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Reactions of aminobenzoic acids with α,β-acetylenic γ-hydroxy nitriles: synthesis of functionalized amino acids and unusually facile esterification and acetylene hydration

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Esterification
Cyanomethylhydroxyalkyl ketones

ABSTRACT

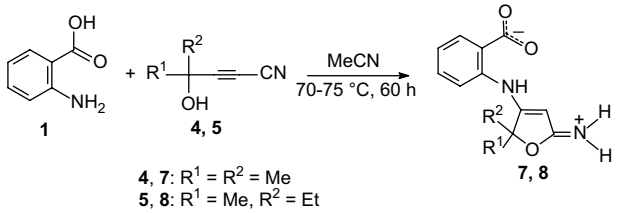
2-Aminobenzoic acid **1** reacts with α,β-acetylenic γ-hydroxy nitriles **4** and **5** to afford 2-[(5-iminio-2,2-dialkyl-2,5-dihydro-3-furanyl)amino]benzenecarboxylates **7** and **8** (yield 73–74%), a new class of unnatural amino acids in a peculiar zwitterionic form, having the positive charge transferred to the remote imino group of the dihydrofuranyl substituent. 3- and 4-Aminobenzoic acids **2** and **3** with α,β-acetylenic γ-hydroxy nitriles **4**–**6** undergo entirely different transformations to deliver the esters of cyanomethylhydroxyalkyl ketones **9**–**12**, which result from the unusually facile esterification of the hydroxyl function and simultaneous hydration of the triple bond. 4-Aminobenzoic acid **3** is found to be an active organic catalyst for the one-pot conversion of α,β-acetylenic γ-hydroxy nitrile **4** to 5-amino-2,2-dimethyl-3(2*H*)-furanone **13**, in 80% yield.

1. Introduction

The ever-growing demand for biological ligands to provide a clear understanding of their function at a molecular level and to pave shorter routes to therapeutic agents puts a special emphasis on the availability of unusual amino acids and their derivatives.[1] Among aromatic amino acids, 2-, 3-, and 4-aminobenzoic acids occupy an important place as intermediates in the synthesis of pharmaceutical products,[2] dyes,[3] and flavors.[4] Aminobenzoic acids are employed as building blocks for the preparation of molecules with targeted biological activity,[5] compounds capable of selectively absorbing harmful solar radiation[6] and materials with luminescent properties.[7] Thus, new and original approaches to the synthesis of unknown classes of unnatural amino acids represent an area of paramount interest for wide circles of diverse specialists. The aim of this work is to develop a new general synthetic methodology of structural modification of aminobenzoic acids **1**–**3** by the reactions with α,β-acetylenic γ-hydroxy nitriles **4**–**6**, which prove to be both worthwhile and available reagents.[8]

2. Results and discussion

Experiments have shown that 2-aminobenzoic acid **1**, on one hand, and 3- and 4-aminobenzoic acids **2** and **3**, on the other hand, react with α,β-acetylenic γ-hydroxy nitriles **4**–**6** in completely different ways, depending on the mutual disposition of the amino and carboxylic functions in the benzene ring. Thus, the reaction between 2-aminobenzoic acid **1** and acetylenes **4** and **5** gives exclusively amino acids with dihydrofuranyl substituents as the



4, **7**: $R^1 = R^2 = Me$
5, **8**: $R^1 = Me$, $R^2 = Et$

Scheme 1.

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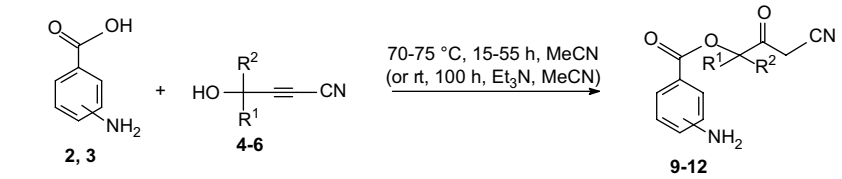


2: 3-$NH_2C_6H_4COOH$
3: 4-$NH_2C_6H_4COOH$

4: $R^1 = R^2$ = Me
5: R^1 = Me, R^2 = Et
6: R^1 - R^2 = $(CH_2)_5$

9: $R^1 = R^2$ = Me, 3-$NH_2C_6H_4COOH$
10: $R^1 = R^2$ = Me, 4-$NH_2C_6H_4COOH$
11: R^1 = Me, R^2 = Et, 4-$NH_2C_6H_4COOH$
12: R^1 - R^2 = $(CH_2)_5$, 4-$NH_2C_6H_4COOH$

Scheme 2.

zwitterions **7** and **8** (in 73–74% yield, 70–75 °C, 60 h, no catalyst, MeCN) (Scheme 1).

On the contrary, 3- and 4-aminobenzoic acids **2** and **3** on reaction with acetylenes **4**–**6** also furnish chemo- and regiospecifically, esters of cyanomethylhydroxyalkyl ketones **9**–**12** (in 14–93% yield, 70–75 °C, 15–55 h, no catalyst, MeCN or in 48–95% yield, rt, 100 h, Et_3N, MeCN) (Scheme 2).

The zwitterion structure of amino acid **7** (and apparently that of **8**) was determined by X-ray analysis of its single crystal (Fig. 1). The benzene and furan cycles are almost planar: maximal deviations of the atoms from the average planes are 0.02 and 0.01 Å, respectively, for C(7) and O(12). The dihedral angle between the planes equals 157.5°. The dihedral angle between the benzene plane and that formed by C(1)O(1)O(2) is 172.4°. The deviation of the N(1) atom out of furan cycle plane is 0.02 Å. In the molecule, the intramolecular H-bond O(2)···H(8)–N(8) is realized, its parameters being O(2)···N(8)—2.558(2) Å, O(2)···H(8)—1.69(2) Å, N(8)–H(8)—0.96(2) Å, O(2) ···H(8)–N(8)—148(2)°.

The zwitterionic character of the molecule **7** explicitly follows from the equivalency of the carboxylic oxygen atoms O(1) and O(2), the absence of the O–H covalent bond in the carboxylic moiety, and the practically equal N–H bonds in the $=N^+H_2$ group. Noteworthy is that the positive charge is transferred to the remote imino group of the dihydrofuran cycle, which is not typical for common amino acids. For the first time such an unusual zwitterionic structure has recently been fixed for the adducts of aliphatic amino acids to α,β-acetylenic γ-hydroxy nitriles.[8f]

NMR (^1H and ^{13}C) and IR spectra of amino acids **7** and **8** correspond to their structure (see Experimental).

The close-to-plane structure of amino acid **7**, its high polarity, and polarizability should provide for through-conjugation and hence easy electron-transfer along the whole system including its supramolecular architectures in solution and crystal state. Consequently, amino acids **7** and **8** are assumed to be highly responsive toward any physical and chemical changes of the surrounding that secure their applications as optoelectronic materials and sensors. Besides, the iminodihydrofuran substituents considerably extend their chemical and pharmaceutical potentials, since the dihydrofuran moiety is known to be a key motif in a number of biologically active compounds and pharmaceutical important molecules.[9]

X-ray analysis of single crystal of ester **10** (Fig. 2) shows that maximal atom deviation out of the benzene ring is 0.01 Å [atom C(4)]. Deviations of the N(1), C(8), O(9), and O(10) atoms out of the benzene ring plane equal to 0.02, 0.09, 0.30, and 0.10 Å, respectively. The dihedral angle between benzene ring and the C(8)O(9)O(10) fragment is 169.5° and the angle between the benzene ring and the C(11)C(13)O(16) fragment is 71.6°. The torsion angles C(11)O(10)C(8)C(5) and C(11)O(10)C(8)O(9) are 161.3(1)° and 18.7(2)°, respectively.

In the crystal structure of ester **10**, the molecules are likely bound in the chain by bifurcate H-bonds between CN and NH_2 groups (the contacts H···N are shorten and the N···N distances are close to the sums of Van der Waals radii).[10]

NMR (^1H, ^{13}C, HMBC) and IR spectra as well as MS spectra of esters **9**–**12** are in agreement with their structure (see Experimental). In the ^{13}C NMR spectrum (DMSO-d_6) of ester **9**, doubling of all the signals except CN and CH_2 groups is observed, maybe due to hindered rotation of the ester carbonyl group, and its different orientation relative to the amino function. Upon chromatography

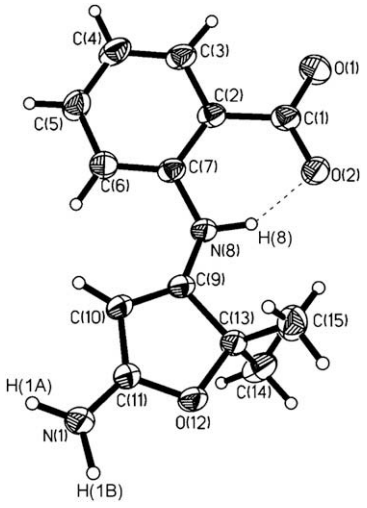


Figure 1. The conformation and designation of atoms in the molecule of 2-[(5-iminio-2,2-dimethyl-2,5-dihydro-3-furanyl)amino]benzenecarboxylate **7**.

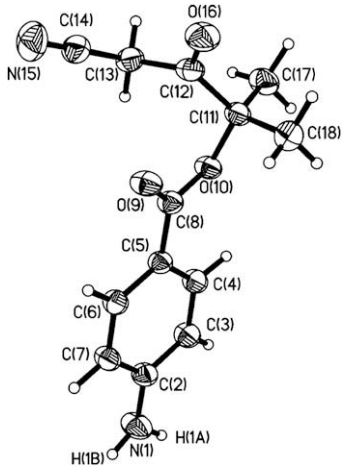
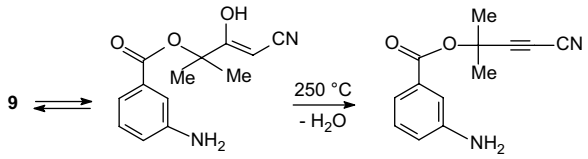
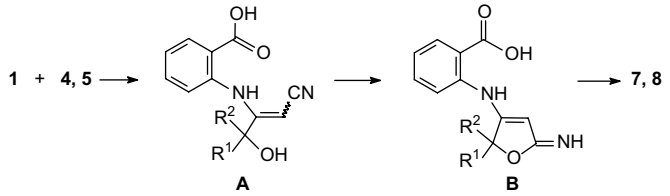


Figure 2. Designation of atoms in the molecule of ester **10**.

(250 °C) a small peak (10–12% $[M]^+$ 228) appears, seemingly a result of water elimination from ester **9**:

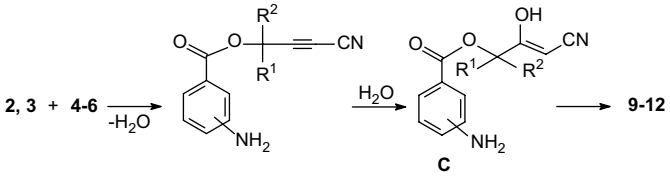


Zwitterions **7** and **8** obviously result from the initial nucleophilic addition of 2-aminobenzoic acid **1** to the triple bond of acetylenes **4** and **5**. The intermediate adducts **A** then undergo the ring closure (in the *E*-configuration) to give iminodihydrofurans **B**, which are finally transformed to their zwitterionic isomers **7** and **8** via the hydrogen transfer from the carboxyl function to the imino group as most basic center (Scheme 3).



4, **7**: $R^1 = R^2 = Me$
5, **8**: $R^1 = Me$, $R^2 = Et$

Scheme 3.



Scheme 4.

It should be emphasized that a similar reaction of aliphatic amino acids with α,β-acetylenic γ-hydroxy nitriles requires an entirely different set of condition (rt, NaOH, H_2O)[8f] owing to the considerable differences in basicity and acidity of their functions as well as the low solubility of 2-aminobenzoic acid **1** in water (<1%).

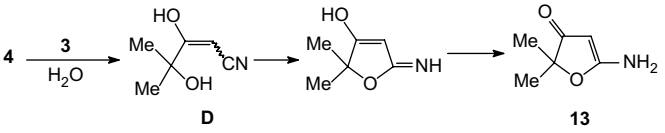
Unlike 2-aminobenzoic acid **1**, 3- and 4-aminobenzoic acids **2** and **3** do not add to acetylenes **4**–**6** by the amino group. Instead, the amazingly easy esterification of the hydroxyl function of acetylenes **4**–**6** is accompanied by unusually facile hydration of the triple bond. It is noteworthy that propargyl alcohol was reported[11] to react with carboxylic acids, including protected amino acids, in the presence of special ruthenium complexes, e.g., $RuCl_2(PMe)_3$(arene), to give in the first step the adducts across the triple bond, neither esterification nor hydration of the acetylenic moiety being occurred.

The easy esterification and the triple bond hydration in the substituted propargyl alcohols **4**–**6** are assumed to be strictly concerted: the molecule of water released from the esterification is scavenged by the triple bond to form enol **C**, which further tautomerizes to the ketone moiety (Scheme 4).

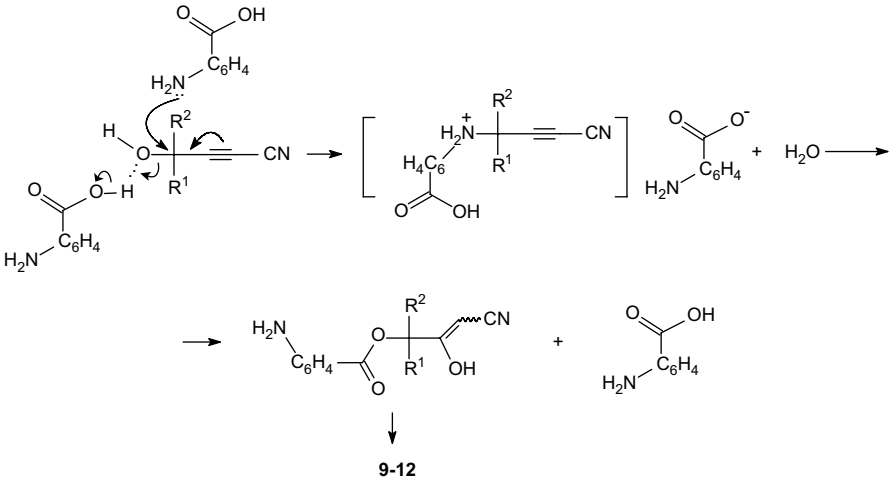
Consequently, it is the combination of carboxylic and amino functions in the 3- and 4-position of the benzene ring that allows the two above classical reactions (esterification and acetylene hydration) to proceed so easily. Apparently, we face here a novel example of organic catalysis. It is known that the presence of carboxylic and amino functions in a molecule is a key prerequisite of organic catalysis.[12]

The mechanism of the catalytic action of 3- and 4-aminobenzoic acids on the tandem esterification–hydration process of acetylenes **4**–**6** is not yet fully understood and deserves to be specially scrutinized. Tentatively, the carboxylic function of amino acids **2** and **3** protonates the hydroxyl of acetylenes **4**–**6**, thus making it a better leaving group, while the remaining propargyl type carbcationic moiety is stabilized by the amino function of the second molecule of the amino acid, until it is quenched with released water (Scheme 5).

Therefore, in this case, 3- and 4-aminobenzoic acids **2** and **3** behave both as reactant and catalyst. Indeed, the experiments show, under the same conditions with benzoic acid, that the above transformation of acetylenes **4**–**6** does not take place. Correspondingly, the methyl ester of 4-aminobenzoic acid proves to be inactive toward acetylene **4** (70–75 °C, 43 h, MeCN). In aqueous media, 4-aminobenzoic acid **3** does not react with acetylene **4**, although it actively catalyzes its hydration, cyclization, and isomerization of the intermediate enol **D** to yield 5-amino-2,2-dimethyl-3(2*H*)-furanone **13** (Scheme 6, Table 1).



Scheme 6.



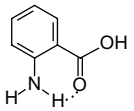
Scheme 5.

Table 1
4-Aminobenzoic acid **4** as catalyst of the acetylene hydration to aminodihydrofuranone **13**

Mol ratio of **3**/**4**	Solvent	Temperature (°C)	Time (h)	Yield of **13** (%)
1:1	H_2O	50–60	18	63
1:9	H_2O	50–60	7.5	56
1:9	H_2O	50–60	30	80
1:1	H_2O–dioxane (4:1)	20–25	4 months	12

Table 1 shows, with a catalytic amount of 4-aminobenzoic acid **3** (mol ratio **3**/**4**=1:9), that the yield of aminodihydrofuranone **13** reaches 80%. Without aminobenzoic acid **3** the reaction is not observed (50–60 °C, 20 h). Further attempts to hydrate acetylene **4** under various conditions gave much lower yields of aminodihydrofuranone **13**: 32% (reflux, 1 h, Et_3N, H_2O),[13] 27% (rt, 6 h, LiOH, H_2O),[14] and 17% (rt, 4 h, KCN, H_2O–dioxane).[15]

As far as 2-aminobenzoic acid **1** is concerned, its inability to form esters like **9**–**12** can be explained in terms of formation of the strong intramolecular H-bond between its amino and carboxyl functions:



The influence of the reaction condition and the reactant structure on the yield of esters **9**–**12** is illustrated in Table 2.

It is notable that Et_3N (6–11 mass %) exhibits a remarkable catalytic effect on the reaction. Under comparable conditions aminobenzoic acid **3** with acetylenes **4** and **5** gave practically the same yield of the corresponding esters. A more noticeable structural effect, mostly of steric character, is displayed by hydroxyalkyl substituents in acetylenes **4**–**6**. Thus, in the case of hydroxycyclohexyl substituent (acetylene **6**) the yield of the corresponding ester **12** drops sharply: from 79 to 14% or from 83 to 48% (under different conditions) as compared to that for acetylene **4** (Table 2).

3. Conclusion

The reaction of 2-aminobenzoic acid with accessible α,β-acetylenic γ-hydroxy nitriles leads to a new type of amino acid having dihydrofuran moieties and existing in a uncommon zwitterionic form with a positive charge located on the remote imino group. X-ray analysis reveals the almost planar structure of the amino acids that secures the through-conjugation between the anionic and cationic centers, and thus making these molecules potentially responsive to chemical and physical surrounding and hence prospective candidates in the design of optoelectronic devices, sensors, and pharmaceuticals.

With 3- and 4-aminobenzoic acids, unusually facile esterification and hydration of α,β-acetylenic γ-hydroxy nitriles occur to give aromatic amino esters having nitrile and ketone moieties, a novel family of potent building blocks for organic synthesis.

The 4-aminobenzoic acid is shown to be an active organic catalyst for one-pot conversion of α,β-acetylenic γ-hydroxy nitriles in aqueous media to aminodihydrofuranones (still inaccessible, so useful as synthetically and pharmaceutically intermediates) and the reaction sequence includes hydration of the acetylenic moieties, intramolecular addition of the hydroxyl to the cyano group, and prototropic rearrangements. The results significantly contribute to basic and preparative chemistry of amino acids and acetylenes.

4. Experimental

4.1. General

IR spectra were measured on a Bruker IFS-25 in KBr pellets. ^1H (400.13 MHz) and ^{13}C (100.62 MHz) spectra were recorded on a Bruker DPX-400 spectrometer in $(CD_3)_2CO$, $CDCl_3$, and DMSO-d_6. Mass spectra were recorded on a GC–MS-QP5050A spectrometer made by Shimadzu Company. Chromatographic column parameters were as follows: SPB™-5, length 60 m, internal diameter 0.25 mm, thickness of stationary phase film 0.25 μm; injector temperature 250 °C, gas carrier helium, flow rate 0.7 mL min^{-1}; detector temperature 250 °C; mass analyzer: quadrupole, electron ionization, electron energy 70 eV, ion source temperature 200 °C; mass range 34–650 Da.

The reaction was controlled by thin-layer chromatography on neutral Al_2O_3 (chloroform–benzene–ethanol, 20:4:1 as eluent). 2-, 3-, and 4-Aminobenzoic acids **1**–**3** are commercial reagents ('Merck'). α,β-Acetylenic γ-hydroxy nitriles **4**–**6** were prepared according to a published method.[16]

4.2. X-ray diffraction

X-ray diffraction studies of **7** and **10** were carried out with an Enraf Nonius CAD-4 diffractometer at room temperature ($\omega/2\theta$-scan mode, Mo for **7** or Cu for **10** Kα radiation, graphite monochromator). Crystalline structure was solved by direct methods followed by Fourier synthesis using SHELXS 97.[17a] The structure was refined using anisotropic full-matrix approximation for all non-hydrogen atoms with SHELXL 97.[17b] Coordinates of hydrogen atoms were defined experimentally and refined isotropically. These data are available via www.ccdc.cam.uk/contsretrieving.html (or from CCDC, 12 Union CambrigeCB2 1EZ, UK, fax: +44(0)1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference

Table 2
Synthesis of esters **9**–**12** (1:1 mol ratio **2**,**3**/**4**–**6**, MeCN)

Aminobenzoic acid	Acetylene	Temperature (°C)	Time (h)	Et_3N[a] (mass %)	Product	Yield (%)
2	**4**	70–75	15	None	**9**	75
2	**4**	70–75	30	None	**9**	85
3	**4**	20–25	60 days	None	**10**	68
3	**4**	70–75	40	None	**10**	79
3	**4**	20–25	100	6	**10**	83
3	**5**	70–75	44	None	**11**	70
3	**5**	70–75	55	None	**11**	93
3	**5**	20–25	100	11	**11**	95
3	**6**	70–75	40	None	**12**	14
3	**6**	20–25	100	7	**12**	48

[a] Relative to the reactant mass.

numbers 705263 and 705262 (for amino acids **7** and **10**, respectively).

4.2.1. Crystallographic data for ***7***

$C_{13}H_{14}N_2O_3$, M=246.26, monoclinic, $P2_1/c$, a=7.809(3) Å, b=13.985(4) Å, c=11.554(3) Å, β=97.52(3)°, U=1250.9(7) Å^3, Z=4, D_{calcd}=1.31 g cm^{-3}, μ=0.094 mm^{-1}, reflection observed/independent 2350/2184, 220 parameters refined, R=0.045 for 1275 reflections with [$F_0>4\sigma(F_0)$].

4.2.2. Crystallographic data for ***10***

$C_{13}H_{14}N_2O_3$, M=246.26, monoclinic, $P2_1/c$, a=10.627(2) Å, b=11.717(2) Å, c=10.674(2) Å, β=102.53(3)°, U=1297.4(4) Å^3, Z=4, D_{calcd}=1.26 g cm^{-3}, μ=0.751 mm^{-1}, reflection observed/independent 2670/2414, 220 parameters refined, R=0.046 for 1974 reflections with [$F_0>4\sigma(F_0)$], $(2\theta)_{max}$=139.9 Å.

4.3. The reaction of 2-aminobenzoic acid 1 with α,β-acetylenic γ-hydroxy nitriles 4 and 5

General method. To a solution of 2-aminobenzoic acid **1** (247 mg, 1.8 mmol) in acetonitrile (4 mL), the appropriate acetylenes **4** or **5** (1.8 mmol) in acetonitrile (2 mL) was added at room temperature. The reaction mixture was stirred at 70–75 °C for 60 h. The solvent was removed in vacuo, and the residue was treated with diethyl ether and dried in vacuo to give compounds **7** and **8**.

4.3.1. 2-[(5-Iminio-2,2-dimethyl-2,5-dihydro-3-furanyl)amino]benzenecarboxylate ***7***

Yield 74%; beige crystals; mp 288–290 °C; IR (KBr) 3500–2500 (NH, =N$^+$H$_2$, C=CH, CH), 1671 (C=O), 1607 (C=C) cm^{-1}; ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.03 (d, J=7.6 Hz, 1H), 7.44 (t, J=7.4 Hz, 1H), 7.28 (d, J=8.0 Hz, 1H), 7.08 (t, J=7.3 Hz, 1H), 5.64 (s, 1H), 1.64 (s, 6H); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ 176.4, 169.9, 168.6, 142.4, 131.3, 131.0, 125.3, 122.6, 116.5, 91.6, 78.4, 24.9. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.59; H, 5.95; N, 11.46.

4.3.2. 2-[(2-Ethyl-5-iminio-2-methyl-2,5-dihydro-3-furanyl)amino]benzenecarboxylate ***8***

Yield 73%; beige crystals; mp 290–292 °C; IR (KBr) 3500–2500 (NH, =N$^+$H$_2$, C=CH, CH), 1681 (C=O), 1624 (C=C) cm^{-1}; ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.00 (d, J=8.0 Hz, 1H), 7.41 (t, J=7.0 Hz, 1H), 7.27 (d, J=7.6 Hz, 1H), 7.07 (t, J=7.4 Hz, 1H), 5.70 (s, 1H), 2.05, 1.94 (dq, ^2J=15.6 Hz, ^3J=7.0 Hz, 2H), 1.59 (s, 3H), 0.75 (t, J=7.0 Hz, 3H); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ 177.2, 169.0, 168.7, 142.2, 131.4, 131.2, 125.4, 122.9, 116.6, 94.5, 79.7, 30.6, 23.8, 7.0. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.66; H, 6.44; N, 10.48.

4.4. The reaction of 3-aminobenzoic acid 2 with α,β-acetylenic γ-hydroxy nitrile 4

To a solution of 3-aminobenzoic acid **2** (247 mg, 1.8 mmol) in acetonitrile (4 mL), acetylene **4** (196 mg, 1.8 mmol) in acetonitrile (2 mL) was added at room temperature. The reaction mixture was stirred at 70–75 °C for 15 h. The solvent was removed in vacuo and the residue was treated with diethyl ether. The filtered residue was dried in vacuo to give 50 mg of 3-aminobenzoic acid **2**. The solvent was removed from diethyl ether fraction, the residue (390 mg, purity 84%, by ^{1}H NMR spectroscopy) was washed by small portions of diethyl ether, and dried in vacuo to give 328 mg ester **9**.

4.4.1. 3-Cyano-1,1-dimethyl-2-oxopropyl 3-aminobenzenecarboxylate ***9***

Yield 75%; yellow powder; mp 150–153 °C; IR (KBr) 3456, 3373, 3236 (NH$_2$), 2261 (CN), 1711, 1625 (C=O), 1607 (C=C) cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.38 (d, J=7.6 Hz, 1H), 7.30 (s, 1H), 7.21 (dd, 1H), 6.89 (d, J=7.4 Hz, 1H), 4.11 (br s, 2H), 3.59 (s, 2H), 1.56 (s, 6H); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ 200.2, 166.0, 149.7, 130.1, 127.5, 120.7, 115.7, 114.4, 113.3, 82.6, 23.1, 22.5; MS m/z (%) (EI): 246 (15), 137 (12), 120 (100), 92 (36), 65 (28), 41 (10), 39 (15). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.53; H, 5.85; N, 11.18.

4.5. The reaction of 4-aminobenzoic acid 3 with α,β-acetylenic γ-hydroxy nitriles 4–6

Method A. To a solution of 4-aminobenzoic acid **3** (247 mg, 1.8 mmol) in acetonitrile (4 mL), a solution of the appropriate acetylenes **4**–**6** (1.0 mmol) in acetonitrile (2 mL) was added at room temperature. The reaction mixture was stirred at 70–75 °C for 40–55 h (Table 2). The solvent was removed in vacuo, the residue was treated with diethyl ether, and dried in vacuo to give compounds **10**–**12**.

Method B. To a solution of 4-aminobenzoic acid **3** (137 mg, 1.0 mmol) and the appropriate acetylenes **4**–**6** (1.0 mmol) in acetonitrile (4 mL), Et_3N (6–11 mass%) was added (Table 2). The reaction mixture was stirred at room temperature for 100 h. The solvent was removed in vacuo, the residue was treated with diethyl ether, and dried in vacuo to give compounds **10**–**12**.

4.5.1. 3-Cyano-1,1-dimethyl-2-oxopropyl 4-aminobenzenecarboxylate ***10***

Method A: yield 83%; method B: 79%; yellow crystals; mp 157–158 °C (acetonitrile); IR (KBr) 3460, 3360, 3230 (NH$_2$), 2255 (CN), 1720, 1665 (C=O), 1605 (C=C) cm^{-1}; ^{1}H NMR [400.13 MHz, $(CD_3)_2O$] δ 7.73 (d, J=8.8 Hz, 2H), 6.68 (d, J=8.8 Hz, 2H), 5.56 (s, 2H), 3.95 (s, 2H), 1.57 (s, 6H); ^{13}C NMR [100.62 MHz, $(CD_3)_2O$] δ 198.7, 165.5, 154.2, 131.7, 115.5, 114.4, 112.6, 81.5, 27.4, 22.9; MS m/z (%) (EI): 246 (6), 137 (6), 120 (100), 92 (16), 65 (23), 41 (11), 39 (14). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.49; H, 5.87; N, 11.17.

4.5.2. 3-Cyano-1-ethyl-1-methyl-2-oxopropyl 4-aminobenzenecarboxylate ***11***

Method A: yield 93%; method B: 95%; yellow powder; mp 142–144 °C; IR (KBr) 3477, 3377, 3230 (NH$_2$), 2259 (CN), 1736, 1681 (C=O), 1601 (C=C) cm^{-1}; ^{1}H NMR [400.13 MHz, $(CD_3)_2O$] δ 7.78–7.74 (m, 2H), 6.70–6.65 (m, 2H), 5.52 (s, 2H), 3.92 (q, $^2J_{AB}$=19.6 Hz, 2H), 2.06, 1.85 (dq, ^2J=11.0 Hz, ^3J=7.6 Hz, 2H), 1.44 (s, 3H), 1.00 (t, J=7.6 Hz, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 197.2, 166.2, 152.1, 132.3, 117.6, 114.1, 113.9, 85.7, 29.4, 26.9, 19.6, 7.7. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.49; H, 5.97; N, 10.57.

4.5.3. 1-(2-Cyanoacetyl)cyclohexyl 4-aminobenzenecarboxylate ***12***

Method A: yield 14%; method B: 48%; yellow powder; mp 146–148 °C; IR (KBr) 3487, 3385 (NH$_2$), 2256 (CN), 1726, 1680 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR [400.13 MHz, $(CD_3)_2O$] δ 7.82 (d, J=8.8 Hz, 2H), 6.73 (d, J=8.8 Hz, 2H), 5.61 (s, 2H), 3.93 (s, 2H), 2.20–2.17 (m, 2H), 1.81–1.60 and 1.37–1.33 (m, 8H); ^{13}C NMR [100.62 MHz, $(CD_3)_2O$] δ 198.2, 165.9, 154.2, 132.3, 116.3, 114.7, 113.2, 83.6, 30.8, 26.5, 24.5, 21.3. Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.34; H, 6.18; N, 9.71.

4.6. 5-Amino-2,2-dimethyl-3(2*H*)-furanone 13

To a solution of 4-aminobenzoic acid **3** (29 mg, 0.2 mmol) in water (4 mL), acetylene **4** (196 mg, 1.8 mmol) was added at room

temperature. The reaction mixture was stirred at 50–60 °C for 30 h. Water was removed and the residue was washed with diethyl ether (4×5 mL) to result in 183 mg (80%) 5-aminodihydrofuranone **13**; mp 228–230 °C. MS, IR, ^{1}H, and ^{13}C NMR spectra correspond to literature data.[12–14]

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