EFFICIENT SYNTHESIS OF 5-SUBSTITUTED ETHYL 1,2,4-TRIAZOLE-3-CARBOXYLATES

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Easily accessible carboxylic acid hydrazides undergo cyclocondensation with ethyl carbethoxyformimidate, giving 5-substituted ethyl 1,2,4-triazole-3-carboxylates. These are important building blocks in organic synthesis. The approach we used to obtain title compounds made possible synthesis of 3-(2-aminophenyl)-1,2,4-triazole

Introduction

The 1,2,4-triazole ring is an ubiquitous structural feature of many synthetic compounds with diversified therapeutic efficacy [1]. For example ethyl 1,2,4-triazole-3-carboxylate is used for obtaining synthetic nucleoside analogue ribavirin [2-4]. There are number of reports on the synthesis of 5-substituted ethyl 1,2,4-triazole-3-carboxylates [5-10]. In all cases 1,2,4-triazoles were generated on a final stage utilizing an intramolecular condensation of acylamidrazones. The required acylamidrazones were obtained employing three different ways from: mixed anhydrides and ethyl 2-amino-2-hydrazono acetate [5]; thioamides or its analogues and acylhydrazides [6-8]; imidoesters and acylhydrazides [9,10]. Last method was used for synthesis only of a few 1,2,4-triazole-3-carboxylates. The aim of the current work is to show possibility of using ethyl

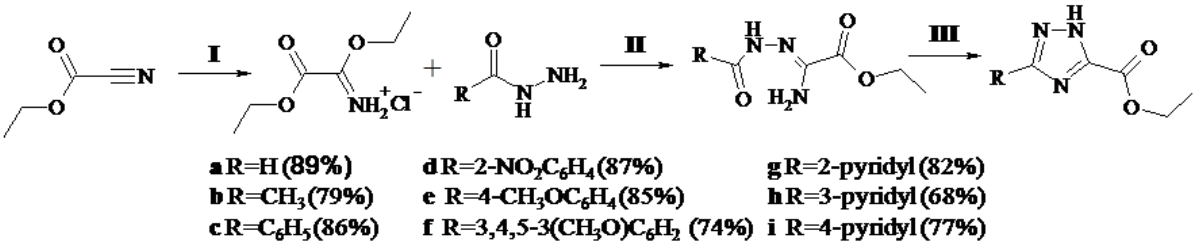

Figure 1. Synthesis of 1,2,4-triazole-3-carboxylates. *Reagents and conditions:* (I) HCl (gas), EtOH, 0˚C. (II) EtOH, NEt_3, room temp., 12 h. (III) PhOPh, reflux, 1 min.

carbethoxyformimidate in synthesis of 5-substituted ethyl 1,2,4-triazole-3-carboxylates from different acylhydrazides **(Figure 1)**.

Results and discussion

5-Substituted ethyl 1,2,4-triazole-3-carboxylates were prepared, starting from corresponding hydrazides **(Figure 1)**. These were first transformed into acylamidrazones **3**, by reaction with carbethoxyformimidate **2**, prepared by the standard procedure from ethylcyanoformate [11]. Thermal intramolecular cyclization of **3** gave title compounds **4**.

Since some derivatives of 1,2,4-triazole-3-carboxylates are widely used in synthetic chemistry, it was interesting to obtain new compounds of this class with different substituents in 5-th position of azole. On the first stage we acylate different type of acylhydrazides, i.e. aliphatic, aromatic and heterocyclic with carbethoxyformimidate **2**. In all cases reaction undergoes in alcohol solution at room temperature. Further heating of **3** in diphenylether solution results in the corresponding triazoles **4**.

It is known that triazolyl carboxylic acid decarboxilates under mild conditions [10]. We used this property for obtaining of 3-(2-aminophenyl)-1,2,4-triazole **7**, which was used by some investigators as synthon for obtaining of potentially biologically active compounds [12,13]. **4d** was hydrolysed under basic condition **(Figure 2)**. Further heating of the obtained acid **5** above its melting point results in 3-(2-nitrophenyl)-1,2,4-triazole **6**. Reduction of **6** catalyzed by Pd/C leads to the formation of 3-(2-aminophenyl)-1,2,4-triazole **7**.

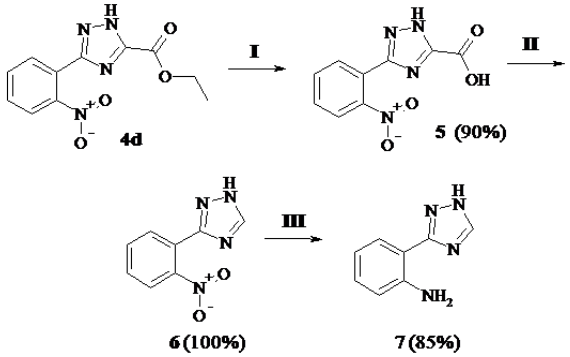

Figure 2. Synthesis of 3-(2-aminophenyl)-1,2,4-triazole. *Reagents and conditions:* (I) NaOH, H_2O, room temp., 6 h.; HCl. (II) heating, 135-140˚C, 5 min. (III) N_2H_4, Pd/C (5%), MeOH, reflux, 5 h.

Conclusions

In summary, 6 new 5-Substituted ethyl 1,2,4-triazole-3-carboxylates were synthesized on a preparative scale through the condensation of easily accessible acylhydrazides and carbethoxyformimidate. Additionally, new route of obtaining 3-(2-aminophenyl)-1,2,4-triazole was developed.

Experimental part

^{1}H NMR (400 MHz) spectra were recorded on Varian 400 spectrometer in $CDCl_3$ solution at room temperature utilizing Me_4Si as internal standard. Melting points were measured with a Buchi melting-point apparatus and are reported uncorrected. Elemental analyses were carried out at Perkin-Elmer 2400 CHN Analyzer. The LC-MS spectra were obtained on an Agilent 1100 Series high-performance liquid

chromatograph equipped with a diode matrix with an Agilent LC/MSD SL mass selective detector; the ionization method is atmospheric-pressure chemical ionization (APCI).

Carbethoxyformimidate **2** was prepared according to the literature method [11]. Acylhydrazides were produced by standard methods from corresponding carboxylic acids [14].

General procedure for the preparation of 5-Substituted ethyl 1,2,4-triazole-3-carboxylates (4a-i)

Acylhydrazide (25 mmol) was added to solution of **2** 4.5g (25 mmol) and triethylamine 4.2 mL (30 mmol) in ethanol (50 ml). The reaction mixture was stirred at room temperature for 12 h and precipitated product **3** was filtered off. The crude product was washed with ethanol and used in the next step without purification. Reflux of **3** in diphenyl ether (50 ml) solution for 1 minute resulted in **4**. Precipitated triazole **4** was filtered off, after the temperature fell down to 40°C, washed with hexane and recristalized from toluene.

Ethyl 1*H*-1,2,4-triazole-5-carboxylate (4a). 3.2 g (89%), white crystals, mp 171-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H= 8.65 (1H, s., CH Trz), 4.50 (2H, q., $^3J_{HH}$= 7.2 Hz, OCH_2), 1.45 (3H, t., $^3J_{HH}$= 7.2 Hz, CH_3). Anal. calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.78; H, 4.93; N, 29.27. LC-MS found m/z 141 $[M+H]^+$.

Ethyl 3-methyl-1*H*-1,2,4-triazole-5-carboxylat (4b). 2.3 g (79%), white crystals, mp 169-172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H= 4.45 (2H, q., $^3J_{HH}$= 7.2 Hz, OCH_2), 2.62 (3H, s., CH_3), 1.39 (3H, t., $^3J_{HH}$= 7.2 Hz, CH_3). Anal. calcd. for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.37; H, 5.93; N, 27.18. LC-MS found m/z 155 $[M+H]^+$.

Ethyl 3-phenyl-1*H*-1,2,4-triazole-5-carboxylate (4c). 2.6 g (86%), white crystals, mp 158-161 °C. ^{1}H NMR (400.13MHz, CD Cl_3): δ_H= 8.01 (2H, d., $^3J_{HH}$= 6.4 Hz, Ar), 7.39 (3H, m., Ar), 4.39 (2H, q., $^3J_{HH}$= 7.2 Hz, OCH_2), 1.31 (3H, t., $^3J_{HH}$= 7.2 Hz, CH_3). Anal. calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.75; H, 5.17; N, 19.21. LC-MS found m/z 217 $[M+H]^+$.

Ethyl 3-(2-nitrophenyl)-1*H*-1,2,4-triazole-5-carboxylate (4d.) Yield 1.8 g (87%), white crystals, mp 167-169 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ_H= 7.95 (1H, d., $^3J_{HH}$= 7.6, Ar), 7.89 (1H, d., $^3J_{HH}$= 8.0, Ar), 7.65 (1 H, t., $^3J_{HH}$= 6.8 Hz, Ar), 7.59 (1H, t., $^3J_{HH}$= 6.4 Hz, Ar), 4.46 (2H, q., $^3J_{HH}$= 7.2 Hz, OCH_2), 1.39 (3H, t., $^3J_{HH}$= 6.4 Hz, CH_3). Anal. calcd. for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 50.23; H, 4.6; N, 20.87. LC-MS found m/z 266 $[M+H]^+$.

Ethyl 3-(4-methoxyphenyl)-1*H*-1,2,4-triazole-5-carboxylate (4e). 2.5 g (85%), white crystals, mp 173-175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H= 7.93 (2H, d., $^3J_{HH}$= 4.4 Hz, Ar), 6.87 (2H, d., $^3J_{HH}$= 4.4 Hz, Ar), 4.38 (2H, q.,

$^3J_{HH}$= 6.8 Hz, OCH_2), 3.79 (3H, s., OCH_3), 1.29 (3H, t., $^3J_{HH}$= 6.4 Hz, CH_3). Anal. calcd. for $C_{12}H_{12}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.38; H, 5.25; N, 17.07. LC-MS found m/z 247 $[M+H]^+$.

Ethyl 3-(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazole-5-carboxylate (4f). 1.3 g (74%), white crystals, mp 185-187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H= 7.28 (2H, s., Ar), 4.4 (2H, q., $^3J_{HH}$= 6.8 Hz, OCH_2), 3.82 (3H, s., OCH_3), 3.72 (6H, s., OCH_3), 1.31 (3H, t., $^3J_{HH}$= 7.2 Hz CH_3). Anal. calcd. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found: C, 54.85; H, 5.43; N, 13.57. LC-MS found m/z 307 $[M+H]^+$.

Ethyl 3-(pyridin-2-yl)-1*H*-1,2,4-triazole-5-carboxylate (4g). Yield 2.4 g (82%), white crystals, mp 164-166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H= 8.77 (1H, d., $^3J_{HH}$= 7.6 Hz , Py), 8.39 (1H, d., $^3J_{HH}$= 7.6 Hz, Py), 7.92 (1H, t., $^3J_{HH}$= 7.2 Hz, Py), 7.47 (1H, t, $^3J_{HH}$= 6.0 Hz, Py), 4.48 (2H, q., $^3J_{HH}$= 7.2 Hz, OCH_2), 1.42 (3H, t., $^3J_{HH}$= 7.2 Hz, CH_3). Anal. calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.37; H, 4.52; N, 24.95. LC-MS found m/z 218 $[M+H]^+$.

Ethyl 3-(pyridin-3-yl)-1*H*-1,2,4-triazole-5-carboxylate (4h). Yield 1.7 g (68%), white crystals, mp 171-174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H= 9.54(1H, s., $^3J_{HH}$= 0.8 Hz, Py), 8.76(1H, s., Py), 8.58 (1H, d., $^3J_{HH}$= 6.8 Hz, Py), 7.52 (1H, t., $^3J_{HH}$= 4.8 Hz, Py), 4.53 (2H, q., $^3J_{HH}$= 6.8 Hz, OCH_2), 1.44 (3H, t., $^3J_{HH}$= 6.8 Hz, CH_3). Anal. calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.19; H, 4.57; N, 24.89. LC-MS found m/z 219 $[M+H]^+$.

Ethyl 3-(pyridin-4-yl)-1*H*-1,2,4-triazole-5-carboxylate (4i). Yield 2.7 g (77%), white crystals, mp 177-179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H= 8.81 (2H, s., $^3J_{HH}$= 4.4 Hz, Py), 8.15 (2H, d., $^3J_{HH}$= 4.8 Hz, Py), 4.52 (2H, q., $^3J_{HH}$= 7.2 Hz, OCH_2), 1.43 (3H, t., $^3J_{HH}$=7.2 Hz, CH_3). Anal. calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.26; H, 4.58; N, 24.55. LC-MS found m/z 218 $[M+H]^+$.

3-(2-nitrophenyl)-1*H*-1,2,4-triazole-5-carboxylic acid (5). A solution of ethyl 3-(2-nitrophenyl)-1*H*-1,2,4-triazole-5-carboxylate **4d** (2.62 g, 10 mmol) and NaOH (1.2 g, 30 mmol) in H_2O (25 mL) was magnetically stirred for 6 h at room temperature. Then HCl (13,2 mL, 2,5 N) was added to solution. After acidification white crystals of **5** have been formed and filtered off. Yield 2,1 g (90%), white crystals, mp 134-135 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H= 8.68 (1H, dd., Ar), 7.93 (1H, dd., Ar), 7.79 (1H, dd., Ar), 7.7 (1H, dd., Ar). Anal. calcd. for $C_9H_6N_4O_4$: C, 46.16; H, 2.58; N, 23.93. Found: C, 46.27; H, 2.52; N, 23.99. LC-MS found m/z 234 $[M+H]^+$.

3-(2-nitrophenyl)-1H-1,2,4-triazole (6). Melting of **5** leads to formation of **6** in quantitative yield, mp 167-168 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H= 14.37 (1H, s., Trz), 8.68 (1H, s., CH Trz), 8.0 (1H, m., Ar), 7.87 (1H, m., Ar), 7.76 (1H, m., Ar), 7.66 (1H, m., Ar). Anal. calcd. for $C_8H_6N_4O_2$: C, 50.53; H,

3.18; N, 29.46. Found: C, 50.37; H, 3.22; N, 29.85. LC-MS found m/z 190 $[M+H]^+$.

2-(1*H*-1,2,4-triazol-3-yl)aniline (7). A mixture of $N_2H_4 \times H_2O$ (1,56 mL 30 mmol) and 5% Pd/C (0,17 g) in MeOH was magnetically stirred for 10-15 min. Then **6** (1,7 g 9 mmol) was added to solution, and the mixture was refluxed for 5 h. The solution was filtered off. Obtained liquor was evaporated in vacuo and recrystallized from toluene. Yield 1.2 g (85 %), white crystals, mp 146-147 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H= 14.4-13.8 (1H, s., Trz), 8.38 (1H, s., CH Trz), 7.82 (1H, m., Ar), 7.1 (1H, t, $^3J_{HH}$= 8.0 Hz, Ar), 6.78 (1H, d., $^3J_{HH}$= 8.4 Hz, Ar), 6.58 (3H, m., Ar, NH_2). Anal. calcd. for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 60.04; H, 5.01; N, 34.95. LC-MS found m/z 160 $[M+H]^+$.

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