Reaction of 2-Acyl-6-methylbenzo[*b*]furan-3-acetic Acids Derivatives with Hydrazine

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Reaction of 2-acyl-6-methylbenzo[*b*]furan-3-acetic acids and their derivatives such as amides and esters with hydrazine does not give expected 1-alkyl-*5H*-benzofuro[2,3-*e*]diazepin-4-ones ones but results in 2-amino-7-methyl-*2H*-benzo[4,5]furo[2,3-*c*]pyridin-3-ones or (3-R-6-methylbenzo[*b*]furan-2-yl)alkyl ketone azines.

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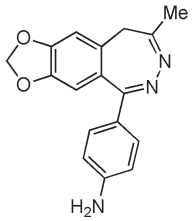
Introduction.

The 2,3-benzodiazepines derivatives are of great interest because of their proven biological action upon the nervous system [1-7]. Among the 2,3-benzodiazepine derivatives tranquilizers and anticonvulsants have been found [2-4,8]. Thus, 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-diazepine (GYKI 52466) was shown to be a highly selective, noncompetitive antagonist of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) and kainate receptor responses [9,10]. Several 2,3-benzodiazepine derivatives are used in clinical practice, *e.g.* tofizopam [1]. Much attention was paid to the synthesis and investigations of the pharmacological activity of diazepines fused with various heterocyclic rings [3,4,6].

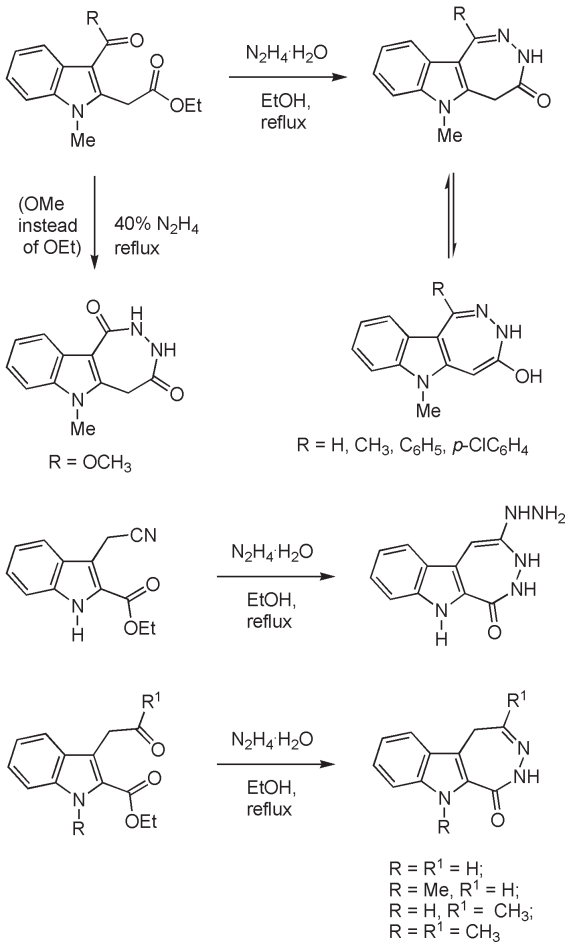


GYKI 52466

Figure 1

Known methods to obtain 2,3-benzodiazepin-4-ones are based on the reaction of 2-aroyl(acetyl)-4,5-dimethoxyphenyl acetic acids with hydrazine [7,11-13]. Thus, 3*H*-[1,2]diazepino[5,6-*b*]indole, 1*H*- and 3*H*-[1,2]diazepino-[4,5-*b*]indole derivatives were obtained by cyclization of derivatives of ethyl indole-2-acetate and indole-2-carboxylate with hydrazine hydrate (Scheme 1) [14-16]. Such transformations for the benzo[*b*]furan series were not described and therefore we were interested if this route to diazepines can be extended onto derivatives with the benzo[*b*]furan fragment.

Scheme 1



This paper describes investigations of reactions of 2-acyl-6-methylbenzo[*b*]furan-3-acetic acid and its derivatives (esters and amides) with hydrazine hydrate, aiming to determine whether the cyclization reactions into benzodiazepine derivatives (of type **BFD**, Schemes 2 and 3) take place in this case.

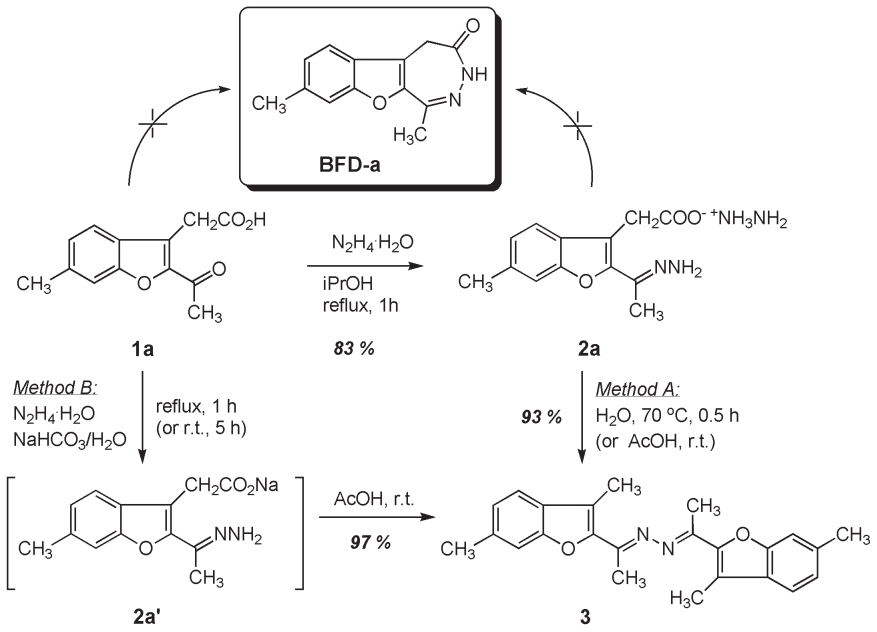
Results and Discussion.

The reaction of acid **1a** with an excess of hydrazine hydrate in 2-propanol at reflux resulted in low-soluble hydrazinium salt of 2-acetyl-6-methylbenzo[*b*]furan-3-acetic acid hydrazone (**2a**). When an aqueous solution of salt **2a** was heated, the decarboxylation was observed resulting in azine **3** (Scheme 2). The same azine **3** was also isolated by the acidification of aqueous solution of hydrazone **2a** with acetic acid.

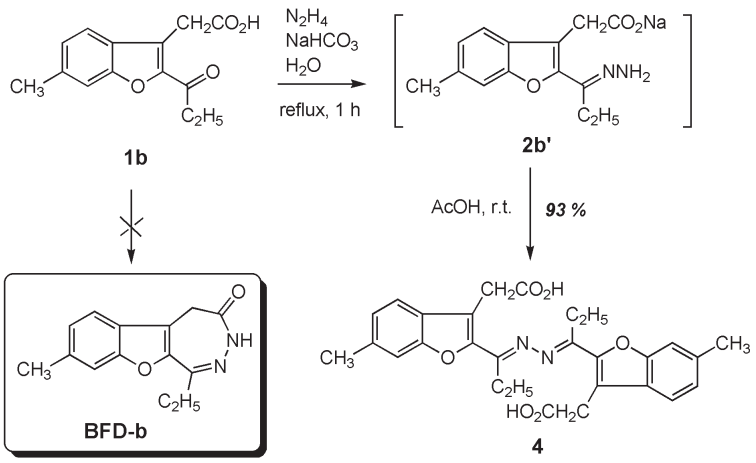
Similar behavior was observed for the sodium salt of ketoacid **1a**, which reacted with hydrazine in water to yield hydrazone **2a''**. The later on attempt to isolate by acidification (even at below the room temperature) gave azine **3**, as confirmed by ^{1}H nmr spectrum (Scheme 2). The temperature of the reaction had no effect on the decarboxylation process in **1a**, and the same azine **3** was formed independently whether compound **1a** reacted with hydrazine hydrate at reflux (1 h) or at room temperature (5 h). In both cases only azine **3** was isolated in high yields (> 90 %). Thus, the reaction of benzo[*b*]furan derivative **1a** with hydrazine does not follow the common cyclization way into 5*H*-benzofuro[2,3-*e*]diazepin-4-ones (**BFD-a**) but results in azine **3**.

Similar reaction of azine **4** (and not diazepinone **BFD-b**) formation was observed in reaction of sodium salt of 6-methyl-2-propionylbenzo[*b*]furan-3-acetic acid **1b** with

Scheme 2



Scheme 3



hydrazine under the same conditions. However, in this case no decarboxylation occurred and the reaction resulted in azine **4**, thus demonstrating the importance of alkyl substituents at 2-carbonyl centre on the stability of the acetic acid fragment in position 3 towards decarboxylation (Scheme 3).

Thus, although the reaction conditions used in the above described studies are not very different from those reported for the preparations of 2,3-benzodiazepinones from 2-aroylacetic acids (excess of hydrazine hydrate, ethanol, reflux 2-3 h) [17], the reaction of 2-acylbenzo[*b*]furan-3-acetic acids **1** does not afford the corresponding benzodiazepinones **BFD** but results in non-cyclized hydrazones **2** or azines **3,4**.

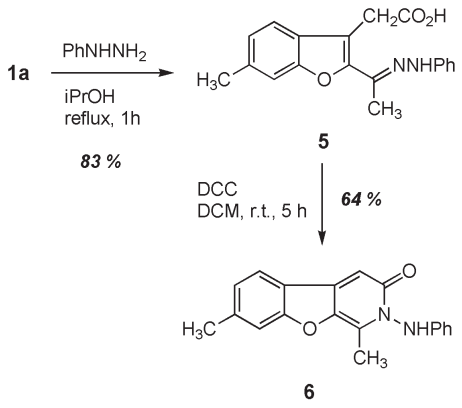
In the next step of variation of hydrazones structure and reaction conditions, we studied cyclization of phenylhydrazone **5** (prepared by reflux of ketoacid **1a** with phenylhydrazine in 2-propanol) in the presence of *N*,*N*-dicyclohexylcarbodiimide (DCC). Similar cyclization of arylhydrazones of 2-acylhomoveratric acid by DCC was shown to yield the corresponding 2,3-benzodiazepinones as a major product with N-phenylaminoisoquinoline derivatives as only minor by-products [.13]. In our case, cyclization of compound **5** in the presence of DCC resulted in 1,7-dimethyl-2-phenylamino-2*H*-benzo[4,5]furo[2,3-*c*]-pyridin-3-one (**6**) in 64 % yield (Scheme 4).

Pyrolytic dehydration of 2-acetylphenylacetic acid phenylhydrazone was shown to give the 2,3-benzodiazepinone derivative, while warming in a 1 *M* solution of sulfuric acid in acetic acid results in cyclization into the 3-isoquinolone derivative [18]. In this context we studied the thermal cyclization of hydrazone **8** (Scheme 5). Ethyl 2-acetylbenzo[*b*]furan-3-acetate (**7**) reacted first with hydrazine yielding compound **8**. Compound **8** was formed even when minimal excess of hydrazine was used. Reflux of compound **8** in ethylene glycol resulted in thermal heterocyclization to afford 1,7-dimethyl-2-amino-*2H*-benzofuro[2,3-*c*]pyridin-3-one (**9**) (Scheme 5).

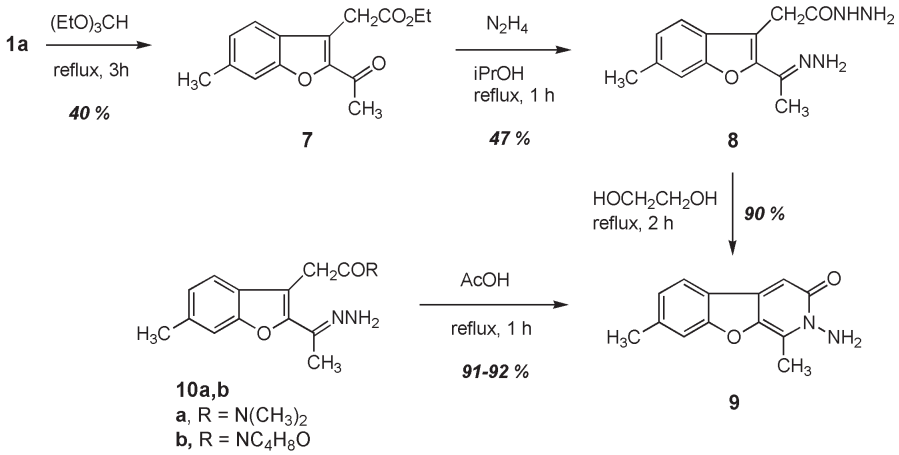
The failed attempts to synthesize 5*H*-benzofuro[2,3-*e*]diazepin-4-ones (**BFD**) from the ketoacids **1a,b** lead us to investigate the interaction of 1,7-dimethyl-3-R-benzofuro[2,3-*c*]pyrylium salts (**11a-e**) [19,20] with hydrazine. However, reflux of perchlorates **11a-d** with hydrazine in 2-propanol resulted in hydrazones **10a-d** only, whereas 1,7-dimethyl-3-hydroxybenzofuro[2,3-*c*]pyrylium perchlorate (**11e**) in these conditions gave azine **3** (see Method C in the Experimental part) (Scheme 6).

Further heterocyclizations of hydrazones **10a-d** proceeded in acidic media only. Thus, the morpholide or dimethylamide of 2-acetylbenzo[*b*]furan-3-acetic acid hydrazones (**10a,b**) underwent a cyclization reaction into 2-amino-2*H*-benzofuro[2,3-*c*]pyridin-3-one (**9**) being refluxed in acetic acid (Scheme 5). In contrast, 2-acetylbenzo[*b*]furan-3-(*N*-arylacetamide) hydrazones (**10c,d**) in the same conditions gave azines **12a,b**, whereas being refluxed in trifluoroacetic acid they also gave pyridone **9**.

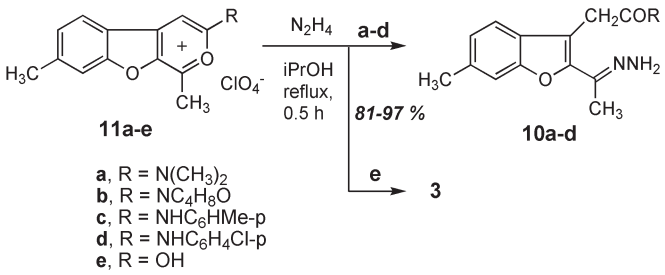
Scheme 4



Scheme 5

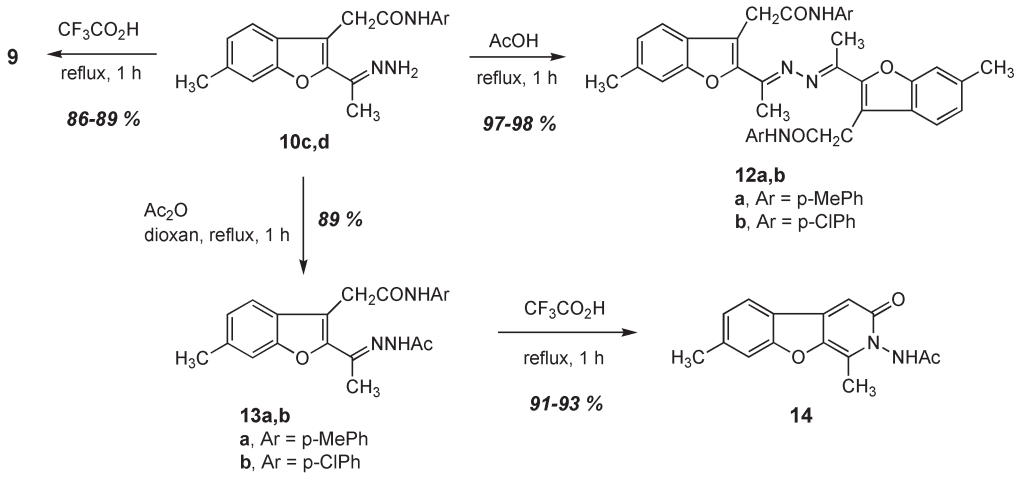


Scheme 6



The acetylhydrazones **13a,b** did not undergowent heterocyclizations in acetic acid, but heating in trifluoroacetic acid resulted in 2-acetylaminopyridone **14** (Scheme 7).

Scheme 7



Conclusion.

In conclusion, hydrazones of 2-acylbenzo[*b*]furan-3-acetic acids (and its derivatives), in contrast to similar phenylacetic and indolylacetic acid derivatives, do not undergo expected heterocyclization into 5*H*-benzofuro[2,3-*e*]diazepin-4-ones (**BFD**). Instead, depending on their structure and the reaction conditions the reaction results in 2-amino-7-methyl-2*H*-benzofuro[2,3-*c*]pyridin-3-ones **6**, **9**, **14** or (3-R-6-methylbenzo[*b*]furan-2-yl)alkyl ketone azines **3**, **4**, **12**.

EXPERIMENTAL

Melting points were determined on a Kofler-type hot-stage microscope apparatus and are uncorrected. The nmr-spectra were recorded on VARIAN VXR-300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) and Bruker DRX500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) spectrometers in DMSO-d_6 or acetone-d_6 solutions. Chemical shifts are given in δ (ppm) and *J* values in Hz. Mass spectra (ms) (electron impact) were determined with Finnigan MAT INCOS 50 and VG7070E mass spectrometers, both operating at an ionizing potential of 70 eV.

(2-Acetyl-6-methylbenzo[*b*]furan-3-yl)acetic Acid (**1a**).

To a suspension of 1,7-dimethyl-3-hydroxybenzofuro[2,3-*c*]-pyrylium perchlorate (**11e**) [19] (3.13 g, 10 mmol) in ethanol (20 ml) an aqueous sodium hydroxide (5 %, 50 ml) was added and the mixture was heated under reflux for 1 hour. After cooling the solution was neutralized with diluted hydrochloric acid. The precipitate was collected by filtration, washed with water, dried and recrystallized from 2-propanol to afford compound **1a** (2.1 g, 90 %) as yellowish needles, mp 160 °C. ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.45 (s, 3H, 6-CH_3), 2.54 (s, 3H, $COCH_3$), 4.06 (s, 2H, CH_2), 7.18 (d, *J* = 8.2 Hz, 1H, C5-H), 7.49 (s, 1H, C7-H), 7.69 (d, *J* = 8.2 Hz, 1H, C4-H), 12.53 (s, 1H, COOH). ^{1}H nmr (acetone-d_6; 300 MHz): δ 2.49 (s, 3H, 6-CH_3), 2.56 (s, 3H, $COCH_3$), 4.18 (s, 2H, CH_2), 7.20 (d, *J* = 8.1 Hz, 1H, C5-H), 7.43 (s, 1H, C7-H), 7.69 (d, *J* = 8.1 Hz, 1H, C4-H). ^{13}C nmr (acetone-d_6, 75 MHz): δ 21.90, 27.56, 29.97, 112.75, 121.46, 122.41, 126.15, 127.13, 140.01, 149.29, 155.21, 171.05, 191.22.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.34; H, 5.16. Found: C, 67.23; H, 5.21.

(2-Propionyl-6-methylbenzo[*b*]furan-3-yl)acetic Acid (**1b**).

This compound was obtained by hydrolysis of the 1-ethyl-3-hydroxy-7-methylbenzofuro[2,3-*c*]pyrylium perchlorate **15** [19] in similar way as described above for **1a**. Yield 97 %, mp 136-137 °C (from toluene-heptane, 1:3). ^{1}H nmr (DMSO-d_6, 500 MHz): δ 1.12 (t, *J* = 7.3 Hz, 3H, CH_3), 2.49 (s, 3H, 6-CH_3), 3.06 (q, *J* = 7.3 Hz, 2H, CH_2), 4.11 (s, 2H, CH_2), 7.22 (d, *J* = 8.1 Hz, 1H, C5-H), 7.52 (s, 1H, C7-H), 7.72 (d, *J* = 8.1 Hz, 1H, C4-H), 12.56 (s, 1H, COOH). ^{1}H nmr (acetone-d_6; 300 MHz): δ 1.15 (t, *J* = 7.3 Hz, 3H, CH_3), 2.49 (s, 3H, 6-CH_3), 3.02 (q, *J* = 7.2 Hz, 2H, CH_2), 4.20 (s, 2H, CH_2), 7.20 (d, *J* = 7.8 Hz, 1H, C5-H), 7.42 (s, 1H, C7-H), 7.68 (d, *J* = 7.8 Hz, 1H, C4-H). ^{13}C nmr (acetone-d_6, 75 MHz): δ 7.62, 21.89, 29.97, 33.34, 112.73, 121.30, 122.35, 126.09, 127.12, 139.87, 149.10, 155.15, 171.11, 194.23.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.40; H, 5.66.

[2-(1-Hydrazono-ethyl)-6-methylbenzo[*b*]furan-3-yl]acetic Acid Hydrazinium Salt (**2a**).

To a solution of **1a** (2.3 g, 10 mmoles) in 2-propanol (50ml) 80 % aqueous hydrazine (2.5 ml, 50 mmol) was added and the mixture was refluxed for 1 hour. After cooling the solid was collected by filtration and washed with 2-propanol to yield compound **2a** (2.3 g, 83 %) as yellowish needles, mp 140 °C (dec.). ^{1}H-nmr (DMSO-d_6 500 MHz): δ 2.11 (s, 3H, 6-CH_3), 2.43 (s, 3H, CH_3C=N), 3.75 (s, 2H, CH_2), 5.25 (m, 5H, ONH_3NH_2), 6.67 (s, 2H, C=NNH_2), 7.02 (d, 1H, *J* = 8.0 Hz, C5-H), 7.30 (s, 1H, C7-H), 7.41 (d, 1H, *J* = 8.0 Hz, C4-H). ^{13}C nmr (acetone-d_6, 75 MHz): δ 11.70, 21.17, 31.83, 110.43, 110.90, 119.67, 123.48, 128.16, 133.23, 136.46, 149.95, 152.65, 173.53.

Anal. Calcd. for $C_{13}H_{18}N_4O_3$: C, 56.10; H, 6.52; N, 20.13. Found: C, 56.23; H, 6.66; N, 20.30.

(3,6-Dimethylbenzo[*b*]furan-2-yl)methyl Ketone Azine (**3**).

Method A.

A solution of compound **2a** (2.0 g, 7.2 mmoles) in water (50 ml) was stirred at 70 °C for 0.5 hour (precipitation was observed after 5 minutes). The mixture was cooled and the yellow solid was collected by filtration and dried. The crude product was recrystallized from DMF to yield azine **3** (1.3 g, 93 %), mp 218–219 °C. ^{1}H nmr (DMSO-d_6, 500 Mhz): δ 2.35 (s, 3H, 3-CH_3), 2.42 (s, 6H, CH_3C=N and 6-CH_3), 7.06 (d, *J* = 8.0 Hz, 1H, C5-H), 7.27 (s, 1H, C7-H), 7.49 (d, *J* = 8.0 Hz, 1H, C4-H). ms: m/z 372 (M^+, 80 %), 185 (100 %).

Anal. Calcd. for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.28; H, 6.37; N, 7.61.

Method B.

A solution of compound **1a** (2.3 g, 10 mmoles) in 0.2 *M* aqueous $NaHCO_3$ (50 ml) and 80 % hydrazine (2.5 ml, 50 mmoles) was refluxed for 1 h. After cooling the solution was acidified by acetic acid to pH < 7. The precipitate was collected by filtration, washed with water and recrystallized from DMF to give compound **3** (1.8 g, 97 %).

Method C.

The mixture of 1,7-dimethyl-3-hydroxybenzofuro[2,3-*c*]-pyrylium perchlorate (**10e**) (3.13 g, 10 mmoles) and 80 % hydrazine (5 ml, 0.1 mol) in ethanol (30 ml) was refluxed for 2 hours. The solid was collected by filtration, washed with ethanol and recrystallized from DMF to give compound **3** (1.43 g, 77 %).

A mixture of the samples of compound **3** prepared by Methods A–C did not gave a depression of the melting point and their ^{1}H nmr spectra were identical.

(3-Carboxymethyl-6-methylbenzo[*b*]furan-2-yl)ethyl Ketone Aazine (**4**).

This compound was obtained by reaction of 2-propionyl-6-methylbenzo[*b*]furan-3-acetic acid (**1b**) (2.46 g, 10 mmol) with 80 % hydrazine (2.5 ml, 50 mmol) similarly to the procedure described for compound **3** (Method B). Yield 2.27 g (93 %), mp 204–205 °C. ^{1}H nmr (DMSO-d_6, 500 MHz): δ 1.17 (t, *J* = 7.4 Hz, 3H, CH_3), 2.48 (s, 3H, 6-CH_3), 3.02 (q, *J* = 7.4 Hz, 2H, CH_2), 4.14 (s, 2H, CH_2), 7.14 (d, *J* = 8.0 Hz, 1H, C5-H), 7.42 (s, 1H, C7-H), 7.57 (d, *J* = 8.0 Hz, 1H, C4-H), 12.32 (s, 1H, COOH).

Anal. Calcd. for $C_{28}H_{28}N_2O_6$: C, 68.84; H, 5.78; N, 5.73. Found: C, 68.72; H, 5.88; N, 5.82.

{6-Methyl-2-[1-(phenylhydrazono)ethyl]-benzo[*b*]furan-3-yl}acetic Acid (**5**).

To a solution of 2-acetyl-6-methylbenzo[*b*]furan-3-acetic acid (**1a**) (2.3 g, 10 mmol) in 2-propanol (20 ml), phenylhydrazine (1.62 g, 15 mmol) was added and the mixture was refluxed for 1 hour. The mixture was cooled, and the solid was collected by filtration, washed with cold 2-propanol and dried to afford compound **5** (2.3 g, 83 %) as yellow needles, mp 173–174 °C (from methanol). ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.32 (s, 3H, 6-CH_3), 2.43 (s, 3H, CH_3C=N), 4.03 (s, 2H, CH_2), 6.78 (m, 1H, C4'-H), 7.07 (d, *J* = 8.0 Hz, 1H, C5-H), 7.21–7.23 (m, 4H, phenyl), 7.33 (s, 1H, C7-H), 7.47 (d, *J* = 8.1 Hz, 1H, C4-H), 9.48 (s, 1H, NH), 12.31 (s, 1H, COOH). ^{13}C nmr (DMSO-d_6, 75 MHz): δ 12.75, 21.20, 30.05, 109.09, 110.77, 112.83 (2C), 119.28 (2C), 124.14, 127.74, 128.81 (2C), 134.04, 135.16, 145.24, 150.22, 152.83, 171.82.

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.91; H, 5.74; N, 8.60.

1,7-Dimethyl-2-phenylamino-*2H*-benzofuro[2,3-*c*]pyridin-3-one (**6**).

To a solution of compound **5** (1.0 g. 3.1 mmol) in dichloromethane (20 ml) *N,N'*-dicyclohexylcarbodiimide (DCC) (0.72 g, 3.5 mmol) was added and the mixture was stirred at room temperature for 5 hours. *N,N'*-Dicyclohexylurea formed in the reaction was removed by filtration, the dichloromethane solution was washed with dilute sodium bicarbonate solution and water. The dichloromethane layer was dried with sodium sulfate and the solvent was evaporated to yield compound **6** as yellow needles. The yield after recrystallization from 2-propanol was 0.6 g (64 %), mp 227-228 °C. ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.48 (s, 3H, 1-CH_3), 2.50 (s, 3H, 7-CH_3), 6.57 (d, *J* = 7.7 Hz, 2H, C2'-H and C6'-H), 6.81 (t, *J* = 7.4 Hz, 1H, C4'-H), 6.88 (s, 1H, C4-H), 7.11-7.19 (m, 3H, C3'-H, C5'-H, C6-H), 7.36 (s, 1H, 8-H), 7.91 (d, *J* = 7.9 Hz, 1H, 5-H), 9.04 (s, 1H, NH). ^{13}C nmr (DMSO-d_6; 75 MHz): δ 12.55, 21.64, 102.92, 111.96, 112.73, 119.02, 120.18, 123.32, 124.52, 128.95, 132.51, 138.12, 138.33, 142.67, 147.60, 159.25, 160.03. ms: m/z 304 (M^+, 100%).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.09; H, 5.22; N, 9.29.

Ethyl 2-Acetyl-6-methyl-3-benzo[*b*]furylacetate (**7**).

2-Acetyl-6-methylbenzo[*b*]furan-3-acetic acid **1a** (2.3 g 10 mmol) was dissolved in triethyl orthoformate (10 ml) and the mixture was refluxed for 3 hours. Evaporation of triethyl orthoformate *in vacuo* gave a white solid, which was recrystallized from cyclohexane to yield compound **7** (1.0 g, 40 %), mp 73–74 °C. ^{1}H nmr (DMSO-d_6, 500 MHz): δ 1.21 (t, *J* = 7.0 Hz, 3H, CH_3), 2.50 (s, 3H, 6-CH_3), 2.56 (s, 3H, CH_3), 4.10 (q, 2H, *J* = 7.0 Hz, CH_2CH_3), 4.13 (s, 2H, CH_2), 7.20 (d, *J* = 8.1 Hz, 1H, C5-H), 7.48 (s, 1H, C7-H), 7.67 (d, 1H, *J* = 8.1 Hz, C4-H). ^{1}H nmr ($CDCl_3$, 300 MHz): δ 1.25 (t, *J* = 7.1 Hz, 3H, CH_3), 2.50 (s, 3H, 6-CH_3), 2.61 (s, 3H, CH_3), 4.16 (s, 2H, CH_2), 4.18 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 7.14 (d, *J* = 8.1 Hz, 1H, C5-H), 7.32 (s, 1H, C7-H), 7.51 (d, 1H, *J* = 8.1 Hz, C4-H). ^{13}C nmr ($CDCl_3$, 75 MHz): δ 14.19, 22.03, 27.59, 30.10, 61.10, 112.22, 120.26, 121.13, 125.40, 126.02, 139.16, 148.40, 154.52, 169.98, 191.30.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.13; H, 6.31.

[2-(1-Hydrazono-ethyl)-6-methylbenzo[*b*]furan-3-yl]acetic Acid Hydrazide (**8**).

To a solution of **7** (1.0 g, 3.8 mmol) in 2-propanol (30 ml) was added 0.2 ml 80 % hydrazine and the mixture was refluxed for 1 hour. After cooling, water was added (100 ml) and the precipitate was collected by filtration, washed with water and recrystallized from 2-propanol to yield compound **8** (0.51 g, 47 %), mp 174–176 °C. ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.08 (s, 3H, 6-CH_3), 2.39 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 4.14 (s, 2H, C=NNH_2), 6.75 (s, 2H, NH_2), 7.04 (d, *J* = 7.9 Hz, 1H, C5-H), 7.30 (s, 1H, C7-H), 7.40 (d, *J* = 7.9 Hz, 1H, C4-H), 8.91 (s, 1H, NH). ^{13}C nmr (DMSO-d_6, 75 MHz): δ 11.65, 21.17, 29.81, 30.97, 108.98, 110.71, 119.37, 123.86, 127.30, 133.77, 136.31, 150.56, 152.71, 169.20.

Anal. Calcd. for $C_{13}H_{16}N_4O_2$: C, 59.99; H, 6.20; N, 21.52. Found: C, 59.86; H, 6.31; N, 21.39.

General Procedure for the Reaction of Pyrylium Perchlorates **11a-d** with Hydrazine.

To a suspension of pyrylium perchlorate **11a-d** [19,20] (10 mmol) in 2-propanol (50 ml) was added 5 ml 80 % hydrazine and the mixture was refluxed for 0.5 hour. After cooling, water was added (50 ml) and the precipitate was collected by filtration, washed with water and recrystallized from 2-propanol to afford compounds **10a-d**, respectively.

[2-(1-Hydrazono-ethyl)-6-methylbenzo[*b*]furan-3-yl]acetic Acid *N,N*-Dimethylamide (**10a**).

This compound was obtained as yellow needles, yield 81 %, mp 127-128 °C (from 2-propanol). ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.06 (s, 3H, 6-CH_3), 2.40 (s, 3H, CH_3C=N), 2.90 [s, 6H, N$(CH_3)_2$], 4.05 (s, 2H, CH_2), 6.74 (s, 2H, C=NNH_2), 7.07 (d, *J* = 8.0 Hz, 1H, C5-H), 7.30 (s, 1H, 7-H), 7.40 (d, *J* = 8.0 Hz, 1H, C4-H).

Anal. Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.83; H, 6.87; N, 15.24.

[2-(1-Hydrazono-ethyl)-6-methylbenzo[*b*]furan-3-yl]acetic Acid Morpholide (**10b**).

This compound was obtained as yellow needles, yield 89 %, mp 124–125 °C (from 2-propanol). ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.06 (s, 3H, 6-CH_3), 2.40 (s, 3H, CH_3C=N), 3.36-3.52 (m, 8H, morpholine), 4.01 (s, 2H, CH_2), 6.77 (s, 2H, C=NNH_2), 7.02 (d, *J* = 8.0 Hz, 1H, C5-H), 7.31 (s, 1H, C7-H), 7.41 (d, *J* = 8.0 Hz, 1H, C4-H).

Anal. Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C 64.83; H 6.81; N 13.24.

[2-(1-Hydrazono-ethyl)-6-methylbenzo[*b*]furan-3-yl]acetic Acid *N*-(4-Methylphenyl)amide (**10c**).

This compound was obtained as yellow needles, yield 97 %, mp 191 °C (from 2-propanol). ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.14 (s, 3H, 6-CH_3), 2.22 (s, 3H, 4'-CH_3), 2.40 (s, 3H, CH_3C=N), 3.87 (s, 2H, CH_2), 6.99 (s, 2H, NH_2), 7.07 (d, *J* = 7.8 Hz, 3H, C3'-H, C5'-H and C5-H), 7.34 (s, 1H, C7-H), 7.43 (d, 3H, *J* = 7.8 Hz, C2'-H, C6'-H and C4-H), 10.20 (1H, c, NH).

Anal. Calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.75; H, 6.22; N, 12.61.

[2-(1-Hydrazono-ethyl)-6-methylbenzo[*b*]furan-3-yl]acetic Acid *N*-(4-Chlorophenyl)amide (**10d**).

This compound was obtained as yellow needles, yield 96 %, mp 201 °C (from 2-propanol). ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.17 (s, 3H, 7-CH_3), 2.43 (s, 3H, CH_3C=N), 3.89 (s, 2H, CH_2), 6.97 (s, 2H, NH_2), 7.07 (d, *J* = 8.0 Hz, 1H, C5-H), 7.30 (d, *J* = 8.6 Hz, 2H, C2'-H and C6'-H), 7.32 (s, 1H, C7-H), 7.46 (d, *J* = 8.0 Hz, 1H, C4-H), 7.60 (d, *J* = 8.6 Hz, 2H, C3'-H and C5'-H), 10.44 (s, 1H, NH). ^{13}C nmr (DMSO-d_6, 75 MHz): δ 11.71, 21.17, 32.83, 108.78, 110.86, 119.16, 120.38, 124.13, 126.46, 127.17, 128.50, 134.07, 136.40, 137.98, 150.69, 152.76, 169.56.

Anal. Calcd. for $C_{19}H_{18}ClN_3O_2$: C, 64.14; H, 5.10; Cl, 9.96; N, 11.81. Found: C, 64.26; H, 5.03; Cl, 9.87; N, 11.73.

1,7-Dimethyl-2-amino-2*H*-benzo[4,5]furo[2,3-*c*]pyridin-3-one (**9**).

Method A.

A solution of **10a** or **10b** (5 mmol) in acetic acid (30 ml) was refluxed for 1 hour. After cooling, water was added (50 ml) and the mixture was neutralized with solution of 10 % aq. ammonia. The solid was collected by filtration, washed with water and recrystallized from 2-propanol to yield compound **9** in 92 and 91 % yields, respectively; mp 255–256 °C. ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.45 (s, 3H, 1-CH_3), 2.61 (s, 3H, 7-CH_3), 6.26 (s, 2H, NH_2), 6.82 (s, 1H, C4-H), 7.15 (d, *J* = 8.0 Hz, 1H, C6-H), 7.38 (s, 1H, C8-H), 7.89 (d, *J* = 8.0 Hz, 1H, C5-H).

^{1}H nmr (acetone-d_6, 300 MHz): δ 2.47 (s, 3H, 1-CH_3), 2.62 (s, 3H, 7-CH_3), 6.31 (s, 2H, NH_2), 6.86 (s, 1H, C4-H), 7.19 (d, *J* = 7.8 Hz, 1H, C6-H), 7.43 (s, 1H, C8-H), 7.94 (d, *J* = 7.8 Hz, 1H, C5-H). ^{13}C nmr (acetone-d_6, 75 MHz): 12.74, 21.55, 99.24, 111.70, 119.28, 122.81, 124.34, 129.58, 134.43, 138.10, 141.55, 158.10, 158.36.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.32; H, 5.19; N, 12.39.

Method B.

The same product **9** was obtained by reflux of compound **8** in ethylene glycol for 2 hours; yield 90 %.

Method C.

A solution of **10c** or **10d** (5 mmol) in trifluoroacetic acid (30 ml) was heated at reflux for 1 hour and then evaporated *in vacuo*. After cooling, water was added (50 ml) and the mixture was neutralized with of 10 % aqueous ammonia. The solid was collected by filtrationered, off, washed with water and recrystallized from 2-propanol to afford compound **9** in 86 or 89 % yields, respectively.

(6-Methyl-3-(*p*-tolylcarbamoyl-methyl)benzo[*b*]furan-2-yl)-methyl Kketone Aazine (**12a**).

Compound **12a** was prepared from compound **10c** similarly to method A described above method A for compound **9**, as yellow crystals; yield 98 %, mp 306-307 °C (from *N,N*-dimethylformamide). ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.23 (s, 3H, 4'-CH_3), 2.42 (s, 3H, 6-CH_3), 2.46 (s, 3H, CH_3C=N), 4.24 (s, 2H, CH_2CO), 7.00 (d, *J* = 8.2 Hz, 2H, C3' and C5'-H), 7.14 (d, *J*= 8.0 Hz, 1H, C5-H), 7.31 (s, 1H, C7-H), 7.39 (d, 2H, C2'-H, C6'-H), 7.60 (d, *J* = 8.0 Hz, 1H, C4-H), 9.75 (s, 1H, NH).

Anal. Calcd. for $C_{40}H_{38}N_4O_4$: C, 75.21; H, 6.00; N, 8.77. Found: C, 75.11; H, 5.89; N, 8.91.

(6-Methyl-3-(*p*-chlorophenylcarbamoyl-methyl)benzo[*b*]furan-2-yl)methyl Ketone Azine (**12b**).

Compound **12b** was prepared from compound **10d** similarly to method A described above for compound **9**, as yellow crystals;

yield 97 %, mp 326–327 °C (*N,N*-dimethylformamide). ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.37 (s, 3H, 6-CH_3), 2.45 (s, 3H, CH_3C=N), 4.26 (s, 2H, CH_2), 7.14 (d, *J* = 8.0 Hz, 1H, C5-H), 7.33 (d, *J* = 8.0 Hz, 2H, C2'-H, C6'-H), 7.45 (s, 1H, C7-H), 7.58-7.64 (m, 3H, C3'-H, C5'-H, C4-H), 10.29 (s, 1H, NH). ^{13}C nmr (DMSO-d_6, 100 °C, 75 MHz): δ 12.43, 21.83, 33.58, 111.96, 116.01, 121.02, 121.84, 125.39, 127.75, 127.96, 129.12, 136.94, 138.79, 150.01, 154.73, 156.24, 168.54.

Anal. Calcd. for $C_{38}H_{32}Cl_2N_4O_4$: C, 67.16, H, 4.75, Cl, 10.43, N, 8.24. Found: C, 67.04, H, 4.88, Cl, 10.32, N, 8.33.

2-{2-[1-(Acetylhydrazono)-ethyl]-6-methylbenzo[*b*]furan-3-yl}-*N*-*p*-tolylacetamide (**13a**).

To a solution of **10c** (1.0 g, 3 mmol) in dioxane (25 ml) acetic anhydride (0.2 g, 4 mmol) was added and the mixture was heated at reflux for 1 h. After cooling, the solid was collected by filtration, washed with cold dioxane to afford compound **13a** (1.0 g, 89 %) as yellow needles, mp 288–289 °C. ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.20 (s, 6H, 4'-and 6-CH_3,), 2.38 (s, 3H, CH_3C=N), 2.43 (s, 3H, CH_3CO), 3.91 (s, 2H, CH_2CO), 7.02 (d, 2H, *J* = 8.0 Hz, C3'-H, C5'-H), 7.17 (d, 1H, *J* = 8.0 Hz, 5-H), 7.43 (s, 1H, C7-H), 7.45 (d, 2H, *J* = 8.0 Hz, C2'-H, C6'-H), 7.70 (d, 1H, *J* = 8.0 Hz, C4-H), 10.21 (s, 1H, CONHAr), 11.07 (s, 1H, CONHN=).

Anal. Calcd. for $C_{22}H_{23}N_3O_3$: C, 70.01, H, 6.14, N, 11.13. Found: C, 70.14, H, 6.25, N, 11.02.

2-{2-[1-(Acetylhydrazono)-ethyl]-6-methylbenzo[*b*]furan-3-yl}-*N*-*p*-chlorophenylacetamide (**13b**).

Compound **13b** was prepared from compound **10d** in a similar way to that described above for compound **13a**, in 89 % yield as colorless needles, mp 289-290 °C (from *N,N*-dimethylformamide). ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.19 (s, 3H, 6-CH_3,), 2.38 (s, 3H, CH_3C=N), 2.45 (s, 3H, CH_3CO), 3.90 (s, 2H, CH_2CO), 7.13 (d, 1H, *J* = 7.6 Hz, C5-H), 7.19 (d, 2H, *J* = 8.0 Hz, C2'-H and C6'-H), 7.32 (s, 1H, C7-H), 7.60 (d, 2H, *J* = 8.0 Hz, C3'-H and C5'-H), 7.69 (d, 1H, *J* = 7.6 Hz, C4-H), 10.32 (s, 1H, CONHAr), 11.03 c (s, 1H, CONHN=).

Anal. Calcd. for $C_{21}H_{20}ClN_3O_3$: C, 63.40, H, 5.07, Cl, 8.91, N, 10.56. Found: C, 63.29, H, 4.91, Cl, 9.02, N, 10.67.

1,7-Dimethyl-2-acetylamino-*2H*-benzo[4,5]furo[2,3-*c*]pyridin-3-one (**14**).

A solution of **13a** or **13b** (1 mmol) in trifluoroacetic acid (30 ml) was heated at reflux for 1 h and then evaporated *in vacuo*. After cooling, water was added (50 ml) and the mixture was neutralized with solution of 10 % aqueous ammonia. The precipitate was collected by filtration, washed with water and recrystallized from 2-propanol to yield compound **14** in 93 and 91 % yields, respectively, mp. 253–254 °C. ^{1}H nmr (DMSO-d_6, 500 MHz): δ 2.09 (s, 3H, 1-CH_3), 2.37 (s, 3H, 7-CH_3), 2.45 (s, 3H, $COCH_3$), 6.88 (s, 1H, C4-H), 7.17 (d, 1H, *J* = 8.0 Hz, C6-H), 7.39 (s, 1H, C8-H), 7.94 (d, 1H, *J* = 8.0 Hz, C5-H), 10.90 (s, 1H, NH). ^{13}C nmr (DMSO-d_6, 75 MHz): δ 12.33, 20.51, 21.63, 102.59, 11.93, 118.81, 123.33, 124.54, 131.45, 138.10, 138.54, 142.88, 159.11, 159.26, 169.65.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.78; H, 10.47

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