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TFA-catalyzed ring transformation of 4-hydroxycyclobutenone: A simple and general route for preparation of 3-substituted 4-aminofuran-2(5*H*)-ones †

Jie Wang,[a] Xin Jiang,[a] Ming Chen,[a] Zongming Ge,[a] Yuefei Hu *[a,b] and Hongwen Hu [a,b]

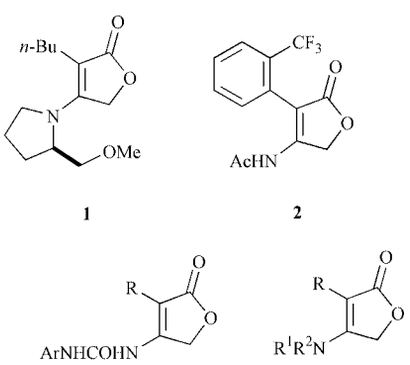
[a] *Department of Chemistry and* [b] *Coordination Chemistry Institute, Nanjing University, Nanjing 210093, People's Republic of China*

Received (in Cambridge, UK) 12th June 2000, Accepted 30th October 2000
First published as an Advance Article on the web 11th December 2000

Following a convenient sequence of alkylation and amination of 3,4-diisopropoxycyclobutene-1,2-dione **11**, three typical substituted groups (H, n-Bu, and Ph) and three typical amino groups (unsubstituted, primary and secondary) are easily introduced onto its C-3 and C-4 positions, respectively, to yield 4-substituted 3-aminocyclobutene-1,2-diones **14**. Reduction of compounds **14** with $NaBH_4$ yield 2-substituted 3-amino-4-hydroxycyclobutenones **15** in high yields. By ring transformation of products **15** catalyzed by TFA, a simple and general route for the preparation of 3-substituted 4-aminofuran-2(5*H*)-ones **4** is developed. A two-step mechanism is proposed to describe the ring transformation of enones **15**. The experimental results show that the process in refluxing *p*-xylene is essential for the initial thermal electrocyclic opening of **15** to yield intermediate hydroxy ketenes **16a** and **16b**. They are then lactonized in the presence of TFA to give furanones **4** in 51–94% yield.

Introduction

Although very few derivatives of 4-aminofuran-2(5*H*)-one occur in nature, their synthetic analogues are widely used in chemical, pharmaceutical and agrochemical research. Some 4-aminofuran-2(5*H*)-ones have been intermediates in the synthesis of natural products.[1] Many have been patented as prodrugs or insecticides and herbicides[2] (for example, see: **1**–**3** in Chart 1).



1 **2** **3** **4**

Chart 1

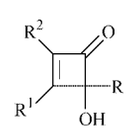
Many methods have been developed for the preparation of 4-aminofuran-2(5*H*)-ones.[3–7] Using cyanohydrin derivatives as starting materials, primary 4-aminofuran-2(5*H*)-ones, being mono- or bis-substituted at C-5 to meet the requirements of the reaction mechanism, were obtained.[4] The sequence of aminoaddition on acetylenecarboxylates followed by intramolecular cyclizations afforded 3-unsubstituted primary or secondary 4-aminofuran-2(5*H*)-ones smoothly.[5] Although 4-halogeno- or 4-hydroxyfuran-2(5*H*)-ones can be aminated to yield the corresponding unsubstituted, primary and secondary 4-aminofuran-2(5*H*)-ones conveniently,[1c,1d,6] the method has been limited by inaccessible precursors.[8] Very few procedures can be employed for direct alkylation of 4-aminofuran-2(5*H*)-ones at C-3.[6a,7]

To continue our agrochemical research project, a series of 3-substituted 4-aminofuran-2(5*H*)-ones (**4** in Chart 1) were designed as targets for synthesis. Herein, we report a novel and practical route for the synthesis of 3-substituted 4-aminofuran-2(5*H*)-ones that overcomes some of the limitations to published procedures.

Results and discussion

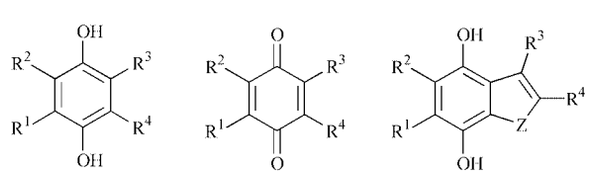
Strategy

4-Hydroxycyclobutenones with an unsaturated substituent at C-4 (**5a**–**c** in Chart 2) undergo thermal electrocyclic ring openings to give a variety of ring-expansion products including highly substituted phenols (**6**),[9] quinones (**7**)[10] and heteroaromatic compounds (**8**) (Chart 2).[11]



5a R = Alkenyl
5b R = Alkynyl
5c R = Aromatic heterocyclics
5d R = H

5



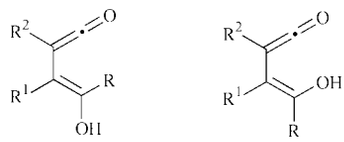
6 **7** **8**

Chart 2

† Elemental analyses results and detailed IR, MS spectra of new compounds **14a**–**o**, **15a**–**o**, **4a**–**m** and **4o** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b004654j/

 DOI: 10.1039/b004654j

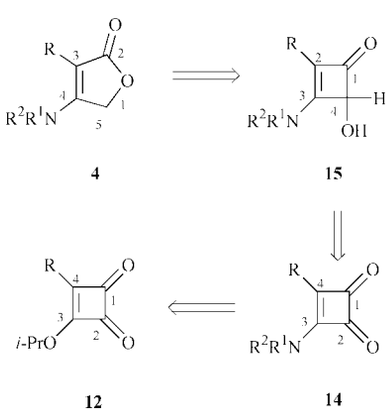
The effect of substituents on the direction of conrotation in electrocyclic reactions of 4-hydroxycyclobutenones has been explained and predicted by Houk's work. The hydroxy group as an electron-donating substituent favors intermediate **9** by outward rotation (Chart 3).[12] For this reason, furan-2(5*H*)-ones formed by intermediate **10** in thermal electrocyclic reactions were believed to be unusual by-products,[13] even though they were obtained as sole products in photochemistry or in metal-catalyzed reactions.[14]



9 (Outward to OH) **10** (Inward to OH)

Chart 3

The thermal electrocyclic opening of 4-substituted 4-hydroxybutenones **5a**–**c** is reversible; hence the final product might arise from trapping intermediate **9** in an equilibrating mixture of **9** and **10**. When the reactivity of R in **9** was inhibited by steric hindrance or a hydrogen bond, the corresponding furan-2(5*H*)-one was obtained by attack of the hydroxy group on the ketene involved in the intermediate **10**.[13,15] It clearly implies that the thermolysis of **5d** (R = H) should yield a furan-2(5*H*)-one because only the hydroxy group as trapping group is present in the molecule. As shown in Scheme 1, this transformation



4 **15** **12** **14**

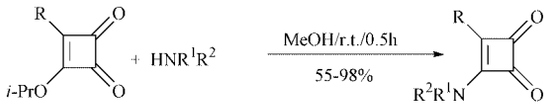
Scheme 1

has been developed as a key step for the preparation of 3-substituted 4-aminofuran-2(5*H*)-ones **4** in our synthetic strategy.

Synthesis of 4-substituted 3-aminocyclobutene-1,2-diones 14

Three typical 4-substituted 3-isopropoxycyclobutene-1,2-diones (**12a**–**c**) were chosen as starting materials, which were routinely prepared in 65–90% yield by known procedures[16] from 3,4-diisopropoxycyclobutene-1,2-dione **11**. The vinylogous ester at C-3 in the structures **12a**–**c** made the substitution of the isopropoxy group by various amines very easy.[17] Thus, a mixture of 3-isopropoxy-4-phenylcyclobutene-1,2-dione **12a** and ammonium hydroxide (28% solution in water, **13a**) in methanol was stirred for 30 min at room temperature, and 3-amino-4-phenylcyclobutene-1,2-dione **14a** was separated in 96% yield. To explore the scope of the reaction, allylic, benzyl and cyclic amines (**13b**–**g**) were tested and all of them gave excellent yields (**14b**–**g**, 88–96%) (Scheme 2).

Similarly, diones **12b**,**c** were treated with amines **13** to give **14h**–**o** in moderate to high yields (55–98%) (Scheme 2 and Table 1). It was noted that the amination of 4-*n*-butyl-substituted compound **12b** usually gave 4-*n*-butyl-3-amino-



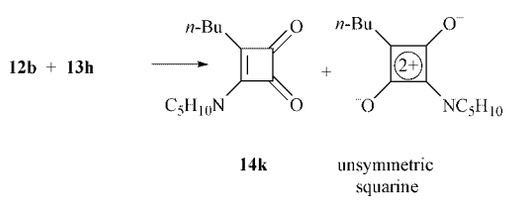
12 **13** **14**

12a R = Ph
12b R = *n*-Bu
12c R = H

13a R^1 = H, R^2 = H
13b R^1 = H, R^2 = CH_2=$CHCH_2$-
13c R^1 = H, R^2 = 3-$CH_3C_6H_4CH_2$-
13d R^1 = H, R^2 = 3-$CF_3C_6H_4CH_2$-
13e R^1 = H, R^2 = 4-$CF_3OC_6H_4CH_2$-
13f R^1R^2 = -$(CH_2)_4$-
13g R^1R^2 = -$(CH_2)_2O(CH_2)_2$-
13h R^1R^2 = -$(CH_2)_5$-
13i R^1 = H, R^2 = 3-$CF_3OC_6H_4CH_2$-
13j R^1 = H, R^2 = 4-$FC_6H_4CH_2$-
13k R^1 = H, R^2 = 3-$FC_6H_4CH_2$-
13l R^1 = H, R^2 = 4-$ClC_3H_4CH_2$-

Scheme 2

cyclobutene-1,2-diones **14h**–**k** in 55–87% yield together with the unsymmetrical squarine by-product in around 10–15% yield.[17a] Unfortunately, more than 20% of squarine by-product was produced in the reaction between **12b** and **13h** (Scheme 3), with the main product being **14k**.

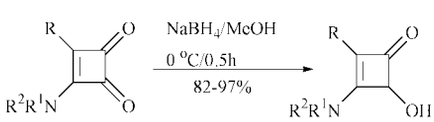


14k unsymmetric squarine

Scheme 3

Synthesis of 2-substituted 3-amino-4-hydroxycyclobutenones 15

In the published procedure, 3-(dibenzylamino)-4-methylcyclobutene-1,2-dione was reduced to 3-(dibenzylamino)-4-hydroxy-2-methylcyclobutenone by Li(*t*-BuO)$_3$AlH in 85% yield.[9a] Realizing that C-2 ketone in compounds **14** is a vinylogous ketone, we used $NaBH_4$ to replace Li(*t*-BuO)$_3$AlH to furnish this conversion. Typically, when a solution of 3-amino-4-phenylcyclobutene-1,2-dione **14a** in methanol was treated with $NaBH_4$ at 0 °C for 30 min, 3-amino-4-hydroxy-2-phenylcyclobutenone **15a** was obtained in 94% yield. In the same way, ketones **14b**–**o** were reduced to the corresponding acyloins **15b**–**o** in 82–97% yield. This new procedure featured short reaction time, low cost and high efficiency (Scheme 4, Table 1).



14a-o **15a-o**

Scheme 4

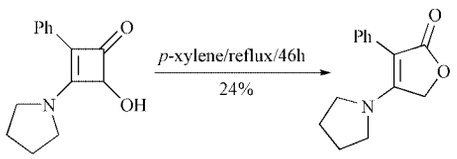
Synthesis of 3-substituted 4-aminofuran-2(5*H*)-ones 4

Following published procedures,[13c,15] 4-hydroxy-2-phenyl-3-pyrrolidinocyclobutenone **15f** was refluxed in *p*-xylene until it disappeared completely by TLC. To our disappointment, this process took 46 h and the desired product, 3-phenyl-4-pyrrolidinofuran-2(5*H*)-one **4f**, was separated in 24% yield by column chromatography (Scheme 5). The low yield may reflect the fact that the electrocyclic opening of **15f** favors 'unsuitable' intermediate **16b** by outward rotation obeying Houk's theory. Then **16b** was converted into 'suitable' intermediate **16a** though

Table 1 Substituents and yields of compounds **14**, **15**, and **4**

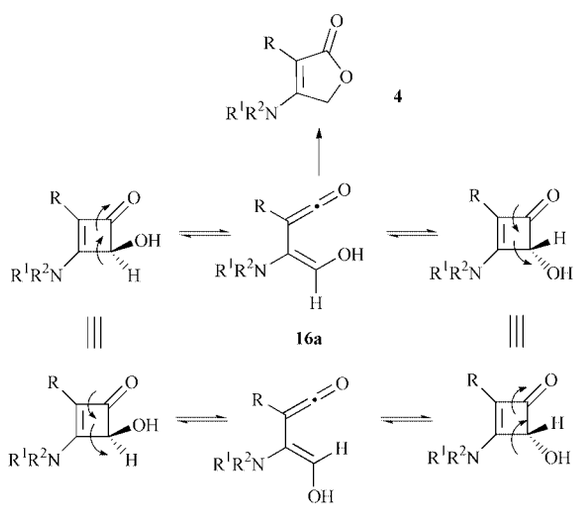
No.	R	R^2 (R^1 = H) or R^1R^2	**14** (%)	**15** (%)	**4** (%)	Time (*t*/h)[a]
a	Ph	H	96	94	84	4.0
b	Ph	$H_2C{=}CHCH_2$	95	91	72	3.0
c	Ph	3-$CH_3C_6H_4CH_2$	95	93	82	2.0
d	Ph	3-$CF_3C_6H_4CH_2$	91	94	80	2.5
e	Ph	4-$CF_3OC_6H_4CH_2$	96	93	70	3.0
f	Ph	$(CH_2)_4$	93	89	68	2.5
g	Ph	$(CH_2)_2O(CH_2)_2$	88	82	62	3.0
h	*n*-Bu	3-$CF_3OC_6H_4CH_2$	87	97	51	3.0
i	*n*-Bu	4-$FC_6H_4CH_2$	82	95	69	2.5
j	*n*-Bu	3-$CF_3C_6H_4CH_2$	82	89	57	3.0
k	*n*-Bu	$(CH_2)_5$	55	89	61	4.0
l	H	4-$ClC_6H_4CH_2$	90	96	94	0.5
m	H	3-$FC_6H_4CH_2$	96	94	72	0.25
n	H	$(CH_2)_4$	98	92	74	2.5
o	H	$(CH_2)_2O(CH_2)_2$	91	89	69	1.0

[a] Reaction time for **4**.



15f **4f**

Scheme 5



Scheme 6

a reversible equilibration illustrated in Scheme 6. Finally, an intramolecular cyclization occurred to give target compound **4** by an attack of the hydroxy group on the ketene in **16a**.

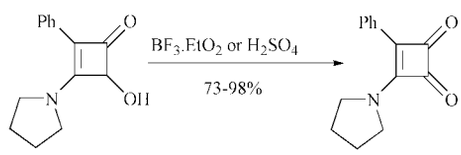
Since the intermediates **16b** and **16a** were hypothesized, the intramolecular cyclization between ketene and hydroxy group should be the key step to affect the reaction time and yield. It has been well known that the reaction between a ketene and a hydroxy group could be promoted significantly by acids and Lewis acids with variable results.[18] Herein, several typical acids and Lewis acids were employed to test their effects on this conversion. As shown in Table 2, the lactonization can be accelerated by most Lewis acids, but without improvement in the yield. Reagents BF_3–Et_2O and H_2SO_4 induced an alternative result to give the oxidized product 3-phenyl-4-pyrrolidinocyclobutene-1,2-dione **14f** (73 and 98% yield respectively) (Scheme 7).

Acetic acid did not benefit either the reaction time or the yield of the reaction. However, the reaction catalyzed by TsOH

Table 2 Effects of catalysts on the reaction of **15f**

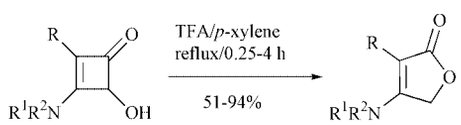
Catalysts	mol%	Time (*t*/h)	**4f** (%)
$AlCl_3$	5	18	28[b]
$ZnCl_2$	5	36	40[b]
$SnCl_2$	5	3	30[b]
BF_3–Et_2O	5	2	75[a]
H_2SO_4	100	0.5	98[b]
HOAc	100	46	34[b]
TsOH	100	10	42[b]
TFA	110	2.5	68[b]
TFA	200	2.0	[b]

[a] An oxidized product was obtained. [b] Compound **15f** disappeared completely on TLC.



15f **14f**

Scheme 7



15a-o **4a-o**

Scheme 8

was completed within 10 h in 42% yield. The best results were obtained in the presence of 1.1 mole equivalents of trifluoroacetic acid (TFA). Thus, a mixture of **15f** (1.0 eq.) and TFA (1.1 eq.) in *p*-xylene was refluxed for 2.5 h gave **4f** in 68% yield (Scheme 8). An attempt to decrease the reaction temperature failed. For example, **15f** was recovered completely after being refluxed in THF for 12 h, even though 2.0 equivalents of TFA were used. This result strongly supported the two-step mechanism proposed in Scheme 6. Similarly, **14a**–**o** were converted to the corresponding lactones **4a**–**o** in 51–94% yield under the same conditions (Table 1).

In conclusion, we have developed a simple and general route for preparation of 3-substituted 4-aminofuran-2(5*H*)-ones. The typical substituted groups, such as H, *n*-Bu, and Ph on C-3 were introduced easily. The derivatives with unsubstituted, primary and secondary amines substituted on C-4 can all be obtained in satisfactory yields.

Experimental

All mps were determined on a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer for samples as KBr pellets. ^1H NMR spectra were recorded on a Bruker MD500 or MD300 spectrometer with TMS as internal reference in $CDCl_3$ unless otherwise specified. *J*-Values are given in Hz. MS spectra were obtained on a VG-ZAB-HS mass spectrometer with 70 eV. Elemental analyses were performed on a Perkin-Elmer 240C instrument and satisfactory results obtained (C ± 0.29, H ± 0.0.24, N ± 0.0.27%) for all new compounds **14a**–**m**, **15a**–**o**, **4a**–**m** and **4o**. Light petroleum refers to the fraction with distillation range 60–90 °C.

General procedure for preparation of 4-substituted 3-aminocyclobutene-1,2-diones 14

A mixture of a 4-substituted 3-isopropoxycyclobutene-1,2-dione **12** (10 mmol) and an amine **13** (10 mmol) in methanol

(30 cm^3) was stirred for 30 min (monitored by TLC). Then it was poured into water (40 cm^3) and the resultant mixture was extracted with EtOAc (3 × 40 cm^3). The combined organic layers were washed successively with water (40 cm^3) and brine (40 cm^3) and dried over $MgSO_4$. The solvent was removed to give the crude product **14**, which was purified by chromatography or recrystallization.

3-Amino-4-phenylcyclobutene-1,2-dione 14a. Mp 257 °C (from EtOH–light petroleum) (Found: C, 69.20; H, 4.18; N, 8.09. $C_{10}H_7NO_2$ requires C, 69.36; H, 4.07; N, 8.09%); ν_{max}/cm^{-1} 3316, 3119, 1791, 1721, 1661, 1600; δ_H (CD_3OD) 7.99–7.97 (m, 2H), 7.53–7.47 (m, 3H); *m/z* 173 (M^+, 13%), 145 (20), 117 (100), 104 (15), 89 (34), 77 (4), 63 (13), 51 (6).

3-Allylamino-4-phenylcyclobutene-1,2-dione 14b. Mp 189–191 °C (from EtOH–light petroleum); ν_{max}/cm^{-1} 1779, 1724; δ_H (acetone-d_6) 8.02–8.00 (m, 2H), 7.54–7.46 (m, 3H), 6.08–6.02 (m, 1H), 5.33 (d, *J* 17.1, 1H), 5.20 (d, *J* 9.9, 1H), 4.48 (d, *J* 4.9, 2H); *m/z* 213 (M^+, 27%), 89 (100).

3-(3-Methylbenzylamino)-4-phenylcyclobutene-1,2-dione 14c. Mp 235–237 °C (from EtOH–light petroleum); ν_{max}/cm^{-1} 1772, 1718; δ_H (acetone-d_6) 8.01–8.00 (m, 2H), 7.51–7.45 (m, 3H), 7.27–7.23 (m, 3H), 7.14–7.13 (m, 1H), 5.04 (s, 2H), 2.32 (s, 3H); *m/z* 277 (M^+, 59%), 105 (100).

3-Phenyl-4-[3-(trifluoromethyl)benzylamino]cyclobutene-1,2-dione 14d. Mp 222–223 °C (from EtOH–light petroleum); ν_{max}/cm^{-1} 1773, 1719; δ_H (acetone-d_6) 8.00–7.99 (m, 2H), 7.83–7.79 (m, 2H), 7.69–7.62 (m, 2H), 7.52–7.46 (m, 3H), 5.20 (s, 2H); *m/z* 331 (M^+, 20%), 89 (100).

3-Phenyl-4-[4-(trifluoromethoxy)benzylamino]cyclobutene-1,2-dione 14e. Mp 216–218 °C (from EtOH); ν_{max}/cm^{-1} 1781, 1722; δ_H (CD_3OD) 7.97–7.96 (m, 2H), 7.53–7.48 (m, 5H), 7.31–7.30 (m, 2H), 5.03 (s, 2H); *m/z* 347 (M^+, 21%), 175 (100).

3-Phenyl-4-pyrrolidinocyclobutene-1,2-dione 14f. Mp 132–133 °C (from EtOH–light petroleum); ν_{max}/cm^{-1} 1752, 1716; δ_H (acetone-d_6) 7.76–7.75 (m, 2H), 7.51–7.48 (m, 2H), 7.44–7.41 (m, 1H), 4.04 (t, *J* 5.4, 2H), 3.69 (d, *J* 5.9, 2H), 2.07–2.05 (m, 4H); *m/z* 227 (M^+, 4%), 171 (100).

3-Morpholino-4-phenylcyclobutene-1,2-dione 14g. Mp 146–147 °C (from EtOH–light petroleum); ν_{max}/cm^{-1} 1778, 1731; δ_H (acetone-d_6) 7.63–7.44 (m, 5H), 4.11 (s, 2H), 3.85 (s, 4H), 3.70 (s, 2H); *m/z* 243 (M^+, 5%), 187 (100).

3-Butyl-4-[3-(trifluoromethoxy)benzylamino]cyclobutene-1,2-dione 14h. Mp 68–71 °C (from C_6H_6–light petroleum); ν_{max}/cm^{-1} 1780, 1722; δ_H 7.47–7.14 (m, 4H), 4.89 (d, *J* 6.3, 1H), 4.67 (d, *J* 5.9, 1H), 2.54 (t, *J* 7.5, 2H), 1.63–1.50 (m, 2H), 1.37–1.26 (m, 2H), 0.88 (t, *J* 7.3, 3H); *m/z* 327 (M^+, 9%), 195 (100).

3-Butyl-4-(4-fluorobenzylamino)cyclobutene-1,2-dione 14i. Mp 104–105 °C (from benzene–light petroleum); ν_{max}/cm^{-1} 1779, 1715; δ_H 7.32–7.25 (m, 2H), 7.12–7.00 (m, 2H), 4.83 (d, *J* 6.3, 1H), 4.60 (d, *J* 5.8, 1H), 2.53 (t, *J* 7.5, 2H), 1.64–1.53 (m, 2H), 1.38–1.29 (m, 2H), 0.90 (t, *J* 7.3, 3H); *m/z* 261 (M^+, 3%), 109 (100).

3-Butyl-4-[3-(trifluoromethyl)benzylamino]cyclobutene-1,2-dione 14j. Mp 85–88 °C (from benzene–light petroleum); ν_{max}/cm^{-1} 1782, 1723; δ_H 7.57–7.43 (m, 4H), 4.91 (s, 2H), 2.52 (t, *J* 7.5, 2H), 1.62–1.55 (m, 2H), 1.35–1.26 (m, 2H), 0.86 (t, *J* 7.3, 3H); *m/z* 311 (M^+, 4%), 159 (100).

3-Butyl-4-piperidinocyclobutene-1,2-dione 14k. An oil; ν_{max}/cm^{-1} 1778, 1731; δ_H 3.94 (s, 2H), 3.52 (s, 2H), 2.65 (t, *J* 7.6, 2H), 1.74 (s, 6H), 1.67–1.59 (m, 2H), 1.51–1.35 (m, 2H), 0.93 (t, *J* 7.3, 3H); *m/z* 221 (M^+, 4%), 164 (100).

3-(4-Chlorobenzylamino)cyclobutene-1,2-dione 14l. Mp 118–119 °C (from benzene); ν_{max}/cm^{-1} 1777, 1741; δ_H 7.93 (s, 1H), 7.39–7.36 (m, 2H), 7.27–7.24 (m, 2H), 4.50 (s, 2H); *m/z* 221 (M^+, 3%), 68 (100).

3-(3-Fluorobenzylamino)cyclobutene-1,2-dione 14m. Mp 69–70 °C (from benzene); ν_{max}/cm^{-1} 1779, 1751; δ_H 7.93 (s, 1H), 7.40–7.00 (m, 4H), 4.87 (s, 1H), 4.52 (s, 2H); *m/z* 205 (M^+, 4%), 68 (100).

3-Pyrrolidinocyclobutene-1,2-dione 14n. Mp 104–105 °C (from benzene–light petroleum) (lit.,[19] 99 °C). Although **14n** had a quite different mp from that of the reference material, it had exactly the same spectral data: ν_{max}/cm^{-1} 1775, 1745; δ_H 7.90 (s, 1H), 3.90–3.86 (m, 2H), 3.54–3.48 (m, 2H), 2.07–2.05 (m, 4H).

3-Morpholinocyclobutene-1,2-dione 14o. Mp 151–152 °C (from *n*-PrOH) (lit.,[19] 141 °C). Although **14o** had a quite different mp from that of the reference material, it had exactly the same spectral data: ν_{max}/cm^{-1} 1779, 1739; δ_H 7.91 (s, 1H), 3.90–3.84 (m, 6H), 3.46–3.40 (m, 2H).

General procedure for preparation of 2-substituted 3-amino-4-hydroxycyclobutenones (15)

To a stirred solution of a 4-substituted 3-aminocyclobutene-1,2-dione **14** (15 mmol) in methanol (50 cm^3) was added partly powdered $NaBH_4$ (1.0 g, 26 mmol) at 0 °C. After the reaction mixture had been kept for another 30 min (monitored by TLC) it was poured into ice–water (60 cm^3). The resultant mixture was extracted with EtOAc (3 × 40 cm^3) and the combined organic layers were washed successively with water (40 cm^3) and brine (40 cm^3) and dried over $MgSO_4$. The solvent was removed to give the crude product **15**, which was purified by chromatography or recrystallization.

3-Amino-4-hydroxy-2-phenylcyclobutenone 15a. Mp 232–233 °C (decomp.) (from EtOH–light petroleum) (Found: C, 68.46; H, 5.13; N, 7.93. $C_{10}H_9NO_2$ requires C, 68.56; H, 5.18; N, 8.00%); ν_{max}/cm^{-1} 3285, 3237, 3102, 1734, 1661, 1600; δ_H (CD_3OD) 7.62–7.61 (m, 2H), 7.34–7.31 (m, 2H), 7.19–7.16 (m, 1H), 4.96 (s, 1H); *m/z* 175 (M^+, 100%), 147 (66), 130 (56), 118 (96), 102 (94), 89 (86), 77 (35), 63 (43), 51 (39), 44 (37).

3-Allylamino-4-hydroxy-2-phenylcyclobutenone 15b. Mp 187–189 °C (from EtOH–light petroleum); ν_{max}/cm^{-1} 3302, 1725; δ_H (acetone-d_6) 7.69–7.67 (m, 2H), 7.32–7.29 (m, 2H), 7.16–7.13 (m, 1H), 6.10–6.06 (m, 1H), 5.32 (d, *J* 17.1, 1H), 5.17 (d, *J* 10.1, 1H), 5.11 (s, 1H), 4.29–4.24 (m, 1H), 4.19–4.16 (m, 1H); *m/z* 215 (M^+, 61%), 174 (100).

4-Hydroxy-3-(3-methylbenzylamino)-2-phenylcyclobutenone 15c. Mp 202–203 °C (from EtOH–light petroleum); ν_{max}/cm^{-1} 3330, 1722; δ_H (acetone-d_6) 7.69–7.68 (m, 2H), 7.26–7.14 (m, 7H), 5.20 (s, 1H), 4.76 (s, 2H), 2.32 (s, 3H); *m/z* 279 (M^+, 21%), 105 (100).

4-Hydroxy-2-phenyl-3-[3-(trifluoromethyl)benzylamino]-cyclobutenone 15d. Mp 200–201 °C (from EtOH–light petroleum); ν_{max}/cm^{-1} 3325, 1727; δ_H (acetone-d_6) 7.85–7.81 (m, 2H), 7.69–7.62 (m, 4H), 7.31–7.28 (m, 2H), 7.16–7.13 (m, 1H), 5.28 (s, 1H), 4.94 (s, 2H); *m/z* 333 (M^+, 53%), 159 (100).

4-Hydroxy-2-phenyl-3-[4-(trifluoromethoxy)benzylamino]-cyclobutenone 15e. Mp 192–194 °C (from EtOH–light petroleum); ν_{max}/cm^{-1} 3316, 1724; δ_H (CD_3OD) 7.63–7.62 (m, 2H),

7.55–7.53 (m, 2H), 7.35–7.27 (m, 4H), 7.20–7.17 (m, 1H), 5.15 (s, 1H), 4.75 (s, 2H); *m*/*z* 349 (M^+, 19%), 175 (100).

4-Hydroxy-2-phenyl-3-pyrrolidinocyclobutenone 15f. Mp 199–201 °C (from EtOH–light petroleum); ν_{max}/cm^{-1} 1725; δ_H (acetone-d_6) 7.49–7.47 (m, 2H), 7.32–7.27 (m, 2H), 7.18–7.15 (m, 1H), 5.05 (s, 1H), 4.06–4.02 (m, 1H), 3.71–3.68 (m, 1H), 3.63–3.58 (m, 1H), 3.40–3.36 (m, 1H), 2.05–1.99 (m, 4H); *m*/*z* 229 (M^+, 43%), 70 (100).

4-Hydroxy-3-morpholino-2-phenylcyclobutenone 15g. Mp 195–197 °C (from EtOH–light petroleum); ν_{max}/cm^{-1} 3216, 1729; δ_H (acetone-d_6) 7.40–7.19 (m, 5H), 5.11 (s, 1H), 3.80 (br s, 6H), 3.56 (br s, 2H); *m*/*z* 245 (M^+, 48%), 87 (100).

2-Butyl-4-hydroxy-3-[3-(trifluoromethoxy)benzylamino]-cyclobutenone 15h. Mp 92 °C (from benzene); ν_{max}/cm^{-1} 3225, 1731; δ_H 7.39–7.12 (m, 4H), 6.15 (br s, 1H), 4.99 (s, 1H), 4.55 (d, *J* 5.5, 2H), 1.90 (t, *J* 7.8, 2H), 1.25–1.23 (m, 2H), 1.17–1.13 (m, 2H), 0.78 (t, *J* 7.2, 3H); *m*/*z* 329 (M^+, 15%), 175 (100).

2-Butyl-4-hydroxy-3-(4-fluorobenzylamino)cyclobutenone 15i. Mp 113–114 °C (from benzene); ν_{max}/cm^{-1} 3239, 1735; δ_H 7.29–7.25 (m, 2H), 7.04–6.94 (m, 2H), 6.16 (br s, 1H), 4.95 (s, 1H), 4.50 (d, *J* 5.6, 2H), 1.91 (t, *J* 7.5, 2H), 1.28–1.14 (m, 4H), 0.80 (t, *J* 7.3, 3H); *m*/*z* 263 (M^+, 6%), 109 (100).

2-Butyl-4-hydroxy-3-[3-(trifluoromethyl)benzylamino]cyclo-butenone 15j. Mp 133 °C (from benzene); ν_{max}/cm^{-1} 3234, 1731; δ_H (CD_3OD) 7.69–7.54 (m, 4H), 5.00 (s, 1H), 4.67 (s, 2H), 2.04 (t, *J* 7.6, 2H), 1.49–1.44 (m, 2H), 1.36–1.29 (m, 2H), 0.90 (t, *J* 7.3, 3H); *m*/*z* 313 (M^+, 12%), 159 (100).

2-Butyl-4-hydroxy-3-piperidinocyclobutenone 15k. Mp 84–86 °C (from benzene); ν_{max}/cm^{-1} 3244, 1737; δ_H 5.05 (s, 1H), 3.65 (s, 2H), 3.48 (s, 2H), 2.11 (t, *J* 7.6, 2H), 1.70 (s, 6H), 1.50–1.40 (m, 2H), 1.37–1.26 (m, 2H), 0.89 (t, *J* 7.3, 3H); *m*/*z* 223 (M^+, 0.6%), 57 (100).

3-(4-Chlorobenzylamino)-4-hydroxycyclobutenone 15l. Mp 148–150 °C (from MeOH–water); ν_{max}/cm^{-1} 3230, 1728; δ_H ($CDCl_3$–CD_3OD) 7.35–7.33 (m, 2H), 7.30–7.25 (m, 2H), 4.93 (s, 1H), 4.43–4.35 (m, 1H), 4.27 (s, 2H); *m*/*z* 223 (M^+, 16%), 125 (100).

3-(3-Fluorobenzylamino)-4-hydroxycyclobutenone 15m. Mp 108–111 °C (from benzene); ν_{max}/cm^{-1} 3201, 1718; δ_H ($CDCl_3$–CD_3OD) 7.40–7.32 (m, 1H), 7.13–7.09 (m, 1H), 7.06–7.00 (m, 2H), 4.95 (s, 1H), 4.45–4.37 (m, 1H), 4.10 (s, 2H); *m*/*z* 207 (M^+, 14%), 109 (100).

4-Hydroxy-3-pyrrolidinocyclobutenone 15n. Mp 133–136 °C (from benzene–light petroleum); ν_{max}/cm^{-1} 3178, 1729; δ_H 6.04 (br s, 1H), 5.12 (s, 1H), 4.82 (s, 1H), 3.98–3.93 (m, 1H), 3.50–3.45 (m, 1H), 3.39–3.37 (m, 2H), 2.05–2.00 (m, 4H); *m*/*z* 153 (M^+, 67%), 95 (100).

4-Hydroxy-3-morpholinocyclobutenone 15o. Mp 117–119 °C (from benzene–light petroleum); ν_{max}/cm^{-1} 3232, 1725; δ_H 6.15 (br s, 1H), 5.17 (s, 1H), 4.93 (s, 1H), 3.86–3.81 (m, 5H), 3.64–3.60 (m, 1H), 3.48–3.41 (m, 2H); *m*/*z* 169 (M^+, 68%), 55 (100).

General procedure for preparation of 3-substituted 4-aminofuran-2(5*H*)-ones 4

A mixture of a 2-substituted 3-amino-4-hydroxycyclobutenone **15** (15 mmol) and TFA (1.88 g, 16.5 mmol) in anhydrous *p*-xylene (35 cm^3) was refluxed until compound **15** had disappeared completely on TLC. Then it was washed with water (35 cm^3) and the organic layer was dried over $MgSO_4$. The solvent was removed to give the crude product **4**, which was purified by chromatography or recrystallization.

4-Amino-3-phenylfuran-2(5*H*)-one 4a. Mp 198–200 °C (from EtOH–water) (Found: C, 68.66; H, 5.26; N, 8.09. $C_{10}H_9NO_2$ requires C, 68.56; H, 5.18; N, 8.00%); ν_{max}/cm^{-1} 3463, 3299, 3177, 1696, 1641, 1609, 1592; δ_H (acetone-d_6) 7.55–7.52 (m, 2H), 7.38–7.35 (m, 2H), 7.22–7.20 (m, 1H), 6.11 (br s, 2H), 4.74 (s, 2H); *m*/*z* 175 (M^+, 100%), 146 (56), 130 (17), 118 (51), 91 (24), 77 (8), 63 (9).

4-Allylamino-3-phenylfuran-2(5*H*)-one 4b. Mp 84–85 °C (from benzene–light petroleum); ν_{max}/cm^{-1} 1708; δ_H 7.48–7.26 (m, 5H), 5.90–5.82 (m, 1H), 5.52 (br s, 1H), 5.29 (s, 1H), 5.25 (d, *J* 9.6, 1H), 4.77 (s, 2H), 3.78 (t, *J* 5.2, 2H); *m*/*z* 215 (M^+, 100%).

4-(3-Methylbenzylamino)-3-phenylfuran-2(5*H*)-one 4c. Mp 98–99 °C (from EtOAc–light petroleum); ν_{max}/cm^{-1} 1713; δ_H 7.48–7.07 (m, 9H), 5.71 (br s, 1H), 4.76 (s, 2H), 4.31 (d, *J* 6.1, 2H), 2.36 (s, 3H); *m*/*z* 279 (M^+, 18%), 106 (100).

3-Phenyl-4-[3-(trifluoromethyl)benzylamino]furan-2(5*H*)-one 4d. Mp 125.5–127 °C (from EtOAc–light petroleum); ν_{max}/cm^{-1} 1714; δ_H 7.61–7.24 (m, 9H), 5.80 (s, 1H), 4.74 (s, 2H), 4.40 (s, 2H); *m*/*z* 333 (M^+, 40%), 159 (100).

3-Phenyl-4-[4-(trifluoromethoxy)benzylamino]furan-2(5*H*)-one 4e. Mp 126–127 °C (from benzene–light petroleum); ν_{max}/cm^{-1} 1714; δ_H 7.46–7.21 (m, 9H), 5.87 (s, 1H), 4.72 (s, 2H), 4.34 (s, 2H); *m*/*z* 349 (M^+, 72%), 175 (100).

3-Phenyl-4-pyrrolidinofuran-2(5*H*)-one 4f. Mp 129–131 °C (from EtOAc–light petroleum); ν_{max}/cm^{-1} 1710; δ_H 7.34–7.24 (m, 5H), 4.74 (s, 2H), 3.17 (br s, 4H), 1.88 (br s, 4H); *m*/*z* 229 (M^+, 67%), 70 (100).

4-Morpholino-3-phenylfuran-2(5*H*)-one 4g. Mp 189–190 °C (from benzene–light petroleum); ν_{max}/cm^{-1} 1713; δ_H 7.38–7.27 (m, 5H), 4.78 (s, 2H), 3.66 (t, *J* 4.8, 4H), 3.18 (t, *J* 4.8, 4H); *m*/*z* 245 (M^+, 56%), 40 (100).

3-Butyl-4-[3-(trifluoromethoxy)benzylamino]furan-2(5*H*)-one 4h. An oil; ν_{max}/cm^{-1} 1725; δ_H 7.41–7.14 (m, 4H), 6.13 (br s, 1H), 4.53 (s, 2H), 4.38 (d, *J* 6.3, 2H), 2.15 (t, *J* 7.7, 2H), 1.45–1.38 (m, 2H), 1.29–1.20 (m, 2H), 0.87 (t, *J* 7.3, 3H); *m*/*z* 329 (M^+, 5%), 175 (100).

3-Butyl-4-(4-fluorobenzylamino)furan-2(5*H*)-one 4i. An oil; ν_{max}/cm^{-1} 1723; δ_H 7.29–7.23 (m, 2H), 7.06–6.96 (m, 2H), 5.97 (br s, 1H), 4.53 (s, 2H), 4.32 (d, *J* 6.1, 2H), 2.14 (t, *J* 7.7, 2H), 1.45–1.38 (m, 2H), 1.26 (m, 2H), 0.87 (t, *J* 7.3, 3H); *m*/*z* 263 (M^+, 7%), 109 (100).

3-Butyl-4-[3-(trifluoromethyl)benzylamino]furan-2(5*H*)-one 4j. An oil; ν_{max}/cm^{-1} 1724; δ_H 7.57–7.48 (m, 4H), 5.94 (s, 1H), 4.54 (s, 2H), 4.41 (s, 2H), 2.16 (t, *J* 7.7, 2H), 1.46–1.39 (m, 2H), 1.32–1.25 (m, 2H), 0.87 (t, *J* 7.2, 3H); *m*/*z* 313 (M^+, 9%), 159 (100).

3-Butyl-4-piperidinofuran-2(5*H*)-one 4k. An oil; ν_{max}/cm^{-1} 1730; δ_H 4.56 (s, 2H), 3.94 (s, 1H), 3.52 (s, 1H), 3.33 (s, 2H), 2.65 (t, *J* 7.6, 1H), 2.31 (t, *J* 7.3, 1H), 1.74 (s, 6H), 1.47–1.32 (m, 4H), 0.93 (t, *J* 7.3, 3H); *m*/*z* 223 (M^+, 13%), 180 (100).

4-(4-Chlorobenzylamino)furan-2(5*H*)-one 4l. Mp 161–162 °C (from $CHCl_3$–light petroleum); ν_{max}/cm^{-1} 1698; δ_H ($CDCl_3$–CD_3OD) 7.37–7.32 (m, 2H), 7.25–7.23 (m, 2H), 4.70 (s, 2H), 4.26 (s, 2H), 3.97 (s, 1H); *m*/*z* 223 (M^+, 15%), 125 (100).

4-(3-Fluorobenzylamino)furan-2(5*H*)-one 4m. Mp 165–166.5 °C (from EtOAc–light petroleum); ν_{max}/cm^{-1} 1701; δ_H ($CDCl_3$–CD_3OD) 7.47–7.01 (m, 4H), 4.62 (s, 1H), 4.42 (s, 2H), 4.31 (s, 2H); *m*/*z* 207 (M^+, 20%), 109 (100).

4-Pyrrolidinofuran-2(5*H*)-one 4n. Mp 119–121 °C (from benzene) (lit.,[6b] 120–121 °C).

4-Morpholinofuran-2(5*H*)-one 4o. Mp 107–109 °C (from benzene); ν_{max}/cm^{-1} 1714; δ_H 4.74 (s, 2H), 4.72 (s, 1H), 3.79 (t, *J* 4.7, 4H), 3.23 (t, *J* 4.7, 4H); *m*/*z* 169 (M^+, 100%).

Acknowledgements

We are grateful to the Education Ministry of China and the Education Department of Jiangsu Province for financial support.

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