Carboxamido-substituted imidazoles from 1,2,3-tricarbonyl derivatives and acetamido-substituted thiazoles from 4-bromo-3-oxo-butanenitriles

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Abstract
Carboxamido-substituted imidazoles obtained from 1,2,3-tricarbonyl compounds and acetamido-substituted thiazoles from 4-bromo-3-oxo-butanenitriles are described.

Keywords: Imidazoles, thiazoles

Introduction

Imidazoles are common compounds which frequently possess therapeutic properties, a variety of which can be found in the Merck Index.[1] In particular Cefpimazole[2] and Dacarbazine[3] are closely related to the substituted imidazoles discussed herein. In the course of investigations dealing with inhibitors of the reverse transcriptase of HIV, we reported[4] on compounds having imidazole rings substituted with a carboxamido functionality, analogs of compound **1** (Figure 1), that were prepared using the Bredereck reaction of α-bromoketones with formamide.[5] In general carboxamido functional groups on an imidazole ring have been prepared by hydration of a nitrile substituent[6] or by conversion of an ester into the corresponding amide.[7] Herein we describe an approach for the preparation carboxamido-substituted imidazoles, involving a three-step sequence from 1,2,3-tricarbonyl reagents.

The initial targets of the reverse transcriptase inhibitors were compounds having an imidazole ring linked directly to a phenyl ring and hence expected to assume a relatively rigid planar conformation as a result of conjugation. Molecular modeling calculations suggested a tricyclic scaffold having a central phenylene ring substituted at the meta positions (**1**), however the calculations did not firmly establish the preferred distance linking the aromatic rings.[4] To study compounds possessing a greater degree of flexibility and rotational freedom we aimed for analogs where the substituents on the phenylene **B** ring were distanced by one carbon atom (see **2**, Figure 1). An additional goal of these studies was to synthesize isosteres of the imidazole ring, such as thiazoles, aminoimidazoles and aminothiazoles.

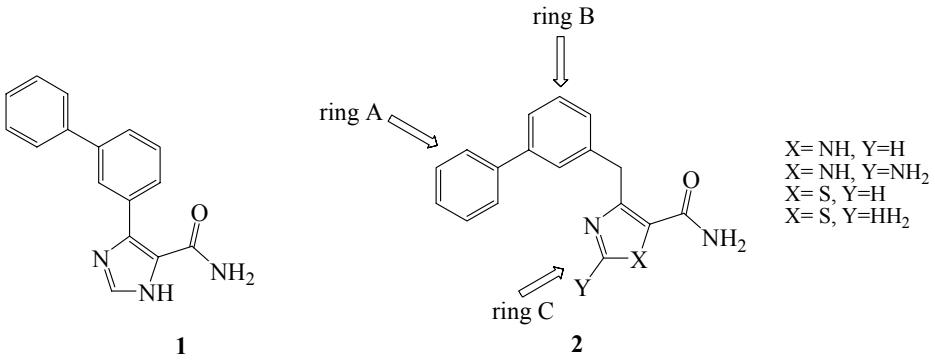
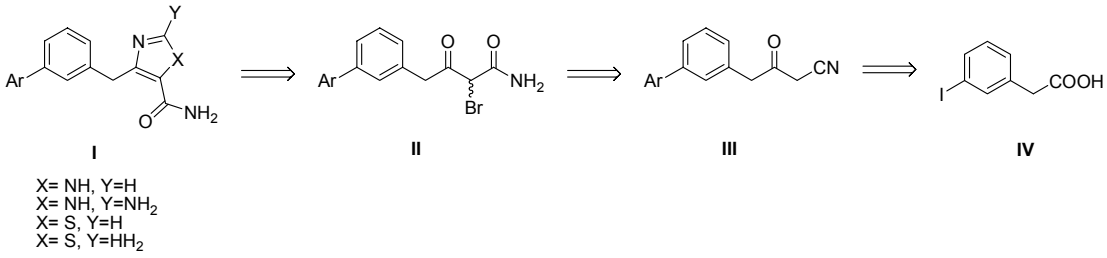


Figure 1. Tricyclic carboxamido substituted imidazoles.

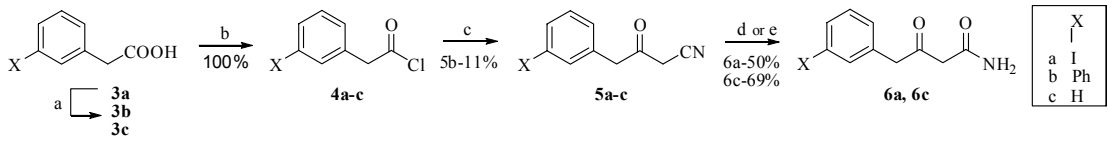
In the retrosynthetic analysis compound **I** was expected to be generated by the Bredereck method from the corresponding α-bromoketone **II** and formamide. The ketone **II** in turn would be the product of nitrile hydration of **III** followed by enol-bromination. Compound **III** was to be prepared in two steps involving condensation of the di-anion of cyanoacetic acid with a suitably activated *meta*-substituted-phenylacetic acid and attachment of the **A** aryl group (see Fig. 1) by a Suzuki-coupling reaction (Scheme 1).



Scheme 1. Retrosynthetic analysis.

Results and Discussion

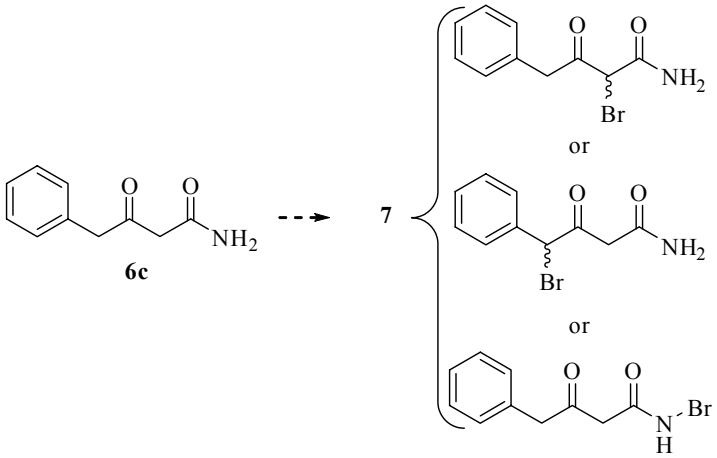
3-Iodophenylacetyl chloride **4**[4]obtained from the acid **3a** was treated with cyanoacetic acid in the presence of n-BuLi to give the cynaomethyl ketone **5a**[4] which upon hydration in the presence of H_2SO_4 (conc.) gave amide **6a**, in about 18% yield. It is conceivable that the organic matter which remained in the aqueous solution was derived from aromatic sulfonation.[8] However hydration of **5a** in the presence of PPA (polyphosphoric acid) led to **6a** in 50% yield. Analogous manipulations were carried out with the *m*-H and *m*-Ph substituted compounds (Scheme 2).



a) $PhB(OH)_2$, H_2O, NaOH, $Pd(OAc)_2$; b) oxalyl chloride, DMF (cat.), CH_2Cl_2; ;c) cyanoacetic acid, n-BuLi, THF, -78 °C, H_2O; d) H_2SO_4; e) PPA, 120 °C

Scheme 2. Synthesis of β-ketoamides.

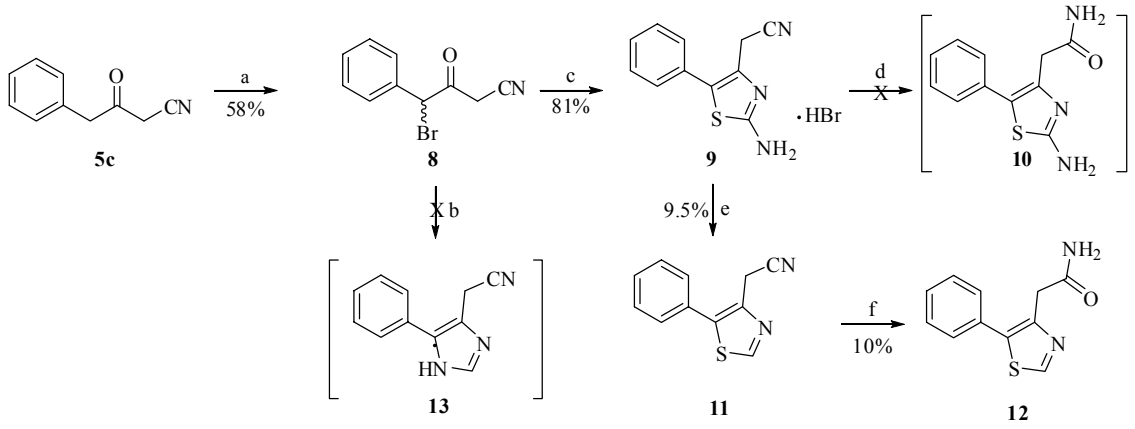
In 3-oxo-4-phenylbutanamides **6**[9] both methylenes are potentially reactive towards bromination, one because it is benzylic and the other because it is part of a β-dicarbonyl system. To determine the position at which the bromination step would take place, **6c** was used as a model. When bromination was carried out in the presence of one equivalent of $CuBr_2$, after 1 h, a major product was detected by tlc mixed with a minor amount of starting material, however all attempts to isolate any product(s) **7** of the reaction failed presumably because of their expected high reactivity (Scheme 3).



Scheme 3. Possible reactive products of β-ketoamide bromination.

In view of the failure to brominate **6c**, the reaction was repeated with the cyanomethyl ketone **5c**[10] where the hydration step was delayed to a later stage. In this case the bromination took place at the benzylic position to give compound **8**, apparently, due to a preferred enol formed in conjugation with the aromatic ring. Although **8** was the undesired brominated isomer, it was further used in the preparation of compounds **9**, **11** and **12** (Scheme 4) isomeric to our target compounds (see Figure 2) and which could assist in structure activity relationship (SAR) studies. Compound **9** was readily prepared by reaction with thiourea, however, attempted hydration of the nitrile group in the presence of hydrogen peroxide and base to give **10**, failed. Deamination of the amino-thiazole group in the presence of sulfuric acid/$NaNO_2$, gave the thiazole **11**, without any sign of nitrile hydration which could have conceivably taken place when **9** was initially

exposed to the aqueous sulfuric acid. Subsequent exposure of **11** to hydration conditions in concentrated H_2SO_4 gave amide **12**. Attempted conversion of **8** into imidazole **13** under Bredereck reaction conditions failed.



a) $CuBr_2$, EtOAc, reflux; b) formamide or formamide/H_2SO_4 (cat.), 160 oC; c) thiourea, EtOH; d) H_2O_2 30%, NH_4OH/MeOH; e) H_2SO_4 40%, $NaNO_2$, H_2O, $Ca(H_2PO_2)_2/H_2O$, 0 °C; f) H_2SO_4 (conc.)

Scheme 4. Thiazoles from β-ketonitriles.

In view of our inability to prepare the target imidazoles by the Bredereck reaction, an alternative approach was undertaken. The synthesis of imidazoles from 1,2-dicarbonyl compounds is well known.[11] Since in our case the final imidazolic compound is substituted by an amide group, it was necessary to initiate the synthesis with the contiguous hydrated tricarbonyl derivative **17a.** When this compound was allowed to stand overnight in an acetone-d_6 solution it dehydrated and was detected in the NMR as the corresponding enol **18a.** The synthesis of the tricarbonyl system (hydrated or dehydrated) required only two steps, and was initially carried out with benzaldehyde **14a** as a model compound. The two first steps, **14→17** are known[12] and both proceeded in ~90% yields. The first one involved a condensation between glyoxal, cyanide and benzaldehyde followed by mild hydrolysis using acidic amberlite leading to the tricarbonyl species **17a-18a**. The structure of intermediate **15b** was established by extensive NMR experiments including Cosy, HMQC and HMBC. We think that the structure of the heterocycle in compound **15b** is unambiguously determined by the carbon chemical shifts and by the CH correlations observed in the HMBC two-dimensional spectrum (typically 2- and 3-bond coupling interactions may be detected), as shown in Fig. 2. In the Figure, the interactions are shown as C→H. Notice that cross-peak between the ***C***-NH_2 and the ring C***H*** indicates that a cycle has indeed been formed.

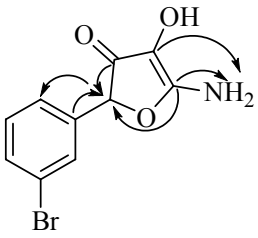
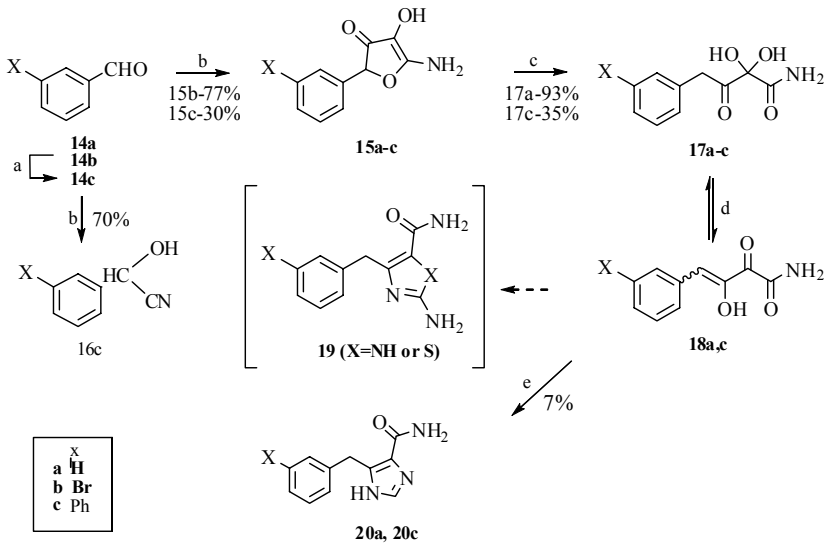


Figure 2. CH correlations observed in the HMBC.

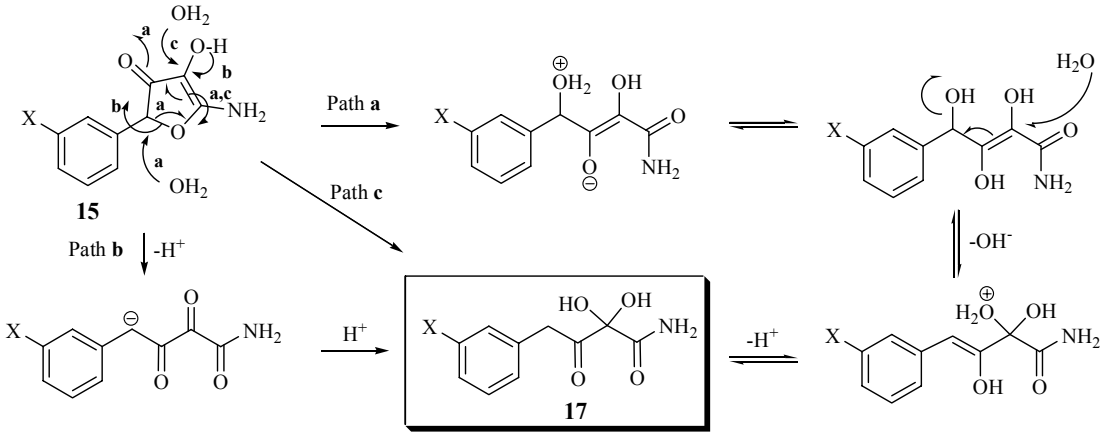
Although the reported[13] treatment of 1,2-dicarbonyl compounds with guanidine leads to aminoimidazoles, in our case treatment of **17a-18a** with guanidinium hydrochloride, guanidine or thiourea, followed by hydrogenation using H_2/Pd or ammonium formate did not afford the aminoimidazole nor the aminothiazole **19** (Scheme 5). Treatment of **17a-18a** with hexamethylenetetramine/ammonium acetate in acetic acid at 65 ^{o}C, led to decomposition products. However, using microwave irradiation[14] or heating in an oil bath, both at 165 ^{o}C, led to the carboxamido substituted imidazole **20a.** Although the various products are structurally similar each required special synthetic conditions. For example, the *m*-phenyl-substituted **15c** was obtained in 30% yield since in this case the cyanohydrin derivative **16c**[15] also formed and was isolated in 70% yield. The reaction involved addition of cyanide to a mixture of two aldehydes, benzaldehyde and glyoxal. In the model case where benzaldehyde was used, apparently the glyoxal was more electrophilic and underwent preferential reaction with the cyanide, leading to a high yield of **15a**. Whereas in the case of the *m*-phenylbenzaldehyde **14c** which is more electrophilic than glyoxal the reaction led to the formation of the cyanohydrin **16c** and a low yield of **15c**. We assumed that pre-stirring of the glyoxal in the presence potassium cyanide without adding the 3-phenylbenzaldehyde **14c** would prevent the formation of the byproduct **16c**, but even with initial stirring (for about 0.5 h), the amount of **16c** was not reduced. Hydrolysis of **15c** even after 5 h (1.5 h in the model) gave 30% yield of **17c**-**18c** (70% in the model). The low yield was attributed to the poor aqueous solubility of **15c**. As an alternative approach to **20c**, it was considered plausible to initiate the synthesis from *m*-bromobenzaldehyde **14b** (using the halogen as a handle for a Suzuki coupling) which was converted in high yield into **16b**, however, attempts to convert the latter into the "tricarbonyl" derivative **17b-18b**, even under exhaustive hydrolytic conditions, gave a mixture of starting material **16b** together with the desired **17b-18b**.



a) Phenylboronic acid, $PdCl_2$, K_2CO_3, EtOH, Bu_4NBr; b) KCN, Na_2CO_3, glyoxal bis(sodium hydrogen sulfite), dioxane, AcOH; c) Amberlite IR 120 (H^+-form), H_2O; d) H_2O; e) hexamethylenetetramine/NH_4OAc, AcOH, microwave irradiation or165 ^oC

Scheme 5. Synthesis of carboxamido-substituted imidazoles.

Alternative pathways for the ring opening of **15** to give the hydrated tricarbonyl species **17** are shown in Scheme 6.



Scheme 6. Hydrolysis paths of 5-amino-4-hydroxy-2-phenylfuran-3(2H)-ones.

Conclusions

The synthesis of carboxamido-substituted imidazoles obtained from 1,2,3-tricarbonyl compounds and acetamido-substituted thiazoles from 4-bromo-3-oxo-butanenitriles, were developed.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra 200, 300 and 600 MHz were obtained on Bruker AC-200 and AM-300 spectrometers, respectively. Chemical shifts are expressed in ppm downfield from Me_4Si used as internal standard. The values are given in δ scale. Mass spectra were obtained on a Varian Mat 731 spectrometer (CI = chemical ionization). HRMS were obtained on a VG AutoSpec E spectrometer. Progress of the reactions was monitored by TLC on silica gel (Merck, Art. 5554) or alumina (Riedel-de Haen, Art. 37349). Flash chromatography was carried out on silica gel (Merck, Art. 9385). The microwave experiments were carried out using a Biotage Initiator EXP EU instrument, at a maximum power of 300 W/frequency 2450 MHz. Commercially available compounds were used without further purification.

4-(Biphenyl-3-yl)-3-oxobutanenitrile (5b). Compound **5b** was obtained as a white solid in 11% yield from compound **4b** using the reported general procedure for the synthesis of cyanoacetonitriles.[4] ^{1}H NMR (300 MHz, acetone-d_6): δ 4.03(s, 2H, CH_2CN), 4.05 (s, 2H, ArCH_2), 7.22-7.68 (m, 9H, Ar). ^{13}C NMR (300 MHz, acetone-d_6) δ 32.2 (CH_2CN), 49.0 (ArCH_2), 115.3 (CN), 126.4, 127.8, 128.3, 129.4, 129.65, 129.7, 129.9, 136.9, 141.6, 142.2, 197 (CO). MS (CI+) *m/z* (%): 235.10 (M^+, 19.5). HRMS: calcd. for $C_{16}H_{13}NO$ 235.0997; found 235.1007

4-(3-Iodophenyl)-3-oxobutanamide (6a). A mixture of **5a**[4] (0.12 g, 0.75 mmol) and polyphosphoric acid (PPA) (0.29 g) was heated at 110-130 ^{o}C for 1 h. The mixture was poured into ice cold water, stirred for 0.5 h, was then slowly basified with solid $NaHCO_3$ to pH~9, and finally extracted with EtOAc. The organic phase was separated, dried ($MgSO_4$), filtered and evaporated to give **6a** as a mixture of ketone and enol forms (1:1.9), as a yellow solid in 50% yield. The NMR data assignment was aided by several two-dimensional spectra including COSY, HMQC and HMBC analysis. ^{1}H NMR (600 MHz, acetone-d_6): δ 7.93-8.00 (m, 2H, *H*-C2 (ket), *H*-C6 (ket)), 7.74-7.76 (m, 1H, *H*-C2 (enol)), 7.69-7.72 (dt, 1H, *J* = 6.9; 2.1 Hz, *H*-C6 (enol)), 7.63-7.67 (ddd, 1H, *J* = 8.1; 2.1; 1.2 Hz, *H*-C4 (ket)), 7.58-7.53 (t, 1H, *J* = 7.8Hz, *H*-C5 (ket)), 7.49-7.44 (m, 2H, *H*-C4 (enol), *H*-C5 (enol)), 7.12 (bs, 1H, *NH* (ket/enol)), 6.68-6.52 (bs, 1H, *NH* (ket/enol)), 5.9 (s, 1H, *CH* (enol)), 3.96 (s, 2H, CH_2 (ket)). ^{13}C NMR (600 MHz, acetone-d_6): δ 194.12 (*CO*(ket)), 175.47 (*CON* (ket)), 169.02 (*CON*(enol)), 139.52 (C1 (ket)), 137.55 (C1 (enol)), 135.12 (C3 (ket)), 134.99 (C3 (enol)), 133.77 (C4 (ket)), 131.26 (C2 (ket)), 131.18 (C4 (enol)), 131.13 (C2 (enol)), 129.1 (C6 (ket)), 127.94 (C5(ket)), 126.2 (C6 (enol)),

124.78 (C5 (enol)), 89.73 (*CH* (enol)), 47.42 (*CH*$_2$ (ket)). MS (CI+) *m/z* (%): 197.03; 198.03 (M^+, 100; 85). HRMS: calcd. for $C_9H_8NO_2Cl$ (M^+, CI+) 197.024; found 197.027.

3-Oxo-4-phenylbutanamide (6c).[9] Using the same procedure as that used in the synthesis of **6b**, compound **6c** was obtained in 69% yield as a cream colored solid from **5c**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (s, 2H, *CH*$_2$CONH$_2$), 3.72 (s, 2H, Ar*CH*$_2$), 5.83 (bs, 1H, *NH*), 6.89 (bs, 1H, *NH*), 7.13 (m, 5H, Ar). ^{13}C NMR (300 MHz, $CDCl_3$): δ 47.92, 50.96 (*CH*$_2$CONH$_2$ and Ar*CH*$_2$), 127.73 (C-4), 129.16, 129.73 (C-2 and C-3), 131.98 (C1), 168.26 ($CONH_2$), 204.15 (CO). MS (CI+) *m/z* (%): 177.08 (M^+, 15), 118.04 ($BnCO^+$, 37.15). HRMS: calcd. for $C_{10}H_{11}NO_2$ 177.0790; found 177.0756.

4-Bromo-3-oxo-4-phenylbutanenitrile (8). A mixture of **5c**[10] (0.14 g, 0.85 mmol) and $CuBr_2$ (0.2 g, 0.85 mmol) in anhydrous EtOAc (20 mL) was heated to reflux for 3.5 h. The mixture was cooled and filtered through a short silica column. The filtrate was evaporated and the residue was purified by flash chromatography (hexane:EtOAc 3:1) to give **8** as a yellow oil in 58% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (ABq, *J* = 14Hz, 2H, *CH*$_2$CN), 5.6 (s, 2H, *CH*Br), 7.41 (m, 5H, Ar). ^{13}C NMR (300 MHz, $CDCl_3$): δ 28.9 (*CH*$_2$), 53.4 (*C*HBr), 113.3 (CN), 128.9, 129.42 (C-*o*, C-*m*), 133.1 (*C*CHBr), 189.7 (CO). MS (CI+) *m/z* (%): 239.99 (MH^+, 16.73), 237.99 (MH^+, 16.77), 211.99 M^+ (MH^+- CN, 48.59%) 209.99 M^+ (MH^+- CN, 48.59), 170.97 ($BnBr^+$, 32.55), 168.97 ($BnBr^+$, 33.67). HRMS: calcd. for $C_{12}H_9NO^{81}Br$ 239.9847; found 239.9855, calcd. for $C_{12}H_9NO^{79}Br$ 237.9868; found 237.9871

2-(2-Amino-5-phenylthiazol-4-yl)acetonitrile hydrobromide (9). Compound **9** was obtained as a white solid in 81% yield from **8** (0.04 g, 0.16 mmol) using the reported general procedure for the synthesis of aminothiazoles,[4] mp (dec.) 207-209 °C. The NMR data assignment was aided by several two-dimensional spectra including COSY, HMQC and HMBC analysis. ^{1}H NMR (600 MHz, CD_3OD): δ 3.93 (s, 2H, C*H*$_2$), 7.47 (m, 2H, *H-o*), 7.54 (m, 3H, *H-m, H-p*). ^{13}C NMR (600 MHz, CD_3OD): δ 16.5 (*C*H$_2$), 116.0 (*C*N), 123.89(*C*S), 125.15 (*C*CH$_2$), 128.8 (*C* ipso to the aminothiazole), 130.22 (*C-m*), 130.74 (*C-o*), 131.22 (*C-p*), 170.47 (*C*NH$_2$). MS (CI+) *m/z* (%): 215.05 (MH^+, 100). HRMS: calcd. for $C_{11}H_9N_3S$ 215.0517; found 215.0519.

2-(5-Phenylthiazol-4-yl)acetonitrile (11). Compound **11** was obtained as a colorless oil in 9.5% yield from compound **9** (0.45 g, 1.5 mmol) using the reported general procedure for the synthesis of thiazoles.[4] ^{1}H NMR (300 MHz, acetone-*d*$_6$): δ 4.09 (s, 2H, C*H*$_2$), 7.54 (m, 5H, *H*-aromatic), 9.04 (s, 1H, *H*-thiazole). ^{13}C NMR (200 MHz, CD_3OD): δ 19.2 (*C*H$_2$), 117.8 (*C*N), 129.09 130.07, 130.09 (*C*-o, *C-m C-p*), 131.1, 135.9, 142.1 (*C*S, *C*CH$_2$, *C* ipso to the aminothiazole), 153.3 (*C*H thiazole). MS (CI+) *m/z* (%): 201.05 (MH^+, 100). HRMS: calcd. for $C_{11}H_9N_2S$ 201.0486; found 201.0456.

2-(5-Phenylthiazol-4-yl)acetamide (12). A solution of compound **11** (0.03 g, 0.15 mmol) in conc. H_2SO_4 was stirred at room temperature for 2 h. To the solution was added EtOAc and concentrated ammonia was added dropwise till pH~10. the organic phase was separated, dried ($MgSO_4$), filtered and evaporated, to give **12** obtained as a white solid in 10% yield, mp 209-211 °C. ^{1}H NMR (300 MHz, acetone-*d*$_6$): δ 3.70 (s, 2H, C*H*$_2$), 6.45 (bs, 1H, N*H*), 6.97 (bs, 1H, N*H*), 6.74(m, 3H, H-*m*, H-*p*), 7.66(m, 2H, H-*o*), 8.95 (s, 1H, *H*-thiazole). ^{13}C NMR (300 MHz,

CD_3OD): δ 37.51 (*C*H_2), 129.2 (*C*-*p*), 127.7, 130.3, (*C*-o, *C*-*m*), 132.2, 135.2, 147.5 (*C*S, *C*CH_2, *C* ipso to the aminothiazole), 152.3 (*C*H thiazole), 171.75 ($CONH_2$). MS (CI+) *m/z* (%): 219.05 (MH^+, 70), 202.03 (M^+-NH_3, 42.6) 175.33 (M^+-$CONH_3$, 65.5). HRMS: calcd. for $C_{11}H_{11}N_2OS$ 219.059; found 219.054.

5-Amino-4-hydroxy-2-phenylfuran-3(2H)-one, (15a).[12] ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.37 (s, 1H, *H*C-CO), 7.34 (m, 5H, *H*-aromatic), 7.8 (bs, 2H, NH_2). ^{13}C NMR (200 MHz, DMSO-d_6) δ 82.6 (*C*H-O), 111.5 (*C*(OH)), 126.35 (C-*o*), 128.1 (C-*p*), 128.2 (C-*m*), 138.2 (C-ipso), 172.5 ($CONH_2$), 182.5 (*C*O ketone).

5-Amino-2-(3-bromophenyl)-4-hydroxyfuran-3(2H)-one (15b): Compound **15b** was obtained as a white solid in 77% yield from compound **14b** as described,[12] mp 176-178 °C. The NMR data assignment was aided by several two-dimensional spectra including COSY, HMQC and HMBC analysis. ^{1}H NMR (600 MHz, DMSO-d_6): δ 5.44 (s, 1H, *H*C-CO), 7.27 (s, 1H, O*H*), 7.28 (d, *J* = 7.8 Hz, 1H, *H*-6), 7.36 (t, *J* = 7.8Hz, 1H, *H*-5), 7.43 (s, 1H, *H*-2), 7.54 (d, *J* = 7.8 Hz, 1H, *H*-4), 7.82 (bs, 2H, NH_2). ^{13}C NMR (600 MHz, DMSO-d_6): δ 81.9 (*C*H-O), 111.2 (*C*(OH)), 121.5 (*C*Br), 125.2 (*C*-6), 128.6 (C-2), 130.7 (C-5), 130.9 (C-4), 138.9 (*C*-CH-O), 172.7 (CNH_2) 182.0 (*C*O ketone). MS (CI+) *m/z* (%): 270.97 (M^+, 31.6), 268.97 (M^+, 32.5), 197.96 (M^+-CO, 66.9), 195.08 (M^+-CO, 66.8), 170.97 ($BrBn^+$, 37.2), 168.97 ($BrBn^+$, 39.6). HRMS: calcd. for $C_{13}H_6NOBr$ 270.963; found 270.967.

5-Amino-2-(biphenyl-3-yl)-4-hydroxyfuran-3(2H)-one (15c). Compound **15c** was obtained in 30% yield from **14c,** as described,[12] mp 164-166 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.47 (s, 1H, *H*C-CO), 7.40 (m, 1H, H-*p*), 7.48 (m, 3H, H-*m*, H-5), 7.54 (s, 1-H, H-2), 7.64 (m, 3H, H-*o*, H-4), 7.86 (bs 2H, N*H*$_2$). ^{13}C NMR (300 MHz, $CDCl_3$): δ 82.5 (*C*H-O), 111.5 (*C*OH), 124.8, 125.3, 126.5, 126.7, 127.6, 129.05, 129.09, (*C*H aromatic), 138.0 (C-ipso CH), 139.9, 140.3 (C-ipso biphenyl, C-ipso biphenyl) 172.7 ($CONH_2$), 182.5 (*C*O ketone). MS (CI+) *m/z* (%): 267.09 (MH^+, 0.63), 250.08 (MH^+-H_2O, 0.42). HRMS: calcd. for $C_{10}H_{11}NO_2$ 267.0900; found 267.092.

2-(Biphenyl-3-yl)-2-hydroxyacetonitrile (16c).[15] Compound **16c** was obtained as a byproduct in the course of the synthesis of **15c** upon exposure of m-phenylbenzaldehyde to aqueous KCN in the presence of Na_2CO_3, glyoxal bis-(sodium hydrogen sulfate), dioxane and AcOH. After precipitation of **15c**, the aqueous solution was extracted with EtOAc. The organic phase was separated, dried ($MgSO_4$), filtered, evaporated and the residue was purified by flash chromatography to give **16c** as a yellow oil in 70% yield. The NMR data assignment was aided by several two-dimensional spectra including COSY, HMQC and HMBC analysis. ^{1}H NMR (600 MHz, acetone-d_6): δ 5.91 (s, 1H, C*H*CN), 6.20 (bs, 1H, OH) 7.38 (m, 1H, H-*p*), 7. 47 (m, 2H, H-*m*), 7.54 (t, *J* = 7.8Hz, 1H, H-5), 7.63 (dm, *J* = 7.8Hz, 1H, H-6), 7.66 (m, 1H, H-*o*), 7.68 (m, 1H, H-4), 7.91 (t, *J* = 0.9Hz, 1H, H-2). ^{13}C NMR (300 MHz, acetone-d_6): δ 63.0 (*C*CN), 120.0 (CN), 125.3 (*C*-2), 125.8 (C-6), 127.0 (C-*o*), 127.2 (C-4), 127.9 (C-*p*), 129.3 (C-*m*), 129.8 (C-5), 137.9 (C-1), 141 (C-3, C-ipso biphenyl). MS (CI+) *m/z* (%): 209.08 (M^+, 32.4), 183.06 (MH^+-HCN, 100). HRMS: calcd. for $C_{14}H_{11}NO$ 209.0841; found 209.0827.

2,2-Dihydroxy-3-oxo-4-phenylbutanamide (17a).[12] ^{13}C NMR (300 MHz, $CDCl_3$): δ 42.7 (*C*H_2), 95.4 (*C*$(OH)_2$), 127.4 (C-*p*), 128.9 (C-*m*), 130.7 (C-*o*), 135.3 (C-ipso), 172.1 ($CONH_2$),

204.3 (*C*O ketone). MS (CI+) (%): 192.067 (MH^+, 15), 174.06 (M^+-NH_3, 7.5) 147.048 (M^+-$CONH_2^+$, 100), 119.06 ($BnCO^+$, 16.3). HRMS: calcd. for $C_{10}H_{10}NO_3$ 192.066; found 192.067

4-(3-Bromophenyl)-2,2-dihydroxy-3-oxobutanamide (17b).[12] Compound **17b** was obtained as a pale white solid yield from compound **15b** as described and was found to be mixed with residual unreacted **15b**. The diagnostic ^{1}H NMR peak for 15b is the *H*C-CO found at 5.72 ppm, whereas that of the product **17b** is the CH_2 found at 4.08 ppm.

4-(Biphenyl-3-yl)-2,2-dihydroxy-3-oxobutanamide (17c).[12] Compound **17c** was obtained as a pale yellow solid in 35% yield from compound **15c** as described,[12] mp 90-92 ^{o}C. ^{1}H NMR (300 MHz, acetone-d_6): δ 4.11 (s, 2H, CH_2), 6.15 (bs, 1H, OH) 7.2 (bs, 1H, NH), 7.34 (m, 9H, *H*-aromatic, NH). ^{13}C NMR (300 MHz, CD_3OD): δ 41.4 (*C*H_2), 97.3 (*C*$(OH)_2$), 123.8, 125.4, 125.7, 127.0, 127.12, 127.15, 127.27 (*C*H-aromatic),133.3 (C-ipso to the methylene), 139.7, 137.9 (C-ipso to the biphenyl), 169.8 ($CONH_2$), 202.1 (*C*O ketone). MS (CI+) *m/z* (%): 267.09 (M-H_2O, 7.4), 212.06 (Ph-Bn-COOH, 40.6). HRMS: calcd. for $C_{16}H_{13}NO_3$ 267.090; found 267.093.

3-Hydroxy-2-oxo-4-phenylbut-3-enamide (18a).[12] Compound **18a** was obtained as a pale yellow solid in 93% yield upon evaporation of a solution of **17a** in acetone. ^{1}H NMR (300 MHz, acetone-d_6): δ 7.06 (s, 1H, enol), 7.36 (m, 3H, H-*m*, H- *p*), 7.93 (m, 2H, *o*). ^{13}C NMR (300 MHz, $CDCl_3$) δ 118.8 (*C*H enolic), 128.5 (C-*m*), 128.8 (C-*p*), 130.7 (C-*o*), 134.6 (C-ipso), 146.9 (*C*OH enolic), 165.3 ($CONH_2$), 184.6 (*C*O ketone).

4-Benzyl-1H-imidazole-5-carboxamide (20a). A solution of **17a** (0.1 g, 0.34 mmol) hexamethylenetetramine (0.1 g, 0.69 mmol), NH_4OAc (0.026 g, 0.34 mmol) in acetic acid (1.5 mL) was heated with stirring at 165 ^{o}C for 5 min under microwave irradiation conditions. The mixture was poured into a saturated aqueous NH_4OH solution cooled to 0 ^{o}C. The brown precipitate formed was filtered and the filtrate was extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and evaporated to give a brown residual oil which was purified by flash chromatography (EtOAc). Compound **20a** was isolated as white needles (crystallized from acetone) in 4% yield (microwave irradiation) or 7% yield (thermal conditions, 1 h 165 ^{o}C, using the same workup). ^{1}H NMR (600 MHz, acetone-d_6): δ 4.48 (s, 2H, CH_2), 6.28 (bs, 1H, N*H*), 7.15 (bs, 1H, NH), 7.16 (t, *J* = 7.2Hz, 1H, H-*p*), 7.25 (t, *J* = 7.2Hz, 2H, H-*m*), 7.3 (d, *J* = 7.2Hz, 2H, H-*o*), 7.50 (s, 1H, C*H*-imidazole). ^{13}C NMR (600 MHz, acetone-d_6): δ 30.3 (*C*H_2), 126.0 (*C*-*p*), 128.2 (C-*m*), 128.5 (C-*o*), 130.4 (C-*m*), 138.2 (C-ipso), 133.5 (*C*H imidazole), 133.7 (*C*$CONH_2$) 139.6 (Bn-*C*), 165.2 ($CONH_2$). MS (CI+) *m/z* (%): 202.10 (MH^+, 4), 185.068 (MH^+-NH_3, 2),159.10 (MH^+-$CONH_3$, 0.81). HRMS (MH^+): calcd. for $C_{11}H_{12}N_3O$ 202.098; found 202.097.

4-(Biphenyl-3-ylmethyl)-1H-imidazole-5-carboxamide (20c). Compound **20c** prepared from **17c-18c** was isolated as described for **20a**, as a yellow oil in 7% yield (microwave irradiation or thermal conditions) from **17c**. ^{1}H NMR (300 MHz, acetone-d_6): δ 4.50 (s, 2H, CH_2), 6.2 (bs, 1H, N*H*), 7.11 (bs, 1H, NH), 7.34 (m, 3H, H-aromatic), 7.42 (m, 3H, H-aromatic), 7.51 (s, 1H, C*H*-imidazole), 7.62 (m, 3H, H-aromatic). ^{13}C NMR (300 MHz, acetone-d_6): δ 31.3 (*C*H_2), 125.6, 127.7, 128.10, 128.16, 128.56, 129.63, 129.77 (*C*H-aromatic) 134.33, 134.55 (*C*$CONH_2$, CH-imidazole). At the concentration of the sample, the quaternary (*C*$CONH_2$ and *C*CH_2) were not observed.

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