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A Green One-Pot Synthesis of *vic*-Amidino (Hetero)aromatic Acids from 1,2-Dinitriles

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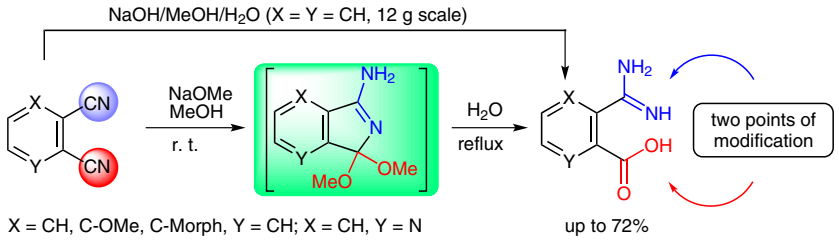

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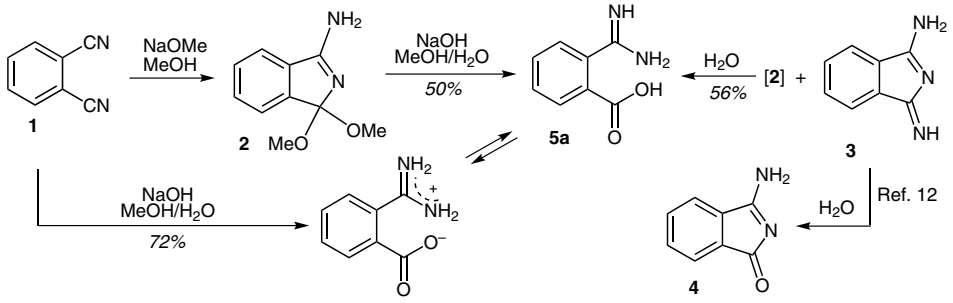
Abstract Phthalonitrile undergoes partial hydration in MeOH–H_2O media in the presence of an equimolar amount of NaOH to afford 2-carbamimidoylbenzoic acid in good yield in one step. This and similar *vic*-amidino (hetero)aromatic acids also could be synthesized from corresponding 1,2-dinitriles by hydrolysis in aqueous MeOH catalyzed by an equimolar amount of NaOH of in situ generated 1,1-dimethoxy-1*H*-isoindol-3-amine or its counterparts. Protonation of the synthesized amidino acids, esterification, and reamination of the parent amidino benzoic acid with N-nucleophiles were performed.

Key words green chemistry, phthalonitrile, partial hydration, 2-carbamimidoylaromatic acids, 3-carbamimidoyl-2-pyridinecarboxylic acid, protonation, esterification, reamination

Acids having both carboxylic and amidinic groups, namely, carbamimidoyl carboxylic acids, are mostly represented by their parent 1,3- and 1,4-isomers and a wide range of substituted derivatives that attracted attention for the first time as arginine mimics.[1] The 1,2-isomer was unknown until recently,[2] and only a very limited number of its derivatives have been described. Usually, the amidinic group is generated from a cyano group through an iminoester by the Pinner protocol,[3] and for 3- and 4-amidino benzoic acids this route can be realized successfully.[4] For 2-cyano benzoic acid/ester/amide bearing bulky substituents at benzene ring into 2-amidino acids, more drastic conditions were described.[5] Other known procedures used phthalic acid derivatives as starting compounds: amides and thioamides,[6a] halogenimides,[6b] mixed esters and amides,[6c,d] *o*-phthalaldehyde.[6e] Only very recently were alkyl 2-amidinobenzoate nitrates obtained from phthalonitrile, acetoxime and $Co(NO_3)_2{\cdot}6H_2O$ via a cobalt intermediate which was transformed into the ester on treatment with $(NH_4)_2S$ in an alcohol.[7] Substituted 2-(*N*-hydroxycarbamimidoyl)benzoic acids demonstrated fungicide[8a,b] and chemokine receptor $CXCR_3$ antagonist activity.[8c] Derivatives of 2-amidino acids with heterocyclic core are even less known. The first reported were 4-[(*N*′-hydroxycarbamimidoyl)imidazol-5-yl]carbamides,[9a] obtained from 4-cyano-5-imidazolecarbamide, and its 1-methyl derivative,[9b] later pyrazine[10a,b] and pyridine[10c] derivatives were prepared. Only one method used β,β,γ,γ-tetracyanoalkanones as aliphatic precursors for the synthesis of pyridine-based substituted amidino acids.[11]

Recently, our group reported that upon preparation of 1-imino-1*H*-isoindol-3-amine **3** by phthalonitrile ammonolysis, 2-carbamimidoylbenzoic acid (**5a**) was isolated in 23% yield.[2] The goal of the present research was to discover how acid **5a** could have formed, in order to develop a method for its preparation. Among the possible ways, a partial hydrolysis of 1-imino-1*H*-isoindol-3-amine **3** was considered by us. According to a literature report[12] it is stable in water, but upon brief boiling can be transformed into 3-imino-1*H*-isoindol-1-one tautomer **4** (Scheme 1). It is stable in water, but upon brief boiling can be transformed into 3-imino-1*H*-isoindol-1-one tautomer **4.** To confirm or contradict this hypothesis, a series of experiments under various neutral, acidic, or basic conditions at variable temperature was conducted. None of these attempts afforded the desired amidino acid **5a**.

We suggested that one of the intermediates in the synthesis of 1-imino-1*H*-isoindol-3-amine **3** – 1,1-dimethoxy-1*H*-isoindol-3-amine (**2**), but not the compound **3** itself, could undergo hydrolysis. It was synthesized by treatment of phthalonitrile with NaOMe in anhydrous MeOH on ice cooling according to a known method.[13] Upon its hydrolysis in aqueous MeOH in the presence of an equimolar amount of NaOH, the expected 2-amidinobenzoic acid **5a** was isolated as its methanol solvate (according to X-ray data) in 50% yield.



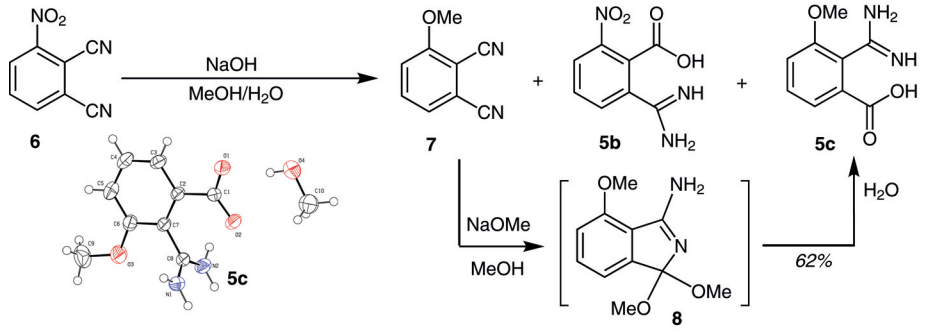
Scheme 1 Synthesis of 2-carbamimidoylbenzoic acid (**5a**)

In the developing of optimum conditions for the efficient synthesis of acid **5a**, phthalonitrile was found to be the best parent compound, and isolation of intermediate dimethoxy derivative **2** was not necessary. Phthalonitrile was easily transformed into acid **5a** upon dissolution in a mixture of MeOH and H_2O with an equimolar amount of NaOH; heating and further reflux for 15–20 minutes led to the elimination of ammonia (method A). The appearance of small colorless crystals of acid **5a** on the liquid surface directly upon cooling of the reaction mixture was evidence of its formation, and the major product **5a** crystallized as its methanol solvate in 72% yield. The yellow-orange reaction solution had a characteristic flower aroma. When necessary, it was hot filtered to remove phthalocyanine impurities before it was allowed to crystallize. Acidification of the mother liquor with AcOH to neutral pH after separation of the major product allowed for additional crystals of **5a** to be isolated, and increase the total yield to about 77%. This simple reaction and isolation procedure can be scaled up easily to give 12 grams of acid **5a**.

It was found that 1-imino-1*H*-isoindol-3-amine (**3**), upon its interaction with 0.5 equivalents of in situ generated dimethoxy derivative **2** could also be transformed into acid **5a** in 56% yield. The analytical data (^{1}H NMR, ^{13}C NMR, X-ray diffraction, mp) of the synthesized acid **5a** were in accordance with previously isolated material.[2] During the performed research it was shown that amidino acid **5a** has a zwitterionic structure both in crystal and in solution due to the formation of intermolecular hydrogen bonds that can lead to stabilization of the zwitterionic form.

A similar reaction for aromatic 1,2-dinitriles had not yet been described, so we explored its scope, firstly for substituted phthalonitriles. Thus, 3-nitrophthalonitrile **6** was subjected to the same reaction conditions (method A) but the major isolated product of the reaction was 3-methoxyphthalonitrile **7** that crystallized upon cooling from the reaction mixture in 59% yield. That was a result of nucleophilic substitution of the nitro group to the methoxy which is typical of 3- and 4-nitrophthalonitriles.[14] The filtrate was allowed to stand overnight, and additional material crystallized. It was found to be a two-component mixture in the ratio of 1:3 as judged by ^{1}H NMR spectroscopy in D_2O. LC–MS analysis led to the identification of 2-amidino-6(3)-nitro- **5b** (210 $[M + H]^+$) and 2-amidino-6(3)-methoxybenzoic acid **5c** (195 $[M + H]^+$; Scheme 2).

When pure 3-methoxyphthalonitrile **7** was introduced by method A, unreacted starting material precipitated while the reaction mixture cooled. Therefore, in order to increase the conversion of nitrile **7**, additional heating of the reaction mixture for 30 minutes was carried out after the beginning of ammonia elimination, and a single crystalline product, 2-carbamimidoyl-3-methoxy benzoic acid **5c**, was isolated in 41% yield. Its structure (as its methanol solvate) was proven by X-ray diffraction data. However, according to LC–MS of the filtrate obtained after separation of **5c**, it ap-

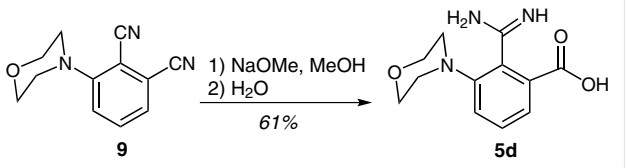


Scheme 2 Synthesis of 3-methoxy-amidinobenzoic acid **5c** and its molecular structure according to the X-ray diffraction

peared that much more complete hydrolysis of **7** was achieved and the yield of target acid **5c** decreased because of formation of 3-methoxy analogues of phthalimide, aminoisoindolone **4**, and phthalamic acid. In order to increase the yield of **5c**, 1,1,4-trimethoxy-1*H*-isoindol-3-amine (**8**) was tested as a starting compound (Scheme 2, method B). It was generated in situ from 3-methoxyphthalonitrile (**7**) by treatment with MeONa in MeOH according to the method[13] and then treated with water. The obtained suspension was refluxed for 20–25 minutes until the solution became clear and liberation of ammonia began. The colorless crystals of **5c** precipitated upon cooling in 62% yield.

The formation of the 3-methoxy isomer can be explained by the nucleophilic attack of the methoxide anion at the more electrophilic carbon atom of the nitrile group at the 1-position while the other nitrile is less electrophilic due to the donor properties of the neighboring MeO group. From this point of view, the 3-nitro group in **6** would instead promote the formation of amidino acid **5b** that was not isolated. In addition, no other isomeric acids of **5c** and **5b** were detected.

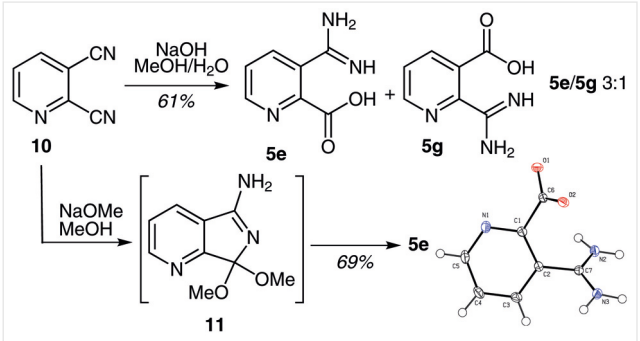
When 3-morpholino dinitrile **9**[15] was subjected to the reaction conditions by method B, the crystals of amidino acid **5d** were obtained in 61% yield (Scheme 3). Only one structural isomer was isolated, as revealed by the presence of only one set of signals in the ^{1}H NMR spectrum. Its structure was assigned as the 3-isomer based on the relative arrangement of the carboxylic and amidinic groups that is expected to be the same as in acid **5c** due to the donor character of morpholine residue.



Scheme 3 Synthesis of morpholine-substituted amidino acid **5d**

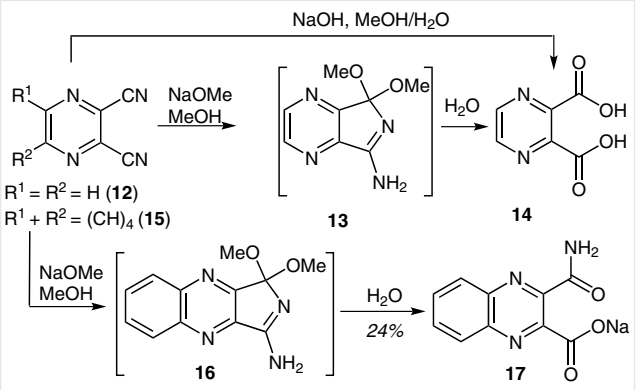
Attempts to obtain the corresponding amidino acid from benzene-1,2,4,5-tetracarbonitrile failed. In an experiment conducted according to method A, the reaction mixture turned blue-black and a precipitate which was supposed to be the corresponding phthalocyanine[16] formed immediately after heating for five minutes. By method B, the pale-rose benzene-1,2,4,5-tetracarbonitrile on treatment with MeONa in MeOH was turned into a gray suspension which after one hour stirring at room temperature and adding water was subjected to heating. Similarly to method A, the solution turned dark within five minutes and a precipitate emerged. Therefore, in the next experiment, after the addition of water the suspension was stirred without heating at room temperature for two hours before ammonia elimination began. The insoluble solid was filtered off, and the filtrate was allowed to stand for one day. Small light-cream-colored crystals were collected but they were not identified because of their insolubility in any appropriate solvent.

Some heterocyclic *vic*-dinitriles were also studied in the reaction. Refluxing of 2,3-dicyanopyridine (**10**) in an aqueous methanolic solution of NaOH was proceeded to 61% conversion and produced crystals that consisted of two compounds **5e** and **5g** in a 3:1 ratio according to the ^{1}H NMR spectrum (Scheme 4). Better results were achieved by method B when dimethoxy derivative **11** was generated in situ from dinitrile **10**. Nucleophilic attack proceeded regioselectively at the more electrophilic α-cyano group, giving rise to 3-carbamimidoylpyridine-2-carboxylic acid (**5e**) in 69% yield. No isomeric acid **5g** was isolated.

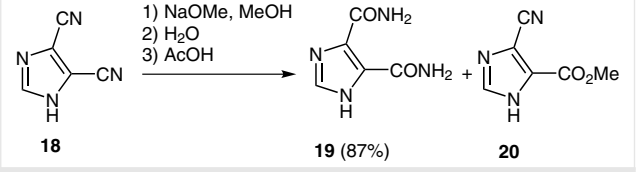


Scheme 4 Synthesis of amidino picolinic acid **5e** and its molecular structure according to X-ray diffraction

Other heterocyclic nitriles – 2,3-dicyanopyrazine (**12**), 2,3-dicyanoquinoxaline (**15**), and 4,5-dicyanoimidazole (**18**) – did not afford the expected acids under any of the applied conditions, but instead underwent hydration of one or two cyano groups (Scheme 5 and Scheme 6). Previously, pyrazine-2,3-dicarbonitrile **15** was found to react with MeOH under basic conditions to form diimino ester; its treatment with HCl afforded a diamide or an amido ester.[17a] Our attempted conversion of 2,3-dicyanopyrazine (**12**) into an amidino acid by methods A or B via in situ formed 5,5-dimethoxy-5*H*-pyrrolo[3,4-*b*]pyrazin-7-ylamine (**13**) failed, probably due to complete hydrolysis to diacid **14** which was identified by LC–MS. The hydrolysis of the individual 5,5-dimethoxy derivative **13** obtained by a literature method[17b] led to the same result. The hydrolysis of 2,3-dicyanoquinoxaline (**15**) under the conditions of method B ceased after the formation of the sodium salt of known 3-carbamoyl-2-quinoxaline carboxylic acid[17c] isolated as its crystalline hydrate **17** (Scheme 5).



Scheme 5 Hydrolysis of 2,3-dicyanopyrazine (**12**) and 2,3-dicyanoquinoxaline (**15**)



Scheme 6 Hydrolysis of 4,5-dicyanoimidazole (**18**)

After sequential treatment of 4,5-dicyanoimidazole (**18**) by method A or B, diamide **19**[18a] was identified as a major product (87% yield, Scheme 6). The latter compound was the only product of 4,5-dicyanoimidazole (**18**) hydrolysis with H_2SO_4.[18b] In one of our experiments, the methyl ester of 4-cyano-1*H*-imidazol-5-carboxylic acid (**20**)[18c] was isolated as crystals suitable for X-ray study, but in poor yield.

Similarly, when 1*H*-1,2,3-triazole-4,5-dicarbonitrile was treated according to methods A and B, hydrolysis of both cyano groups led to the formation of a mixture of 5-cyano-1*H*-1,2,3-triazole-4-carboxamide (74%) and 1*H*-1,2,3-triazole-4,5-dicarboxamide (26%, LC–MS).

Amidino acid formation via 1,1-dimethoxy-3-aminoisoindolenines or their aza analogues could be explained on the basis of pyrrole ring opening of the corresponding intermediate by nucleophilic attack of the hydroxide anion at the dimethoxy carbon followed by hydrolysis.

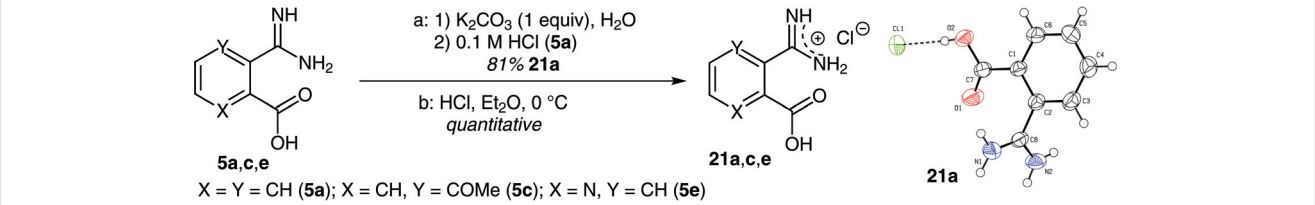
Among the alcohols used, only aqueous MeOH allowed to produce final products in preparative yields by method A. The progress of the reaction was equally well promoted by equimolar amounts of the bases NaOH and KOH. When smaller amounts of bases were used, the yields decreased due to the formation of (aza-) phthalocyanines as side products. With excess base, an acid remained in solution as the potassium or sodium salt, and could be recovered by evaporation of the solvent. Salts have a much better solubility compared to acids. Use of K_2CO_3, Na_2CO_3, or $NaHCO_3$ instead of NaOH decreased the yields of the desired products. It is interesting to note that each nitrile reaction mixture had its own specific floral scent.

Like parent amidino acid **5a**, the acids **5c–e** also exist in zwitterionic form both in crystal and in solution. Due to their (hetero)aromatic nature, they are not readily soluble in water at ambient temperature; however, they can be crystallized from water without undesirable hydrolysis. Amidino acids **5a**,**c–e** exhibit a high stability under reflux in water in a neutral medium and moderate stability in an alkaline or weakly acid medium. They readily form water-soluble salts with alkali from which they can be recovered upon acidification to the equivalence point. It should be mentioned that their low water-solubility did not allow for a full set of signals to be detected by ^{13}C NMR spectroscopy, nor for the molecular ions to be visible in LC–MS spectra.

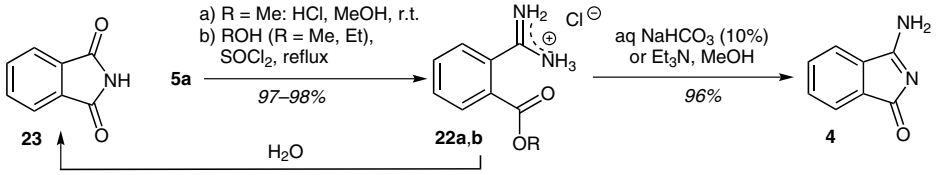
Hydrochloride **21a** was crystallized in 81% yield from an aqueous solution of the potassium salt of acid **5a**, itself generated in situ from **5a** and K_2CO_3, after addition of diluted 0.1 M HCl to adjust the slight acidic pH and slow the evaporation of the mixture at ambient temperature (Scheme 7). Hydrochlorides **21a**,**c**,**e** were readily obtained in quantitative yields by bubbling dry HCl through a stirred suspension of the powdered amidino acids **5a**,**c**,**e** in anhydrous Et_2O in an ice bath for 1–2 hours.

When Et_2O was changed to anhydrous MeOH, HCl bubbling at ambient temperature afforded methyl 2-amidinobenzoate **22a**. In anhydrous EtOH or *i*-PrOH, esterification failed, probably due to formation of insoluble hydrochloride **21a**. Nevertheless, methyl **22a** and ethyl 2-amidinobenzoate hydrochloride **22b** were successfully prepared under reflux of **5a** with excess $SOCl_2$ in methanol or ethanol (Scheme 8).

Crystalline ester hydrochlorides **22a**,**b** are stable for a long period of time, but when in contact with moisture, and especially in aqueous solution, they hydrolyze slowly to form phthalimide **23**. The latter is easily identified by ^1H NMR spectroscopic analysis of a DMSO-d_6 solution, where-



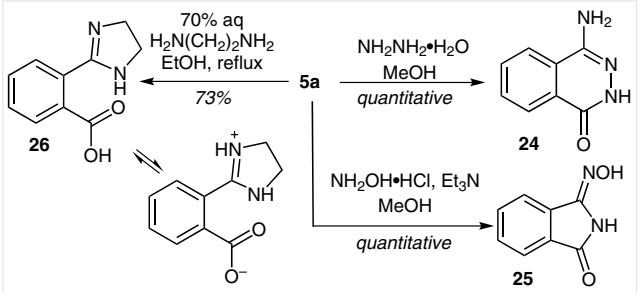
Scheme 7 Synthesis of hydrochlorides **21a**,**c**,**e** and the molecular structure of **21a** according to X-ray diffraction



Scheme 8 Esterification of **5a** and transformations of esters **22a**,**b**

in a singlet of aromatic protons at δ = 7.78 ppm is observed. Free bases are unstable: an attempted transformation of ester hydrochlorides **22a**,**b** into bases on treatment with $NaHCO_3$ or Et_3N in MeOH immediately led to intramolecular cyclization to 3-amino-1*H*-isoindol-1-one (**4**, Scheme 8) that had been synthesized earlier from 2-cyanobenzamide in 80% yield.[19] The tautomeric structure of **4** has been proven by X-ray diffraction.

Re-amination is a characteristic feature of amidines, and selected transformations of amidino acid **5a** with hydrazine hydrate, hydroxylamine, and ethylenediamine were performed (Scheme 9). Six-membered heterocyclization occurred upon interaction with hydrazine hydrate in MeOH and afforded 4-aminophthalazin-1(2*H*)-one (**24**) in quantitative yield. Its structure was confirmed by LC–MS, ^1H, ^{13}C NMR data, and comparative analysis with data of phthalazinone **24** that was known to be prepared from **4**.[20] When amidino acid **5a** was treated with hydroxylamine in MeOH, five-membered heterocyclization resulted, quantitatively, in the known 3-(hydroxyimino)-2,3-dihydro-1*H*-isoindol-1-one (**25**).[21] Heating of a suspension of **5a** in EtOH with an excess of 70% aqueous 1,2-ethylenediamine followed by acidification with 10 M HCl to neutral pH afforded 2-(4,5-dihydro-1*H*-imidazol-2-yl)benzoic acid (**26**) in 66% yield. Its water-solubility and the structure bearing protonated cyclic amidinic pattern are similar to the parent compound **5a**.



Scheme 9 Selected re-amination reactions of **5a**

In summary, a one-pot green synthesis of *vic*-amidino (hetero)aromatic acids from the corresponding 1,2-dinitriles by hydrolysis in aqueous MeOH catalyzed by equimolar amount of NaOH of in situ generated 1,1-dimethoxy-1*H*-isoindol-3-amine or its counterparts was elaborated.[22,23] This transformation appears to be a general phenomenon which provides a simple direct synthetic entry to a new type of 1,2-amidino acids from *vic*-dinitriles when the steric arrangement of cyano groups would allow the pyrrole ring closure. The crystalline amidino acids exist in zwitterionic form. This new variety of compounds has potential to be modified at both the carboxylic and the amidinic functions. Selected examples of chemical behavior of the simplest amidino benzoic acid were demonstrated: protonation, esterification, re-amination with N-nucleophiles including hydrazine hydrate, hydroxylamine, and 1,2-ethylenediamine. The bifunctional scaffolds of this type could be introduced into peptide chain to mimic an arginine turn. The studies of *vic*-amidino (hetero)aromatic acids are in progress in our laboratory and will be reported soon.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588933.

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(22) **Synthesis of Amidino Acids 5a,c–e; General Procedure**

Method A

To a solution of NaOH (0.4 g, 10 mmol) in aq MeOH (25 mL; MeOH–H_2O, 3:2) 1,2-dinitrile (10 mmol) was added, and the obtained suspension was brought to reflux with stirring. The resulting clear solution was refluxed for 15–20 min before the elimination of ammonia began. Then the hot reaction mixture, if necessary, was filtered through cotton wool in order to separate the phthalocyanine impurities. The solution was left to cool at r.t. overnight during which time well-firmed crystals were formed. The crystals were filtered off, washed with MeOH (10 mL), and dried in air. Acidification of the mother liquior with AcOH (ca. 1 mL) to neutral pH produced an additional portion of target product.

Method B

To a freshly prepared solution of MeONa obtained by dissolving sodium metal (0.23 g, 10 mmol) in MeOH (15 mL), 1,2-dinitrile (10 mmol) was added. The resulting suspension was stirred at ambient temperature until TLC showed no starting nitrile. The obtained solution or suspension was diluted with distilled water (10 mL), brought to reflux with stirring, and kept under reflux for 20–25 min before the elimination of ammonia began. The further workup was as in method A.

2-Carbamimidoylbenzoic Acid (5a)

Method A; colorless crystals of MeOH solvate (ca. 1:0.7) which lost MeOH on standing in air; yield 1.34 g (72%); mp 179–180 °C. IR (KBr): 3395, 3232, 3092, 2954, 2829, 1667, 1579, 1538, 1468, 1437, 1384 cm^{-1}. ^1H NMR of MeOH solvate (400 MHz, D_2O, 25 °C): δ = 3.32 (s, 2 H, MeOH), 7.52 (d, J = 7.6 Hz, J_m = 0.8 Hz, 1 H, H_3), 7.56 (dd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_m =1.2 Hz, 1 H, H_4), 7.63 (dd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_m =1.2 Hz, 1 H, H_5), 7.73 (d, J = 7.6 Hz, 1 H, H_6). ^1H NMR (400 MHz, D_2O, 25 °C): δ = 7.72–7.80 (m, 2 H, H_3 + H_4), 7.85 (dd, J_1 = 7.2 Hz, J_2 = 7.2 Hz, 1 H, H_5), 7.93 (d, J = 7.6 Hz, 1 H, H_6). ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 171.3 (COOH), 166.9 (C(NH_2)=NH), 135.2 (C1), 129.8, 127.7, 126.7, 125.8 (C2), 125.7. Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.24; H, 4.99; N, 17.38.

2-Carbamimidoyl-3-methoxybenzoic Acid (5c)

Method B; colorless crystals of MeOH solvate (ca. 1:1); yield 1.40 g (62%); mp 190–191 °C (subl.). IR (KBr): 3338, 3069, 1686, 1615, 1579, 1522, 1466, 1432, 1377 cm^{-1}. ^1H NMR (400 MHz, D_2O, 25 °C): δ = 3.33 (s, 3 H, CH_3OH), 3.89 (s, 3 H, OCH_3), 7.25 (d, J = 8.4 Hz, 1 H, H_{Ar}), 7.36 (d, J = 8.0 Hz, 1 H, H_{Ar}), 7.58 (dd, J_1 = 8.0 Hz, J_2 = 8.4 Hz, 1 H, H_5). ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 175.2 (COOH), 168.5 (C(NH_2)=NH), 157.9, 140.3, 134.8, 123.1, 119.4, 115.8, 58.5 (CH_3O), 50.9 (CH_3OH). Anal. Calcd for $C_9H_{10}N_2O_3$×CH_3OH: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.30; H, 6.31; N, 12.76.

2-Carbamimidoyl-3-morpholin-4-ylbenzoic Acid (5d)

Method B; pale yellow crystals of MeOH solvate (ca. 1:1); yield 1.71 g (61%); mp 194–195 °C (dec.). IR (KBr): 3360, 3244, 3064, 2962, 2924, 2858, 2826, 1688, 1610, 1574, 1520, 1430, 1386 cm^{-1}. ^1H NMR (400 MHz, D_2O, 25 °C): δ = 3.10 (m, 4 H, H_{morph}), 3.45 (s, 4 H, MeOH), 3.95 (m, 4 H, H_{morph}), 7.55 (d, J = 7.6 Hz, 1 H, H_4), 7.60 (d, J = 7.6 Hz, 1 H, H_6), 7.71 (2×d, J_1 = 7.6 Hz, J_2 = 7.6 Hz, 1 H, H_5). ^1H NMR (400 MHz, D_2O + HCl, 25 °C): δ = 2.88 (m, 4 H, H_{morph}), 3.20 (s, 2 H, MeOH), 3.72 (m, 4 H, H_{morph}), 7.58–7.64 (m, 2 H, $H_{4,5}$), 7.82 (d, J = 6.4 Hz, 1 H, H_6). ^{13}C NMR (100 MHz, D_2O + HCl, 25 °C): δ = 168.0 (COOH), 167.0 (C(NH_2)=NH), 150.6, 132.8, 129.3, 128.2, 127.7, 127.6, 66.9, 52.7, 48.8. Anal. Calcd for $C_{12}H_{15}N_3O_3$·CH_3OH: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.84; H, 6.78; N, 14.63.

3-Carbamimidoylpyridine-2-carboxylic Acid (5e)

Method B; colorless crystals; yield 1.14 g (69%); mp 250–251 °C. IR (KBr): 3016, 2360, 1706, 1583, 1565, 1526, 1446, 1428, 1377 cm^{-1}. ^1H NMR (400 MHz, D_2O, 25 °C): δ = 7.61 (dd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, 1 H, H_5), 8.04 (d, J = 8 Hz, J_M = 1.2 Hz, 1 H, H_4), 8.70 (d, J = 4.4 Hz, 1 H, H_6). ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 170.3, 169.0, 162.5, 153.6, 139.6, 133.0, 126.7. ^1H NMR (400 MHz, D_2O + HCl, 25 °C): δ = 8.03–8.06 (m, 1 H, H_5), 8.49 (d, J = 7.2 Hz, 1 H, H_4), 8.80 (d, J = 4 Hz, 1 H, H_6). ^{13}C NMR (100 MHz, D_2O + HCl, 25 °C): δ = 164.0 (COOH), 161.7 (C(NH_2)=NH), 146.6, 144.6, 143.1, 129.2, 128.2. Anal. Calcd for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 51.28; H, 4.34; N, 25.75.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)benzoic Acid (26)

To a suspension of 2-carbamimidoylbenzoic acid (**5a**, 0.328 g, 2 mmol) in EtOH (10 mL) was added an excess of 70% ethylenediamine solution in water (1.5 mL, 18 mmol). This reaction mixture was refluxed until no more ammonia gas was fixed by pH paper. The obtained clear solution was evaporated under reduced pressure to a volume of about 5 mL and acidified with a few drops of 10 M HCl to neutral pH with stirring. After standing for 2 h, fine colorless crystals were formed and separated by filtration, washed with EtOH (2 mL), and dried. Colorless crystals of hydrate (1:1); yield 0.277 g (73%); mp 222–223 °C. IR (KBr): 3382, 3218, 3106, 2944, 2896, 2686, 1628, 1604, 1577, 1556, 1380, 1286 cm^{-1}. ^1H NMR (400 MHz, D_2O, 25 °C): δ = 4.07 (s, 4 H, CH_2), 7.55 (d, J = 7.6 Hz, 1 H, H_3), 7.59 (2 × d, J_1 = 7.6 Hz, J_2 = 7.2 Hz, 1 H, H_4), 7.68 (2 × d, J_1 = 7.2 Hz, J_2 = 7.2 Hz, 1 H, H_5),

7.76 (d, J = 7.2 Hz, 1 H, H_6). ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 173.6 (COOH), 168.7 (C(NH)=NH), 138.0, 132.8, 130.1, 129.0, 128.4, 122.0, 45.0 (2 CH_2). Anal. Calcd for $C_{10}H_{10}N_2O_2{\cdot}H_2O$: C, 57.68; H, 5.81; N, 13.45. Found: C, 58.03; H, 6.19; N, 13.80. LC–MS: m/z (%) = 191 (100) $[M + H]^+$.

(23) X-ray diffraction studies of compounds **5c**,**e**, **17**, **20**, **21a**, and **4** were performed on an 'Xcalibur 3' diffractometer (graphite-monochromated Mo Kα radiation (λ = 0.71073), CCD detector, ω scans). Structure **4** was studied at both low and room temperature. Structures were solved by direct method and refined against F^2 within anisotropic approximation for all nonhydrogen atoms using OLEX2 program package[24] with SHELXS and SHELXL modules.[25] Crystallographic data, details of the data collection and processing, structure solution and refinement are summarized in Table S1 (see Supporting Information). CCDC numbers 1509778 (**20**) and 1509780–1509785 (**5e**, **4**, **21a**, **5c**, **17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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