Moroccan Journal of Chemistry
ISSN: 2351-812X
http://revues.imist.ma/?journal=morjchem&page=login
Achmlale & al. / Mor. J. Chem. Vol 9 N°1 (2021) 109-115

Synthesis of Some New *N*-protected 2-(Substituted-1*H*-1,2,3-Triazol-1-yl)glycine Derivatives by Selective Saponification

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Received 30 *Aug 2019,*
Revised 09 Jan 2021,
Accepted 12 Feb 2021

Abstract

We report in this paper the synthesis of some new *N*-protected 2-(substituted-1*H*-1,2,3-triazol-1-yl)glycine derivatives through selective saponification reaction in basic medium. The structures of obtained products were established on the basis of NMR spectroscopy (^{1}H, ^{13}C), MS data and elemental analysis.

Keywords: *Amino acids, N-protected glycine, 1,2,3-triazole, saponification.*

1. Introduction

Aminoacids have a wide range of activities, particularly in medicine: Antibiotics, antiepileptics, neuroexcitators, fungicides [1], biochemistry [2] and enzymology especially as enzyme inhibitors [3]. The literature describes a large number of work on molecules carrying the 1,2,3-triazole ring. These play a fundamental role in different areas. Thus, they present activities in pharmacology [4] as an antimicrobial chemical species [5] whose active principles are derivatives of 1,2,3-coumarin substituted in the 4-position, as anti-cancer molecules [6], such as 1,2,3-triazole condensed derivatives of N-arylpyrazole. Active substances have antifungal properties [7,8], especially with 1,2,3-triazole analogs [7] and 1,2,3-triazole phenylhydrazone derivatives [8]. Finally, two works concerning the biological interest of these nitrogen heterocycles recently cited on 1,2,3-triazole hydrazide derivatives having antiphytopathogenic activity [9] and on 1,2,3-triazole fatty acid derivatives, which have antituberculous remedies [10].

2. Experimental Section

2.1 Materials

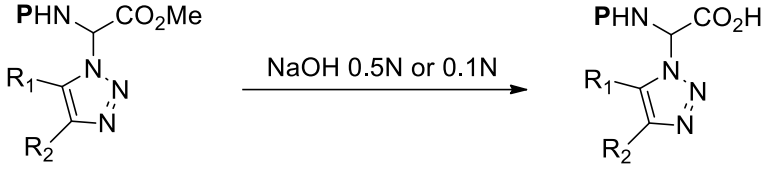
Uncorrected melting points were measured using a capillary Buchi. ^{1}H NMR and ^{13}C NMR spectra were recorded on the BRUKER apparatus (200 MHz, Montpellier II Faculty of Sciences and Technology). The multiplicity of the observed signals is indicated by a lowercase letter: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and se (extended signal). Mass spectra were recorded on JEOL JMS DX 300 Chemical Ionization (IC/NH_3) at LSPCO-UPS in Toulouse. The elementary analyzes were carried out by the central microanalysis department of the CNRS in Montpellier.

2.2 General procedure for saponification

To the starting product (1 mmol) in solution in 10 mL of a dioxane-water mixture (9/1) is added dropwise a 0.5N or 0.1N sodium hydroxide solution (1 to 1.5 mmol). After 4-16 hours of reaction, at room temperature or at cold temperature (0°C), the dioxane is evaporated and then 15 mL of water are added. The mixture is extracted 3 times with CH_2Cl_2, the aqueous phase is neutralized with 1N hydrochloric acid solution to pH = 2 to 3 and then extracted with ethyl acetate. The organic phase is dried with Na_2SO_4, the concentrated solvent; the acid is thus recovered, which is recrystallized from an acetone-ether mixture.

3. Results and discussion

After the synthesis of *N*-protected triazole amino esters, according to the synthesis strategy already adopted [11]; when the 1,3-dipolar cycloaddition reaction of *N*-protected methyl α-azidoglycinates by various protecting groups on various acetylenic dipolarophils is the key step in this synthesis method, we proceeded to the saponification of the ester function of these products (Scheme 1).



P = PhCO, Cl_3CCH_2OCO (Troc), F_3CCO **1** - **10**

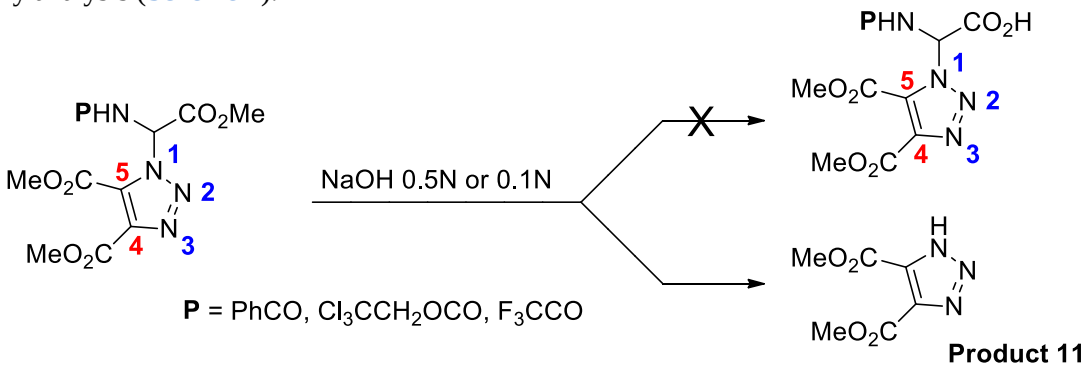
Scheme 1. Synthesis strategy of *N*-protected 2-(substituted-1*H*-1,2,3-triazol-1-yl)glycine **1** - **10**.

The cleavage of the methyl ester of the glycine unit of the various cycloadducts is by saponification at room temperature or at cold 0°C in the presence of a sodium hydroxide solution in a 9/1 dioxane-water mixture. The Table 1 summarizes the operating conditions and the results obtained.

Table 1. The operating conditions and the results obtained for compounds **1** - **10**.

Product	P	R_1	R_2	Time (h)	Yield (%)	Eq. of Na^+OH^- solution	Conc. of Na^+OH^- solution
1	PhCO	H	CO_2Et	16	60	1	0.5M
2	PhCO	H	Ph	16	92	1.5	0.5M
3	PhCO	CH_2Cl	H	16	83	1.5	0.5M
4	PhCO	H	$CH(OH)CH_3$	16	74	1.5	0.5M
5	PhCO	H	$CH(OH)C_2H_5$	16	82	1.5	0.5M
6	Troc	H	Ph	4	62	1	0.1M
7	Troc	H	CH_2Cl	4	50	1	0.1M
8	Troc	H	CO_2Et	4	35	1	0.1M
9	F_3CCO	H	Ph	16	74	1.5	0.5M
10	F_3CCO	H	CH_2Cl	16	70	1.5	0.5M

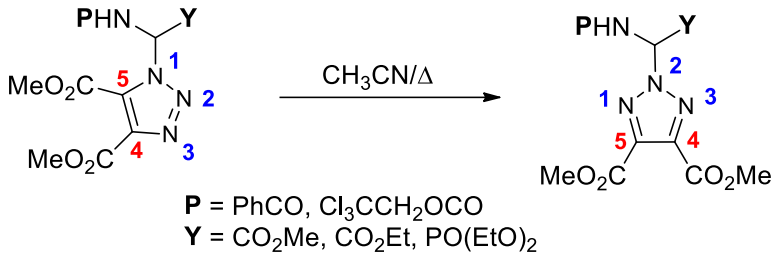
The saponification of the triazolic derivative of the methyl ester glycine *N*-protected by trichloroethoxycarbonyl group CCl_3CH_2OCO (Troc) requires milder conditions. Thus the action of a sodium hydroxide solution 0.1M at cold temperature (0°C) for only 4 hours was used to isolate the corresponding acids with yields ranging from 35% to 62%.
It should be noted that saponification of cycloadducts with 1,2,3-triazole ring bisubstituted by two methoxycarbonyl groups at positions 4 and 5, on glycine α-carbon, under the same conditions as before, notably with sodium hydroxide solution 0.5M or 0.1M, for only two hours causes degradation of the starting product and the bisubstituted 1,2,3-triazole ring was essentially obtained **11**, the latter is identified and characterized by different spectroscopic methods and elementary analysis (Scheme 2).



Scheme 2. Synthesis way of compound **11**

This degradation of the cycloadducts can be explained by the fragility of the bond between the carbon atom (CH) of the glycine and the nitrogen atom (N^1) of the triazole ring disubstituted by the 4,5-dimethoxycarbonyl groups. These have an electroattractor mesomeric effect (-M) which favors the easy cleavage of this bond. The fragile nature of the CH-N^1 bond was observed during the work carried out on the thermal isomerization in a neutral medium of these same

triazole derivatives of N-protected α-amino esters and their phosphonic analogue of glycine [12] (Scheme 3). It should be noted that in the case where the triazolic ring carries an ethyl ester function, we have succeeded in the selective hydrolysis of the methyl ester of the glycine unit. In the case where the triazolic ring carries two methyl ester functions, the use of three equivalents of the basic solution to hydrolyze the three ester functions causes the degradation of the molecule, only the 4,5-dicarboxymethyl-1,2,3-triazole ring **11** is recovered. The use of a single equivalent did not allow isolating the acid either.



Scheme 3. Thermal isomerization of triazole derivatives

We give below a model of ^{13}C NMR spectrum of the product (Figure 1) of hydrolysis of the function methyl ester in carboxylic acid **9**, in mixture of chloroform and deuterated dimethyl sulfoxide ($CDC1_3$/DMSO-d_6). Thus, it is observed, among others, the coupling between the carbon atom and the fluorine atoms which give two quadruplets at 114.28 ppm and 156.8 ppm respectively with the coupling constants $^1J_{C-F}$ = 287 Hz and $^2J_{C-F}$ = 38.4 Hz.

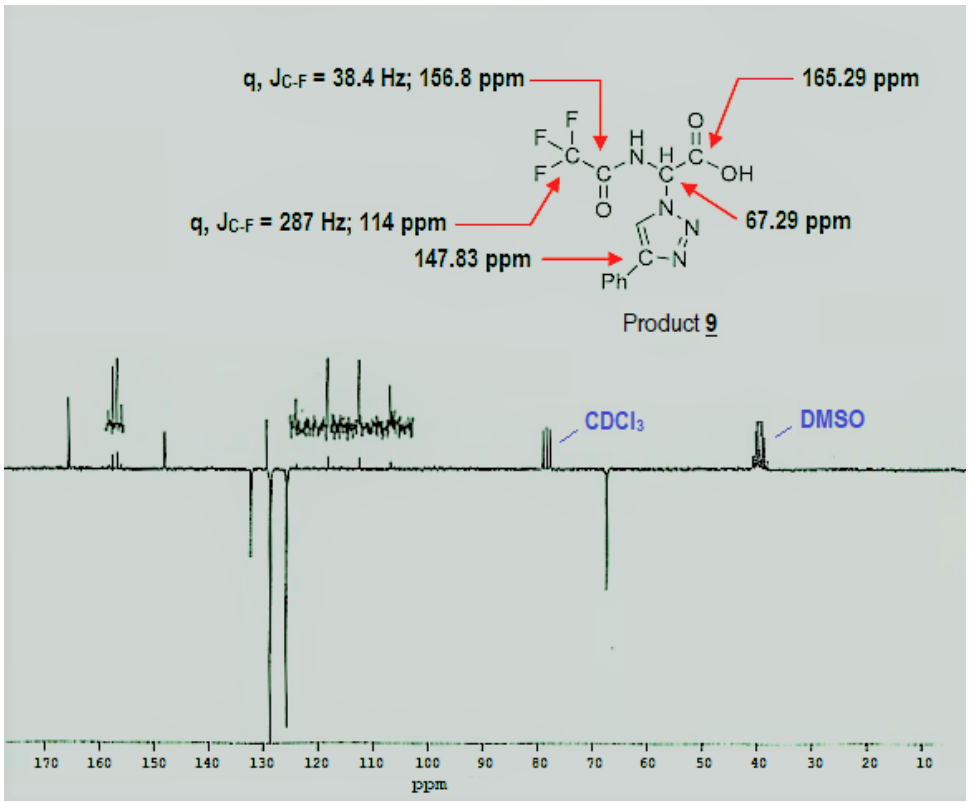


Figure 1. ^{13}C NMR spectrum of compound **9**.

Spectral Data

2-Benzamido-2-(4-(ethoxycarbonyl)-1H-1,2,3-triazol-1-yl)acetic acid (1):

Yield = 60%; m.p. = 174°C; **^{1}H NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 1.30 (3H, C**H$_3$**-CH_2, t, *J* = 7 Hz); 4.29 (2H, CH_3-C**H$_2$**-O, q, *J* = 7 Hz); 6.99 (1H, -C**H**-N^1, d, *J* = 8 Hz); 7.39-7.90 (5**H**$_{arom}$, m); 8.70 (1H, **H**^{5}-(triazole), s); 9.95 (1H, -**H**NCO, d, *J* = 8 Hz). **^{13}C NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 13.90 (**C**H_3-CH_2); 60.41 (CH_3-**C**H_2-O); 64.97 (-**C**H-N^1); 127.44, 127.66, 128.02, 128.31 and 131.96 (**C**^{5}-(triazole) + 6**C**$_{arom}$); 139.01 (**C**^{4}-(triazole)); 159.95, 166.54 and 166.60 (3C, **C**O). **Calcd**. for $C_{14}H_{14}N_4O_5$ (%): C, 52.83; H, 4.43; N, 17.6; **Found** (%): C, 52.28; H, 4.37; N, 17.26.

2-Benzamido-2-(4-phenyl-1H-1,2,3-triazol-1-yl)acetic acid (2):

Yield = 92%; m.p. = 152°C; **^{1}H NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 7.10 (1H, -C**H**-N^1, d, *J* = 8 Hz); 7.3-8.33 (11**H**$_{arom}$, m); 8.73 (1H, **H**^{5}-(triazole), s); 10.9 (1H, -**H**NCO, d, *J* = 8 Hz). **^{13}C NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 64.94 (-**C**H-N^1); 120.93 (**C**^{5}-(triazole)); 125.20, 127.7, 127.94, 128.45, 128.86, 130.32, 132.25 and 132.3 (12**C**$_{arom}$); 146.2 (**C**^{4}-(triazole)); 166.5 and 167.0 (2C, **C**O). **Calcd**. for $C_{17}H_{14}N_4O_3$ (%): C, 63.35; H, 4.38; N, 17.38; **Found** (%): C, 62.42; H, 4.31; N, 17.20.

2-*Benzamido-2-(5-(chloromethyl)-1H-1,2,3-triazol-1-yl)acetic acid (3):*

Yield = 83%; m.p. = 139°C; **^{1}H NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 4.81 (2H, -C**H$_2$**-Cl, s); 7.10 (1H, -C**H**-N^1, d, *J* = 8 Hz); 7.38-8.0 (5**H**$_{arom}$, m); 7.90 (1H, **H**^{4}-(triazole), s); 10.50 (1H, -**H**NCO, d, *J* = 8 Hz). **^{13}C NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 35.75 (-**C**H_2-Cl); 68.16 (-**C**H-N^1); 127.8, 128.3, 132.14 and 132.4 (6**C**$_{arom}$); 134.4 (**C**^{4}-(triazole)); 144.83 (**C**^{5}-(triazole)); 166.5 and 166.80 (2C, **C**O). **Calcd**. for $C_{12}H_{11}ClN_4O_3$ (%): C, 48.91; H, 3.76; N, 19.01; **Found** (%): C, 49.42; H, 3.93; N, 18.78.

2-Benzamido-2-(4-(1-hydroxyethyl)-1H-1,2,3-triazol-1-yl)acetic acid (4):

Yield = 74%; m.p. = 170°C; **^{1}H NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 1.56 (3H, C**H$_3$**-CH, d, *J* = 7 Hz); 3.0 (1H, -CHO**H**, se); 5.10 (1H, CH_3-C**H**, q, *J* = 7 Hz); 6.81 (1H, -C**H**-N^1, d, *J* = 8 Hz); 7.3-7.6 (5**H**$_{arom}$, m); 8.01 (1H, **H**^{5}-(triazole), s); 9.5 (1H, -**H**NCO, d, *J* = 8 Hz). **Calcd**. for $C_{13}H_{14}N_4O_4$ (%): C, 53.79; H, 4.86; N, 19.30; **Found** (%): C, 53.81; H, 4.87; N, 18.66.

2-Benzamido-2-(4-(1-hydroxypropyl)-1H-1,2,3-triazol-1-yl)acetic acid (5):

Yield = 82%; m.p. = 158°C; **^{1}H NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 0.86 (3H, C**H$_3$**-CH_2-, t, *J* = 7 Hz); 1.6-1.86 (2H, CH_3-C**H$_2$**-, m) ; 4.64 (1H, -CH_2-C**H**-, t, *J* = 7 Hz) ; 6.91 (1H, -C**H**-N^1, d, *J* = 8 Hz) ; 7.3-7.9 (5**H**$_{arom}$, m); 7.98 (1H, **H**^{5}-(triazole), s) ; 9.67 (1H, -**H**NCO, d, *J* = 8 Hz). **^{13}C NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 9.54 (**C**H_3-CH_2-); 29.93 (-**C**H_2-CH-); 64.38 (-CH_2-**C**H-); 67.17 (-**C**H-N^1); 120.96 (**C**^{5}-(triazole)); 127.38, 127.95, 131.8 and 132.14 (6**C**$_{arom}$); 151.63 (**C**^{4}-(triazole)); 166.41 and 166.89 (2C, **C**O). **Calcd**. for $C_{14}H_{16}N_4O_4$ (%): C, 55.26; H, 5.30; N, 18.41; **Found** (%): C, 54.98; H, 5.23; N, 18.04.

2-(4-Phenyl-1H-1,2,3-triazol-1-yl)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)acetic acid (6):

Yield = 62%; m.p. = 126°C; **^{1}H NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 4.78 (2H, Cl_3C-C**H$_2$**-, s); 6.72 (1H, -C**H**-N^1, d, *J* = 8 Hz); 7.33-7.81 (5**H**$_{arom}$, m); 8.22 (1H, **H**^{5}-(triazole), s); 9.63 (1H, -**H**NCO, d, *J* = 8 Hz). **^{13}C NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 69.83 (-**C**H-N^1); 73.81 (Cl_3C-**C**H_2-); 95.18 (Cl_3**C**-CH_2-); 125.13 125.57, 128.96, 129.7 and 132.12 (6**C**$_{arom}$ + **C**^{5}-(triazole)); 147.5 (**C**^{4}-(triazole)); 154.16 and 165.93 (2C, **C**O). **Calcd**. for $C_{13}H_{11}Cl_3N_4O_4$ (%): C, 39.67; H, 2.82; N, 14.23; **Found** (%): C, 39.43; H, 2.57; N, 14.83.

2-(4-(Chloromethyl)-1H-1,2,3-triazol-1-yl)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)acetic acid (7):

Yield = 50%; m.p. = 172°C; **^{1}H NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 4.8 (2H, -C**H$_2$**-Cl, s); 4.83 (2H, Cl_3C-C**H$_2$**-, s); 6.78 (1H, -C**H**-N^1, d, *J* = 8 Hz); 8.20 (1H, **H**^{5}-(triazole), s); 9.54 (1H, -**H**NCO, d, *J* = 8 Hz). **^{13}C NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 36.19 (-C**H$_2$**-Cl); 66.35 (-**C**H-N^1); 73.89 (Cl_3C-C**H$_2$**-); 95.43 (Cl_3**C**-CH_2-); 123.62 (**C**^{5}-(triazole)); 143.48 (**C**^{4}-(triazole)); 154.10 and 166.30 (2C, **C**O). **Calcd**. for $C_8H_8Cl_4N_4O_4$ (%): C, 26.25; H, 2.20; N, 15.31; **Found** (%): C, 27.36; H, 2.57; N, 15.03.

2-(4-(Ethoxycarbonyl)-1H-1,2,3-triazol-1-yl)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)acetic acid (8):

Yield = 35%; m.p. = 148°C; **^{1}H NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 1.33 (3H, C**H$_3$**-CH_2-, t, *J* = 7 Hz); 4.33 (2H, CH_3-C**H$_2$**-, q, *J* = 7 Hz); 4.8 (2H, Cl_3C-C**H$_2$**-, s); 6.76 (1H, -C**H**-N^1, d, *J* = 8 Hz); 8.54 (1H, **H**^{5}-(triazole), s); 8.94 (1H, -**H**NCO, d, *J* = 8 Hz). **^{13}C NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 14.7 (**C**H_3-CH_2-); 62.0 (CH_3-**C**H_2-); 68.0 (-**C**H-N^1); 75.5 (Cl_3C-**C**H_2-); 96.31(Cl_3**C**-CH_2-); 129.5 (**C**^{5}-(triazole)); 140.80 (**C**^{4}-(triazole)); 155.5, 161.4 and 167.35 (3C, **C**O). **Calcd**. for $C_{10}H_{11}Cl_3N_4O_6$ (%): C, 30.83; H, 2.85; N, 14.38; **Found** (%): C, 30.36; H, 2.67; N, 14.08.

2-(4-Phenyl-1H-1,2,3-triazol-1-yl)-2-(2,2,2-trifluoroacetamido)acetic acid (9):

Yield = 74%; m.p. = 166°C; **^{1}H NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 6.95 (1H, -C**H**-N^1, d, *J* = 8 Hz); 7.3-7.8 (5**H$_{arom}$**, m); 8.10 (1H, **H**^{5}-(triazole), s); 11.0 (1H, -**H**NCO, d, *J* = 8 Hz). **^{13}C NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 67.29 (-**C**H-N^1); 114.28 (-**C**F_3, q, $J_{C\text{-}F}$ = 287 Hz); 125.58, 128.45, 128.56, 129.02 and 132.06 (6**C$_{arom}$** + **C**^{5}-(triazole)); 147.83 (**C**^{4}-(triazole)); 156.80 (CF_3**C**O, q, $J_{C\text{-}F}$ = 38.4 Hz); 165.29 (1C, **C**O). **Calcd**. for $C_{12}H_9F_3N_4O_3$ (%): C, 45.87; H, 2.89; N, 17.83; **Found** (%): C, 44.97; H, 2.87; N, 17.64.

2-(4-(Chloromethyl)-1H-1,2,3-triazol-1-yl)-2-(2,2,2-trifluoroacetamido)acetic acid (10):

Yield = 70%; m.p. = 172°C; **^{1}H NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 4.65 (2H, -C**H$_2$**-Cl, s); 6.8 (1H, -C**H**-N^1, d, *J* = 8 Hz); 8.07 (1H, **H**^{5}-(triazole), s); 10.71 (1H, -**H**NCO, d, *J* = 8 Hz). **^{13}C NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 35.60 (-C**H$_2$**-Cl); 63.73 (-**C**H-N^1); 115.12 (-**C**F_3, q, $J_{C\text{-}F}$ = 287 Hz); 123.43 (**C**^{5}-(triazole)); 143.64 (**C**^{4}-(triazole)); 156.80 (CF_3**C**O, q, $J_{C\text{-}F}$ = 38.80 Hz); 165.26 (1C, **C**O). SM (DCI/NH_3) m/z: 287.5 $[M+H]^+$, 309.5 $[M+Na]^+$.

Dimethyl 1H-1,2,3-triazole-4,5-dicarboxylate (11):

Yield = 60%; m.p. = 131°C; **^{1}H NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 3.46 (6H, 2 x C**H$_3$**-O-, s). **^{13}C NMR** ($CDCl_3$/DMSO-d_6, δ ppm): 52.30 (2 x C**H$_3$**-O-); 137.67 (**C**^{4} + **C**^{5}-(triazole)); 160.21 (2C, **C**O). **Calcd**. for $C_6H_7N_3O_4$ (%): C, 38.92; H, 3.81; N, 22.70; **Found** (%): C, 38.20; H, 3.01; N, 22.13.

4. Conclusion

In summary, we have successfully selective hydrolysis of the methyl ester despite the presence of an ethyl ester function on the heterocycle of products. The cycloadducts whose amine function is protected by the benzoyl and trifluroacethyl groups, the saponification is carried out without particular difficulty, with 0.5M sodium hydroxide solution at room temperature for 16 hours. While their *N*-protected analogs by the trichloroethoxycarbonyl group require much milder saponification conditions, in particular, handling at zero degrees and a 0.1M soda solution five times less concentrated for only 4 hours.

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