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

Dmytro M. Khomenko*, Roman O. Doroschuk, and Rostyslav D. Lampeka

Department of Chemistry, Taras Shevchenko National University of Kyiv, Volodymyrska Str. 64, Kyiv, Ukraine.
dkhomenko@ukr.net

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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, NEt₃, 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.

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

1H NMR (400 MHz) spectra were recorded on Varian 400 spectrometer in CDCl3 solution at room temperature utilizing Me₄Si 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).

Carbethoxyformiminate 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 recrystallized from toluene.

**Ethyl 1H-1,2,4-triazole-5-carboxylate (4a).** 3.2 g (89%), white crystals, mp 171-173 °C. 1H NMR (400 MHz, CDCl3): δH= 8.65 (1H, s., CH Trz), 4.50 (2H, q., 3JHH= 7.2 Hz, OCH2), 1.45 (3H, t., 3JHH= 7.2 Hz, CH3). Anal. calcd. for C3H7N2O: C, 50.90; H, 5.19; N, 29.77. Found: C, 50.90; H, 5.19; N, 29.77. MS-found m/z 141 [M+H]+.

**Ethyl 3-methyl-1H-1,2,4-triazole-5-carboxylat (4b).** 2.3 g (79%), white crystals, mp 169-172 °C. 1H NMR (400 MHz, CDCl3): δH= 4.45 (2H, q., 3JHH= 7.2 Hz, OCH2), 2.62 (3H, s., CH3), 1.39 (3H, t., 3JHH= 7.2 Hz, CH3). Anal. calcd. for C9H12N4O2: C, 46.37; H, 5.93; N, 27.08. Found: C, 46.37; H, 5.93; N, 27.18. LC-MS found m/z 155 [M+H]+.

**Ethyl 3-phenyl-1H-1,2,4-triazole-5-carboxylate (4c).** 2.6 g (86%), white crystals, mp 158-161 °C. 1H NMR (400.13MHz, CDCl3): δH= 8.01 (2H, d., 3JHH= 6.4 Hz, Ar), 7.39 (3H, m., Ar), 4.39 (2H, q., 3JHH= 7.2 Hz, OCH2), 1.31 (3H, t., 3JHH= 7.2 Hz, CH3). Anal. calcd. for C11H11N3O2: 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)-1H-1,2,4-triazole-5-carboxylate (4d).** Yield 1.8 g (87%), white crystals, mp 167-169 °C. 1H NMR (400 MHz, CDCl3): δH= 7.95 (1H, d., 3JHH= 7.6, Ar), 7.89 (1H, d., 3JHH= 8.0, Ar), 7.65 (1H, t., 3JHH= 6.8 Hz, Ar), 7.59 (1H, t., 3JHH= 6.4 Hz, Ar), 4.46 (2H, q., 3JHH= 7.2 Hz, OCH2), 1.39 (2H, q., 3JHH= 6.4 Hz, CH3). Anal. calcd. for C11H12N4O4: 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)-1H-1,2,4-triazole-5-carboxylate (4e).** 2.5 g (85%), white crystals, mp 173-175 °C. 1H NMR (400 MHz, CDCl3): δH= 7.93 (2H, d., 3JHH= 4.4 Hz, Ar), 6.87 (2H, s., 3JHH= 4.4 Hz, Ar), 4.38 (2H, q.,
Ethyl 3-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole-5-carboxylate (4f). Yield 1.3 g (74%), white crystals, mp 185-187 °C. 1H NMR (400 MHz, CDCl3): δH= 7.28 (2H, s., Ar), 4.4 (2H, q., JHH= 6.8 Hz, OCH2), 3.82 (3H, s., OCH3), 3.72 (6H, s., OCH3), 1.31 (3H, t., JHH= 7.2 Hz CH3). Anal. calcd. for C14H17N3O3: 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)-1H-1,2,4-triazole-5-carboxylate (4g). Yield 2.4 g (82%), white crystals, mp 164-166 °C. 1H NMR (400 MHz, CDCl3): δH= 8.77 (1H, d., JHH= 7.6 Hz, Py), 8.39 (1H, d., JHH= 7.6 Hz, Py), 7.92 (1H, t., JHH= 7.2 Hz, Py), 7.47 (1H, t., JHH= 7.2 Hz, OCH2), 1.42 (3H, t., JHH= 7.2 Hz, CH3). Anal. calcd. for C10H10N3O2: 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)-1H-1,2,4-triazole-5-carboxylate (4h). Yield 1.7 g (68%), white crystals, mp 171-174 °C. 1H NMR (400 MHz, CDCl3): δH= 9.54(1H, s., JHH= 0.8 Hz, Py), 8.76(1H, s., Py), 8.58 (1H, d., JHH= 6.8 Hz, Py), 7.52 (1H, t., JHH= 4.8 Hz, Py), 4.53 (2H, q., JHH= 6.8 Hz, OCH2), 1.44 (3H, t., JHH= 6.8 Hz, CH3). Anal. calcd. for C10H10N4O2: 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)-1H-1,2,4-triazole-5-carboxylate (4i). Yield 2.7 g (77%), white crystals, mp 177-179 °C. 1H NMR (400 MHz, CDCl3): δH= 8.81 (2H, s., JHH= 4.4 Hz, Py), 8.15 (2H, d., JHH= 4.8 Hz, Py), 4.52 (2H, q., JHH= 7.2 Hz, OCH2), 1.43 (3H, t., JHH=7.2 Hz, CH3). Anal. calcd. for C10H10N4O2: 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)-1H-1,2,4-triazole-5-carboxylic acid (5). A solution of ethyl 3-(2-nitrophenyl)-1H-1,2,4-triazole-5-carboxylate 4d (2.62 g, 10 mmol) and NaOH (1.2 g, 30 mmol) in H2O (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.). 1H NMR (400 MHz, DMSO-d6): δH= 8.68 (1H, dd., Ar), 7.93 (1H, dd., Ar), 7.79 (1H, dd., Ar), 7.7 (1H, dd., Ar). Anal. calcd. for C8H6N4O4: 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. 1H NMR (400 MHz, DMSO-d6): δH= 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 C8H6N4O2: 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-(1H-1,2,4-triazol-3-yl)aniline (7). A mixture of N$_2$H$_4$×H$_2$O (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, $^3$J$_{HH}$= 8.0 Hz, Ar), 6.78 (1H, d, $^3$J$_{HH}$= 8.4 Hz, Ar), 6.58 (3H, m., Ar, NH$_2$). Anal. calcd. for C$_8$H$_8$N$_4$: 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]^+.

References