(New) 5-Substituted-4*H*-4-amino-3-mercapto-1,2,4-triazoles with Increased Complexing Capabilities

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Five 5-substituted-4H-4-amino-3-mercapto-1,2,4-triazoles have been synthesized, in a single step, through the reaction of hydrazides of o-hydroxy-benzoic, p-hydroxy-benzoic, 3,4,5-trihydroxy-benzoic, o-amino-benzoic and p-amino-benzoic acids with carbon disulfide in ethanolic potassium hydroxide, followed by the reaction of the intermediate N''-acyl-dithiocarbazates with hydrazine hydrate. The products were characterized by mass, IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Keywords : 4H-4-amino-5-(hydroxy-phenyl)-substituted-3-mercapto-1,2,4-triazole, 5-(amino-phenyl)-substituted-4H-4-amino-3-mercapto-1,2,4-triazole

5-Substituted-4*H*-4-amino-3-mercapto-1,2,4-triazoles, their derivatives, as well as their coordination complexes, are biologically active compounds, showing antibacterial [1-4], anti-fungal [1,5], tuberculostatic [6,7], antihelmintic [8], antimicrobial [9], antiviral [10], anti-HIV [11], and antitumoral [12,13] activities.

The purpose of our work was to synthesize (new) 4*H*-4-amino-5-aryl-3-mercapto-1,2,4-triazoles (**1**) with -OH and -NH_2 groups on the benzenic ring, compounds with increased complexing capabilities and which can serve as starting material for new functional derivatives with potential biological activity (Schiff bases, Mannich bases, glycosidic derivatives [14-16]).

Among the synthesis methods of 5-substituited 4*H*-4-amino-3-mercapto-1,2,4-triazoles (**1**) presented in literature, the ones using accessible starting materials are shown in scheme 1.

According to the literature data, 4*H*-4-amino-5-aryl-3-mercapto-1,2,4-triazoles (**1**) with R= 2-HO-C_6H_4- and 2(4)-H_2N-C_6H_4- substituents can be synthesized by treating thiocarbohydrazide (**6**) with the corresponding carboxylic acids [8].

Among the synthetic routes presented in scheme 1, we choose for the synthesis of 4*H*-4-amino-3-mercapto-5-aryl-1,2,4-triazoles (**1a-e**) the reaction of the corresponding hydrazides with carbon disulfide in ethanolic potassium hydroxide, followed by the cyclization with hydrazine hydrate of the intermediate N''-acyl-dithiocarbazates, without their isolation, method which we used for the synthesis of others 5-substituted 4*H*-4-amino-3-mercapto-1,2,4-triazoles [17].

Experimental part

Materials and methods

The reagents were commercial products (Chimopar, Merck, Fluka) and used as received. Hydrazides (**4a-e**) were obtained according to the literature, by hydrazinolysis of the corresponding ethylic esters (**3a-e**) [18].

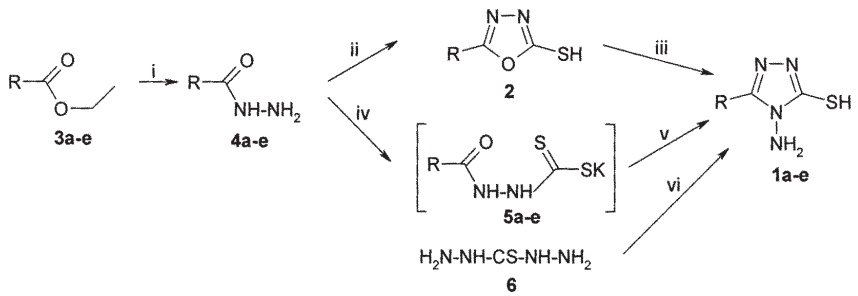
Mass spectra GS-MS was performed on a Agilent G1701DA apparatus using methanol as carrier solvent.

Melting points were determined on a Böetius PHMK (Veb Analytik Dresden) instrument, and thin-layer chromatography was carried out on silica gel-coated plates 60 F_{254} Merck using benzene : ethyl acetate 1:1 (v/v) as eluant.

IR spectra were recorded in KBr pellet, on a Jasco FT/IR-410 spectrophotometer (br-broad; s-strong; m-medium; w-weak, γ-out of plane vibration; sk-skeletal vibration; ν-stretching vibration; δ-deformation vibration). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance AC200 and Bruker Avance DRX400 spectrometer in DMSO-d_6, using TMS as reference; chemical shifts are reported in ppm and the coupling constants in Hz.

*Preparation of 5-substituted-4H-4-amino-3-mercapto-1,2,4-triazoles (**1a-e**)*

Hydrazide (**4a-e**) (0.02 mol) was dissolved in a solution of 0.03 mol KOH / 20 mL ethanol and 0.03 mol carbon disulfide was added dropwise, at room temperature. The



Scheme 1.Synthetic routes to 5-substituted 4*H*-4-amino-3-mercapto-1,2,4-triazoles(1)

i=$N_2H_4{\cdot}H_2O$ reflux; ii= a) CS_2 / KOH / EtOH / Δt, b) HCl; iii= $N_2H_4{\cdot}H_2O$ reflux; iv=CS_2 / KOH /EtOH / r.t.; v=$N_2H_4{\cdot}H_2O$ r.t., reflux; vi=RCOOH / Δ t

R=2-HO-C_6H_4-(**a**), 4-HO-C_6H_4-(**b**), 3,4,5-$(HO)_3C_6H_2$-(**c**), 2-H_2N-C_6H_4-(**d**), 4-H_2N-C_6H_4-(**e**)

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formed suspension was maintained at room temperature for 2 h, then 0.04 mol hydrazine hydrate was added dropwise. After 2 h, half of the reaction volume was distilled, 0.04 mol hydrazine hydrate was added, the solution was refluxed for 4 h, then cooled at room temperature, adjusted to *p*H ~ 1 with concd. HCl, filtered and products (**1a-e)** were separated by filtration and recrystallyzed from ethanol 50%.

4H-4-amino-5-(2-hydroxy-phenyl)-3-mercapto-1,2,4-triazole (**1a**)

Crem-coloured powder η=65%, m.p.= 210-213°C;

GS-MS(m/z)= 208(100%, $M^{+\cdot}$); 137 (17,52%); 120 (20,61%).

IR(KBr, cm^{-1}): ν_{OH}=3428; ν^{as}_{NH2}=3294m; ν^{s}_{NH2}=3196m; ν_{CHar}=3028w; $\nu_{C=N}$=1616m; $\nu_{SK,ar}$=1493s; $\gamma_{SK,ar}$=746m, 693m;

δ_H (DMSO-*d*6, 200 MHz): 13.79 (s, 1H, -$\underline{NH}_{tr.}$); 10.30 (s, 1H, -$\underline{OH}$); 7.48(d, 1H, *J*=7.5 Hz, 6'-H), 7.37 (t, 1H, *J*=7.8 Hz, 4'-H), 7.05 (d, 1H, *J*=8.0 Hz, 2'-H), 6.92 (t, 1H, J=7.5 Hz, 5'-H), 5.65 (s, 2H, -$\underline{NH}_2$)

δ_C (DMSO-*d*6, 50 MHz): 164.9 (5-C); 155.9 (2'-C); 148.9 (3-C); 131.9 (4'-C); 130.6 (6'-C); 119.0 (5'-C); 116.2 (3'-C); 112.9 (1'-C)

*4H-4-amino-5-(4-hydroxy-phenyl)-3-mercapto-1,2,4-triazol*e (**1b**)

White powder η=80%, m.p.= 260-263°C;

GS-MS(m/z)= 208 (100%, $M^{+\cdot}$); 137 (35.10%); 119 (23.40%).

IR(Kbr, cm^{-1}): ν_{OH}=3475; ν^{as}_{NH2}=3306m; ν^{s}_{NH2}=3279m; ν_{CHar}=3017w, $\nu_{C=N}$=1612m; $\nu_{SK,ar}$=1481s; $\gamma_{SK,ar}$=733m, 697m;

δ_H (DMSO-*d*6, 400 MHz): 13.76 (s, 1H, -$\underline{NH}_{tr}$); 10.02 (s, 1H, -$\underline{OH}$); 7.90 (d, 2H, *J*=8.6 Hz, 2'-H, 6'-H), 6.91(d, 2H, *J*= 8.6 Hz, 3'-H, 5'-H); 5.75 (s, 2H, -$\underline{NH}_2$)

δ_C (DMSO-*d*6, 100 MHz): 166.4 (5-C); 159.4 (4'-C); 149.6 (3-C); 129.7 (2'-C, 6'-C); 116.5 (1'-C); 115.3 (3'-C, 5'-C);

4H-4-amino-5-(3,4,5-trihydroxy-phenyl)-3-mercapto-1,2,4-triazole (**1c**)

Brown powder η=50%, m.p.>250°C;

IR(KBr, cm^{-1}): ν_{OH}=3391; ν^{as}_{NH2}=3318m; ν^{s}_{NH2}=3285m; ν_{CHar}=3017w;$\nu_{C=N}$=1618m;$\nu_{SK,ar}$=1526s; $\gamma_{SK,ar}$=754m;

δ_H (DMSO-*d*6, 200 MHz): 13.68 (s, 1H, $\underline{NH}_{tr}$); 9.15 (br.s, 3H, 3'-$\underline{OH}$, 4'-$\underline{OH}$, 5'-$\underline{OH}$); 7.13 (s, 2H, 2'-H, 6'-H), 5.73 (s, 2H, -$\underline{NH}_2$)

δ_C (DMSO-*d*6, 50 MHz): 166.0 (5-C); 149.1 (3-C); 145.6 (3'-C, 5'-C); 135.6 (4'-C); 115.6 (1'-C); 107.1 (2'-C, 6'-C);

Mixture of *4H-4-amino-5-(2-amino-phenyl)-3-mercapto-1,2,4-triazole (**1d**)* and *5-(2-amino-phenyl)-2-mercapto-1,3,4-oxadiazole* (**2**)

Yellow powder (1.8 g crude product); m.p.= 152-160°C;

GS-MS(m/z)= 207 (100%, $M^{+\cdot}$ triazole); 136 (17.64%); 118 (30.4%); 193 (100%, $M^{+\cdot}$oxadiazole); 120 (77.5%); 104 (31.25%)

4H-4-amino-5-(4-amino-phenyl)-3-mercapto-1,2,4-triazole (**1e**)

Yellow powder η=83%, m.p.= 243-247°C;

IR (Kbr, cm^{-1}): ν^{as}_{NH2} = 3351m; ν^{s}_{NH2} = 3269m; ν_{CHar}=3017w; $\nu_{SK,ar}$=1505m; $\gamma_{SK,ar}$=751m, 689m;

δ_H (DMSO-d_6, 400 MHz): 13.61 (s, 1H, $\underline{NH}_{tr}$); 7.74 (d, 2H, J= 8.5 Hz, 2'-H, 6'-H), 6.64 (d, 2H, J=8.5 Hz, 3'-H, 5'-H); 5.71 (s, 2H, 4-$\underline{NH}_2$) 5.63 (s, 2H, 4'-$\underline{NH}_2$)

δ_C (DMSO-d_6, 100 MHz): 165.9 (5-C); 150.8 (4'-C); 149.9 (3-C); 129.0 (2'-C, 6'-C); 113.0 (3'-C, 5'-C); 112.5 (1'-C)

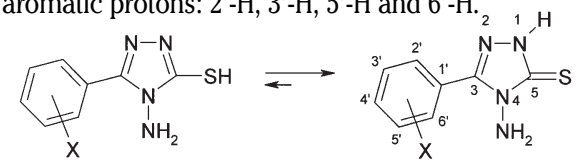
Results and discussions

Reaction of hydrazides (**4a-e**) with carbon disulfide in ethanolic KOH, was performed without the isolation of the intermediate N''-acyl-dithiocarbazates (**5a-e)**, which treated with hydrazine hydrate at reflux, lead to 5-aryl-4*H*-4-amino-3-mercapto-1,2,4-triazoles (**1a-e**), with good yields in the case of para-oriented substituents and modest yields in the case of ortho-oriented substituents.

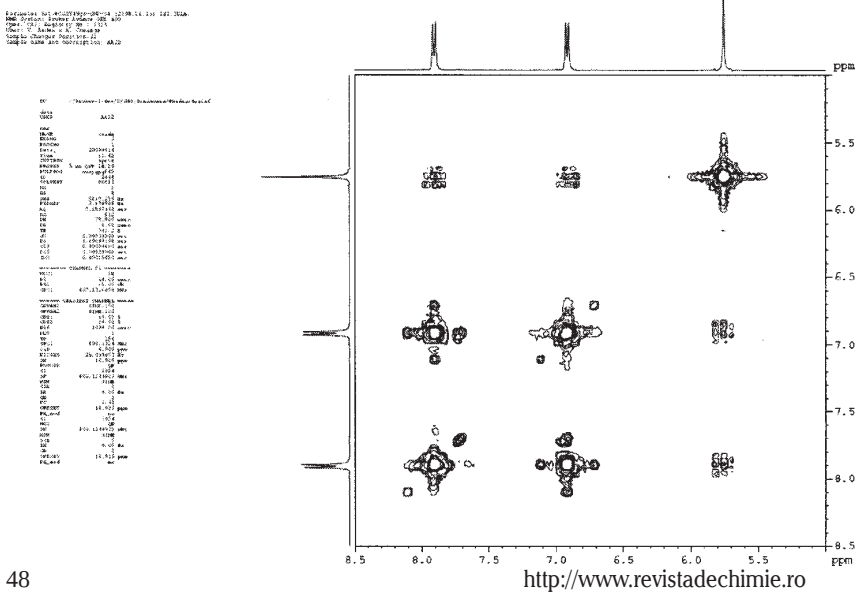
In our attempt to synthesize the compound with the -NH_2 group in the ortho position, a mixture of triazole (**1d**) and oxadiazole (**2**) was obtained. The ^{1}H-NMR spectra of this mixture indicates a ratio beetween the 4*H*-4-amino-5-(2-amino-phenyl)-3-mercapto-1,2,4-triazole (**1d**) and 5-(2-amino-phenyl)-2-mercapto-1,3,4-oxadiazole (**2**) of 2:1. The GS-MS results indicated, as well, the presence of the two compounds. The two compounds could not be separated by recrystallization.

The ^{13}C-NMR spectra of compounds (**1a-e)** evidence only the presence of thione tautomeric form (C=S) through the signals with δ = 164.9-166.4 ppm, corresponding to exocyclic C=S bonds and through the signals with δ = 13.61-13.79 ppm corresponding to ^{1}N-H proton.

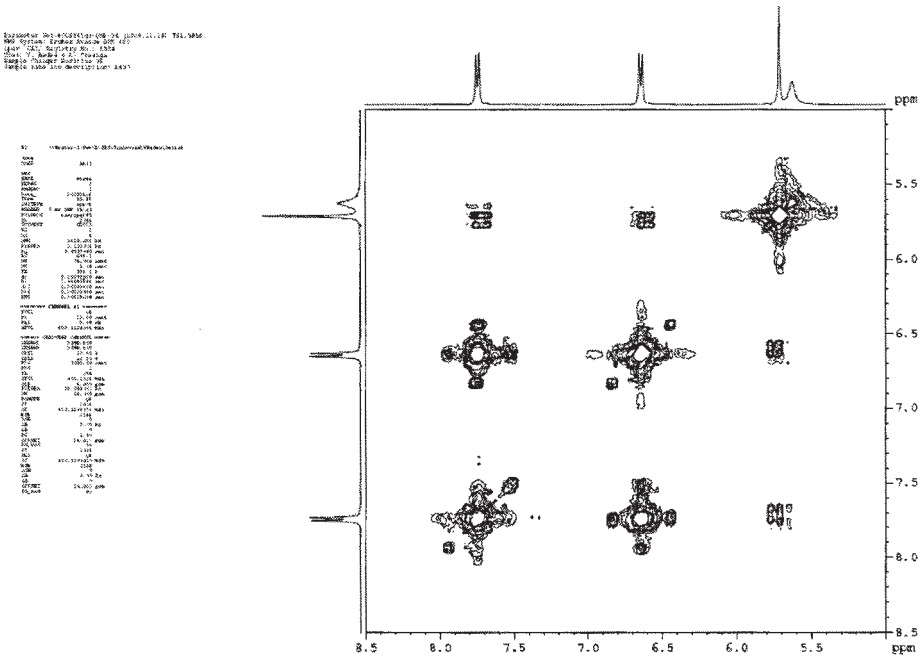
The COSY NMR spectra of compounds (**1b, e)** evidence the direct coupling of the amino group protons (-$\underline{NH}_2$) with the aromatic protons: 2'-H, 3'-H, 5'-H and 6'-H.



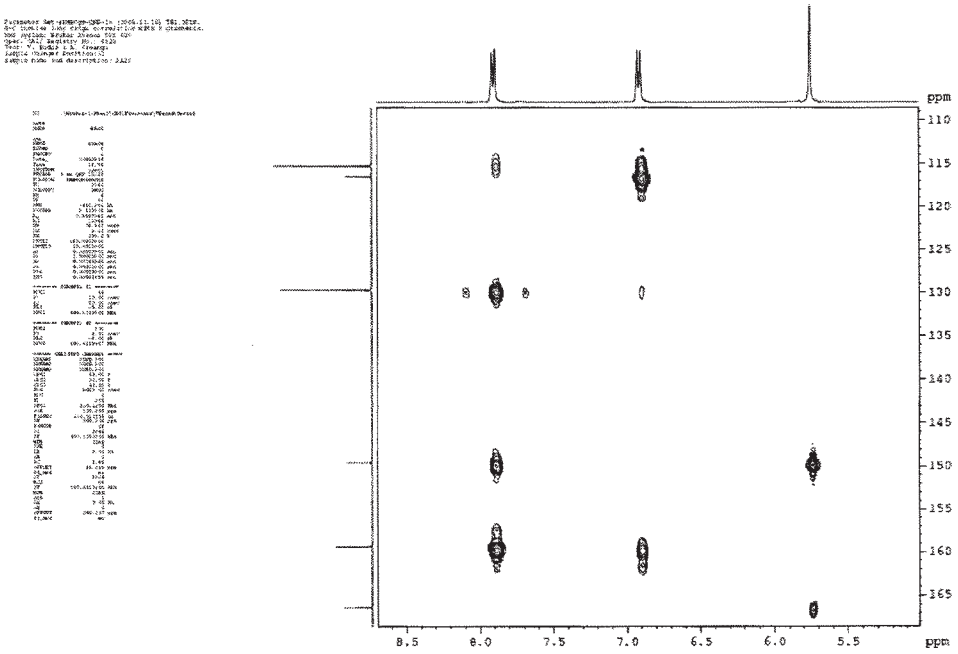
1a-e X= 2-HO- (**a**); 4-HO-(**b**); 3,4,5-(HO-)$_3$ (**c**); 2-H_2N- (**d**); 4-H_2N- (**e**)



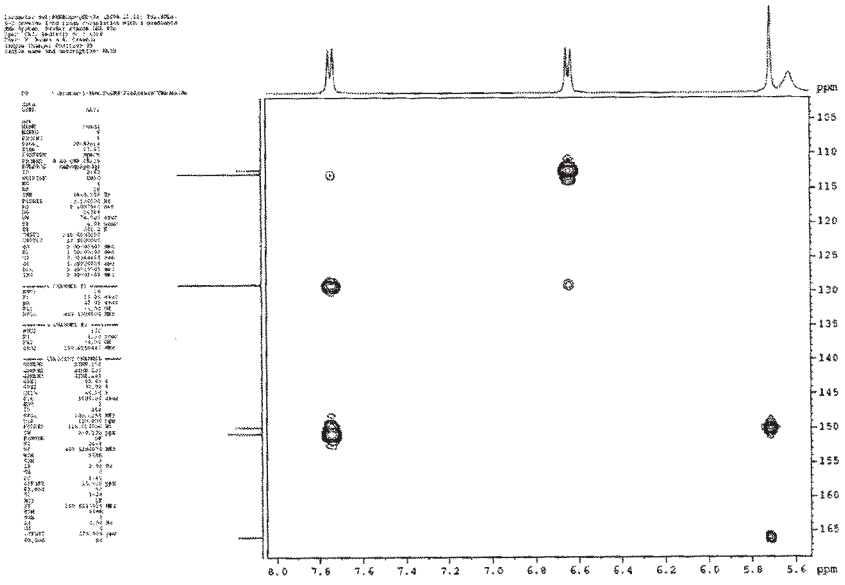
COSY spectra of compound **1b**



COSY spectra of compound **1e**



2D ^{1}H -^{13}C HMBC spectra of compound **1b**



2D ^{1}H-^{13}C HMBC spectra of compound **1e**

Analyzing 2D ^{1}H-^{13}C HMBC spectra, long distance coupling $^{3}J_{3\text{-}C,\text{-}NH2}$ and $^{3}J_{5\text{-}C,\text{-}NH2}$ of 3-C and 5-C carbon atoms with the protons of the NH_2 group is observed, coupling which confirms the presence of the amino group grafted on the triazolic ring.

Conclusions

Four compounds, 4*H*-4-amino-5-(2-hydroxy-phenyl)-3-mercapto-1,2,4-triazole (**1a**), 4*H*-4-amino-5-(4-hydroxy-phenyl)-3-mercapto-1,2,4-triazole (**1b**), 4*H*-4-amino-5-(3,4,5-trihydroxy-phenyl)-3-mercapto-1,2,4-triazole (**1c**) and 4*H*-4-amino-5-(4-amino-phenyl)-3-mercapto-1,2,4-triazole (**1e**), have been synthesized using a different method from the one presented in literature. The four compounds were characterized accordingly.

References

1. MOHAN, J., VERMA P., J. Indian Chem. Soc., **69**, nr.5, 1992, p.268
2. ZHANG, Z., CHEN, X., WEI, L., MA, Z., Chem. Res. Chin. Univ., **7**, nr.2, 1991, p.129
3. MOHAN, J., ANJANEYULU, G.S.R, YAMINI, K.V.S., J. Indian Chem. Soc., **68**, nr.8, 1991, p.474
4. RAO, V., RAVINDER, P., SHARMA, V.M., Indian J. Pharm. Sci., **54**, nr.5, 1992, p.193
5. PRASAD, M.V, NAIDU, M.S., J. Indian Chem. Soc., **68**, nr.11, 1991, p.619
6. GLOTOVA, T.E., NAKHMANOVICH, A., Khim-Farm. Zh., **23**, nr.11, 1989, p.1338
7. KANDEMIRLI, F., SHVETS, N., ÜNSALAN, S., KÜÇÜKGÜZEL, I., ROLLAS , S., KOVALISHYN, V., DIMOGLO, A., Medicinal Chemistry, **2**, 2006, p.415
8.CHENDE, M., KARNIK, B. M., Indian J. Heterocycl. Chem., **1**, nr.3, 1991, p.117
9. EWEISS, N.F., BAHAJAJ, A.A., ELSHERBINI, E.A., J. Heterocycl. Chem., **23**, 1986, p.1451
10. AL-MASOUDI, I.A., AL-SOUD, Y.A., AL-SALIHI, N.J., AL-MASOUDI, N.A., Chem. Heterocycl. Compd., **42**, nr.11, 2006, p.1377
11. WU, J., LIU, X., CHENG, X., CAO, Y., WANG, D., LI, Z., XU, W., PANNECOUQUE, C., WITVROUW, M., ERIK DE CLERCQ, Molecules, **12**, 2007, p.2003
12. YANG, J-G., PAN, F-Y., Lett. Org. Chem., **4**, 2007, p.137
13. TOMAŠČIKOVA, J., IMRICH, J., DANIHEL, I., BÖHM, S., KRISTIAN, P., PIARČIKOVA, J., SABOL, M., KLIKA, K.D., Molecules, **13**, 2008, p.501
14. ŞIŞU, E., LASCU, A., BERCEAN, V., CAPROIU, M., ZAMFIR, A., ŞIŞU, I., NEANU, C., CSUNDERLIK, C., RUSU, V., KATALINIC, J.P., Rev. Chim. (Bucharest), **54**, nr.2, 2003, p.181
15. SISU, I., BERCEAN, V., BADEA, V., CAPROIU, M.T., SISU, E., Rev. Chim. (Bucharest), **60**,. nr. 9, 2009, p.884
16. LASCU, A., ŞIŞU, I., BERCEAN, V., LUPEA, A.X., CĂPROIU, M.T., ŞIŞU, E., Rev. Roum. Chim., **55**, nr. 3, 2010, p.205
17. CREANGĂ, A.A., BERCEAN, V.N., BADEA, V., PATRAS, A.I., COCÂRŢÎ, A.I., TATU, C. A., CSUNDERLIK, C. , Rev. Chim. (Bucharest), **61**, no. 3, 2010, p. 1169
18.a) *** BEILSTEINS, Handbuck der Organischen Chemie, Springer-Verlag Berlin-Heidelberg-New York, Tokyo, **10**, IV, 1983, p.194
18.b) *** BEILSTEINS, Handbuck der Organischen Chemie, Springer-Verlag Berlin-Heidelberg-New York, Tokyo, , **10**, IV, 1983, p.360
18.c) *** BEILSTEINS, Handbuck der Organischen Chemie, Verlag von Julius Springer, **10**, H, 1927, p.488
18.d) *** BEILSTEINS, Handbuck der Organischen Chemie, Springer-Verlag Berlin-Heidelberg, **14**, III, 1971, p.894
18.e) *** BEILSTEINS, Handbuck der Organischen Chemie, Verlag von Julius Springer, **14**, I, 1933, p.570

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