolet FTIR-6700 instrument. TLC analyses were performed on silica gel plates and column chromatography was conducted over silica gel (mesh 200–300).

4.2. Representative experimental procedure

To a mixture of 1 mmol of 2-triisopropylsiloxylfuran, 2 mmol of *N*,*N*-dimethyl aniline, and 0.05 mmol of CuBr in 1 mL of CH_3OH was added 1.2 mmol of TBHP (5–6 M in decane) (or 1.2 mmol of T-HYDRO (70% ^{t}BuOOH in water) or 1 atm O_2 or 1.2 mmol of H_2O_2 (30% in water)). The mixture was heated to 55 °C for 3 h before it was cooled to room temperature. The mixture was diluted and extracted with ether. Solvent was evaporated and the residue was purified by column chromatography on silica gel to give the desired product (4:1 hexanes/EtOAc).

4.2.1. Synthesis of 5-[(methylphenylamino)methyl]-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J*=5.6 Hz, 1H), 7.26 (t, *J*=8.0 Hz, 2H), 6.79–6.72 (m, 3H), 6.13 (dd, *J*=5.6, 1.6 Hz, 1H), 5.27 (dd, *J*=5.6, 1.6 Hz, 1H), 3.69 (d, *J*=5.6 Hz, 2H), 3.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.46, 154.43, 147.98, 129.04 (2C), 121.61, 116.88, 111.93 (2C), 81.85, 54.49, 39.12; IR (neat) 1757 cm^{-1} (C=O); MS (CI) *m*/*z*: 204 $[M+1]^+$; HRMS (EI) calcd for $C_{12}H_{13}NO_2$ $[M]^+$ 203.0946, found 203.0948.

4.2.2. Synthesis of 5-{[methyl(4-methylphenyl)amino]methyl}-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J*=5.6, 1.6 Hz, 1H), 7.07 (d, *J*=8.0 Hz, 2H), 6.65 (d, *J*=8.8 Hz, 2H), 6.13 (dd, *J*=6.0, 2.0 Hz, 1H), 5.28–5.25 (m, 1H), 3.65 (d, *J*=6.0 Hz, 2H), 3.00 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.69, 154.55, 146.19, 129.92 (2C), 126.77, 122.09, 112.63 (2C), 81.97, 55.37, 39.66, 20.18; IR (neat) 1751 cm^{-1} (C=O); MS (CI) *m*/*z*: 218 $[M+1]^+$; HRMS (EI) calcd for $C_{13}H_{15}NO_2$ $[M]^+$ 217.1103, found 217.1109.

4.2.3. Synthesis of 5-{[(4-bromophenyl)methylamino]methyl}-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J*=5.2, 1.2 Hz, 1H), 7.25 (d, *J*=8.8 Hz, 2H), 6.51 (d, *J*=8.8 Hz, 2H), 6.08 (dd, *J*=6.0, 2.0 Hz, 1H), 5.19–5.16 (m, 1H), 3.63 (dd, *J*=15.2, 5.6 Hz, 1H), 3.56 (dd, *J*=15.6, 6.0 Hz, 1H), 2.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.43, 152.96, 146.27, 131.05 (2C), 121.47, 112.89 (2C), 108.39, 80.83, 53.88, 38.66; IR (neat) 1756 cm^{-1} (C=O); MS (CI) *m*/*z*: 282 $[M+1]^+$; HRMS (EI) calcd for $C_{12}H_{12}BrNO_2$ $[M]^+$ 281.0051, found 281.0047.

4.2.4. Synthesis of 5-[(biphenyl-4-yl-methylamino)methyl]-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.41 (m, 5H), 7.33 (t, *J*=7.6 Hz, 2H), 7.22–7.17 (m, 1H), 6.70 (d, *J*=8.8 Hz, 2H), 6.07 (dd, *J*=5.6, 2.0 Hz, 1H), 5.23–5.20 (m, 1H), 3.70–3.59 (m, 2H), 2.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.60, 153.29, 146.55, 139.71, 129.09 (2C), 127.69 (2C), 126.97 (2C), 125.26 (2C), 121.29, 111.50 (2C), 80.95, 53.91, 38.62; IR (neat) 1753 cm^{-1} (C=O); MS (CI) *m*/*z*: 280 $[M+1]^+$; HRMS (EI) calcd for $C_{18}H_{17}NO_2$ $[M]^+$ 279.1259, found 279.1250.

4.2.5. Synthesis of 4-{[(2,5-bihydro-5-oxo-2-furanyl)methyl]methylamino}benzaldehyde

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.76 (d, *J*=8.8 Hz, 2H), 7.53 (dd, *J*=5.6, 1.2 Hz, 1H), 6.76 (d, *J*=8.8 Hz, 2H), 6.18 (dd, *J*=5.6, 2.0 Hz, 1H), 5.33–5.30 (m, 1H), 3.91 (dd, *J*=15.6, 4.8 Hz, 1H), 3.73 (dd, *J*=15.2, 6.0 Hz, 1H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.27, 172.12, 153.38, 152.66, 132.02 (2C), 126.13, 122.80, 111.25 (2C), 81.72, 54.14, 39.86; IR (neat) 1755, 1595 cm^{-1} (C=O); MS (CI) *m*/*z*: 232 $[M+1]^+$; HRMS (EI) calcd for $C_{13}H_{13}NO_3$ $[M]^+$ 231.0895, found 231.0891.

4.2.6. Synthesis of 5-{[methyl(3-methylphenyl)amino]methyl}-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J*=5.6, 1.2 Hz, 1H), 7.16–7.11 (m, 1H), 6.59 (d, *J*=7.2 Hz, 1H), 6.52 (d, *J*=5.6 Hz, 2H), 6.12 (dd, *J*=6.0, 2.0 Hz, 1H), 5.26–5.25 (m, 1H), 3.66 (d, *J*=6.0 Hz, 2H), 3.00 (s, 3H),

2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.62, 154.51, 148.22, 139.05, 129.14, 121.96, 118.20, 112.95, 109.41, 81.93, 54.90, 39.45, 21.82; IR (neat) 1754 cm^{-1} (C═O); MS (CI) *m*/*z*: 218 [M+1]$^+$; HRMS (EI) calcd for $C_{13}H_{15}NO_2$ [M]$^+$ 217.1103, found 217.1108.

4.2.7. Synthesis of 5-[(ethylphenylamino)methyl]-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J*=5.6, 1.2 Hz, 1H), 7.19–7.15 (m, 2H), 6.68–6.62 (m, 3H), 6.07 (dd, *J*=5.6, 2.0 Hz, 1H), 5.19–5.15 (m, 1H), 3.61 (dd, *J*=15.2, 6.0 Hz, 1H), 3.50 (dd, *J*=15.2, 6.0 Hz, 1H), 3.46–3.26 (m, 2H), 1.09 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.69, 153.75, 145.95, 128.49 (2C), 121.08, 116.06, 111.43 (2C), 80.84, 51.88, 44.77, 10.85; IR (neat) 1752 cm^{-1} (C═O); MS (CI) *m*/*z*: 218 [M+1]$^+$; HRMS (EI) calcd for $C_{13}H_{15}NO_2$ [M]$^+$ 217.1103, found 217.1104.

4.2.8. Synthesis of 5-{[ethyl(4-methylphenyl)amino]methyl}-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J*=5.2 Hz, 1H), 6.99 (d, *J*=8.4 Hz, 2H), 6.56 (d, *J*=8.4 Hz, 2H), 6.06 (dd, *J*=5.6, 1.6 Hz, 1H), 5.17–5.14 (m, 1H), 3.60 (dd, *J*=15.2, 6.0 Hz, 1H), 3.45 (dd, *J*=15.2, 6.4 Hz, 1H), 3.41–3.25 (m, 2H), 2.18 (s, 3H), 1.07 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.76, 153.93, 143.85, 128.99 (2C), 125.53, 120.96, 111.98 (2C), 80.90, 52.20, 45.01, 19.15, 10.92; IR (neat) 1755 cm^{-1} (C═O); MS (CI) *m*/*z*: 232 [M+1]$^+$; HRMS (EI) calcd for $C_{14}H_{17}NO_2$ [M]$^+$ 231.1259, found 231.1247.

4.2.9. Synthesis of 5-{[n-butyl(4-methylphenyl)amino]methyl}-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J*=5.6, 0.8 Hz, 1H), 6.98 (d, *J*=8.8 Hz, 2H), 6.55 (d, *J*=8.8 Hz, 2H), 6.05 (dd, *J*=5.6, 1.6 Hz, 1H), 5.17–5.14 (m, 1H), 3.62 (dd, *J*=15.2, 6.0 Hz, 1H), 3.46 (dd, *J*=14.8, 6.4 Hz, 1H), 3.32–3.14 (m, 2H), 2.18 (s, 3H), 1.49–1.46 (m, 2H), 1.29–1.23 (m, 2H), 0.86 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.76, 153.97, 143.97, 128.97 (2C), 125.41, 120.86, 111.95 (2C), 80.74, 52.69, 50.73, 27.92, 19.16 (2C), 12.94; IR (neat) 1754 cm^{-1} (C═O); MS (CI) *m*/*z*: 260 [M+1]$^+$; HRMS (EI) calcd for $C_{16}H_{21}NO_2$ [M]$^+$ 259.1572, found 259.1545.

4.2.10. Synthesis of 5-(1-phenyl-2-pyrrolidinyl)-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2H), 7.30–7.22 (m, 4H), 6.78–6.72 (m, 4H), 6.58 (d, *J*=8.4 Hz, 2H), 6.18–6.16 (m, 2H), 5.40–5.38 (m, 1H), 5.04–5.01 (m, 1H), 4.39–4.36 (m, 1H), 3.86 (t, *J*=7.2 Hz, 1H), 3.63–3.55 (m, 2H), 3.23–3.16 (m, 2H), 2.15–1.68 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.82 (2C), 154.97, 152.64, 146.02, 145.83, 128.49 (2C), 128.32 (2C), 121.79, 120.67, 116.26, 116.04, 111.67 (2C), 111.43 (2C), 83.07, 81.42, 59.54, 58.11, 48.41, 48.21, 26.90, 24.24, 23.12, 22.24; IR (neat) 1757 cm^{-1} (C═O); MS (CI) *m*/*z*: 230 [M+1]$^+$; HRMS (EI) calcd for $C_{14}H_{15}NO_2$ [M]$^+$ 229.1103, found 229.1109.

4.2.11. Synthesis of 5-[1-(4-methylphenyl)-2-pyrrolidinyl]-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (m, 1H), 7.03–6.97 (m, 2H), 6.57 (d, *J*=8.4 Hz, 1H), 6.41 (d, *J*=8.4 Hz, 1H), 6.11–6.07 (m, 1H), 5.31–5.29 (m, 0.62H) [4.93–4.90 (m, 0.37H)], 4.27–4.24 (m, 0.63H) [3.72 (t, *J*=7.6 Hz, 0.38H)], 3.55–3.46 (m, 1H), 3.12–3.03 (m, 1H), 2.19 (d, *J*=4.8 Hz, 3H), 2.05–1.62 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.90 (2C), 155.20, 152.77, 143.96, 143.81, 128.99 (2C), 128.81 (2C), 125.45, 125.20, 121.75, 120.54, 111.71 (2C), 111.43 (2C), 83.28, 81.55, 59.80, 58.25, 48.66, 48.49, 27.07, 24.19, 23.20, 22.27, 19.21 (2C); IR (neat) 1757 cm^{-1} (C═O); MS (CI) *m*/*z*: 244 [M+1]$^+$; HRMS (EI) calcd for $C_{15}H_{17}NO_2$ [M]$^+$ 243.1259, found 243.1250.

4.2.12. Synthesis of 5-[1-(4-methoxyphenyl)-2-pyrrolidinyl]-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.39 (m, 1H), 6.89–6.83 (m, 2H), 6.68 (d, *J*=9.2 Hz, 1H), 6.53 (d, *J*=9.2 Hz, 1H), 6.19–6.15 (m, 1H), 5.35–5.34 (m, 0.36H) [4.99–4.97 (m, 0.51H)], 4.30–4.27 (m, 0.42H) [3.80–3.77 (m, 0.61H)], 3.76 (d, *J*=3.6 Hz, 3H), 3.61–3.54 (m, 1H), 3.17–3.08 (m, 1H), 2.14–1.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.96 (2C), 156.13, 153.78, 151.75, 151.57, 141.72, 141.50, 122.71, 121.52, 115.06 (2C), 114.87 (2C), 113.60 (2C), 113.31 (2C), 84.38, 82.72, 61.08, 59.57, 55.77, 55.74, 50.13, 49.90, 28.10, 25.24, 24.27, 23.36; IR (neat) 1758 cm^{-1} (C═O); MS (CI) *m*/*z*: 260 [M+1]$^+$; HRMS (EI) calcd for $C_{15}H_{17}NO_3$ [M]$^+$ 259.1208, found 259.1212.

4.2.13. Synthesis of 5-(1,2,3,4-tetrahydro-2-phenyl-1-isoquinolinyl)-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J*=6.0, 1.6 Hz, 1H), 7.28 (dd, *J*=6.0, 2.0 Hz, 1H), 7.23–7.05 (m, 12H), 6.89 (d, *J*=8.0 Hz, 2H), 6.79 (d, *J*=8.0 Hz, 2H), 6.75–6.70 (m, 2H), 6.00 (dd, *J*=5.6, 2.0 Hz, 1H), 5.81 (dd, *J*=5.6, 1.6 Hz, 1H), 5.34–5.32 (m, 1H), 5.24–5.22 (m, 1H), 5.07 (d, *J*=4.4 Hz, 1H), 4.81 (d, *J*=6.0 Hz, 1H), 3.70–3.64 (m, 1H), 3.53–3.45 (m, 2H), 3.36–3.30 (m, 1H), 3.94–2.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.60, 171.48, 153.74, 152.68, 147.93, 147.88, 134.71, 134.33, 131.41, 130.95, 128.46 (2C), 128.39 (2C), 127.62, 127.43, 127.12, 126.81, 126.75, 126.55, 125.37, 124.98, 121.48, 121.18, 117.82, 117.66, 113.51 (2C), 113.44 (2C), 84.89, 84.44, 60.66, 59.54, 42.96, 42.41, 27.24, 26.22; IR (neat) 1759 cm^{-1} (C═O); MS (CI) *m*/*z*: 292 [M+1]$^+$; HRMS (EI) calcd for $C_{19}H_{17}NO_2$ [M]$^+$ 291.1259, found 291.1253.

4.2.14. Synthesis of 5-methyl-5-[(methylphenylamino)methyl]-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J*=5.6 Hz, 1H), 7.19–7.13 (m, 2H), 6.66 (t, *J*=7.2 Hz, 1H), 6.59 (d, *J*=8.4 Hz, 2H), 5.87 (d, *J*=5.6 Hz, 1H), 3.63 (d, *J*=15.6 Hz, 1H), 3.57 (d, *J*=16.0 Hz, 1H), 2.91 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.08, 156.84, 147.77, 128.20 (2C), 120.35, 116.00, 110.96 (2C), 89.65, 57.80, 39.03, 20.88; IR (neat) 1753 cm^{-1} (C═O); MS (CI) *m*/*z*: 218 [M+1]$^+$; HRMS (EI) calcd for $C_{13}H_{15}NO_2$ [M]$^+$ 217.1103, found 217.1104.

4.2.15. Synthesis of 5-methyl-5-{[methyl(4-methylphenyl)-amino]methyl}-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J*=6.0 Hz, 1H), 7.03 (d, *J*=8.8 Hz, 2H), 6.58 (d, *J*=8.8 Hz, 2H), 5.94 (d, *J*=6.0 Hz, 1H), 3.68–3.59 (m, 2H), 2.96 (s, 3H), 2.24 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.13, 157.95, 146.76, 129.71 (2C), 126.22, 121.29, 112.15 (2C), 90.70, 59.16, 40.15, 21.89, 20.14; IR (neat) 1751 cm^{-1} (C═O); MS (CI) *m*/*z*: 232 [M+1]$^+$; HRMS (EI) calcd for $C_{14}H_{17}NO_2$ [M]$^+$ 231.1259, found 231.1257.

4.2.16. Synthesis of 5-methyl-5-{[methyl(3-methylphenyl)amino]-methyl}-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J*=5.6 Hz, 1H), 7.13–7.09 (m, 1H), 6.56 (d, *J*=7.6 Hz, 1H), 6.47 (d, *J*=6.0 Hz, 2H), 5.95 (d, *J*=5.6 Hz, 1H), 3.72–3.61 (m, 2H), 2.98 (s, 3H), 2.31 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.10, 156.87, 147.85, 137.95, 128.00, 120.28, 116.94, 111.73, 108.21, 89.68, 57.80, 39.06, 20.93, 20.90; IR (neat) 1753 cm^{-1} (C═O); MS (CI) *m*/*z*: 232 [M+1]$^+$; HRMS (EI) calcd for $C_{14}H_{17}NO_2$ [M]$^+$ 231.1259, found 231.1250.

4.2.17. Synthesis of 5-methyl-5-(1-phenyl-2-pyrrolidinyl)-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 1H), 7.18–7.12 (m, 2H), 6.70–6.64 (m, 1H), 6.62–6.60 (m, 2H), 5.96 (d, *J*=5.6 Hz, 0.87H) [5.74 (d, *J*=5.6 Hz, 0.21H)], 4.03 (d, *J*=8.4 Hz, 0.24H) [3.90 (d, *J*=7.6 Hz, 0.98H)], 3.60–3.50 (m, 1H), 3.20–3.10 (m, 1H), 2.10–1.97 (m, 4H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ171.18 (2C), 159.31, 157.06, 147.11, 147.04, 128.04 (2C), 127.97 (2C), 119.34, 119.12, 116.28, 115.89, 112.65 (2C), 112.07 (2C), 83.18, 81.45, 62.53, 61.32, 49.90, 49.63, 26.66, 26.23, 23.16, 22.97, 21.02, 19.31; IR (neat) 1755 cm^{-1} (C═O); MS (CI) *m*/*z*: 244 [M+1]$^+$; HRMS (EI) calcd for $C_{15}H_{17}NO_2$ [M]$^+$ 243.1259, found 243.1266.

4.2.18. Synthesis of 5-allyl-5-[(methylphenylamino)methyl]-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J=6.0 Hz, 1H), 7.26–7.20 (m, 2H), 6.73 (t, J=7.2 Hz, 1H), 6.65 (d, J=8.8 Hz, 2H), 5.96 (d, J=6.0 Hz, 1H), 5.74–5.63 (m, 1H), 5.21–5.16 (m, 2H), 3.79 (d, J=15.6 Hz, 1H), 3.66 (d, J=15.6 Hz, 1H), 2.97 (s, 3H), 2.66–2.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.95, 156.32, 148.74, 130.12, 129.17 (2C), 122.37, 120.56, 116.99, 111.95 (2C), 92.24, 57.58, 40.08, 39.63; IR (neat) 1755 cm^{-1} (C=O); MS (CI) m/z: 244 $[M+1]^+$; HRMS (EI) calcd for $C_{15}H_{17}NO_2$ $[M]^+$ 243.1259, found 243.1264.

4.2.19. Synthesis of 5-allyl-5-{[methyl(4-methylphenyl)amino]-methyl}-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J=5.6 Hz, 1H), 7.02 (d, J=8.4 Hz, 2H), 6.56 (d, J=8.4 Hz, 2H), 5.95 (d, J=5.6 Hz, 1H), 5.70–5.62 (m, 1H), 5.19–5.14 (m, 2H), 3.74 (d, J=15.6 Hz, 1H), 3.62 (d, J=15.6 Hz, 1H), 2.93 (s, 3H), 2.65–2.53 (m, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.00, 156.47, 146.71, 130.16, 129.65 (2C), 126.13, 122.23, 120.42, 112.10 (2C), 92.26, 57.89, 40.15, 39.54, 20.09; IR (neat) 1755 cm^{-1} (C=O); MS (CI) m/z: 258 $[M+1]^+$; HRMS (EI) calcd for $C_{16}H_{19}NO_2$ $[M]^+$ 257.1416, found 257.1402.

4.2.20. Synthesis of 5-allyl-5-{[methyl(3-methylphenyl)amino]-methyl}-2(5H)-furanone

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J=6.0 Hz, 1H), 7.12–7.08 (m, 1H), 6.55 (d, J=7.2 Hz, 1H), 6.46 (d, J=6.0 Hz, 2H), 5.95 (d, J=5.6 Hz, 1H), 5.73–5.62 (m, 1H), 5.20–5.15 (m, 2H), 3.77 (d, J=16.0 Hz, 1H), 3.63 (d, J=15.6 Hz, 1H), 2.95 (s, 3H), 2.66–2.54 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.98, 156.39, 148.79, 138.86, 130.11, 128.94, 122.24, 120.46, 117.88, 112.68, 109.16, 92.25, 57.54, 40.06, 39.52, 21.88; IR (neat) 1751 cm^{-1} (C=O); MS (CI) m/z: 258 $[M+1]^+$; HRMS (EI) calcd for $C_{16}H_{19}NO_2$ $[M]^+$ 257.1416, found 257.1411.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.078.

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