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Short Note

3-[1-(4-Methylphenyl)-3-oxo-1,3,4,5,6,7-hexahydro-2*H*-isoindol-2-yl]propanoic Acid

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Abstract: A simple solvent-free synthesis of 3-[1-(4-methylphenyl)-3-oxo-1,3,4,5,6,7-hexahydro-2*H*-isoindol-2-yl]propanoic acid **3** was achieved by fusion of *cis*-2-[(4-methylphenyl)carbonyl]cyclohexanecarboxylic acid **1** with 3-aminopropanoic acid **2**. The structure of this new compound was confirmed by elemental analysis, IR, EI-MS, ^{1}H-NMR and ^{13}C-NMR spectral data.

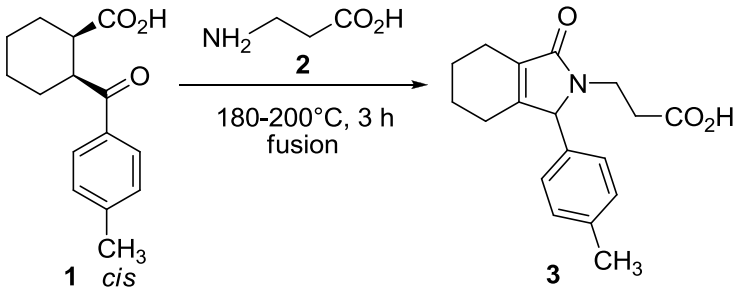
Keywords: isoindolone; 4-oxocarboxylic acid; β-aminoacid

2,3-Dihydro-1*H*-isoindolin-1-one (phthalimidine) as an important hetero ring system is core unit in various naturally occurring alkaloids or synthetic compounds. Several isoindolone derivatives have a range of biological activities including anti-inflammatory (indoprofen) [1], antiarrhytmic (ubisindine) [2,3], nootropic [4], anxiolytic and sedative (pazinaclone and pagoclone) [5,6] or diuretic and antihypertensive activity (chlorthalidone) [7]. Other derivatives have potent 5-HT_{1A} and 5-HT_{2c} receptor antagonist [8,9], antispasmodic [10], antinociceptive (JM-1232) [11] and hypnotic activity [12] while *N*,*N*-phthaloyl derivative of α-, β- and γ-amino acids showed anticonvulsant activity [13]. The isoindolinone moiety is also an integral part of a variety of natural products, such as fumaridine, lennoxamine, nuevamine, or aristoyagonine [14-16].

Recently, we studied of the condensation reaction of the *cis*-cyclohexane-fused γ-oxocarboxylic acid **1** with several primary alkyl-, aryl- and arylalkyl amines [17] or with bifunctional amines [18] to give the corresponding hexahydroisoindolones in good yields. The reactions were performed in refluxing toluene solution in the presence of catalytic amount of *p*-toluenesulfonic acid (PTSA).

In continuation of previous works to develop new isoindole derivatives we investigated the reactivity of naturally occurring amino acids with γ-oxocarboxylic acids. We observed that application of the usual reaction condition (refluxing toluene) was unsuccessful for the condensation of oxocarboxylic acid and amino acid, thus we had to find a more powerful, more effective method. The current work describes the synthesis of 3-[1-(4-methylphenyl)-3-oxo-1,3,4,5,6,7-hexahydro-2*H*-isoindol-2-yl]propanoic acid **3**, which molecule include an isoindoline and a β-alanine moiety (unit) simultaneously.

Scheme 1. Synthesis of the title compound **3**.



Experimental

In a round-bottom flask, a mixture of oxocarboxylic acid **1** (2.46 g, 0.01 mol) and an excess of 3-aminopropanoic acid (β-alanine) **2** (1.07 g, 0.012 mol) was heated at 180–200 ℃ for 3 hours. After cooling to room temperature the mixture was solved in chloroform and purified by column chromatography with chloroform, then EtOAc eluent on silica gel packing. The collected fractions were evaporated and the residue was treated with diethyl ether (15 mL) and kept in refrigerator overnight then was collected and recrystallized from diethyl ether to give the title compound **3** as a white crystalline solid.

Yield: 59%; m.p. 151–153 ℃ R_f: 0.11 (benzene-EtOH-*n*-hexane = 4:1:3, visualization with iodine vapor or by UV light).

IR (KBr) $\nu_{max}cm^{-1}$: 3041 (OH), 2941, 2925 (C-H aliphatic), 1735 (C=O, lactam), 1639 (C=O, carboxylic acid), 1455, 1412, 1287, 1302, 1186, 1173, 1058, 814, 803, 520.

^{1}H NMR (400 MHz, $CDCl_3$) (δ/ ppm): 1.57–2.05 (m, 5H, aliphatic), 2.26 (m, 3H), 2.34 (s, 3H, CH_3), 2.46 (m, 1H) 2.64 (m, 1H), 3.48 (m, 1H), 3.80 (m, 1H), 4.88 (s, 1H, Ar-CH), 6.98 (d, 2H, *J* = 2.4 Hz, Ar-H), 7.22 (d, 2H, *J* = 2.4 Hz, Ar-H), 9.36 (s, br, 1H, COOH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8, 21.7, 22.4, 22.6, 23.7, 36.9 (CH_2-COOH)), 68.5 (N-CH_2-), 77.6 (CH benzylic), 128.0, 130.4, 131.3, 132.8, 139.1, 156.3(C-anellation), 173.3 (C=O), 175.8 (COOH).

Elemental analysis: calculated for $C_{18}H_{21}NO_3$: C, 72.22%, H, 7.07%, N, 4.68%. Found C, 72.25%, H, 7.09%, N, 4.65%.

EI-MS (70eV) *m/z*: 299 (M^+, 82), 281 (22), 238 (100), 212 (27), 185 (18), 105 (93) 91 (71) 77 (50).

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