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Synthesis of 1,4-Dihydropyridine Carboxylic Acids (III)

Jung Jin Suh, You Hwa Hong and Myn Bae
Yuhan Research Center, Kunpo-Shi 435-030, Korea
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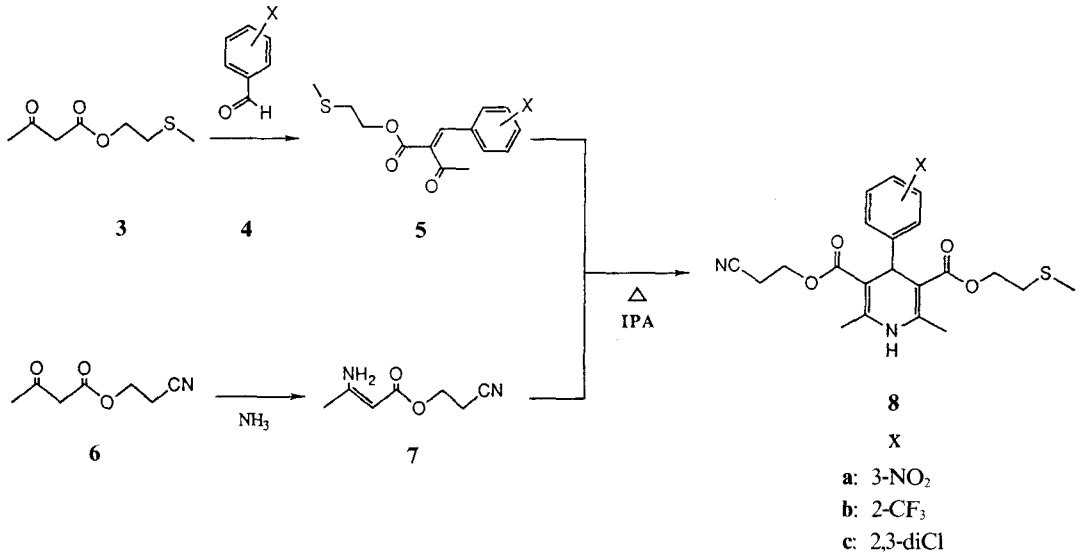
Abstract □ 2,6-Dimethyl-4-(3′-nitrophenyl)1,4-dihydropyridine-3,5-dicarboxylic acid 5-(2′-cyanoethyl) ester **10a** reacted with chloromethyl methylsulfide to give 2,6-dimethyl-4-(3′-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methylthiomethyl 5-(2′-cyanoethyl) ester **11a** in 88.1% yield. The synthesis of 2,6-dimethyl-4-(3′-nitrophenyl)-1,4-dihydropyridine-3,5-dicrboxylic acid 3-methylthiomethyl ester **2a** was achieved in 83% yield by alkaline hydrolysis of compound **11a** in aqueous EtOH.

Keywords □ 1,4-Dihydripyridine. Ca-antagonist. hydrolysis 1,4-dihydropyridine carboxylic acids.

The aryldihydropyridines first prepared by Hantzsch have been found to be highly effective calcium antagonist with suitable pharmacological profile. The discovery of the therapeutic activity of these compouds initiated the various modification of the Hantzsch condensation and the synthesis of numerous 4-aryldihydropyridines and related compounds[1-4]. In a recent study, the pharmacological activity of dissymmetrically substituted ester derivatives of 1,4-dihydropyridine were shown to be superior to those of corresponding symmetrically substituted ester derivaties in many cases[5,6]. Thus, as a part of our continuing effort to develop novel 1,4-dihydropyridine compounds, we have tried to synthesize various dissymmetric 1,4-dihydropyridine derivatives. These compounds were tested for the effect on vascular smooth muscle and a few of them were selected for preclinical tests. The one compound, YH-334 (2,6-dimethyl-4-(3′-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methyl 5-methylthiomethyl ester) showed potent blocking effect on the voltage dependent Ca-channels of vascular smooth muscles. The activity of YH-334 was about 10 times more potent than that of nitrendipine[7]. This result promoted us to extend the methylthiomethyl ester derivatives. To make these compounds conveniently, methylthiomethyl ester mono acid **2** was needed. This compound **2** will be the expected metabolite of YH-334, **1** (Fig. 1).

In this paper we wish to discribe a new synthesis of 1,4-dihydropyridine mono carboxylic acids containing methylthiomethylester moiety, which was important intermediate of YH-334 derivatives. 1,4-Dihydropyridine mono carboxylic acids could be prepared from the 1,4-dihydropyridine 3,5-dicarboxylic acid ester by the modified methods of alkaline hydrolysis. Four researchers developed the hydrolysis methods of symmetric 1,4-dihydropyridine dicarboxylic acid esters, but none of the methods gave selectively 1,4-dihydropyridine mono carboxylic acid in good yield[8-11]. In case of selective hydrolysis, Wehinger *et al.*[12] reported the hydrolysis of cyanoethyl ester and Suh *et al.*[13] selected methylthioethyl ester derivatives. So we tried to combine the two selective hydrolysis methods for preparting compound **2**. The starting compound **8**, 1,4-dihydropyridine 3,5-dicarboxylic acid 3-cyanoethyl 5-methylthioethyl ester, were prepared by the modified Hantzsch condensation in 33-58% yield (Scheme 1).

The starting compound **8a** was refluxed with iodomethane for 16 hrs. to give the corresponding methyliodide salt **9a** yield. The reaction of **8b** and **8c** needed prolong reaction time (4-7 days) and gave corresponding **9a** and **9c** in 67% and 76% yield respectively. The methyliodide salt **9a** was selectively hydrolyzed in aqueous EtOH at pH 11-12 to give, 1,4-dihydropyridine 3,5-dicarboxylic acid 3-cyanoethyl ester **10a** in 92% yield. Muto *et al.* synthesized



Scheme 1

compound **10** in 45% yield from symmetric 1,4-dihydropyridine 3,5-dicarboxylic acid 3-cyanoethyl 5-cyanoethyl ester to confirm the structure of metabolite of benidipine[11].

Compound **9b** and **9c** gave compound **10b** and **10c** in 79.3% and 71.7% yield respectively. 1,4-Dihydropyridine cyanoethyl ester **10a** reacted with chloromethyl methylsulfide in the presence of triethylamine and CH_3CN to give 1,4-dihydropyridine cyanoethyl methylthiomethyl ester **11a** in 88.1% yield. Compound **10b** and **10c** gave compound **11b** and **11c** in 39.2% and 71.85% yield. The synthesis of 1,4-dihydropyridine methylthiomethyl ester **2a** could be achieved in 83% yield by alkaline hydrolysis of compound **11a** in aqueous EtOH. Compound **2b** and **2c** were obtained in 23.3% and 52.4% yield resepectively (Scheme 2). All reaction steps of 4-(2'-trifluoromethylphenyl) and 4-(2',3'-dichlorophenyl)-1,4-dihydropyridine gave somewhat lower yield than the counterpart of 4-(3'-nitrophenyl) 1,4-dihydropyridine compound.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Capilary melting point apparatus and are uncorrected. The pmr spectra were recorded on a Varian VXR-5200 (200 MHz). Chemical shifts are recorded in ppm with tetramethylsilane as the internal standard. The IR spectra were recorded with a Shimazu IR-435 spectrometer.

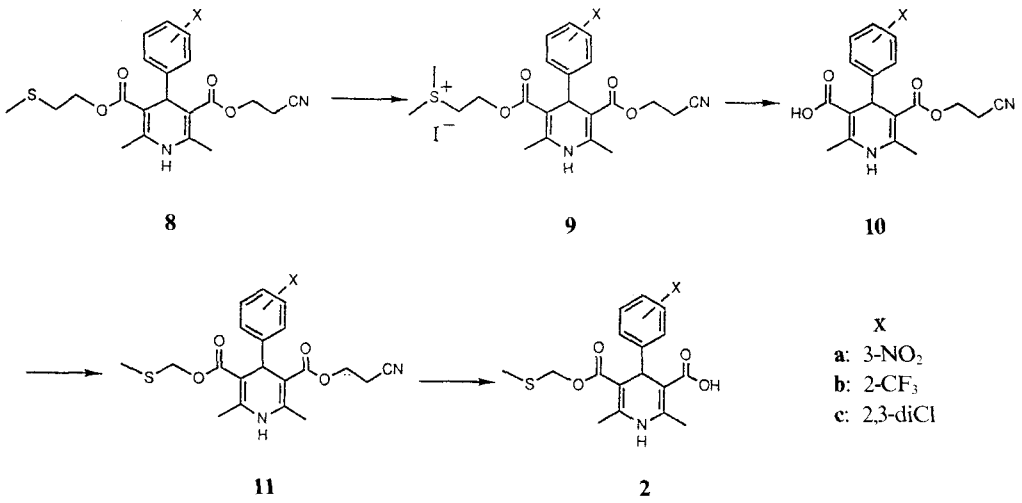
***2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl)-5-(2'-methylthioethyl) ester 8a*[14]**

A mixture of 2-methylthioethyl acetoacetate (**3**, 7.05g, 0.04 mole), 3-nitrobenzaldehyde (**4**, 5.63g, 0.037 mole) and piperidine (0.5 m*l*) in anhydrous benzene (50 m*l*) was heated to reflux for 3 hrs. and then evaporated *in vacuo*. To the residue were added 2'-cyanoethyl 3-aminocrotonate (**7**, 5.7g, 0.037 mole) and IPA (150 m*l*). The reaction mixture was refluxed for 12 hrs. The solvent was evaporated *in vacuo*. The residual oil was purified on silica gel column (EtOAc/*n*-Hexane=1 : 1).

Yield: 7g (42.5%); mp: 148-150℃ (lit. 152℃); ^{1}H-NMR (DMSO-d_6): δ 2.05 (s, 3H, -SCH_3), 2.17 (s, 6H, -CH_3X2), 2.63 (m, 2H, -CH_2S-), 2.85 (m, 2H, -CH_2CN), 4.0-4.2 (m, 4H, -OCH_2-X2), 5.02 (s, 1H, C_4-H), 7.45-8.05 (m, 4H, Ar-H), 9.20 (s, 1H, -NH-); IR (KBr) cm^{-1}: 3360 (NH), 1703 (C=O).

2,6-Dimethyl-4-(2'-trifluoromethylphenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) 5-(2'-methylthioethyl) ester 8b

Yield: 32.8%; mp: 109-111℃; ^{1}H-NMR (DMSo-d_6): δ 2.01 (s, 3H, -SCH_3), 2.27 (s, 6H, -CH_3X2), 2.61 (t, 2H, -CH_2S-), 2.8 (t, 2H, -CH_2CN), 4.0-4.2 (m, 4H,



Scheme 2

-OCH_2-X2), 5.42 (s, 1H, C_4-H), 7.3-7.6 (m, 4H, Ar-H), 9.0 (s, 1H, -NH-); IR (KBr) cm^{-1}: 3351.5 (NH), 1700.5 (C=O).

2,6-dimethyl-4-(2',3'-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) 5-(2'-methylthioethyl) ester 8c

Yield: 57.9%; mp: 90-92℃; ^{1}H-NMR (DMSO-d_6): δ 2.05 (s, 3H, -SCH_3), 2.3 (s, 6H, -CH_3X2), 2.6 (t, 2H, -CH_2S-), 2.8 (t, 2H, -CH_2CN), 4.2 (m, 4H, -OCH_2-X2), 5.4 (s, 1H, C_4-H), 7.2-7.5 (m, 3H, Ar-H), 9.1 (s, 1H, -NH-); IR (KBr) cm^{-1}: 3333.0 (NH), 1699.9 (C=O).

2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) 5-(2'-methylthioethyl) ester methyliodide salt 9a

A mixture of 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) 5-(2'-methylthioethyl) ester (**8a**, 11.14g, 0.025 mole) and iodomethane (50 m*l*) was heated for 16 hrs. The solvent was evaporated. The residue was treated with ether (50 m*l*) and yellow precipitate were filtered and dried.

Yield: 13.64g (92%); mp: 140-142℃; ^{1}H-NMR (DMSO-d_6): δ 2.25 (s, 3H, -CH_3), 2.26 (s, 3H, -CH_3), 2.91 (s, 3H, -SCH_3), 2.93 (s, 3H, -SCH_3), 2.91 (m, 2H, -CH_2CN), 3.65 (m, 2H, -CH_2S-), 4.18 (m, 2H, -OCH_2-), 4.42 (m, 2H, -OCH_2-), 5.01 (s, 1H, C_4-H), 7.51-8.03 (m, 4H, Ar-H), 9.31 (s, 1H, -NH-); IR (KBr) cm^{-1}: 3357 (NH), 1696 (C=O).

2,6-Dimethyl-4-(2'-trifluoromethylphenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) 5-(2'-methylthioethyl) ester methyliodide salt 9b

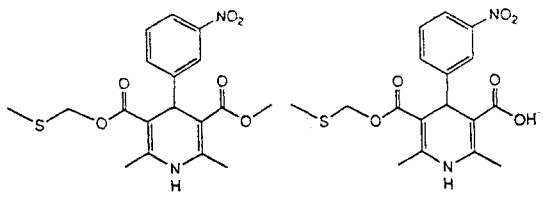
A mixture of 2,6-dimethyl-4-(2'-trifluoromethylphenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) 5-(2'-methylthioethyl) ester (**8b**, 0.6g, 1.3 mmole) and iodomethane (20 m*l*) was heated to reflux for 4 days. After cooling to room temperature, ether (30 m*l*) was added to the reaction mixture. The reaction mixture was stirred for 30 min. and filtered.

Yield: 66.7%; mp: 112-114℃; ^{1}H-NMR (DMSO-d_6): δ 2.27 (s, 6H, -CH_3X2), 2.80 (t, 2H, -CH_2CN), 2.85 (s, 3H, -SCH_3), 2.88 (s, 3H, -SCH_3), 3.56 (t, 2H, -CH_2 S-), 3.9-4.6 (m, 4H, -OCH_2-X2), 5.40 (s, 1H, C_4-H), 7.3-7.6 (m, 4H, Ar-H), 9.15 (s, 1H, -NH-); IR (KBr) cm^{-1}: 3349 (NH), 1709 & 1684 (C=O).

2,6-Dimethyl-4-(2',3'-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) 5-(2'-methylthioethyl) ester methyliodide salt 9c

A mixture of 2,6-dimethyl-4-(2',3'-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) 5-(2'-methylthioethyl) ester **8c** and iodomethane was heated to reflux for 7 days.

Yield: 76.3%; mp: 120-122℃; ^{1}H-NMR (DMSO-d_6): δ 2.3 (s, 6H, -CH_3X2), 2.8-3.0 (m, 8H, -SCH_3X2 & -CH_2CN), 3.6 (t, 2H, -CH_2S-), 4.2 (t, 2H, -OCH_2-),



1(YH-334) 2

Fig. 1. Structures of 1 and 2.

4.4 (m, 2H, -OCH_2-), 5.32 (s, 1H, C_4-H), 7.2-7.5 (m, 3H, Ar-H), 9.2 (s, 1H, -NH-); IR (KBr) cm^{-1}: 3403.0 (NH), 1668.6 & 1709.5 (C=O).

2,6-Dimethyl-4-(3'-nitrophenyl)1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) ester 10a

To the mixture of 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) 5-(2'-methylthioethyl) ester methyliodide salt (**9a**, 11.75g, 0.02 mole) and 50% aqueous EtOH (200 m*l*) was added 2N-NaOH solution slowly at pH 11-12. The solution was stirred for 1 hr. and acidified with d-HCl at pH 1-2. The yellow precipitate was filtered and dried *in vacuo* over P_2O_5.

Yield: 7.43g (lit. 196-198℃); ^{1}H-NMR (DMSO-d_6): δ 2.35 (s, 6H, -CH_3X2), 2.83 (m, 2H, -CH_2CN), 4.18 (m, 2H, -OCH_2-), 5.05 (s, 1H, C_4-H), 7.5-8.05 (m, 4H, Ar-H), 9.1 (s, 1H, -NH-), 11.9 (br, 1H, -COOH); IR (KBr) cm^{-1}: 3351 (NH), 1709 (C=O).

2,6-Dimethyl-4-(2'-trifluoromethylphenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) ester 10b

Yield: 79.3%; mp: 150-151℃; ^{1}H-NMR (DMSO-d_6): δ 2.20 (s, 3H, -CH_3), 2.25 (s, 3H, -CH_3), 2.75 (t, 2H, -CH_2CN), 3.9-4.2 (m, 2H, -OCH_2), 5.38 (s, 1H, C_4-H), 7.27-7.51 (m, 4H, Ar-H), 8.83 (s, 1H, -NH-); IR (KBr) cm^{-1}: 3395 (NH), 1686 (C=O).

2,6-Dimethyl-4-(2',3'-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) ester 10c

Yield: 71.7%; mp: 156-159℃; ^{1}H-NMR (DMSO-d_6): δ 2.3 (s, 6H, -CH_3X2), 2.8 (t, 2H, -CH_2CN), 4.2 (t, 2H, -OCH_2-), 5.3 (s, 1H, C_4-H), 7.2-7.5 (m, 3H, Ar-H), 8.92 (s, 1H, -NH-), 11.7 (br, 1H, -COOH); IR (KBr) cm^{-1}: 3330.0 (NH), 1663.5 & 1695.0 (C=O).

2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methylthiomethyl 5-(2'-cyanoethyl) ester 11a

To the mixture of 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) ester (**10a**, 6.68g, 0.018 mole) and acetonitrile (100 m*l*) was added Et_3N (5 m*l*). After the mixture was stirred for 30 min., chloro methyl methylsulfide (2.3 m*l*) was added to the mixture. The reaction mixture was stirred at room temperature for 3 days. The solvent was evaporated *in vacuo*.

The residue was dissolved in EtOAc (100 m*l*) and the solution was washed with water and saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous $MaSO_4$ and evaporated *in vacuo*. The yellow precipitate was crystallized from EtOH.

Yield: 7.22g (88.1%); mp: 147-149℃; ^{1}H-NMR (DMSO-d_6): δ 2.04 (s, 3H, -SCH_3), 2.32 (s, 6H, -CH_3 X2), 2.84 (m, 2H, -CH_2CN), 4.15 (m, 2H, -OCH_2-), 4.99 (s, 1H, C_4-H), 5.12 (q, 2H, -OCH_2S-), 7.54-8.03 (m, 4H, Ar-H), 9.23 (s, 1H, -NH-); IR (KBr) cm^{-1}: 3370 (NH), 1697 (C=O).

2,6-Dimethyl-4-(2'-trifluoromethylpohenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) 5-methylthiomethyl ester 11b

Yield: 39.2% [after column (EtOAc/*n*-Hexane=1 : 2)]; mp: amorphous form; ^{1}H-NMR ($CDCl_3$): δ 2.07 (s, 3H, -SCH_3), 2.30 (s, 3H, -CH_3), 2.33 (s, 3H, -CH_3), 2.63 (t, 2H, -CH_2CN), 4.16-4.36 (m, 2H, -OCH_2-), 5.05 (q, 2H, -OCH_2S-), 5.56 (s, 1H, C_4-C), 6.29 (s, 1H, -NH-), 7.24-7.54 (m, 4H, Ar-H); IR (KBr) cm^{-1}: 3335 (NH), 1698 (C=O).

2,6-Dimethyl-4-(2',3'-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2'-cyanoethyl) 5-methylthiomethyl ester 11c

Yield: 71.85%; mp: oil; ^{1}H-NMR (DMSO-d_6): δ 2.0 (s, 3H, -SCH_3), 2.3 (s, 6H, -CH_3X_2), 2.8 (t, 2H, -CH_2CN), 4.1 (m, 2H, -OCH_2-), 5.1 (q, 2H, -OCH_2 S-), 5.4 (s, 1H, C_4-H), 7.2-7.5 (m, 3H, Ar-H), 9.2 (s, 1H, -NH-) IR (KBr) cm^{-1}: 3334.0 (NH), 1698.9 (C=O).

2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methylthiomethyl ester 2a

2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-methylthiomethyl 5-(2'-cyanoethyl) ester (**11a**, 4.31g, 0.01 mole) was suspended in 50% EtOH (100 m*l*). To the suspension was added 2N-NaOH (6 m*l*) and the mixture was stirred at room temperature for 4 hrs. To the reaction solution was added N-HCl at pH 1-2. The precipitate was filtered and dried.

Yield: 3.14g (83%); mp: 184-186℃; ^{1}H-NMR (DMSO-d_6) δ 2.03 (s, 3H, -SCH_3), 2.29 (s, 3H, -CH_3), 2.33 (s, 3H, -CH_3), 5.02 (s, 1H, C_4-H), 5.15 (q, 2H, -OCH_2S-), 7.56-8.04 (m, 4H, Ar-H), 9.09 (s, 1H, -NH-), 12.0 (br, 1H, -COOH); IR (KBr) cm^{-1}: 3339 (NH), 1706 (C=O).

2,6-Dimethyl-4-(2′-trifluoromethylphenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 5-methylthiomethyl ester 2b

Yield: 23.3% [after column (EtOAc/*n*-Hexane=1 : 2)]; mp: 155-157℃; ^{1}H-NMR ($CDCl_3$): δ 2.05 (s, 3H, -SCH_3), 2.30 (s, 3H, -CH_3), 2.35 (s, 3H, -CH_3), 5.04 (q, 2H, -OCH_2S-), 5.55 (s, 1H, C_4-H), 5.75 (s, 1H, -NH-), 7.26-7.48 (m, 4H, Ar-H); IR (KBr) cm^{-1}: 3347 (NH), 1688 (C=O).

2,6-Dimethyl-4-(2′,3′-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 5-methylthiomethyl ester 2c

Yield: 52.4%; mp: 175-177℃; ^{1}H-NMR (DMSO-d_6): δ 2.0 (s, 3H, -SCH_3), 2.3 (d, 6H, -CH_3X2), 5.05 (q, 2H, -OCH_2S-), 5.3 (s, 1H, C_4-H), 7.2-7.5 m, 3H, Ar-H), 9.03 (s, 1H, -NH-), 11.72 (s, 1H, -COOH); IR (KBr) cm^{-1}: 3332.0 (NH), 1664.6 (C=O).

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