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STUDY OF HYDRAZINOLYSIS OF METHYL-3-(4-ALLYL-3--SUBSTITUTED-5-THIOXO-4,5-DIHYDRO-1*H*-1,2,4-TRIAZOL-1--YL)PROPANOATES

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By hydrazinolysis of the methyl esters of 3-(4-allyl-3-substituted-5-thioxo--4,5-dihydro-1*H*-1,2,4-triazol-1-yl)propanoic acids it was established that depending on the reaction conditions (solvent, additive, temperature, time, etc.) as the end product hydrazide with both an allyl and propyl group can be obtained. It is also shown that the allyl group contained in hydrazides can be selectively reduced by hydrazine hydrate in the presence of air.

***Keywords*:** hydrazide, hydrazinolysis, triazole, reduction.

Introduction. It is known that 1,2,4-triazole derivatives with a wide range of useful properties have found application in medicine, pharmacology, microbiology, agriculture, photo and textile industries, etc. [1, 2]. Analysis of the literature data shows, that a change in the nature of the substituent in the triazole ring or a change of its position in the ring leads to a sharp change in the nature of the pharmacological action [3, 4].

Along with the mentioned properties, 4,5-disubstituted-1,2,4-triazolo-3-thiols have a great synthetic potential and can be successfully used in fine organic synthesis. Specifically, some representatives of this class of compounds are used as nucleophiles for the asymmetric synthesis of non-proteinogenic α-amino acids [5, 6].

It was previously established that in the reactions of nucleophilic substitution of 4,5-disubstituted-1,2,4-triazolo-3-thiols in the presence of bases (potassium carbonate, sodium or potassium hydroxides), in the medium of absolute acetone, *S*-derivatives of the starting compounds are formed [7, 8], while in the addition reactions of conjugated systems, e.g. acrylates, acrylonitriles – *N*-derivatives of the starting compounds [8–11].

Materials and Methods. In order to further study the chemical properties of 4,5-disubstituted-1,2,4-triazolo-3-thiols we have investigated the behavior of the latter with methyl ester of acrylic acid under the Michael reaction conditions. It is established that the condensation catalyzed by sodium methylate resulted in formation of methyl esters of 3-(3,4-disubstituted-5-thioxo-4,5-dihydro-1*H*-1,2,4--triazol-1-yl)propanoic acids (**2**, **a**–**c**).

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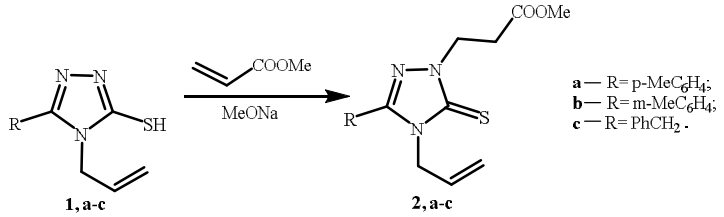
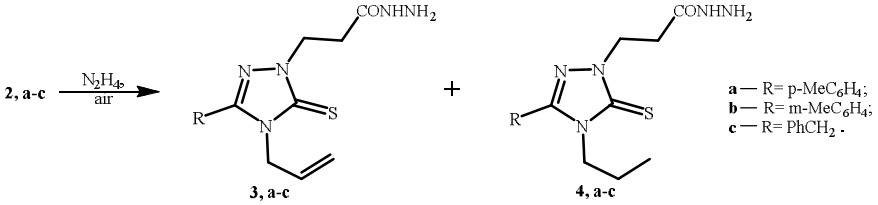


Scheme 1.

To study the chemical properties of 4-allyl derivatives of 1,2,4-triazoles, the reaction of hydrazinolysis in the presence of air was carried out, which led to an unexpected result with partial reduction of the allyl group.



Scheme 2.

The mixture of **3** and **4** is practically applicable for further use, since it is not separated by known methods. Due to this fact, the alternative ways of synthesis to produce **3** and **4** separately were explored. To obtain hydrazides **4**, **a**–**c**, the process of complete reduction of the allyl group was optimized (Tab. 1).

Table 1

Ester **2**	Solvent	Atmosphere	$N_2H_4 \cdot H_2O$ equivalent	*T*, °*C*	Duration, *h*	Ratio of end products 3 : 4	Total yield , %
a	C_2H_5OH	air	1.5	50	8*	1.2 : 1	89
a	C_2H_5OH	air	3	25	24*	1 : 1	91
a	C2H5OH	air	3	60	8*	1 : 6	90
a	C_2H_5OH	air	10	80	12*	0 : 1	93

* with stirring.

Table 2

Ester **2**	Solvent	Atmosphere	Additives, mol %	$N_2H_4 \cdot H_2O$ equivalent	*T* , °*C*	Duration, *h*	Ratio of end products 3 : 4	Total yield, %
c	C_2H_5OH	air-ethanol	–	1.5	50	8*	1.2 : 1	85
c	CH_3OH	vacuum	–	1.2	25	72*	8.3 : 1	91
c	C_2H_5OH	vacuum	–	1.5	70	10*	8.6 : 1	87
c	CH_3OH	N_2	–	1.1	25	5**	10 : 1	87
c	C_2H_5OH	vacuum	–	1.5	25	72*	11.2 : 1	90
c	CH_3OH	vacuum	–	1.5	25	48*	11 : 1	93
c	CH_3OH	vacuum	$Na_2S_2O_3$, 10	1.5	25	48*	9 : 1	94
c	CH_3OH	vacuum	Na_2SO_3, 10	1.5	25	48*	10 : 1	92
c	CH_3OH	vacuum	Na_2SO_3, 150	1.5	25	24*	11 : 1	92
c	CH_3OH	air-ethanol	Na_2SO_3, 50	2	25	48*	15.3 : 1	93
c	C_2H_5OH	air-ethanol	Na_2SO_3***, 20	10	25	5*	1 : 0	95

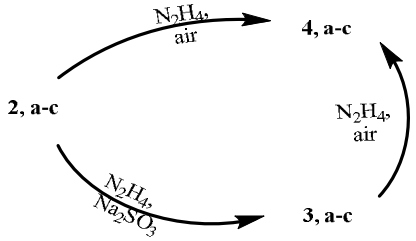
* without stirring; ** with stirring; *** purification with sodium sulfite solution.

For the synthesis of hydrazides **3**, **a–c**, containing the allyl group, numerous attempts were made under various conditions: in an atmosphere of inert gases, in vacuum, in different ratios of hydrazine hydrate, with a change of the solvent, with or without stirring, etc., but the obtained end product always contained a mixture of hydrazides **3** and **4**.

The anticipated hydrazide **3** containing the allyl group was obtained in a medium of ethanol in the presence of sodium sulfite with a tenfold excess of hydrazine hydrate.

Optimization of the process of hydrazinolysis without reduction is shown in Tab. 2.

Compounds **4**, **a–c** were also synthesized from hydrazides **3**, **a–c** by reduction with hydrazine hydrate in an air atmosphere.



Scheme 3.

The structures of the compounds obtained were determined by NMR spectral analysis data.

Experimental Part.

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury-300 *MHz* in DMSO–CCl_4 mixture (1:3). Chemical shifts (δ, *ppm*) are reported as quoted relative to the residual signals of DMSO-d_6 (2.5 for ^{1}H NMR and 39.5 for ^{13}C NMR) as internal references. All reagents were of reagent grade and were used as such or distilled prior to use. Starting 1,2,4-triazoles were prepared as previously reported [12]. Melting points were determined on "Boetius" micro-heating stage.

General Procedure for the Preparation of Esters (2, a–c). To a mixture of 8 *mmol* of the corresponding triazole in 40 *mL* of acetonitrile were added 0.8 *mL* of 1 *M* solution of sodium methylate in methanol, 9.7 *mmol* of methyl acrylate and the whole was stirred for 4 *h* at room temperature and 5 *h* at 50–60°C. The mixture was cooled, and the solvent is removed in vacuum. The crystals formed were recrystallized.

*Methyl 3-(4-allyl-5-thioxo-3-p-tolyl-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanoate (**2 a**)*. White powder (90% yield); mp. 60–62°*C* (EtOH : H_2O = 2 : 1). Found, %: C 60.66; H 6.02; N 13.12; S 10.11. $C_{16}H_{19}N_3O_2S$. Calculated, %: C 60.54; H 6.03; N 13.24; S 10.10.

^{1}H NMR (300 *MHz*, DMSO : CCl_4 = 1 : 3), δ, *ppm*: 7.58–7.46 m ($2H_{arom.}$); 7.30 d (*J*=7.9 *Hz*, $2H_{arom.}$), 5.91 ddt (*J* = 17.2; 10.3; 5.1 *Hz*, 1H, =CH); 5.27–5.16 m ($1H^a$, $=CH_2$); 5.09–4.95 m ($1H^b$, $=CH_2$); 4.70 dt (*J*=5.1; 1.7 *Hz*, 2H, $N\underline{CH_2}CH=CH_2$); 4.51–4.39 m (2H, $N\underline{CH_2}CH_2$); 3.68 (s, 3H, OCH_3); 2.93–2.86 m (2H, $NCH_2\underline{CH_2}$); 2.44 s (3H, $\underline{CH_3}$ Ar).

^{13}C NMR (75 *MHz*, DMSO:CCl_4=1:3), δ: 169.6; 166.7; 149.8; 140.2; 131.1; 129.0; 127.9; 122.5; 117.4; 51.0; 46.9; 44.1; 31.6; 20.9.

*Methyl 3-(4-allyl-5-thioxo-3-m-tolyl-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanoate (**2 b**)*. White powder (89% yield); mp. 74–76°*C* (EtOH : H_2O = 2 : 1). Found, %: C 60.66; H 6.02; N 13.12; S 10.11. $C_{16}H_{19}N_3O_2S$. Calculated, %: C 60.54; H 6.03; N 13.24; S 10.10.

^{1}H NMR (300 *MHz*, DMSO : CCl_4 = 1 : 3), *δ, ppm*: 7.49–7.28 m ($4H_{arom.}$); 5.92 ddt (*J* = 17.2; 10.4; 5.2 *Hz*, 1H, CH=); 5.23 dq (*J* = 10.4; 1.5 *Hz*, $1H^a$, CH_2=); 5.03 dq (*J* = 17.2; 1.5 *Hz*, $1H^b$, CH_2=); 4.70 dt (*J* = 5.2; 1.7 *Hz*, 2H, $\underline{CH_2}CH{=}CH_2$); 4.45 t (*J* = 7.3 *Hz*, 2H, $N\underline{CH_2}CH_2$); 3.68 s (3H, CH_3O); 2.89 t (*J* = 7.3 *Hz*, 2H, $NCH_2\underline{CH_2}$); 2.43 s (3H, $\underline{CH_3}$ Ar).

^{13}C NMR (75 *MHz*, DMSO:CCl_4=1:3), *δ, ppm*: 169.6; 166.7; 149.8; 137.9; 131.1; 130.9; 128.6; 128.2; 125.2; 125.1,; 117.4; 51.0; 47.0; 44.2; 31.6; 20.7.

*Methyl 3-(4-allyl-3-benzyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanoate (**2 c**)*. White powder (85% yield); mp.74–77°*C* (Hexane). Found, %: C 60.46; H 6.13; N 13.41; S 10.01. $C_{16}H_{19}N_3O_2S$. Calculated, %: C 60.54; H 6.03; N 13.24; S 10.10.

^{1}H NMR (300 *MHz*, DMSO : CCl_4 = 1 : 3), *δ, ppm*: 7.35–7.16 m (5H, Ph); 5.83–5.63 m (1H, CH=); 5.13 dd (*J* = 10.3; 1.2 *Hz*, $1H^a$, CH_2=); 5.04 dd (*J* = 17.1; 1.2 *Hz*, $1H^b$, CH_2=); 4.52 dt (*J* = 5.5; 1.5 *Hz*, 2H, $N\underline{CH_2}CH{=}CH_2$); 4.37 t (*J* = 7.2 *Hz*, 2H, $N\underline{CH_2}CH_2$); 4.03 s (2H, $\underline{CH_2}$Ph); 3.64 s (3H, CH_3); 2.82 t (*J* = 7.3 *Hz*, 2H, $NCH_2\underline{CH_2}$).

^{13}C NMR (75 *MHz*, DMSO:CCl_4=1:3), *δ, ppm*: 169.6; 166.3; 149.2; 133.7; 130.3; 128.2; 128.2; 126.7; 117.6; 51.0; 45.8; 43.9; 31.7; 30.7.

General Procedure for the Synthesis of the Hydrazides (3, a–c). To the mixture of 5.2 *mL* (95 *mmol*) of an 80% solution of hydrazine hydrate, 0.24 *g* (1.9 *mmol*) of sodium sulfite and 10 *mL* of ethanol was added 9.5 *mmol* of the corresponding ester. The resulting mixture was left for 5 *h* without access to air. 15 *mL* of a 3% aqueous solution of sodium sulfite was added to the reaction mixture. The precipitated crystals were filtered off, 50 *mL* of a 3% aqueous solution of sodium sulfite, were washed with water, and dried.

*3-(4-Allyl-5-thioxo-3-p-tolyl-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanehydrazide (**3 a**)*. White powder (84% yield); mp. 104–106°*C*. Found, %: C 56.65; H 6.03; N 22.17; S 9.76. $C_{15}H_{19}N_5OS$. Calculated, %: C 56.76; H 6.03; N 22.06; S 10.10.

^{1}H NMR (300 *MHz*, DMSO : CCl_4= 1 : 3), *δ, ppm*: 9.02 s (1H, NH); 7.53 d (*J* = 8.0 *Hz*, 2H, C_6H_4); 7.30 d (*J* = 8.0 *Hz*, 2H, C_6H_4); 5.91 ddt (*J* = 15.6; 10.3; 5.0 *Hz*, 1H, =CH); 5.20 d (*J* = 10.4 *Hz*, $1H^a$, $=CH_2$); 5.02 d (*J* = 17.3 *Hz*, $1H^b$, $=CH_2$); 4.69 d (*J* = 4.9 *Hz*, 2H, $N\underline{CH_2}CH{=}CH_2$); 4.46–4.33 m (2H, $N\underline{CH_2}CH_2$); 3.96 s (2H, NH_2); 2.70–2.56 m (2H, $NCH_2\underline{CH_2}$); 2.43 s (3H, CH_3).

^{13}C NMR (75 *MHz*, DMSO:CCl_4=1:3), *δ, ppm*: 168.3, 166.5, 149.7, 140.1, 131.2, 129.0, 128.0, 122.6, 117.4, 46.9, 45.0, 31.6, 20.9.

*3-(4-Allyl-3-benzyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanehydrazide (**3 c**)*. White powder (91% yield); mp. 99–101°*C*. Found, %: C 56.36; H 6.08; N 22.15; S 10.27. $C_{15}H_{19}N_5OS$. Calculated, %: C 56.76; H 6.03; N 22.06; S 10.10.

^{1}H NMR (300 *MHz*, DMSO : CCl_4 = 1 : 3), *δ, ppm*: 8.99 s (1H, NH); 7.46–7.07 m (5H, Ph); 5.72 ddt (*J* = 15.9; 10.7; 5.5 *Hz*, 1H, =CH); 5.12 dd (*J* = 10.4; 0.7 *Hz*, $1H^a$, CH_2=); 5.04 dd (*J* = 17.2, 0.6 *Hz*, $1H^b$, CH_2=); 4.51 d (*J* = 5.5 *Hz*, 2H, $N\underline{CH_2}CH{=}CH_2$); 4.40–4.25 m (2H, $N\underline{CH_2}CH_2$); 4.04 s (*J* = 13.0 *Hz*, 2H, $\underline{CH_2}$Ph); 3.93 br.s. (*J* = 20.5 *Hz*, 2H, NH_2); 2.62–2.52 m (2H, $NCH_2\underline{CH_2}$).

^{13}C NMR (75 *MHz*, DMSO:CCl_4 =1:3), *δ*: 168.3; 166.0; 149.0; 133.9; 130.4; 128.2; 128.2; 126.6; 117.6; 45.8; 44.7; 31.6; 30.7.

*3-(4-Allyl-5-thioxo-3-m-tolyl-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanehydrazide (**3 b**)*. White powder (97% yield); mp. 146–148°*C*. Found, %: C 56.38; H 6.05; N 22.21; S 10.28. $C_{15}H_{19}N_5OS$. Calculated, %: C 56.76; H 6.03; N 22.06; S 10.10.

^{1}H NMR (300 *MHz*, DMSO : CCl_4 = 1 : 3), *δ, ppm*: 9.04 s (1H, NH); 7.51–7.27 m ($4H_{arom}$); 5.91 ddd (*J* = 22.3; 10.3; 5.1 *Hz*, 1H, CH=); 5.21 d (*J* = 10.4 *Hz*, $1H^a$, CH_2=); 5.02 d (*J* = 17.3 *Hz*, $1H^b$, CH_2=); 4.69 d (*J* = 5.0 *Hz*, 2H, $N\underline{CH_2}CH{=}CH_2$); 4.52–4.30 m (2H, $N\underline{CH_2}CH_2$); 3.08 br.s. (2H), 2.69–2.55 m (2H, $NCH_2\underline{CH_2}$); 2.42 s (3H, CH_3).

^{13}C NMR (75 *MHz*, DMSO:CCl_4=1:3), *δ, ppm*: 168.5; 166.5; 150.0; 138.2; 131.4; 131.2; 128.8; 128.5; 125.4; 125.3; 117.6; 47.1; 45.1; 31.7; 20.9.

General Procedure for the Synthesis of the Hydrazides (4, a–c).

Method A. To the mixture of 9.5 *mmol* of the corresponding ester in 20 *mL* of ethanol, 5.2 *mL* of an 80% solution of hydrazine were added, stirred for 1 *h* at room temperature and 12 *h* at 75–80°*C* with air access. After cooling, the mixture was diluted with water; the precipitate formed was filtered off, washed with water and dried.

Method B. To the mixture of 9.5 *mmol* of the corresponding hydrazide **3** in 20 *mL* of ethanol, 5.2 *mL* of an 80% solution of hydrazine was added, stirred for 1 *h* at room temperature and 8 *h* at 70–80°*C* with air access. After cooling, the mixture was diluted with water; the precipitate was filtered off, washed with water and dried.

*3-(4-Propyl-5-thioxo-3-p-tolyl-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanehydrazide (**4 a**)*. White powder (77% yield); mp. 108–109°*C*. Found, %: C 56.26; H 6.58; N 22.03; S 10.31. $C_{15}H_{21}N_5OS$. Calculated, %: C 56.40; H 6.63; N 21.92; S 10.04.

^{1}H NMR (300 *MHz*, DMSO : CCl_4 = 1 : 3), *δ, ppm*: 9.00 s (1H, NH); 7.58–7.45 m ($2H_{arom.}$); 7.32 d (*J* = 8.0 *Hz*, $2H_{arom.}$); 4.45–4.31 m (2H, $N\underline{CH_2}CH_2$); 4.08–3.96 m (2H, $N\underline{CH_2}CH_2CH_3$); 3.95 br.s. (2H, NH_2); 2.67–2.55 m (2H, $NCH_2\underline{CH_2}$); 2.45 s (3H, $Ar\underline{CH_3}$); 1.79–1.59 m (2H, $NCH_2\underline{CH_2}CH_3$); 0.85 t (*J* = 7.4 *Hz*, 3H, $NCH_2CH_2\underline{CH_3}$).

^{13}C NMR (75 *MHz*, DMSO:CCl_4=1:3), *δ*: 168.3; 166.1; 140.0; 129.1; 128.0; 122.9; 46.1; 44.8; 31.6; 20.9; 10.5.

*3-(4-Propyl-5-thioxo-3-m-tolyl-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanehydrazide (**4 b**)*. White powder (80% yield); mp. 135–136°*C*. Found, %: C 56.26; H 6.48; N 22.13; S 10.21. $C_{15}H_{21}N_5OS$. Calculated, %: C 56.40; H 6.63; N 21.92; S 10.04.

^{1}H NMR (300 *MHz*, DMSO:CCl_4=1:3), *δ, ppm*: 9.00 s (1H, NH); 7.47–7.30 m ($4H_{arom.}$); 4.43–4.34 m (2H, $N\underline{CH_2}CH_2CO$); 4.07–3.98 m (2H, $N\underline{CH_2}CH_2CH_3$); 3.99 br.s. (2H, NH_2); 2.67–2.56 m (2H, $NCH_2\underline{CH_2}CO$); 2.45 s (3H, CH_3Ar); 1.79–1.56 m (2H, $NCH_2\underline{CH_2}CH_3$); 0.85 t (*J* = 7.4 *Hz*, 3H, $NCH_2CH_2\underline{CH_3}$).

^{13}C NMR (75 *MHz*, DMSO:CCl_4=1:3), *δ*: 168.6; 166.2; 149.5; 138.0; 130.8; 128.8; 128.3; 125.7; 125.1; 46.1; 44.8; 31.6; 20.9; 20.8; 10.5.

*3-(3-Benzyl-4-propyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanehydrazide (**4 c**)*. White powder (87% yield); mp. 86–89°*C* (benzene). Found, %: C 56.36; H 6.58; N 22.23; S 9.95. $C_{15}H_{21}N_5OS$. Calculated, %: C 56.40; H 6.63; N 21.92; S 10.04.

^{1}H NMR (300 *MHz*, DMSO : CCl_4 = 1 : 3), *δ, ppm*: 8.99 s (1H,NH); 7.37–7.18 m (5H, Ph); 4.36–4.26 m (2H, N$\underline{CH_2}CH_2CO$); 4.09 s (2H), 3.96 br.s. (2H), 3.81–3.70 m (2H, N$\underline{CH_2}CH_2CH_3$); 2.60–2.52 m (2H, $NCH_2\underline{CH_2}CO$); 1.54–1.34 m (2H, $NCH_2\underline{CH_2}CH_3$); 0.84 t (*J* = 7.4 *Hz*, 3H, $NCH_2CH_2\underline{CH_3}$).

^{13}C NMR (75 *MHz*, DMSO : CCl_4 = 1 : 3), *δ, ppm*: 168.4; 165.8; 14.0; 134.3; 128.3; 128.4; 126.7; 45.5; 44.6; 31.7; 30.8; 20.4; 10.6.

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