CONCISE SYNTHESIS OF SOME (4-AMINOPHENOXY)ALKANOIC ACIDS BASED ON PARACETAMOL

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ABSTRACT. Starting from *N*-(4-hydroxyphenyl)acetamide (*Paracetamol*), a three steps synthesis of (4-aminophenoxy)acetic acid and 4-(4-aminophenoxy) butyric acid is comparatively discussed.

Keywords: (4-aminophenoxy)acetic acid, 4-(4-aminophenoxy)butyric acid, Williamson etherification, acidolysis

INTRODUCTION

(4-Aminophenoxy)acetic acid **1a** and 4-(4-aminophenoxy)butyric acid **1b** (Scheme 1) are known compounds as early as for the end of XIX-century and the starting of XX-century [1-4].

1a (n=1), **1b** (n=3)
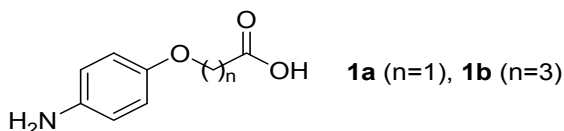
Scheme 1

The first reported synthesis of (4-aminophenoxy)acetic acid consisted of reduction of its corresponding nitro precursor, the last one being available from Williamson etherification of 4-nitrophenol with monochloroacetic acid in alkaline conditions [1-3]. Closer to our days, the same etherification strategy still was actual by using, in the key step, *N*-(4-hydroxyphenyl)acetamide (*Paracetamol*) in reaction with monochloroacetic acid [5, 6] with yields around 60%. However, the expected soft nucleophilicity of the conjugated *p*-substituted phenoxides[1] prompted other authors to explore the use of
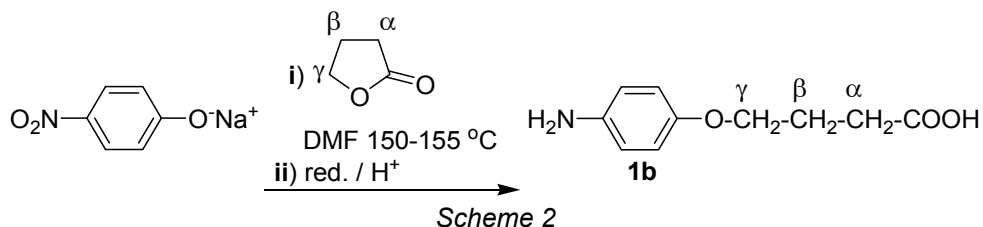
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[1] pKa (*Paracetamol*): 9.38; pKa (4-nitrophenol): 7.16

bromoacetic acid [7] or of its low alkyl esters against deprotonated forms of *Paracetamol* [8a] or even *p*-nitrophenol [8b]. Overall, the nowadays increased interest in (*N*,*O*-masked) forms of (4-aminophenoxy)acetic acid arises from their bioimpact, i.e. when targeting new analgesic, antipyretic and anti-inflammatory agents [6], new potential antisickling agents [7], bioabsorbable as biocompatible polyurethanes and polyamides for medical [8] devices.

In contrast, there are very few reports concerning the synthesis of 4-(4-aminophenoxy)butyric acid **1b** (Scheme 1) in spite of its first mentioning in the literature in 1917 [4]. Similar to its lower homologue **1a**, **1b** can be obtained by reduction of 4-(4-nitrophenoxy)butyric acid resulted, from the regioselective ring cleavage of γ-butyrolactone upon treatment with sodium 4-nitrophenoxide (Scheme 2) [9a, 9b] or by Williamson etherification of the latter, as reported very recently [9c, 9d].

$$O_2N-\!\!\!\!\bigcirc\!\!\!\!-O^- Na^+ \quad \xrightarrow[\text{ii}) red. / H^+]{\begin{array}{c}\text{i}) \text{(γ-butyrolactone)}\\ \text{DMF } 150\text{-}155\,^oC\end{array}} \quad H_2N-\!\!\!\!\bigcirc\!\!\!\!-O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}COOH$$

i) β α γ (γ-butyrolactone)

DMF 150-155 °C

ii) red. / H⁺

H₂N— —O-CH₂-CH₂-CH₂-COOH   γ β α

1b

Scheme 2

Lately, the use of **1b** as polyconjugate for delivery of RNA triggers to tumor cells *in vivo* [9c], as intermediate in the synthesis of new anti-*Helicobacter pylori* agents [10] and side-chain component of some cancer inhibitors of the cellular checkpoint kinase Wee1 [11] was reported.
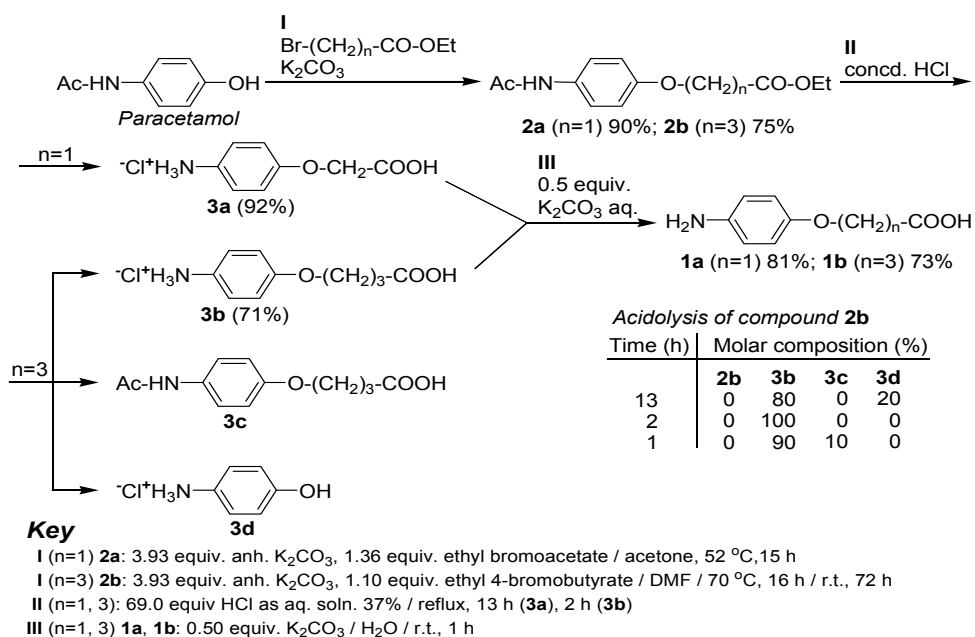
Therefore, the aim of the present preliminary communication is to present a common and concise synthetic pathway towards (4-aminophenoxy)alkanoic acids **1a** and **1b** (Scheme 1) based on a Williamson approach.

RESULTS AND DISCUSSION

The chemistry we performed is resumed in Scheme 3.

(4-Aminophenoxy)acetic acid hydrochloride **3a** was prepared in two steps, **I** and **II**, both inspired from Bezwada's recent Patent [8a]. They consisted of Williamson etherification of *Paracetamol* (**I**, 90% yield against lit. 80% [8a]) followed by acidolysis of the amidoester **2a** (**II**, 92% yield against lit. 77.6% [8a]), hence, an overall yield of 83% (lit. 62%, [8a]). In step **III**, we isolated the free amine **1a** by manipulating its solubility in water in such a way that we avoided contamination with potassium chloride.

In order to access 4-(4-aminophenoxy)butyric acid **1b**, we first planned the ring opening of γ-butyrolactone with the use of sodium phenoxide of *Paracetamol* in similar conditions with those already reported in the case of sodium 4-nitrophenoxide (Scheme 2) [9a]. In our hands no reaction occurred, the starting *N*-(4-hydroxyphenyl)acetamide being recovered. That is, once more we moved our interest towards Williamson

Key
 I (n=1) **2a**: 3.93 equiv. anh. K_2CO_3, 1.36 equiv. ethyl bromoacetate / acetone, 52 °C,15 h
 I (n=3) **2b**: 3.93 equiv. anh. K_2CO_3, 1.10 equiv. ethyl 4-bromobutyrate / DMF / 70 °C, 16 h / r.t., 72 h
 II (n=1, 3): 69.0 equiv HCl as aq. soln. 37% / reflux, 13 h (**3a**), 2 h (**3b**)
 III (n=1, 3) **1a**, **1b**: 0.50 equiv. K_2CO_3 / H_2O / r.t., 1 h

Scheme 3

methodology. Thus, inspired from the similar reactivity of *N*-(4-hydroxyben-zyl)acetamide [10], we obtained (**I**) the amidoester **2b** with good yield[2]. However, acidolysis (**II**) of **2b** carried out in identical conditions as for **2a**, resulted in a crude reaction mixture whose ^{1}H NMR spectrum revealed, besides formation of the desired **3b**, the existence of the hydrochloride of 4-aminophenol **3d** issued from the acidolysis of the etheric connection (Figure 1). ^{1}H NMR monitoring of the process showed the reaction reaching completion within 2 h, i.e. in a much shorter time in comparison with **3a** (Scheme 3). As for **1a**, the free amine **1b** was isolate simply (**III**) by modulating its solubility in water against that of potassium chloride. To conclude, the overall yield in the synthesis of **1b** was 39%.

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[2] Compound **2b** was previously mentioned by Katsura and co-workers in 2000 (Ref. [10]) with no experimental assignment (synthesis and / or analytical data)

CONCLUSIONS

Starting from *N*-(4-hydroxyphenyl)acetamide, we described a three steps expeditious synthetic pathway in the direction of two (4-aminophenoxy)alkanoic acids. The common key step, a Williamson etherification yielding amidoesters of the target aminoacids, appears to be a good option if ethyl bromoalkanoates are used. In contrast, the key step,
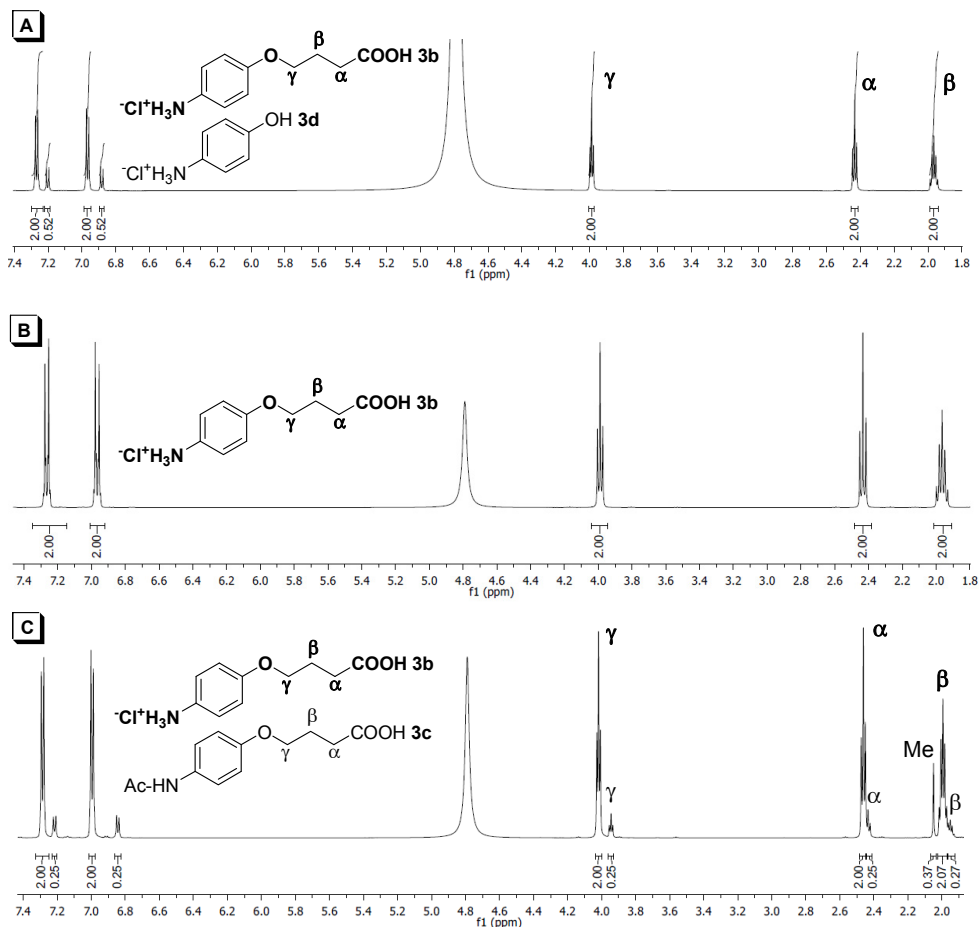

Figure 1. ^{1}H NMR monitoring of acidolysis of amidoester **2b** (600 MHz, D$_2$O, 298 K): crude reaction mixture after 13 h (**A**), 2 h (**B**), 1 h (**C**).

N,O-deprotection of the resulting amidoesters by acidolysis, strongly depends on the size of the (poly)methylenic chain (n=1 vs. n=3).

EXPERIMENTAL SECTION

General. Melting points were measured on an Electrothermal® instrument and are not corrected. NMR spectra were recorded on Bruker® AV 400, or AV 600 instruments operating at 400 or 600 MHz for ^{1}H and at 100 or 150 MHz for ^{13}C nuclei respectively. All chemical shifts (δ values) are given in parts per million (ppm); all homocoupling patterns ($^nJ_{H,H}$ values) are given in Hertz. TLC was performed by using aluminium sheets with silica gel 60 F$_{254}$ (Merck®). IR spectra were recorded on a Bruker® FT-IR Vector 22 Spectrometer. Microanalyses were performed on a Carlo Erba® CHNOS 1160 apparatus. Mass spectra were carried out on a Schimadzu® GC-MS QP-2010 PLUS instrument equipped with a Column HP-5MS under EI (70 eV) ionisation. All solvents and reagents were of analytical grade and required no purification prior to use.

***Typical procedure for Williamson etherification. Preparation of compound* 2b**. Into a DMF (30 mL) solution containing *N*-(4-hydroxyphenyl) acetamide (3.00 g, 19.85 mmol) and ethyl 4-bromobutyrate (3.14 mL, 4.26 g, 21.83 mmol), anhyd. K$_2$CO$_3$ (10.81 g, 78.2 mmol) was added with vigorous stirring. The resulted suspension was heated at 70 °C for 16 h then let to stir at room temperature for additional 72 h. Water (50 mL) and ethyl acetate (100 mL) were added to the reaction mixture with stirring, then the resulted two layers were separated. The organic layer was washed with water to complete removal of DMF (5 × 50 mL), dried over anhyd. Na$_2$SO$_4$ and evaporated under reduced pressure. The crude solid product was crystallised from min. amount of ethyl acetate to afford 3.95 g pure compound **2b** [75% yield with respect to *N*-(4-hydroxyphenyl)acetamide] as a white solid.

Ethyl (4-N-acetylamino)phenoxyacetate (**2a**); yield 90% [1.41 g **2a** starting from 1.00 g *N*-(4-hydroxyphenyl)acetamide], white powder, mp 102.3-103.5 °C (toluene/hexane 1:5 v/v) (Lit. [8a]: 104.2-106.2 °C); [Found: C, 61.05; H, 6.57; N, 6.24%. C$_{12}$H$_{15}$NO$_4$ (237.10) requires: C, 60.75; H, 6.37; N, 5.90 %]; R_f (ligroin/acetone 2:1 v/v) 0.51. $\nu_{max.}$ (KBr) 3382 (m), 2994 (w), 1741(s), 1678 (m), 1532 (m), 1510 (s), 1428 (w), 1408 (w), 1322 (w), 1251 (m), 1215 (s), 1175 (w), 1089 (m), 1015 (w), 833 (m), 810 (m), 678 (w), 595 (w) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ_H 1.20 (3 H, t, $^3J_{H,H}$=7.0 Hz, CH$_2$C*H$_3$*), 2.00 (3 H, s, CH$_3$), 4.15 (2 H, q, $^3J_{H,H}$=7.0 Hz, C*H$_2$*CH$_3$), 4.71 (2 H, s, CH$_2$), 6.86 (2 H, d, $^3J_{H,H}$=9.2 Hz, H-3, -5, Ar), 7.47 (2 H, d, $^3J_{H,H}$=9.2 Hz, H-2, -6, Ar), 9.83 (1 H, s, NH) ppm. ^{13}C NMR in J_{mod} (100 MHz, DMSO-d_6, 298 K) δ_C 14.1 (CH$_2$*C*H$_3$), 23.8 (CH$_3$), 60.6 (*C*H$_2$CH$_3$), 64.9 (CH$_2$), 114.6 (C-3, -5, Ar), 120.5 (C-2, -6, Ar), 133.2 (C-4, Ar), 153.4 (C-1, Ar), 167.9 (NH-CO), 168.9 (COO) ppm. GC-MS (MeOH) *m*/*z* (rel. int. %) 223 [M, - CH$_3$] (23); [APCI(+), MeCN] *m*/*z* (rel. int. %) 238.11 [M+1].

Ethyl 4-(4-N-acetylamino)phenoxybutyrate (**2b**); yield 75% [3.95 g **2b** starting from 3.00 g *N*-(4-hydroxyphenyl)acetamide], white crystals, mp 88-90 °C (ethyl acetate); [Found: C, 63.56; H, 7.10; N, 5.34%. $C_{14}H_{19}NO_4$ (265.13) requires: C, 63.38; H, 7.22; N, 5.28%]; R_f (CHCl$_3$/MeOH 5:0.5 v/v) 0.51. $\nu_{max.}$ (KBr) 3325 (m), 2992 (w), 2944 (w), 2914 (w), 2874 (w), 1730 (s), 1659 (s), 1533 (s), 1513 (m), 1409 (m), 1377 (m), 1319 (m), 1266 (m), 1249 (m), 1179 (s), 1101 (w), 1055 (m), 1032 (w), 965 (m), 943 (w), 828 (m), 603 (w) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ_H 1.16 (3 H, t, $^3J_{H,H}$=7.2 Hz, CH$_2$CH_3), 1.93 (2 H, tt app. qv., $^3J_{H,H}$=6.8 Hz, β-CH$_2$), 1.99 (3 H, s, CH$_3$), 2.43 (2 H, t, $^3J_{H,H}$=6.0 Hz, α-CH$_2$), 3.92 (2 H, t, $^3J_{H,H}$=6.2 Hz, γ-CH$_2$), 4.05 (2 H, q, $^3J_{H,H}$=7.2 Hz, CH_2CH$_3$), 6.83 (2 H, d, $^3J_{H,H}$=9.2 Hz, H-3, -5, Ar), 7.45 (2 H, d, $^3J_{H,H}$=8.8 Hz, H-2, -6, Ar), 9.79 (1 H, s, NH) ppm. ^{13}C NMR in J_{mod} (100 MHz, DMSO-d_6, 298 K) δ_C 14.2 (CH$_2$$CH_3$), 23.9 (CH$_3$), 24.4 (β-CH$_2$), 30.3 (α-CH$_2$), 60.0 (γ-CH$_2$), 66.7 (C$H_2CH_3$), 114.5 (C-3, -5, Ar), 120.6 (C-2, -6, Ar), 132.6 (C-4, Ar), 154.3 (C-1, Ar), 167.9 (NH-CO), 172.7 (COO) ppm. GC-MS (MeOH) *m/z* (rel. int. %) 265.1 [M$^+$] (5).

Typical procedure for acidolysis. Preparation of compound 3b. Ethyl 4-(4-*N*-acetylamino)phenoxybutyrate **2b** (3.95 g, 14.90 mmol) was added to aq. concd. 37% HCl soln. (86 mL solution, 1028.10 mmol HCl) and the reaction mixture was refluxed for 2 h. The resulted white suspension was cooled at 0 °C for 24 h, filtered off and washed with anh. THF to afford 2.45 g pure compound **3b** (71% yield with respect to **2b**) as white crystals.

(4-Aminophenoxy)acetic acid hydrochloride (**3a**); yield 92% (5.31 g **3a** starting from 6.70 g **2a**), beige powder, mp 219.6-220.9 °C (aq. HCl) (Lit. [8a]: 224-226 °C); [Found: C, 47.51; H, 4.64; N, 6.94%. $C_8H_{10}ClNO_3$ (203.03) requires: C, 47.19; H, 4.95; N, 6.88%]; R_f (EtOH 100%) 0.43. $\nu_{max.}$ (KBr) 3101 (s), 3016 (s), 2968 (s), 2850 (s), 2585 (m), 1761 (m), 1736 (s), 1614 (w), 1574 (w), 1500 (s), 1435 (w), 1407 (w), 1309 (w), 1277 (w), 1242 (w), 1178 (s), 1073 (m), 1053 (m), 812 (m), 771 (m), 732 (m), 672 (w), 629 (w) cm^{-1}. ^{1}H NMR (400 MHz, D$_2$O, 298 K) δ_H 4.68 (2 H, s, CH$_2$), 7.00 (2 H, ddd app. dt, $^3J_{H,H}$=9.6 Hz, $^4J_{H,H}$=$^5J_{H,H}$= 2.8 Hz, H-3, -5, Ar), 7.29 (2 H, ddd app. dt, $^3J_{H,H}$=9.7 Hz, $^4J_{H,H}$=$^5J_{H,H}$= 2.8 Hz, H-2, -6, Ar) ppm. ^{13}C-RMN in J_{mod} (100 MHz, D$_2$O, 298 K) δ_C 65.0 (CH$_2$), 115.8 (C-3, -5, Ar), 123.4 (C-4, Ar) 124.4 (C-2, -6, Ar), 157.3 (C-1, Ar), 173.1 (C=O) ppm. GC-MS (MeOH) *m/z* (rel. int. %) 169 [M, - HCl, + CH$_3$] (24).

4-(4-Aminophenoxy)butyric acid hydrochloride (**3b**); yield 71% (2.45 g **3b** starting from 3.95 g **2b**), white crystals, mp 191-193 °C (aq. HCl); [Found: C, 52.06; H, 6.15; N, 5.96%. $C_{10}H_{14}ClNO_3$ (231.07) requires: C, 51.84;

H, 6.09; N, 6.05%]; R_f (ligroin/acetone 1:1 v/v) 0.5. $\nu_{max.}$ (KBr) 3119 (m), 3026 (s), 2918 (s), 2868 (s), 2604 (w), 2559 (w), 1734 (s), 1616 (m), 1565 (m), 1503 (s), 1465 (m), 1440 (w), 1406 (m), 1378 (w), 1345 (w), 1261 (s), 1172 (s), 1118 (w), 1050 (m), 943 (m), 840 (m), 814 (m), 768 (w), 645 (w) cm^{-1}. ^{1}H NMR (400 MHz, D_2O, 298 K) δ_H 1.96 (2 H, tt app. qv., $^3J_{H,H}$=6.7 Hz, β-CH$_2$), 2.43 (2 H, t, $^3J_{H,H}$=7.0 Hz, α-CH$_2$), 3.99 (2 H, t, $^3J_{H,H}$=6.0 Hz, γ-CH$_2$), 6.97 (2 H, ddd app. dt, $^3J_{H,H}$=9.6 Hz, $^4J_{H,H}$=$^5J_{H,H}$= 3.1 Hz, H-3, -5, Ar), 7.26 (2 H, ddd app. dt, $^3J_{H,H}$=9.6 Hz, $^4J_{H,H}$=$^5J_{H,H}$=3.1 Hz, H-2, -6, Ar) ppm. ^{13}C NMR in J_{mod} (100 MHz, D_2O, 298 K) δ_C 23.8 (β-CH$_2$), 30.5 (α-CH$_2$), 67.6 (γ-CH$_2$), 115.8 (C-3, -5, Ar), 122.6 (C-4, Ar), 124.2 (C-2, -6, Ar), 158.3 (C-1, Ar), 178.1 (C=O) ppm. GC-MS (MeOH) m/z (rel. int. %) 209 [M -HCl, + CH$_3$] (20).

Typical procedure for isolation of (4-aminophenoxy)alkanoic acids as free amine. Isolation of compound 1b. 4-(4-aminophenoxy)butyric acid hydrochloride **3b** (2.45 g, 10.60 mmol) was dissolved in distilled water (20 mL). To this solution, anhyd. K_2CO_3 (0.73 g, 5.30 mmol) was added portionwise. The resulted suspension was stirred for 1 h at r.t. then filtered off to give 1.51 g pure compound **1b** (73% yield with respect to **3b**) as a white powder.

(4-Aminophenoxy)acetic acid (**1a**); yield 81% (0.20 g **1a** starting from 0.30 g **3a**), white powder, mp 214 °C (dec.) (Lit. 312 °C [2], 220 °C [3], 215-220 °C [7]); [Found: C, 57.58; H, 5.88; N, 8.25%. $C_8H_9NO_3$ (167.06) requires: C, 57.48; H, 5.43; N, 8.38%]; R_f (EtOH 100%) 0.54. $\nu_{max.}$ (KBr) 2931 (m), 2870 (m), 2630 (m), 2100 (w), 1619 (m), 1592 (m), 1544 (m), 1511 (s), 1411 (m), 1338 (w), 1301 (w), 1258 (m), 1227 (m), 1182 (w), 1057 (m), 916 (w), 822 (m), 729 (m), 596 (w), 578 (w) cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, 298 K) δ_H 4.47 (2 H, s, CH$_2$), 5.51 (3 H, br s, NH$_2$ ⇆ COOH exchangeable), 6.52 (2 H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ar), 6.64 (2 H, d, $^3J_{H,H}$=9.0 Hz, H-2, -6, Ar) ppm. ^{13}C-RMN in J_{mod} (150 MHz, DMSO-d_6, 298 K) δ_C 65.5 (CH$_2$), 115.2 (C-3, -5, Ar), 115.5 (C-2, -6, Ar), 142.5 (C-4, Ar), 149.5 (C-1, Ar), 170.9 (C=O) ppm. GC-MS (MeOH) m/z (rel. int. %) 109 [M+1, - CO$_2$, - CH$_3$] (100).

4-(4-Aminophenoxy)butyric acid (**1b**); yield 73% (1.51 g **1b** starting from 2.45 g **3b**), white powder, mp 143-145 °C (H$_2$O) (Lit. 145.5-146 °C [4]).; [Found: C, 61.75; H, 6.48; N, 6.95%. $C_{10}H_{13}NO_3$ (195.09) requires: C, 61.53; H, 6.71; N, 7.18;%]; R_f (ligroin/acetone 1:1 v/v) 0.5. $\nu_{max.}$ (KBr) 2959 (m), 2872 (m), 2590 (m), 2148 (w), 1623 (m), 1601 (m), 1519 (s), 1507 (s), 1405 (m), 1387 (w), 1302 (m), 1216 (w), 1174 (w), 1077 (w), 1050 (w), 1024 (w), 832 (m), 810 (w), 766 (w), 663 (w) cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, 298 K) δ_H 1.86 (2 H, tt app. qv., $^3J_{H,H}$=6.9 Hz, β-CH$_2$), 2.35 (2 H, t, $^3J_{H,H}$=7.2 Hz, α-CH$_2$), 3.81 (2 H, t, $^3J_{H,H}$=6.3 Hz, γ-CH$_2$), 6.51 (2 H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ar),

6.64 (2 H, d, $^3J_{H,H}$=8.4 Hz, H-2, -6, Ar) ppm. ^{13}C NMR in J_{mod} (100 MHz, DMSO-d_6, 298 K) δ_C 24.6 (β-CH$_2$), 30.3 (α-CH$_2$), 67.1 (γ-CH$_2$), 115.1 (C-3, -5, Ar), 115.5 (C-2, -6, Ar), 142.3 (C-4, Ar), 150.0 (C-1, Ar), 174.4 (C=O) ppm. GC-MS (MeOH) m/z (rel. int. %) 195 [M$^+$] (10).

ACKNOWLEDGMENT

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