PEG 400 as a Reusable Solvent for 1,4-Dipolar Cycloadditions via a Three-Component Reaction

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Abstract: Isocyanides, dialkyl acetylenedicarboxylates, and α,β-unsaturated aldehydes undergo smooth condensation in poly(ethylene glycol) (PEG 400) to afford the corresponding styrylfuran derivatives in good yields. This method provides a convenient route for a wide range of styrylfurans in a one-pot operation via a three-component reaction. The solvent can be recycled and reused for further reactions.

Key words: poly(ethylene glycol), three-component reaction, zwitterions, styrylfurans

Multicomponent reactions (MCRs) are highly important because of their wide range of applications in the pharmaceutical chemistry for the production of diversified structural scaffolds and combinatorial libraries for drug discovery.[1] They are extremely convergent, producing a remarkably high increase of molecular complexity in just one step.[2] The cycloaddition of 1,4-dipoles with various electrophiles such as aldehydes, imines, quinones, activated alkenes, and aza-aromatic systems has been reported to generate a wide range of heterocycles including aminofurans, pyrroles, and novel spirolactones.[3,4] Furthermore, the cycloaddition of zwitterions derived from isocyanides and dimethyl acetylenedicarboxylate with phenyl isocyanate, diethyl mesoxalate, and dimethyl azodicarboxylate has also been reported to produce six-membered heterocycles.[5,6] Though, the cycloaddition of zwitterions derived from isocyanides and dimethyl acetylenedicarboxylate has been known with simple aldehydes,[3] no examples are reported using 3-formylchromenones to produce chromenylfurans. Keeping in mind the challenges posed by traditional solvents and also the limitation of ionic liquids and supercritical fluids, we are particularly interested in the use of readily available and biologically compatible poly(ethylene glycol) (PEG) as a recyclable solvent for cycloaddition reactions.[7–9] Although, ionic liquids have been demonstrated to be a recyclable reaction media, they are relatively expensive and are toxic compared to PEG.[10,11] The preparation of ionic liquids requires tedious purification techniques.

Following our interest in zwitterionic chemistry,[12] we attempted the annulation of α,β-unsaturated aldehydes with zwitterions derived from dimethyl acetylenedicarboxylate and isocyanides to produce seven-membered oxepins, however, instead of the expected annulated product (Figure 1) a 2-aminofuran was isolated as the sole product. Thus treatment of 3-formylchromone **1** (R^1 = H) with cyclohexyl isocyanide (**2**, R^2 = cyclohexyl) and dimethyl acetylenedicarboxylate (**3a**) in PEG 400 gave dimethyl 2-(cyclohexylamino)-5-(4-oxo-4*H*-chromen-3-yl)furan-3,4-dicarboxylate (**4a**) in 80% yield (Table 1). The structure of **4a** was confirmed by X-ray crystallography (Figure 2).

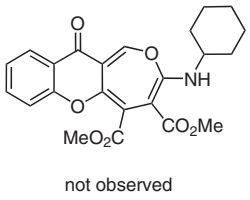

Figure 1 Expected annulated product

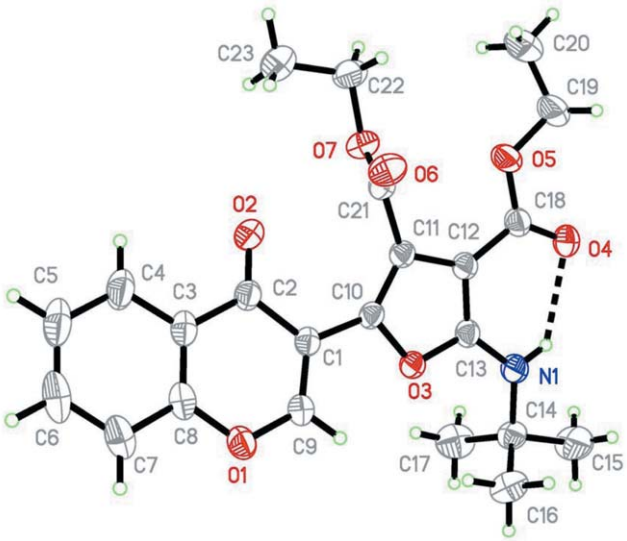

Figure 2 X-ray crystal structure of **4a**

Similarly, *tert*-butyl isocyanide also participated well in the reaction and the results are presented in Table 1.

Encouraged by the results obtained with 3-formylchromone **1**, we turned our attention to other α,β-unsaturated aldehydes **5**, isocyanides **2**, and dialkyl acetylenedicarboxylates **3**. Interestingly, the coupling of cinnamaldehyde (**5**, $R^1 = R^2$ = H) with zwitterions derived from cy-

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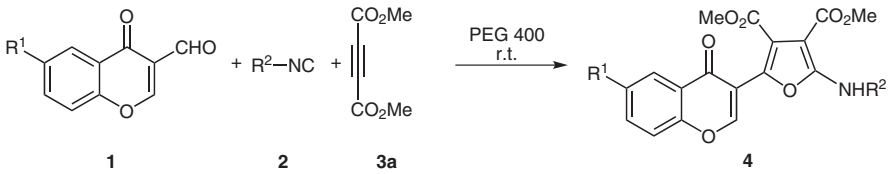
Table 1 Three-Component Reaction for the Synthesis of Chromenylfurans **4** in PEG 400



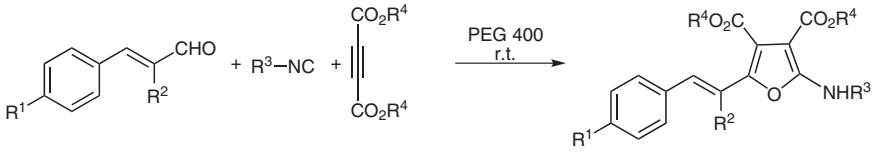
Entry	R^1	R^2	Product[a]	Time (h)	Yield[b] (%)
1	H	*c*-Hex	**4a**	3.0	90
2	H	*t*-Bu	**4b**	3.0	75
3	Me	*c*-Hex	**4c**	3.0	82

[a] All products were characterized by NMR, IR, and MS.
[b] Yield refers to pure products after purification.

clohexyl isocyanide (**2**, R^3 = cyclohexyl) and dimethyl acetylenedicarboxylate (**3a**) at room temperature in PEG 400 afforded dimethyl 2-(cyclohexylamino)-5-styrylfuran-3,4-dicarboxylate (**6a**) in 90% yield (Table 2, entry 1).

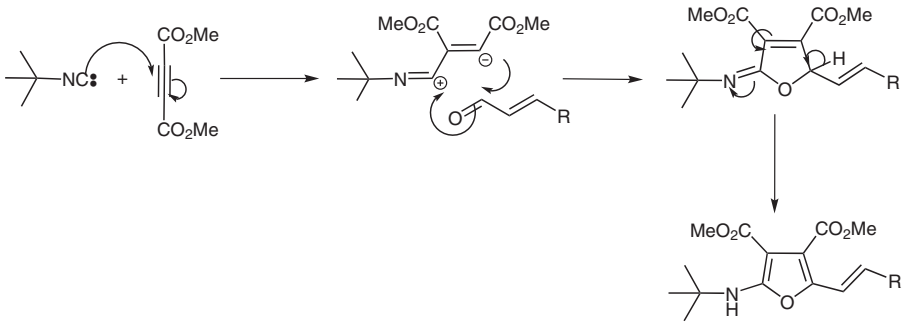
Similarly, various conjugated aldehydes such as α-methyl- and 4-(dimethylamino)cinnamaldehydes **5** reacted effectively with zwitterions to produce styrylfurans **6g–n** in good yields (Table 2, entries 7–14). Other isocyanides, including *tert*-butyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide, also participated in this reaction (Table 2). However, α,β-unsaturated ketones, such as cyclopentenone and cyclohexenone, failed to give the 2-aminofuran derivatives under identical conditions. Similarly, aliphatic α,β-unsaturated aldehydes, such as acrolein and crotonaldehyde, also did not give the desired product. The reaction was only successful with aryl-substituted α,β-unsaturated aldehydes. Diethyl acetylenedicarboxylate (**3b**) was also

Table 2 Three-Component Reaction for the Synthesis of Styrylfurans Using PEG 400



Entry	R^1	R^2	R^3	R^4	Time (h)	Product[a]	Yield[b] (%)
1	H	H	*c*-Hex	Me	3.0	**6a**	90
2	H	H	*t*-Bu	Me	3.0	**6b**	90
3	H	H	CMe_2CH_2*t*-Bu	Me	3.5	**6c**	95
4	H	H	*c*-Hex	Et	3.0	**6d**	96
5	H	H	*t*-Bu	Et	3.0	**6e**	94
6	H	H	CMe_2CH_2*t*-Bu	Et	3.5	**6f**	93
7	H	Me	*c*-Hex	Me	3.0	**6g**	92
8	H	Me	*t*-Bu	Me	3.0	**6h**	89
9	H	Me	CMe_2CH_2*t*-Bu	Me	3.0	**6i**	85
10	H	Me	*c*-Hex	Et	3.0	**6j**	88
11	H	Me	*t*-Bu	Et	3.0	**6k**	87
12	H	Me	CMe_2CH_2*t*-Bu	Et	3.5	**6l**	89
13	NMe_2	H	*c*-Hex	Me	4.0	**6m**	75
14	NMe_2	H	CMe_2CH_2*t*-Bu	Me	4.0	**6n**	76

[a] All products were characterized by NMR, IR, and MS.
[b] Isolated yields after purification.



Scheme 1 A plausible reaction mechanism

equally effective for this conversion (Table 2, entries 4–6 and 10–12). The structure of **6a** was characterized by ^{1}H and ^{13}C NMR, IR, and HRMS. Mechanistically, the isocyanide may initially react with dimethyl acetylenedicarboxylate to generate a 1,4-dipole. This highly reactive zwitterion undergoes subsequent cyclization with the α,β-unsaturated aldehyde to give the desired styrylfuran (Scheme 1).

The effects of various solvents, such as water, tetrahydrofuran, and benzene, were studied for this conversion to **6a**: PEG 400 appeared to give the best results. None of the desired product was formed in water at room temperature. The reaction proceeded well at room temperature in PEG 400, whereas the same reaction was successful in benzene under reflux conditions. After completion of the reaction, the mixture was diluted with anhydrous diethyl ether and stirred for 10 minutes and then allowed the layers were allowed to separate out and the ether layer was decanted. This process was repeated twice to obtain the product in diethyl ether whereas the mother liquor (PEG) was kept aside for further runs. A second run was performed without any modification using recovered PEG 400. Thus treatment of cinnamaldehyde (1 mmol) with cyclohexyl isocyanide (1 mmol) and dimethyl acetylenedicarboxylate (1 mmol) in recovered PEG 400 gave the product **6a** in 89% yield with the same purity as in first run. The efficient recycling of the reaction medium was then proved by additional experiments until a fifth run. Similar yields and reaction rates were achieved in all the runs.

In summary, we have demonstrated the use of PEG 400 as an efficient reaction medium for the 1,4-dipolar cycloaddition of α,β-unsaturated aldehydes with zwitterions derived from isocyanides and dialkyl acetylenedicarboxylates. The cycloaddition is more rapid and high-yielding in PEG 400 at room temperature over conventional solvents.

IR spectra were recorded on Perkin-Elmer FT-IR 240-c spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a Bruker AV-300 NMR spectrometer with respect to internal TMS. MS were obtained on Finnigan MAT1020B and Agilent technologies LC/MSD trapSL spectrometer operating at 70 eV using a direct inlet system.

Dimethyl (*E*)-2-(Cyclohexylamino)-5-styrylfuran-3,4-dicarboxylate (6a); Typical Procedure

A mixture of cyclohexyl isocyanide (197 mg, 1.8 mmol) and DMAD (257 mg, 1.8 mmol) in PEG-400 (5 mL) was purged with N_2 at r.t. After 15 min, cinnamaldehyde (200 mg, 1.51 mmol) was added and then the resulting mixture was allowed to stir at r.t. for 3–4 h. After completion of the reaction (TLC monitoring), the mixture was extracted with Et_2O (2 ×). The combined ether layers were concentrated in vacuo. The resulting crude product was purified by column chromatography (silica gel, EtOAc–hexanes) to give the pure styrylfuran derivative as a yellow liquid.

IR (KBr): 3351, 2934, 2855, 1722, 1670, 1612, 1473, 1225, 1149, 1083 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.3 Hz, 2 H), 7.28 (t, *J* = 7.7 Hz, 2 H), 7.16 (m, 1 H), 7.05 (d, *J* = 16.0 Hz, 1 H), 6.92 (d, *J* = 8.1 Hz, 1 H), 6.84 (d, *J* = 16.2 Hz, 1 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 3.70 (m, 1 H), 2.11–1.21 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 163.8, 161.7, 145.0, 136.4, 128.8, 128.4, 127.6, 127.6, 126.2, 113.9, 86.5, 51.7, 51.1, 50.8, 33.1, 25.2, 24.2.

MS (ESI): *m*/*z* = 384 [M + H]$^+$, 406 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{25}NO_5Na$: 406.1630; found: 406.1641.

Dimethyl 2-(Cyclohexylamino)-5-(4-oxo-4*H*-chromen-3-yl)furan-3,4-dicarboxylate (4a)

Yellow solid; mp 138–139 °C.

IR (KBr): 3355, 2930, 1736, 1667, 1613, 1464, 1226, 1097 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27–8.21 (m, 2 H), 7.68–7.62 (m, 1 H), 7.41–7.32 (m, 2 H), 6.72 (d, *J* = 7.7 Hz, 1 H), 3.82 (s, 3 H), 3.72 (s, 3 H), 3.69 (m, 1 H), 2.11–1.20 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 164.9, 161.2, 155.6, 152.9, 133.7, 133.1, 126.4, 125.4, 123.7, 117.9, 117.8, 115.6, 105.3, 87.2, 52.3, 51.3, 51.1, 33.3, 29.6, 24.4.

MS (ESI): *m*/*z* = 426 [M + H]$^+$, 448 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{23}NO_7Na$: 448.1372; found: 448.1361.

Dimethyl 2-(*tert*-Butylamino)-5-(4-oxo-4*H*-chromen-3-yl)furan-3,4-dicarboxylate (4b)

Yellow solid; mp 144–145 °C.

IR (KBr): 3448, 2924, 2854, 1737, 1664, 1609, 1558, 1464, 1404, 1350, 1311, 1215, 1093 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27–8.24 (m, 2 H), 7.68–7.63 (m, 1 H), 7.46–7.38 (m, 2 H), 6.94 (s, 1 H), 3.87 (s, 3 H), 3.76 (s, 3 H), 1.48 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 164.9, 161.2, 155.6, 152.9, 133.7, 133.1, 126.4, 125.4, 123.7, 117.9, 117.8, 115.6, 105.3, 87.2, 52.3, 51.3, 51.1, 33.3.

MS (ESI): *m*/*z* = 400 $[M + H]^+$, 422 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{22}NO_7$: 400.1396; found: 400.1388.

Dimethyl 2-(Cyclohexylamino)-5-(6-methyl-4-oxo-4*H*-chromen-3-yl)furan-3,4-dicarboxylate (4c)
Yellow solid; mp 154–155 °C.

IR (KBr): 3363, 2928, 1742, 1668, 1476, 1228, 1100 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 8.05 (s, 1 H), 7.52–7.34 (m, 2 H), 6.65 (d, *J* = 8.1 Hz, 1 H), 3.91 (s, 3 H), 3.72 (s, 3 H), 3.68 (m, 1 H), 2.42 (s, 3 H), 2.02–1.33 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 164.9, 161.2, 153.9, 152.9, 135.4, 134.9, 133.4, 126.5, 125.6, 124.2, 123.3, 117.7, 115.3, 87.25, 52.7, 51.3, 51.08, 33.3, 25.3, 24.4, 20.8.

MS (ESI): *m*/*z* = 440 $[M + H]^+$, 462 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{25}NO_7Na$: 462.1528; found: 462.1518.

Dimethyl (*E*)-2-(*tert*-Butylamino)-5-styrylfuran-3,4-dicarboxylate (6b)
Pale yellow liquid.

IR (KBr): 3332, 2924, 2854, 1726, 1669, 1606, 1470, 1212, 1086 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.3 Hz, 2 H), 7.28 (t, *J* = 7.7 Hz, 2 H), 7.25 (d, *J* = 7.1 Hz, 1 H), 7.13 (s, 1 H), 7.05 (d, *J* = 16.2 Hz, 1 H), 6.84 (d, *J* = 16.2 Hz, 1 H), 3.81 (s, 3 H), 3.70 (s, 3 H), 1.50 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 164.0, 162.1, 145.4, 136.5, 128.9, 128.5, 127.8, 127.7, 126.4, 114.0, 87.5, 52.7, 51.8, 50.9, 29.6.

MS (ESI): *m*/*z* = 358 $[M + H]^+$, 380 $[M + Na]^+$.

HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{23}NO_5Na$: 380.1473; found: 380.1466.

Dimethyl (*E*)-2-Styryl-5-(2,4,4-trimethylpentan-2-ylamino)furan-3,4-dicarboxylate (6c)
Pale yellow liquid.

IR (KBr): 3333, 2947, 1726, 1669, 1607, 1472, 1217, 1085 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.5 Hz, 2 H), 7.30–7.23 (m, 4 H), 7.05 (d, *J* = 16.6 Hz, 1 H), 6.85 (d, *J* = 15.8 Hz, 1 H), 3.87 (s, 3 H), 3.75 (s, 3 H), 1.81 (s, 2 H), 1.56 (s, 6 H), 1.04 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 163.8, 161.9, 144.9, 136.5, 128.5, 127.6, 127.3, 126.3, 114.6, 114.0, 87.5, 60.8, 59.4, 56.3, 52.9, 31.5, 31.3, 30.1.

MS (ESI): *m*/*z* = 436 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{31}NO_5Na$: 436.2099; found: 436.2107.

Diethyl (*E*)-2-(Cyclohexylamino)-5-styrylfuran-3,4-dicarboxylate (6d)
Dark brown liquid.

IR (KBr): 3342, 2930, 1726, 1668, 1610, 1472, 1222, 1074 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.5 Hz, 2 H), 7.25 (t, *J* = 7.5 Hz, 2 H), 7.15 (d, *J* = 6.7 Hz, 1 H), 7.08 (d, *J* = 15.8 Hz, 1 H), 6.93 (d, *J* = 8.3 Hz, 1 H), 6.84 (d, *J* = 15.8 Hz, 1 H), 4.25 (q, *J* = 7.5 Hz, 2 H), 4.22 (q, *J* = 6.7 Hz, 2 H), 3.71 (s, 1 H), 2.06–1.42 (m, 10 H), 1.37 (t, *J* = 7.5 Hz, 3 H), 1.25 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.89, 163.8, 161.8, 144.7, 136.7, 128.9, 128.6, 127.6, 127.3, 126.3, 114.1, 86.8, 60.8, 59.5, 51.3, 33.3, 29.6, 24.4, 14.3, 14.2.

MS (ESI): *m*/*z* = 434 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{29}NO_5Na$: 434.1943; found: 434.1957.

Diethyl (*E*)-2-(*tert*-Butylamino)-5-styrylfuran-3,4-dicarboxylate (6e)
Yellow liquid.

IR (KBr): 3327, 2978, 1728, 1666, 1604, 1466, 1210, 1086 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.8 Hz, 2 H), 7.25–7.3 (m, 2 H), 7.18 (t, *J* = 7.8 Hz, *J* = 6.8 Hz, 1 H), 7.12 (s, 1 H), 7.07 (d, *J* = 15.6 Hz, 1 H), 6.82 (d, *J* = 15.6 Hz, 1 H), 4.32 (q, *J* = 7.8 Hz, 2 H), 4.21 (q, *J* = 6.8 Hz, 2 H), 1.50 (s, 9 H), 1.38 (t, *J* = 7.8 Hz, 3 H), 1.31 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 163.8, 162.1, 145.0, 136.6, 128.5, 127.7, 127.4, 126.3, 114.56, 114.08, 87.75, 60.9, 59.5, 52.6, 29.6, 14.3, 14.2.

MS (ESI): *m*/*z* = 386 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{27}NO_5Na$: 408.1793; found: 408.1786.

Diethyl (*E*)-2-Styryl-5-(2,4,4-trimethylpentan-2-ylamino)furan-3,4-dicarboxylate (6f)
Brown liquid.

IR (KBr): 3421, 2923, 1728, 1664, 1604, 1467, 1216, 1085 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.3 Hz, 2 H), 7.24–7.31 (m, 3 H), 7.16–7.21 (m, 1 H), 7.05 (d, *J* = 16.2 Hz, 1 H), 6.81 (d, *J* = 16.2 Hz, 1 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 1.81 (s, 2 H), 1.55 (s, 6 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.0 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 163.8, 161.9, 144.9, 136.5, 128.5, 127.6, 127.3, 126.3, 114.6, 114.0, 87.5, 60.8, 59.4, 56.3, 52.9, 31.5, 31.3, 30.1, 14.3, 14.2.

MS (ESI): *m*/*z* = 442 $[M + H]^+$, 464 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{35}NO_5Na$: 464.2419; found: 464.2412.

Dimethyl (*E*)-2-(Cyclohexylamino)-5-(1-phenylprop-1-en-2-yl)furan-3,4-dicarboxylate (6g)
Brown liquid.

IR (KBr): 3356, 2932, 2855, 1737, 1679, 1614, 1475, 1223, 1148, 1103 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 4 H), 7.20–7.11 (m, 1 H), 6.80 (s, 1 H), 6.60 (d, *J* = 8.3 Hz, 1 H), 3.83 (s, 3 H), 3.74 (s, 3 H), 3.70 (m, 1 H,), 2.03 (s, 3 H), 1.81–1.22 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 164.5, 160.6, 142.0, 136.9, 129.1, 128.0, 126.5, 125.2, 125.0, 114.0, 87.3, 52.4, 51.3, 50.9, 33.2, 29.5, 25.3, 14.1.

MS (ESI): *m*/*z* = 398 $[M + H]^+$, 420 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{27}NO_5Na$: 420.1786; found: 420.1779.

Dimethyl (*E*)-2-(*tert*-Butylamino)-5-(1-phenylprop-1-en-2-yl)furan-3,4-dicarboxylate (6h)
Brown liquid.

IR (KBr): 3341, 2961, 1737, 1677, 1609, 1461, 1212, 1092 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 4 H), 7.22–7.17 (m, 1 H), 6.84 (d, *J* = 10 Hz, 2 H), 3.83 (s, 3 H), 3.73 (s, 3 H), 2.04 (s, 3 H), 1.49 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 164.6, 160.9, 142.5, 136.9, 129.1, 128.0, 126.6, 125.3, 125.0, 113.7, 88.2, 52.5, 52.4, 50.9, 29.5, 14.1.

MS (ESI): *m*/*z* = 372 $[M + H]^+$, 394 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{25}NO_5Na$: 394.163; found: 394.1620.

Dimethyl (*E*)-2-(1-Phenylprop-1-en-2-yl)-5-(2,4,4-trimethylpentan-2-ylamino)furan-3,4-dicarboxylate (6i)
Yellow liquid.

IR (KBr): 3342, 2952, 1737, 1676, 1609, 1472, 1214, 1091 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.18 (m, 5 H), 6.91 (s, 1 H), 6.81 (s, 1 H), 3.82 (s, 3 H), 3.71 (s, 3 H), 2.05 (s, 3 H), 1.70 (s, 2 H), 1.50 (s, 6 H), 1.04 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 164.9, 161.0, 142.5, 137.2, 129.3, 128.3, 126.8, 125.4, 125.2, 114.0, 88.3, 56.4, 53.3, 52.6, 51.1, 31.5, 30.2, 29.8, 14.3.

MS (ESI): *m*/*z* = 428 $[M + H]^+$, 450 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{33}NO_5Na$: 450.2256; found: 450.2258.

Diethyl (*E*)-2-(Cyclohexylamino)-5-(1-phenylprop-1-en-2-yl)furan-3,4-dicarboxylate (6j)
Yellow liquid.

IR (KBr): 3354, 2930, 1743, 1675, 1466, 1219, 1073 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.20 (m, 4 H), 7.21–7.12 (m, 1 H), 6.81 (s, 1 H), 6.63 (d, *J* = 7.9 Hz, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 3.69 (s, 1 H), 2.01 (s, 3 H), 1.82–1.21 (m, 10 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 164.1, 160.5, 141.6, 136.9, 128.9, 127.9, 126.4, 125.0, 124.9, 114.4, 87.5, 61.2, 59.3, 51.1, 33.1, 29.4, 25.2, 24.2, 14.1, 13.8.

MS (ESI): *m*/*z* = 426 $[M + H]^+$, 448 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{32}NO_5$: 426.228; found: 426.2287.

Diethyl (*E*)-2-(*tert*-Butylamino)-5-(1-phenylprop-1-en-2-yl)furan-3,4-dicarboxylate (6k)
Yellow liquid.

IR (KBr): 3339, 2978, 1734, 1673, 1465, 1208, 1094, 1047 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 5 H), 6.82 (s, 2 H), 4.25 (q, *J* = 7.5 Hz, 2 H), 4.15 (q, *J* = 7.5 Hz, 2 H), 2.06 (s, 3 H), 1.40 (s, 9 H), 1.35 (t, *J* = 7.5 Hz, 3 H), 1.28 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 164.3, 160.9, 142.1, 136.9, 129.0, 128.0, 126.5, 125.1, 125.0, 114.1, 88.3, 61.4, 59.4, 52.4, 29.5, 14.2, 14.1, 13.9.

MS (ESI): *m*/*z* = 400 $[M + H]^+$, 422 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{29}NO_5Na$: 422.1943; found: 422.1945.

Diethyl (*E*)-2-(1-Phenylprop-1-en-2-yl)-5-(2,4,4-trimethylpentan-2-ylamino)furan-3,4-dicarboxylate (6l)
Pale yellow liquid.

IR (KBr): 3339, 2978, 1735, 1672, 1609, 1472, 1249, 1084 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.22 (m, 4 H), 7.20–7.12 (m, 1 H), 6.91 (s, 1 H), 6.80 (s, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 2.07 (s, 3 H), 1.70 (s, 2 H), 1.50 (s, 6 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.04 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 164.3, 160.9, 142.1, 136.9, 129.0, 128.0, 126.5, 125.1, 125.0, 114.1, 88.3, 61.4, 59.4, 52.4, 33.6, 31.7, 29.7, 22.5, 14.2, 14.1, 13.9.

MS (ESI): *m*/*z* = 456 $[M + H]^+$, 478 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{38}NO_5$: 456.2749; found: 456.2736.

Dimethyl (*E*)-2-(Cyclohexylamino)-5-[4-(dimethylamino)styryl]furan-3,4-dicarboxylate (6m)
Dark brown liquid.

IR (KBr): 3423, 2923, 2853, 1731, 1672, 1611, 1466, 1228, 1083 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.7 Hz, 2 H), 6.91–6.86 (m, 2 H), 6.81–6.75 (m, 3 H), 3.82 (s, 3 H), 3.76 (s, 3 H), 3.70 (m, 1 H), 3.01 (s, 6 H), 2.01–1.27 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 165.4, 161.8, 150.1, 146.7, 136.2, 128.7, 127.7, 127.7, 112.2, 110, 82.9, 51.7, 51.3, 50.9, 40.3, 33.4, 29.6, 24.5.

MS (ESI): *m*/*z* = 427 $[M + H]^+$, 449 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{30}NO_5Na$: 449.2052; found: 449.2057.

Dimethyl (*E*)-2-[4-(Dimethylamino)styryl]-5-(2,4,4-trimethylpentan-2-ylamino)furan-3,4-dicarboxylate (6n)
Dark brown liquid.

IR (KBr): 3447, 2995, 1729, 1664, 1604, 1464, 1217, 1084 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.3 Hz, 2 H), 6.95 (d, *J* = 16.2 Hz, 2 H), 6.68 (d, *J* = 16 Hz, 2 H), 3.82 (s, 3 H), 3.71 (s, 3 H), 3.68 (m, 1 H), 3.02 (s, 6 H), 1.81 (s, 2 H), 1.48 (s, 6 H), 1.01 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 164.5, 162.0, 150.2, 146.9, 135.6, 129.7, 128.7, 127.8, 112.3, 110.1, 86.7, 56.3, 53.1, 51.8, 50.9, 40.4, 31.4, 30.2, 29.6.

MS (ESI): *m*/*z* = 457 $[M + H]^+$, 479 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{36}NO_5Na$: 479.2521; found: 479.2510.

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