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A domino amino-lactonisation of arylidene pyruvic acids (APAs) by amines in aqueous media

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ABSTRACT

The aqueous reaction of arylidene pyruvic acids (APAs) with arylamines or urea under refluxing conditions leading to the formation of 3-(amino)-5-aryl-furan-2(5*H*)-one, without catalyst, is described. Also (*E*)-4-(4-chlorophenyl)-2-oxobut-3-enoic acid reacts with 1,2-phenylenediamine to form (*E*)-3-(4-chlorostyryl) quinoxalin-2(1*H*)-one under the same conditions. Excellent yields were observed after filtration of the product and washing with brine solution.

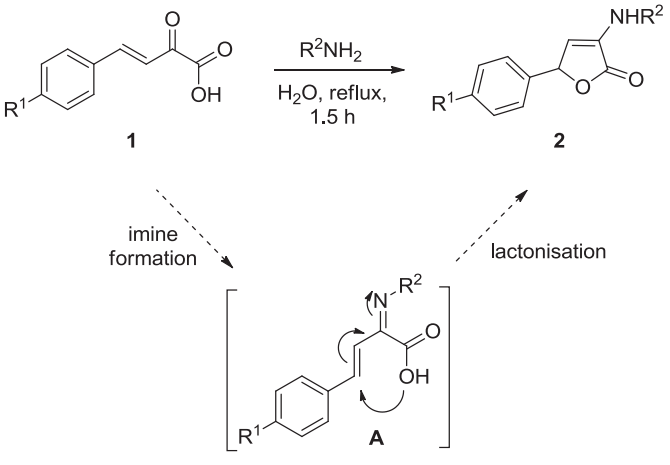
1. Introduction

Nowadays green and sustainable chemistry present huge challenges for the various branches of science.[1] Green chemistry involves the planning and execution of reactions with the aim to reduce the use and production of harmful chemicals. Two major sources of pollution in conventional reaction media for organic reactions are solvents and catalysts. The drive for greener methods has led to numerous exciting advances in the design of reactions under solvent- and catalyst-free conditions or to introduce environmentally benign solvents and catalysts.[1]

Water is the most suitable green solvent since it comes from the heart of nature and it is safe, not to mention its cost-effectiveness. In some cases it was reported that certain organic reactions in water without any additives proceed better than in conventional organic solvents. Sharpless named these '*on water*' reactions.[2,3] In addition, certain reactions in water forms water-insoluble products, which facilitate easier isolation and purification of the products.

γ-Lactone derivatives are important heterocyclic compounds and they display a wide range of applications in medicinal chemistry.[4–6] In particular, unsaturated γ-lactones or butenolides are known to exhibit significant biological and pharmacological importance and are also present in many natural products.[7–15]

Arylidene pyruvic acids (APAs) **1** have a versatile structure and have been used as starting materials for the synthesis of a large diversity of organic compounds.[16] Although there are some erroneous reports[17,18] on the identification of the main product isolated from the reaction of amines and APAs, the correct structures, namely 3-(amino)-5-aryl-furan-2(5*H*)-ones **2** have subsequently been established by the same group (Scheme 1).[19] Inspection of the



Scheme 1.

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reaction mechanism (see Scheme 1) suggests that the imine intermediate **A** and also product **2** are sensitive to water, therefore the reaction was reported in absolute ethanol.[17–19]

Following our initial study on the chemistry of APAs,[20] herein we wish to report the reaction APAs with amines in water without any additive leading to 3-amino-5-arylbutenolides.

2. Results and discussion

We first investigated the reaction of (*E*)-4-(4-chlorophenyl)-2-oxobut-3-enoic acid (**1a**) and aniline in water. Although the reaction did not proceed at room temperature, it was completed after 1.5 h under reflux conditions and the precipitate was filtered and washed with brine to give **2a** as the sole product in 80% yield without any further purification (Scheme 1 and Table 1, entry 1). The reaction was repeated for other derivatives of aniline, which also gave good yields for both electron-donating groups (such as Me and OMe) and electron-withdrawing groups (such as Cl, Br, CF_3 and NO_2) (Table 1, entries 2–8).

Afterwards the scope of the reaction was evaluated using methyl and methoxy derivatives of APAs (Scheme 1). To our delight, all the aniline derivatives screened yielded the expected 3-amino-5-arylbutenolides **2i**–**2u** in good isolated yields (Table 1, entries 9–21).

Table 1
Tandem amino-lactonisation of arylidene pyruvic acids (APAs) with different amines

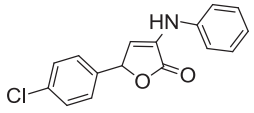
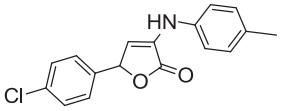
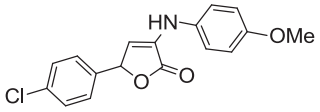
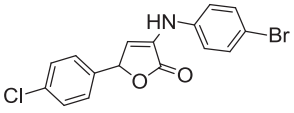
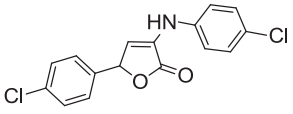
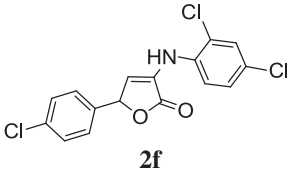
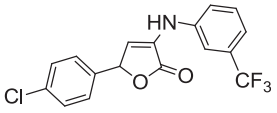
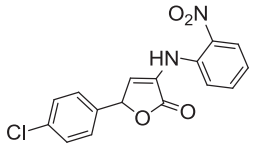
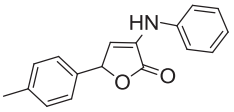
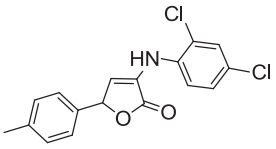
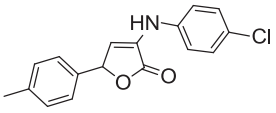
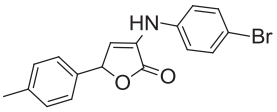
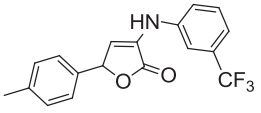
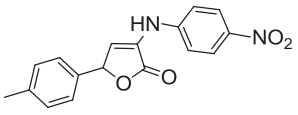
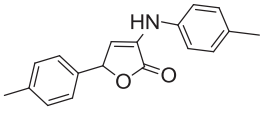
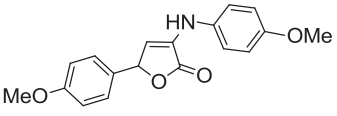
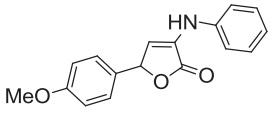
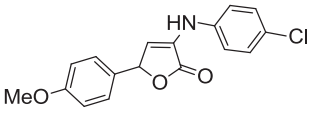
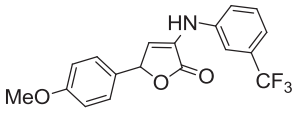
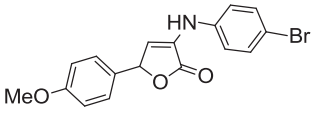
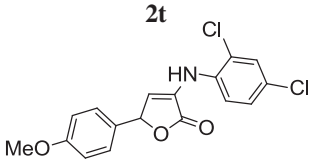
Entry	APA	Amine	Product	Isolated yield (%)
1	**1a**	Aniline	 **2a**	80
2	**1a**	4-Methylaniline	 **2b**	75
3	**1a**	4-Methoxyaniline	 **2c**	77
4	**1a**	4-Bromoaniline	 **2d**	81
5	**1a**	4-Chloroaniline	 **2e**	83
6	**1a**	2,4-Dichloroaniline	 **2f**	80
7	**1a**	3-(Trifluoromethyl) aniline	 **2g**	75
8	**1a**	2-Nitroaniline	 **2h**	72

Table 1 (*continued*)

Entry	APA	Amine	Product	Isolated yield (%)
9	**1b**	Aniline	 **2i**	78
10	**1b**	2,4-Dichloroaniline	 **2j**	82
11	**1b**	4-Chloroaniline	 **2k**	79
12	**1b**	4-Bromoaniline	 **2l**	75
13	**1b**	3-(Trifluoromethyl)aniline	 **2m**	78
14	**1b**	4-Nitroaniline	 **2n**	81
15	**1b**	4-Methylaniline	 **2o**	78
16	**1c**	4-Methoxyaniline	 **2p**	81
17	**1c**	Aniline	 **2q**	79
18	**1c**	4-Chloroaniline	 **2r**	78

(*continued on next page*)

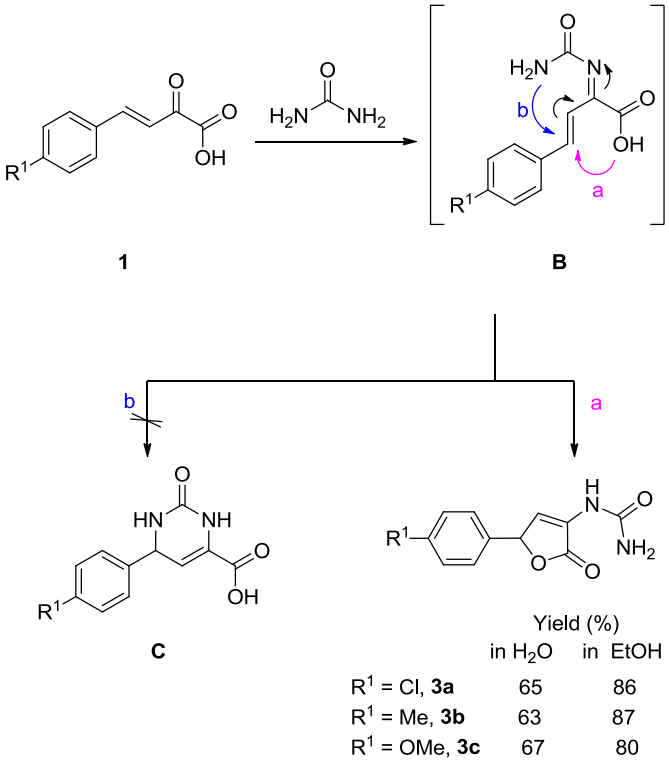
Table 1 (*continued*)

Entry	APA	Amine	Product	Isolated yield (%)
19	**1c**	3-(Trifluoromethyl)aniline	 **2s**	76
20	**1c**	4-Bromoaniline	 **2t**	79
21	**1c**	2,4-Dichloroaniline	 **2u**	75

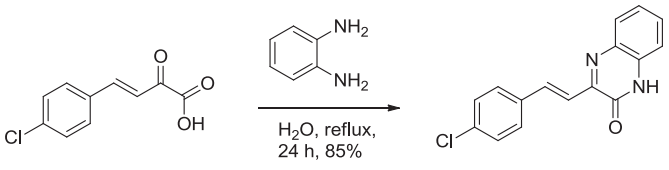
The reaction of the bromo- and chloro-aniline derivatives can potentially be expanded by transition metal catalysed coupling to the more complex structures similar to reports in the literature.[21]

Aliphatic amines did not produce the desired corresponding products, but when urea was utilised as an alternative to anilines, some interesting results were obtained. Unlike in the synthesis of 3,4-dihydropyrimidin-2-one **C** through the reaction of urea and α,β-unsaturated carbonyl compounds, the reaction of **1** with urea also gave butenolides **3a**–**3c** in 63–67% when reacted at reflux in water. The products form via tandem imination and lactonisation reactions (Scheme 2). The yield of **3a**–**3c** was increased to 80–87% when heated at reflux 96% ethanol (Scheme 2).

In addition it was discovered that **1a** undergoes cyclisation with benzene-1,2-diamine to give (*E*)-3-(4-chlorostyryl)quinoxalin-2(1*H*)-one (**4**) in 85% yield after 24 h of reflux in water without catalyst (Scheme 3).



Scheme 2.



Scheme 3.

3. Conclusions

In summary, we have developed a green and direct entry to 3-amino-5-arylbutenolides through the reaction of arylidene pyruvic acids and arylamines or urea with water as solvent and at reflux temperature without any catalyst and/or additive. The products were solely purified by filtration and washing with a brine solution without using column chromatography.

4. Experimental section

4.1. General

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. IR spectra were recorded on a Shimadzu Infra Red Spectroscopy IR-435. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 and 600 MHz Spectrometers in $CDCl_3$ and DMSO-d_6 as solvent. High-resolution mass spectrometric data were obtained using a Bruker micro TOF-Q II instrument operating at ambient temperatures and a Leco CHNS, model 932 was used for elemental analysis.

4.2. General procedure for the reaction of APAs and amines

To a stirring solution of arylidene pyruvic acids (0.5 mmol) in H_2O (5 mL), was added the amine (0.5 mmol). The aqueous solution was heated at reflux and the reaction was monitored by TLC. After the appropriate time, the reaction mixture was filtered when still hot and the products were washed with brine. Usually the crude material was pure, but in a few cases, for example, the urea

derivatives, it was necessary to wash filtrate with ethanol to obtain pure products.

The copies of ^{1}H NMR and ^{13}C NMR spectra for the all products are presented as Supplementary data.

4.3. Spectral data and physical properties

*4.3.1. 5-(4-Chlorophenyl)-3-(phenylamino)furan-2(5H)-one (**2a**).* Yield 114 mg, 80% as a pale yellow powder; mp 144–146 °C; ν_{max} (KBr plate) 3339, 1741, 1661, 1601 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 6.02 (d, *J* 2.2 Hz, 1H), 6.39 (d, *J* 2.2 Hz, 1H), 6.45 (s, NH, 1H), 7.03 (t, *J* 7.4 Hz, 1H), 7.08 (d, *J* 8.0 Hz, 2H), 7.28–7.31 (m, 2H), 7.34–7.40 (m, 4H); δ_C (150 MHz, $CDCl_3$) 81.7, 112.5, 117.1, 122.4, 128.5, 129.4, 129.8, 135.0, 135.4, 140.8, 171.0; HRMS calculated for $C_{16}H_{12}^{35}ClNNaO_2$ $[M+Na]^+$ 308.0450, found 308.0442.

*4.3.2. 5-(4-Chlorophenyl)-3-(p-tolylamino)furan-2(5H)-one (**2b**).* Yield 112 mg, 75% as a pale yellow powder; mp 133–135 °C; ν_{max} (KBr plate) 3371, 1741, 1665, 1614 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 2.33 (s, 3H), 6.00 (d, *J* 2.2 Hz, 1H), 6.31 (d, *J* 2.2 Hz, 1H), 6.33 (s, 1H, NH), 6.98 (d, *J* 6.8 Hz, 2H), 7.15 (d, *J* 8.3 Hz, 2H), 7.28–7.30 (m, 2H), 7.37–7.39 (m, 2H); δ_C (150 MHz, $CDCl_3$) 20.5, 81.3, 111.3, 116.9, 128.1, 128.9, 129.3, 129.9, 131.6, 134.8, 134.9, 137.9, 170.6; HRMS calculated for $C_{17}H_{14}^{35}ClNNaO_2$ $[M+Na]^+$ 322.0621, found 322.0613.

*4.3.3. 5-(4-Chlorophenyl)-3-(4-methoxyphenylamino)furan-2(5H)-one (**2c**).* Yield 121 mg, 77% as a yellow powder; mp 129–131 °C; ν_{max} (KBr plate) 3440, 1623, 1578, 1532 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 3.71 (s, 3H), 6.18 (d, *J* 2.3 Hz, 1H), 6.60 (d, *J* 2.3 Hz, 1H), 6.87 (d, *J* 6.9 Hz, 2H), 7.22 (d, *J* 6.9 Hz, 2H), 7.41(d, *J* 6.7 Hz, 2H), 7.48 (d, *J* 6.7 Hz, 2H), 8.19 (s, 1H, NH); δ_C (150 MHz, DMSO-d_6) 55.7, 80.9, 112.9, 114.8, 119.1, 129.2, 129.2, 129.8, 133.8, 135.6, 136.8, 154.3, 170; HRMS calculated for $C_{17}H_{14}^{35}ClNNaO_3$ $[M+Na]^+$ 338.0576, found 338.0565.

*4.3.4. 3-(4-Bromophenylamino)-5-(4-chlorophenyl)furan-2(5H)-one (**2d**).* Yield 146 mg, 81% as a pale yellow powder; mp 155–157 °C; ν_{max} (KBr plate) 3372, 1740, 1665, 1591 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.00 (d, *J* 1.6 Hz, 1H), 6.33 (d, *J* 1.9 Hz, 1H), 6.43 (s, 1H, NH), 6.94 (d, *J* 8.7 Hz, 2H), 7.26–7.28 (m, 2H), 7.37 (d, *J* 8.4 Hz, 2H), 7.43 (d, *J* 8.7 Hz, 2H); δ_C (100 MHz, $CDCl_3$) 81.6, 112.9, 114.4, 118.4, 128.2, 128.9, 129.2, 132.5, 134.5, 135.3, 139.6, 170.5; HRMS calculated for $C_{16}H_{11}^{81}Br^{35}ClNNaO_2$ $[M+Na]^+$ 387.9557, found 387.9533.

*4.3.5. 5-(4-Chlorophenyl)-3-(4-chlorophenylamino)furan-2(5H)-one (**2e**).* Yield 133 mg, 83% as a pale yellow powder; mp 147–149 °C; ν_{max} (KBr plate) 3371, 1739, 1665, 1594 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 6.02 (d, *J* 2.2 Hz, 1H), 6.35 (d, *J* 2.2 Hz, 1H), 6.44 (s, 1H, NH), 7.01 (d, *J* 8.9 Hz, 2H), 7.29 (d, *J* 8.7 Hz, 2H), 7.31 (d, *J* 8.9 Hz, 2H), 7.39 (d, *J* 8.6 Hz, 2H); δ_C (150 MHz, $CDCl_3$) 81.5, 112.7, 118.1, 127.1, 128.2, 129.0, 129.2, 129.6, 134.6, 135.3, 139.2, 170.5; HRMS calculated for $C_{16}H_{12}^{35}Cl_2NO_2$ $[M+H]^+$ 320.0432, found 320.0390.

*4.3.6. 5-(4-Chlorophenyl)-3-(2,4-dichlorophenylamino)furan-2(5H)-one (**2f**).* Yield 141 mg, 80% a pale yellow powder; mp 162–164 °C. Found: C, 54.2; H, 2.8; N, 3.9. $C_{16}H_{10}Cl_3NO_2$ requires C, 53.9; H, 2.9; N, 3.7%. ν_{max} (KBr plate) 3368, 1744, 1663, 1596 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.02 (d, *J* 1.3 Hz, 1H), 6.40 (d, *J* 1.7 Hz, 1H), 6.92 (s, 1H, NH), 7.17 (d, *J* 8.8 Hz, 1H), 7.23–7.25 (m, 1H), 7.28 (d, *J* 7.8 Hz, 2H), 7.39 (d, *J* 8.4 Hz, 2H), 7.44 (d, *J* 2.0 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 81.4, 114.2, 116.6, 123.1, 126.8, 127.9, 128.2, 128.4, 129.2, 129.8, 134.3, 135.4, 135.9, 170.1.

*4.3.7. 5-(4-Chlorophenyl)-3-(3-(trifluoromethyl)phenylamino)furan-2(5H)-one (**2g**).* Yield 132 mg, 75% as a pale yellow powder; mp 94–96 °C; ν_{max} (KBr plate) 3337, 1753, 1659, 1618 cm^{-1}; δ_H (600 MHz, $CDCl_3$) δ=6.05 (d, *J* 1.9 Hz, 1H), 6.43 (d, *J* 2.2 Hz, 1H), 6.61 (s, 1H, NH), 7.23 (d, *J* 8.1 Hz, 1H), 7.28–7.30 (m, 4H), 7.40 (d, *J* 8.6 Hz, 2H), 7.47 (t, *J* 7.9 Hz, 1H); δ_C (150 MHz, $CDCl_3$) 81.6, 113.1, 113.6, 118.8, 120.0, 124.7, 128.2, 128.7, 129.2, 130.2, 132.0, 134.3, 135.4, 141.1, 170.4; HRMS calculated for $C_{17}H_{11}^{35}ClF_3NNaO_2$ $[M+Na]^+$ 376.0353, found 376.0338.

*4.3.8. 5-(4-Chlorophenyl)-3-(2-nitrophenylamino)furan-2(5H)-one (**2h**).* Yield 118 mg, 72% as a yellow powder; mp 154–156 °C; ν_{max} (KBr plate) 3442, 3323, 1765, 1661, 1613 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 6.08 (d, *J* 2.1 Hz, 1H), 6.68 (d, *J* 2.2 Hz, 1H), 7.06–7.09 (m, 1H), 7.30 (d, *J* 8.3 Hz, 2H), 7.41 (d, *J* 8.3 Hz, 2H), 7.45 (d, *J* 8.0 Hz, 1H), 7.62–7.65 (m, 1H), 9.93 (s, 1H, NH); δ_C (150 MHz, $CDCl_3$) 81.3, 117.1, 118.2, 120.8, 127.2, 128.0, 128.1, 129.3, 130.6, 134.0, 135.5, 135.9, 169.7; HRMS calculated for $C_{16}H_{11}^{35}ClN_2NaO_4$ $[M+Na]^+$ 353.0331, found 353.0315.

*4.3.9. 3-(Phenylamino)-5-p-tolylfuran-2(5H)-one (**2i**).* Yield 103 mg, 78% as a yellow powder; mp 153–155 °C; ν_{max} (KBr plate) 3340, 1739, 1621, 1601 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 2.32 (s, 3H), 6.16 (d, *J* 2.2 Hz, 1H), 6.76 (d, *J* 2.3 Hz, 1H), 6.90 (t, *J* 6.6 Hz, 1H), 7.22 (d, *J* 8.0 Hz, 2H), 7.26–7.30 (m, 6H), 8.35 (s, 1H, NH); δ_C (150 MHz, DMSO-d_6) 21.3, 81.7, 114.5, 117.3, 121.2, 127.3, 129.0, 129.8, 130.2, 134.5, 138.8, 142.3, 170.9; HRMS calculated for $C_{17}H_{15}NNaO_2$ $[M+Na]^+$ 288.1067, found 288.1052.

*4.3.10. 3-(2,4-Dichlorophenylamino)-5-p-tolylfuran-2(5H)-one (**2j**).* Yield 136 mg, 82% as a pale yellow powder; mp 151–153 °C; ν_{max} (KBr plate) 3367, 1744, 1664, 1597 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 2.34 (s, 3H), 5.98 (d, *J* 2.2 Hz, 1H), 6.38 (d, *J* 2.6 Hz, 1H), 6.88 (s, 1H, NH), 7.13–7.23 (m, 6H), 7.39 (d, *J* 2.8 Hz, 1H); δ_C (150 MHz, $CDCl_3$) 21.2, 82.3, 115.1, 116.4, 122.9, 126.5, 126.8, 127.8, 128.1, 129.7, 129.7, 132.7, 136.1, 139.5, 170.4; HRMS calculated for $C_{17}H_{15}Cl_2NO_2$ $[M+H]^+$ 334.0426, found 334.0411.

*4.3.11. 3-(4-Chlorophenylamino)-5-p-tolylfuran-2(5H)-one (**2k**).* Yield 118 mg, 79% as a pale yellow powder; mp 148–150 °C; ν_{max} (KBr plate) 3338, 1735, 1659, 1597 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 2.38 (s, 3H), 6.02 (d, *J* 2.2 Hz, 1H), 6.37 (d, *J* 2.2 Hz, 1H), 6.44 (s, 1H, NH), 7.01 (d, *J* 6.9 Hz, 2H), 7.21–7.24 (m, 4H), 7.28–7.31 (m, 2H); δ_C (150 MHz, $CDCl_3$) 21.2, 82.4, 113.6, 118.0, 126.9, 128.7, 129.5, 129.6, 133.0, 139.4, 170.8; HRMS calculated for $C_{17}H_{14}^{35}ClNNaO_2$ $[M+Na]^+$ 322.0613, found 322.0609.

*4.3.12. 3-(4-Bromophenylamino)-5-p-tolylfuran-2(5H)-one (**2l**).* Yield 128 mg, 75% as a pale yellow powder; mp 152–154 °C; ν_{max} (KBr plate) 3339, 1735, 1660, 1592 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 2.38 (s, 3H), 6.01 (d, *J* 2.2 Hz, 1H), 6.38 (d, *J* 2.2 Hz, 1H), 6.48 (s, 1H, NH), 6.96 (d, *J* 7.1 Hz, 2H), 7.21–7.24 (m, 4H), 7.44 (d, *J* 7.0 Hz, 2H); δ_C (150 MHz, $CDCl_3$) 21.2, 82.4, 113.8, 114.1, 118.3, 126.9, 128.6, 129.6, 132.4, 132.9, 139.4, 139.9, 170.8; HRMS calculated for $C_{17}H_{15}^{79}BrNO_2$ $[M+H]^+$ 344.0430, found 344.0415.

*4.3.13. 5-p-Tolyl-3-(3-(trifluoromethyl)phenylamino)furan-2(5H)-one (**2m**).* Yield 130 mg, 78% as a pale yellow powder; mp 133–135 °C; ν_{max} (KBr plate) 3347, 1751, 1659, 1609 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 2.39 (s, 3H), 6.05 (d, *J* 2.1 Hz, 1H), 6.45 (d, *J* 2.1 Hz, 1H), 6.59 (s, 1H, NH), 7.22–7.24 (m, 5H), 7.27–7.31 (m, 2H), 7.46 (t, *J* 7.92 Hz, 1H); δ_C (150 MHz, $CDCl_3$) 21.2, 82.4, 113.0, 114.4, 118.5, 119.8, 126.9, 128.4, 129.7, 130.1, 132.1, 132.7, 139.5, 141.3, 170.9; HRMS calculated for $C_{18}H_{14}F_3NNaO_2$ $[M+Na]^+$ 356.0901, found 356.0885.

*4.3.14. 3-(4-Nitrophenylamino)-5-p-tolylfuran-2(5H)-one (**2n**).* Yield 125 mg, 81% as a yellow powder; mp 182–184 °C. Found: C, 65.8; H, 4.5; N, 9.0. $C_{17}H_{14}N_2O_4$ requires C, 56.1; H, 4.6; N, 8.8%. ν_{max} (KBr plate) 3327, 1747, 1714, 1607 cm^{-1}; δ_H (600 MHz,

$CDCl_3$) 2.39 (s, 3H), 6.08 (d, *J* 2.2 Hz, 1H), 6.63 (d, *J* 2.2 Hz, 1H), 6.95 (s, 1H, NH), 7.12 (d, *J* 9.1 Hz, 2H), 7.24 (m, 4H), 8.25 (d, *J* 9.2 Hz, 2H); δ_C (150 MHz, $CDCl_3$) 21.3, 82.5, 115.6, 117.5, 126.0, 126.9, 127.5, 129.8, 132.1, 139.7, 141.7, 146.3, 170.3.

*4.3.15. 5-p-Tolyl-3-(p-tolylamino)furan-2(5H)-one (**2o**).* Yield 108 mg, 78% as a pale yellow powder; mp 132–134 °C; ν_{max} (KBr plate) 3343, 1737, 1658, 1614 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 2.28 (s, 3H), 2.33 (s, 3H), 5.95 (d, *J* 2.1 Hz, 1H), 6.29 (d, *J* 2.3 Hz, 1H), 6.30 (s, 1H, NH), 6.93 (d, *J* 8.3 Hz, 2H), 7.09 (d, *J* 8.3 Hz, 2H), 7.16 (d, *J* 8.1 Hz, 2H), 7.20 (d, *J* 8.1 Hz, 2H); δ_C (150 MHz, $CDCl_3$) 20.9, 21.4, 82.5, 112.6, 117.2, 127.1, 129.4, 129.7, 130.2, 131.7, 133.6, 138.5, 139.4, 171.3; HRMS calculated for $C_{18}H_{17}NNaO_2$ $[M+Na]^+$ 302.1208, found 302.1180.

*4.3.16. 5-(4-Methoxyphenyl)-3-(4-methoxyphenylamino)furan-2(5H)-one (**2p**).* Yield 125 mg, 81% as a yellow powder; mp 143–145 °C; ν_{max} (KBr plate) 3441, 1597, 1569, 1511 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 3.71 (s, 3H), 3.77 (s, 3H), 6.11 (d, *J* 2.2 Hz, 1H), 6.55 (d, *J* 2.3 Hz, 1H), 6.86 (d, *J* 6.9 Hz, 2H), 6.96 (d, *J* 6.7 Hz, 2H), 7.22 (d, *J* 6.8 Hz, 2H), 7.29 (d, *J* 8.5 Hz, 2H), 8.14 (s, 1H, NH); δ_C (150 MHz, DMSO-d_6) 55.7, 55.8, 81.6, 113.2, 114.6, 114.9, 118.9, 122.6, 129.0, 129.8, 135.7, 154.2, 160.2, 170.9; HRMS calculated for $C_{18}H_{18}NO_4$ $[M+H]^+$ 312.1265, found 312.1248.

*4.3.17. 5-(4-Methoxyphenyl)-3-(phenylamino)furan-2(5H)-one (**2q**).* Yield 111 mg, 79% as a pale yellow powder; mp 152–154 °C; ν_{max} (KBr plate) 3334, 1742, 1661, 1603 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 3.84 (s, 3H), 6.01 (d, *J* 2.2 Hz, 1H), 6.40 (d, *J* 2.2 Hz, 1H), 6.43 (s, 1H, NH), 6.92 (d, *J* 6.7 Hz, 2H), 7.02 (t, *J* 7.5 Hz, 1H), 7.09 (d, *J* 7.74 Hz, 2H), 7.29 (d, *J* 6.4 Hz, 2H), 7.35 (t, *J* 7.9 Hz, 2H); δ_C (150 MHz, $CDCl_3$) 55.4, 82.3, 112.9, 114.3, 116.8, 122.0, 128.1, 128.6, 129.0, 129.5, 140.8, 171.0; HRMS calculated for $C_{17}H_{15}NNaO_3$ $[M+Na]^+$ 304.0985, found 304.0965.

*4.3.18. 3-(4-Chlorophenylamino)-5-(4-methoxyphenyl)furan-2(5H)-one (**2r**).* Yield 123 mg, 78% as a pale yellow powder; mp 133–135 °C; ν_{max} (KBr plate) 3313, 1783, 1657, 1598 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 3.84 (s, 3H), 6.01 (d, *J* 2.2 Hz, 1H), 6.36 (d, *J* 2.2 Hz, 1H), 6.42 (s, 1H, NH), 6.93 (d, *J* 2.5 Hz, 2H), 7.02 (d, *J* 8.9 Hz, 2H), 7.28 (m, 2H), 7.31 (d, *J* 8.6 Hz, 2H); δ_C (150 MHz, $CDCl_3$) 55.4, 82.3, 113.4, 114.3, 118.0, 126.9, 127.8, 128.5, 128.9, 129.5, 139.4, 160.5, 170.7; HRMS calculated for $C_{17}H_{15}^{35}ClNO_3$ $[M+H]^+$ 316.0749, found 316.0742.

*4.3.19. 5-(4-Methoxyphenyl)-3-(3-(trifluoromethyl)phenylamino)furan-2(5H)-one (**2s**).* Yield 133 mg, 76% as a pale yellow powder; mp 139–141 °C. Found: C, 61.2; H, 4.0; N, 4.0. $C_{18}H_{14}F_3NO_3$ requires C, 59.1; H, 4.2; N, 4.0%. ν_{max} (KBr plate) 3348, 1752, 1659, 1611 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 3.84 (s, 3H), 6.04 (d, *J* 2.0 Hz, 1H), 6.44 (d, *J* 2.2 Hz, 1H), 6.58 (s, 1H, NH), 6.94 (d, *J* 8.5 Hz, 2H), 7.24 (d, *J* 8.2 Hz, 1H), 7.27–7.31 (m, 4H), 7.46 (t, *J* 7.9 Hz, 1H); δ_C (150 MHz, $CDCl_3$) 55.4, 82.4, 113.0, 114.2, 114.4, 118.5, 119.8, 127.6, 128.6, 130.1, 132.2, 141.3, 160.5, 170.6.

*4.3.20. 3-(4-Bromophenylamino)-5-(4-methoxyphenyl)furan-2(5H)-one (**2t**).* Yield 142 mg, 79% as a pale yellow powder; mp 144–146 °C; ν_{max} (KBr plate) 3315, 1783, 1657, 1593 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 3.84 (s, 3H), 6.01 (d, *J* 2.2 Hz, 1H), 6.37 (d, *J* 2.2 Hz, 1H), 6.45 (s, 1H, NH), 6.94 (d, *J* 6.5 Hz, 2H), 6.97 (d, *J* 6.8 Hz, 2H), 7.28 (d, *J* 6.2 Hz, 2H), 7.44 (d, *J* 6.9 Hz, 2H); δ_C (150 MHz, $CDCl_3$) 55.4, 82.3, 113.6, 114.1, 114.3, 118.3, 127.8, 128.5, 128.8, 132.4, 139.9, 160.5, 170.8; HRMS calculated for $C_{17}H_{15}^{79}BrNO_3$ $[M+H]^+$ 360.0244, found 360.0237.

*4.3.21. 3-(2,4-Dichlorophenylamino)-5-(4-methoxyphenyl)furan-2(5H)-one (**2u**).* Yield 130 mg, 75% as a pale yellow powder; mp 128–130 °C. Found: C, 58.3; H, 3.7; N, 4.0. $C_{17}H_{13}Cl_2NO_3$ requires C, 58.1; H, 3.5; N, 4.1%. ν_{max} (KBr plate) 3369, 1745, 1664, 1607 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 3.84 (s, 3H), 6.02 (d, *J* 2.1 Hz, 1H), 6.42 (d, *J* 2.2 Hz, 1H), 6.93 (d, *J* 8.8 Hz, 2H), 7.20 (d, *J* 8.5 Hz, 1H), 7.24–7.28 (m, 4H), 7.45 (d, *J* 2.8 Hz, 1H); δ_C (150 MHz, $CDCl_3$) 55.4, 82.2, 114.4, 114.8, 116.4, 123.0, 126.5, 127.5, 127.8, 128.3, 128.5, 129.7, 136.2, 160.5, 170.3.

*4.3.22. 1-(5-(4-Chlorophenyl)-2-oxo-2,5-dihydrofuran-3-yl)urea (**3a**).* Yield 83 mg, 65% (in H_2O) and 108 mg, 86% (in EtOH) as a pale yellow powder; mp 210–212 °C; ν_{max} (KBr plate) 3460, 3369, 3270, 3221, 3069, 1751, 1660, 1624 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 6.21 (d, *J* 2.0 Hz, 1H), 6.37 (br s, 2H, NH_2), 7.12 (d, *J* 1.9 Hz, 1H), 7.39 (d, *J* 8.4 Hz, 2H), 7.50 (d, *J* 8.7 Hz, 2H), 8.63 (s, 1H, NH); δ_C (150 MHz, $CDCl_3$) 81.4, 124.1, 127.0, 129.1, 129.3, 134.0, 135.9, 155.7, 170.2; HRMS calculated for $C_{11}H_9^{35}ClN_2NaO_3$ $[M+Na]^+$ 275.0301, found 275.0299.

*4.3.23. 1-(2-Oxo-5-p-tolyl-2,5-dihydrofuran-3-yl)urea (**3b**).* Yield 74 mg, 63% (in H_2O) and 101 mg, 87% (in EtOH) as a pale yellow powder; mp 213–215 °C; ν_{max} (KBr plate) 3431, 3363, 3252, 3169, 1750, 1725, 1656, 1629 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.30 (s, 3H), 6.11 (d, *J* 1.6 Hz, 1H), 6.33 (br s, 2H, NH_2), 7.05 (d, *J* 1.5 Hz, 1H), 7.21 (d, *J* 9.0 Hz, 4H), 8.56 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 21.2, 82.2, 124.4, 126.9, 127.2, 129.8, 133.8, 138.8, 155.7, 170.4; HRMS calculated for $C_{12}H_{12}N_2NaO_3$ $[M+Na]^+$ 255.0907, found 255.0863.

*4.3.24. 1-(5-(4-Methoxyphenyl)-2-oxo-2,5-dihydrofuran-3-yl)urea (**3c**).* Yield 83 mg, 67% (in H_2O) and 99 mg, 80% (in EtOH) as a pale yellow powder; mp 209–211 °C; ν_{max} (KBr plate) 3423, 3367, 3170, 1749, 1728, 1638, 1612 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 3.77 (s, 3H), 6.11 (d, *J* 2.0 Hz, 1H), 6.34 (br s, 2H, NH_2), 6.96 (d, *J* 8.5 Hz, 2H), 7.05 (d, *J* 2.2 Hz, 1H), 7.25 (d, *J* 8.8 Hz, 2H), 8.57 (s, 1H, NH); δ_C (150 MHz, $CDCl_3$) 55.7, 82.2, 114.6, 124.3, 127.0, 128.5, 128.9, 155.7, 160.2, 170.4; HRMS calculated for $C_{12}H_{12}N_2NaO_4$ $[M+Na]^+$ 271.0735, found 271.0713.

*4.3.25. (E)-3-(4-Chlorostyryl)quinoxalin-2(1H)-one (**4**).* Yield 120 mg, 85% as a yellow powder; mp 260 °C (dec); ν_{max} (KBr plate) 3426, 1661, 1624, 1591 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.34–7.36 (m, 2H), 7.51–7.55 (m, 3H), 7.66 (d, *J* 16.3 Hz, 1H), 7.80–7.82 (m, 3H), 8.08 (d, *J* 16.3 Hz, 1H), 12.56 (s, 1H, NH); δ_C (150 MHz, $CDCl_3$) 15.8, 123.3, 124.0, 128.9, 129.5, 129.8, 130.5, 132.2, 132.8, 134.2, 135.4, 136.1, 153.3, 155.2; HRMS calculated for $C_{16}H_{11}^{35}ClN_2NaO$ $[M+Na]^+$ 305.0412, found 305.0432.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.02.036.

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