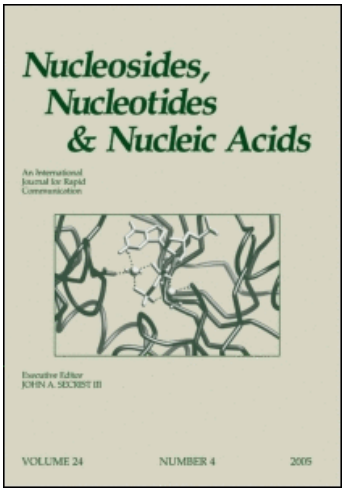

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Microwave-Assisted Organic Synthesis of 3-(D-*gluco*- Pentitol-1-Yl)-1*H*-1,2,4-Triazole

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MICROWAVE-ASSISTED ORGANIC SYNTHESIS OF 3-(D-*GLUCO*-PENTITOL-1-YL)-1*H*-1,2,4-TRIAZOLE

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□ *The condensation of* D*-glucono- and* D*-galactono-1,5-lactone and thiocarbohydrazide to give 3-(*D*-alditol-1-yl)-4-amino-5-mercapto-1,2,4-triazoles* ***4*** *and* ***5*** *is accelerated by the use of microwave-assisted organic reaction (MAOS). The deamination and dethiolation of compound* ***4*** *to give* ***6*** *was also accelerated by the use of MAOS. Condensation of* ***4*** *and* ***5*** *with p-nitrobenzaldehyde afforded Schiff bases* ***8*** *and* ***9****, respectively, within 4 min under microwave irradiation (MWI), whereas with ethyl chloroacetate the thioalkylated products* ***14*** *and* ***15*** *were obtained in 8 min. The structures of the synthesized compounds were confirmed by* ^{1}*H NMR, 2D NMR, and mass spectra.*

Keywords MAOS; MWI; 1,2,4-Triazoles; Acyclonucleosides; *Seco C*-Nucleosides

INTRODUCTION

Microwave-assisted organic synthesis (MAOS) has experienced exponential growth in the last several years. The use of MAOS often provides higher yields and purities when compared to traditional synthetic method.[1] A part of our ongoing program has been devoted to the use of microwave irradiation (MWI) to achieve and/or accelerate organic reactions.[2–9] 1,2,4-Triazoles have gained an important place in medicinal chemistry as a result of their pharmacological activities,[10–15] especially those having 4-amino-5-mercapto-3–substituted derivatives.[16–18] Moreover, the syntheses of their respective nucleosides and acyclonucleoside analogues have been undertaken to enhance their biological activities.[19–25] We report herein the details for our preliminary results[26] for the synthesis of *seco C*-nucleosides of 1,2,4-triazole under the influence of microwave irradiation (MWI).

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EXPERIMENTAL

General Methods

Melting points were determined on a Mel-temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Jeol spectrometer (500 MHz). The chemical shifts are expressed on the δ-scale using Me_4Si as a standard, and coupling–constant values are given in Hz. The assignments of ^{1}H NMR spectra were based on chemical-shift correlation DQFCOSY spectra. TLC was preformed on Merck silica gel 60F254 with detection by charring in sulfuric acid and by UV light. Irradiation was achieved using a domestic microwave oven EM-230 M (800 Watt output power). Microanalyses were preformed in the Microanalysis Unit at the Faculty of Science, Cairo University.

3-(D-Alditol-1-yl)-4-amino-5-mercapto-1,2,4-triazoles (4, 5). General procedure. A mixture of **1** or **2** (0.028 mole, 4.98 g) and thiocarbohydazide **3** (0.028 mol, 2.63 g) in dry pyridine (2 mL) was placed in a Teflon screw-capped vessel and was irradiated for 5–6 min in a microwave oven, then it was left to cool. The product was washed with alcohol and crystallized.

4-Amino-3-(D-*gluco*-pentitol-1-yl)-5-mercapto-1,2,4-triazole (4). The product was crystallized from methanol-water in white needles (88% yield); mp 201–203°C; lit[18] mp 201–202 °C.

4-Amino-3-(D-*galacto*-pentitol-1-yl)-5-mercapto-1,2,4-triazole (5). The product was crystallized from methanol-water in white needles (80% yield); mp 215–217°C; lit[18] mp 214–215°C.

3-(1,2,3,4,5-Penta-*O*-acetyl-D-*gluco*-pentitol-1-yl)-1*H*-1,2,4-triazole (7). A suspension of **4** (1.35 g, 5 mmol) in orthophosphoric acid (10 mL) was treated with sodium nitrite (5N, 35 mL) at 0°C. The reaction mixture was irradiated in a microwave oven for 2 min, neutralized with 10% sodium hydroxide, and then evaporated. The crude product was boiled with ethanol and filtered, and the filtrate was evaporated to dryness. The resulting syrup was dissolved in pyridine (15 mL), cooled to 0°C, and then treated with acetic anhydride (25 mL) and kept for overnight at room temperature. The reaction mixture was poured into ice water and extracted with methylene chloride. The organic layer was washed with water, dried over sodium sulfate, and evaporated to give a syrup, which crystallized from ethanol to give **17** as colorless crystals, 63% yield; mp 177–179°C; lit[21] mp 177–178°C.

3-(D-*Gluco*-pentitol-1-yl)-1*H*-1,2,4-triazole (6). To a stirred solution of **7** (0.429 g, 1 mmol) in methanol (30 mL), ammonium hydroxide (20%, 7 ml) was added. The reaction mixture was allowed to stand overnight at

room temperature, then evaporated under reduced pressure. The crude product was recrystallized from methanol-ether (70%, yield), mp 158–160°C; ^{1}H NMR (DMSO-d_6 + D_2O) δ: 3.20 (dd, 1 H, $J_{5'',4'} = 3.8$ Hz, $J_{5'',5'} = 10.7$ Hz, H-5″), 3.29 (dd, 1 H, $J_{5',4'} = 4.5$ Hz, $J_{5',5''} = 10.7$ Hz, H-5′), 3.42–3.45 (m, 1 H, H-4′), 3.51 (dd, 1 H, $J_{3',2'} = 3.05$ Hz, $J_{3',4'} = 10.7$ Hz, H-3′), 3.92 (d, 1 H, $J_{2',1'} = 6.8$ Hz, H-2′), 4.76 (d, 1 H, $J_{1',2'} = 6.8$ Hz, H-1′), 8.02 (s, 1 H, H-5 arom), 13.33 (s, 1 H, D_2O exchangeable, NH).

3-(D-Alditol-1-yl)-4-(*p*-nitrobenzylidene)amino-5-mercapto-1*H*-1,2,4-triazoles (8, 9).

Method (a). A mixture of the triazole **4** or **5** (0.27 g, 1 mmol), *p*-nitrobenzaldehyde (0.15 g, 1 mmol), in DMF (10 mL) and *p*-toluenesulfonic acid (0.08 g) was heated at reflux for 8 h, cooled to room temperature, and poured into ice water. The product was filtered off and recrystallized from ethanol.

Method (b). A mixture of the triazole **4** or **5** (0.27 g, 1 mmol), *p*-nitrobenzaldehyde (0.15 g, 1 mmol), and *p*-toluenesulfonic acid (0.08 g) in dry DMF (5 mL) was placed in an Erlenmeyer flask (100 mL) and irradiated for 4 min. The reaction mixture was cooled to room temperature.

3-(D-*Gluco*-pentitol-1-yl)-4-(*p*-nitrobenzylidene)amino-5-mercapto-1*H*-1,2,4-triazole (8). The product was crystallized from ethanol to give yellow crystals (61% from method a and 82% from method b); mp 220–222°C; ^{1}H NMR (DMSO-d_6 + D_2O) δ: 3.13 (dd, 1 H, $J_{5'',4'} = 8.4$, $J_{5'',5'} = 11.3$ Hz, H-5″), 3.31 (dd, 1 H, $J_{5',4'} = 5.3$ Hz, $J_{5',5''} = 11.3$ Hz, H-5′), 3.58–3.48 (m, under solvent, 2 H, H-3′, H-4′), 4.20 (d, 1 H, $J_{2',1'} = 8.5$ Hz, H-2′), 4.84 (d, 1 H, $J_{1',2'} = 8.5$ Hz, H-1′), 8.15 (d, 2 H, $J = 7.6$ Hz, H-2, H-6), 8.33 (d, 2 H, $J = 8.4$ Hz, H-3, H-5), 10.15 (s, 1 H, CH=N), 14.00 (s, 1 H, D_2O exchangeable, SH).

3-(D-*Galacto*-pentitol-1-yl)-4-(*p*-nitrobenzylidene)amino-5-mercapto-1*H*-1,2,4-triazole (9). The product was crystallized from ethanol to give yellow crystals (63% from method a and 80% from method b); mp 255–257°C; ^{1}H NMR (DMSO-d_6 + D_2O) δ: 3.32–3.39 (m, 2 H, H-5′, H-5″), 3.53 (dd, 1 H, $J_{3',2'} = 9.2$ Hz, H-3′), 3.71 (m under solvent, 1 H, H-4′), 3.89 (dd, 1 H, $J_{2',1'} = 2.3$ Hz, $J_{2',3'} = 9.2$ Hz, H-2′), 5.06 (d, 1 H, $J_{1',2'} = 2.3$ Hz, H-1′), 8.15 (d, 2 H, $J = 7.7$ Hz, H-2, H-6), 8.32 (d, 2 H, $J = 8.4$ Hz, H-3, H-5), 10.37 (s, 1 H, CH=N), 13.90 (s, 1 H, D_2O exchangeable, SH).

3-(1,2,3,4,5-Penta-*O*-acetyl-D-alditol-1-yl)-4-(*p*-nitrobenzylidene)amino-5-mercapto-1*H*-1,2,4-triazole (11, 12). A cold solution of **8** or **9** (0.133 g, 0.33 mmol) in dry pyridine (1 ml) was treated with acetic anhydride (1.5 mL), the reaction mixture was kept overnight at room temperature, and poured into ice-cold water.

3-(1,2,3,4,5-Penta-*O*-acetyl-D-*gluco*-pentitol-1-yl)-4-(*p*-nitrobenzylidene)-amino-5-mercapto-1*H*-1,2,4-triazole (11). The crude product was recystallized from ethanol to give yellow crystals (85% yield), mp 187–189°C; ^{1}H NMR ($CDCl_3$) δ: 2.01, 2.02, 2.06, 2.07, 2.08 (5s, 15 H, 5 × OAc), 4.12 (dd, 1 H, $J_{5'',4'} = 5.3$ Hz, $J_{5'',5'} = 12.3$ Hz, H-5″), 4.22 (dd, 1 H, $J_{5',4'} = 3.05$ Hz, $J_{5',5''} = 12.3$ Hz, H-5′), 5.16 (ddd, 1 H, $J_{4',5''} = 5.3$ Hz, $J_{4',5'} = 3.05$ Hz, $J_{4',3'} = 8.4$ Hz, H-4′), 5.39 (dd, 1 H, $J_{3',4'} = 8.4$ Hz, $J_{3',2'} = 2.3$ Hz, H-3′), 6.0 (dd, 1 H, $J_{2',3'} = 2.3$ Hz, $J_{2',1'} = 8.4$ Hz, H-2′), 6.3 (d, 1 H, $J_{1',2'} = 8.4$ Hz, H-1′), 8.08 (d, 2 H, $J = 9.2$ Hz, H-2, H-6), 8.41 (d, 2 H, $J = 8.4$ Hz, H-3, H-5), 10.93 (s, 1 H, CH=N), 11.05 (s, 1 H, D_2O exchangeable, SH).

3-(1,2,3,4,5-Penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-4-(*p*-nitrobenzylidene)-amino-5-mercapto-1*H*-1,2,4-triazole (12). The crude product was recystallized from ethanol to give yellow crystals (83% yield), mp 183–185°C; ^{1}H NMR ($CDCl_3$) δ: 2.01, 2.03, 2.17, 2.18, 2.21 (5s, 15 H, 5 × OAc), 3.93 (dd, 1 H, $J_{5'',4'} = 7.6$ Hz, $J_{5'',5'} = 11.5$ Hz, H-5″), 4.32 (dd, 1 H, $J_{5',4'} = 4.3$ Hz, $J_{5',5''} = 11.5$ Hz, H-5′), 5.41 (m, 1 H, H-4′), 5.58 (m, 2 H, H-3′, H-2′), 6.14 (d, 1 H, $J_{1',2'} = 1.9$ Hz, H-1′), 8.07 (d, 2 H, $J = 8.6$ Hz, H-2, H-6), 8.38 (d, 2 H, $J = 8.6$ Hz, H-3, H-5), 10.21 (s, 1 H, CH=N), 11.01 (s, 1 H, D_2O exchangeable, SH).

4-Amino-3-(1,2,3,4,5-penta-*O*-acetyl-D-alditol-1-yl)-5-(ethoxycarbonylmethyl)thio-1,2,4-triazoles (18, 19).

Method (a). A mixture of **4** or **5** (0.27 g, 1 mmol), ethyl chloroacetate (0.122 g, 1mmol), and sodium acetate (0.016 g, 0.2 mmol) in absolute ethanol (25 mL) was refluxed for 18 h. The solvent was evaporated under reduced pressure to dryness. The resulting syrup was dissolved in pyridine (3 mL), cooled to 0°C, and then treated with acetic anhydride (5 mL). The reaction mixture was kept overnight at room temperature, poured into ice water, and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to give a syrup, which was purified by column chromatography.

Method (b). A mixture of **4** or **5** (0.27 g, 1 mmol), ethyl chloroacetate (0.122 g, 1 mmol), and sodium acetate (0.016 g, 0.2 mmol) in absolute ethanol (5 mL) was placed in a Teflon screw-capped vessel and microwave-irradiated for 8 min. Then the reaction mixture was process as in method a.

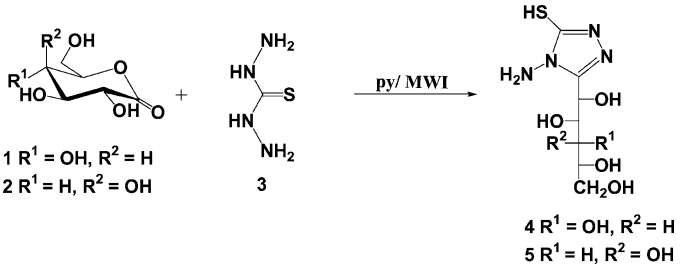
4-Amino-3-(1,2,3,4,5-penta-*O*-acetyl-D-*gluco*-pentitol-1-yl)-5-(ethoxycarbonylmethyl)thio-1,2,4-triazole (18). The crude product was eluted with (petroleum ether/ethyl acetate, 1:4) to give **18** as a syrup (51% method a and 61% method b), ^{1}H NMR ($CDCl_3$) δ: 1.28 (t, 3 H, $J = 7.6$ Hz, CH_3), 1.96, 2.01, 2.10, 2.11, 2.13 (5s, 15 H, 5 × OAc), 3.89, 3.97 (2d, 2 H,

J_{gem} = 16.8 Hz, SCH_2), 4.08 (dd, 1 H, $J_{5'',4'}$ = 7.6 Hz, $J_{5'',5'}$ = 12.3 Hz, H-5″), 4.15 (dd, 1 H, $J_{5',4'}$ = 3.1 Hz, $J_{5',5''}$ = 12.3 Hz, H-5′), 4.23 (q, 2 H, OCH_2), 4.98 (dd, 1 H, $J_{3',4'}$ = 9.2 Hz, $J_{3',2'}$ = 1.5 Hz, H-3′), 5.03 (m, 1 H, H-4′), 5.32 (s, 2 H, D_2O exchangeable, NH_2), 5.69 (d, 1 H, $J_{1',2'}$ = 9.2 Hz, H-1′), 6.18 (dd, 1 H, $J_{2',3'}$ = 1.5 Hz, $J_{2',1'}$ = 9.2 Hz, H-2′).

4-Amino-3-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-5-(ethoxy carbonylmethyl)thio-1,2,4-triazole (19). The crude product was eluted with (petroleum ether/ethyl acetate, 1:4) to give **19** as a syrup (53% method a and 63% method b), ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.25 (t, 3 H, J = 7.6 Hz, CH_3), 1.94, 2.01, 2.03, 2.07, 2.11 (5s, 15 H, 5 × OAc), 3.78, 3.84 (2d, 2 H, J_{gem} = 17.6 Hz, SCH_2), 3.92 (dd, 1 H, $J_{5'',4'}$ = 7.65 Hz, $J_{5'',5'}$ = 11.5 Hz, H-5″), 4.18 (q, 2 H, OCH_2), 4.28 (dd, 1 H,$J_{5',4'}$ = 6.1 Hz, $J_{5',5''}$ = 11.5 Hz, H-5′), 5.25 (s, 2 H, D_2O exchangeable, NH_2), 5.38 (dd, 1 H, $J_{4',5'}$ = 6.1 Hz,$J_{4',3'}$ = 6.9 Hz, H-4′), 5.55-5.59 (m, 2 H, H-2', H-3′), 6.07 (d, 1 H, $J_{1',2'}$ = 2.3 Hz, H-1′).

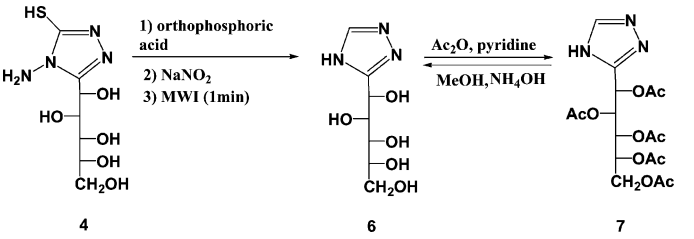
RESULTS AND DISCUSSION

D-Glucono- and D-galactono-1,5-lactones (**1, 2**) and thiocarbohydrazide (**3**) were chosen as building blocks for constructing certain *seco C*-nucleosides; for example, using these building blocks, we obtained 4-amino-3-(D-*gluco*- and D-*galacto*-pentitol-1-yl)-5-mercapto-1,2,4-triazoles (**4** and **5**) in 88 and 80% yield, respectively, under microwave irradiation (MWI) within a shorter reaction times (5–6 min) compared to conventional heating (Scheme 1).[18] Recently, we published a new method for a one-pot deamination and dethiolation of 4-amino-3-(D-*gluco*-pentitol-1-yl)-5-mercapto-1,2,4-triazole **4** using sodium nitrite in orthophosphoric acid.[21] Attempted acceleration of the reaction with MWI for 2 min gave similar results.



SCHEME 1

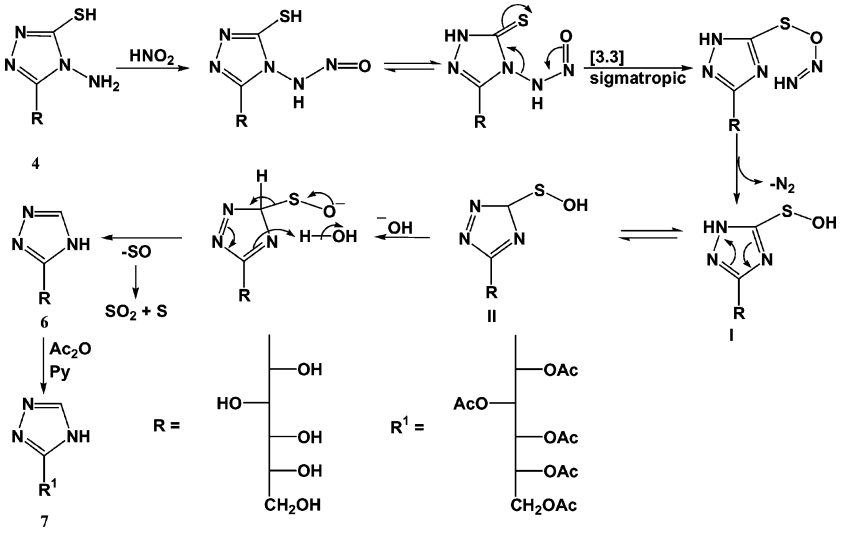
The reaction mixture was neutralized with sodium hydroxide and acetylated to give **7** in an improved yield (63%) compared to that obtained by conventional heating (52%).[21] Deacetylation of **7** with ammonium hydroxide



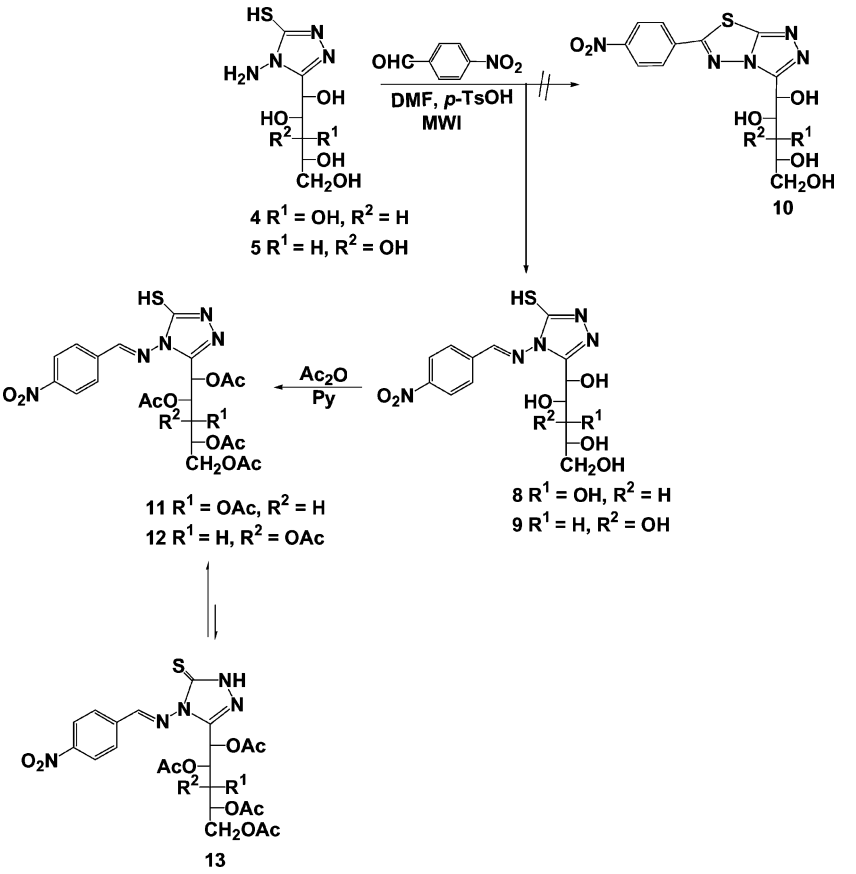
SCHEME 2

in methanol afforded the respective acyclo *C*-nucleoside **6** (Scheme 2). The ^{1}H NMR spectrum of **6** showed in addition to the sugar five hydroxyl exchangeable protons, an exchangeable singlet in the low field region at δ 13.33 due to the NH proton. H-5 of the triazole moiety was assigned to a singlet at δ 8.02. At higher field, the sugar protons H-1′ and H-2′ resonated at δ 4.76 and 3.92, respectively, whereas H-3′, H-5′ and H-5″ each resonated as a doublet of doublets at δ 3.51, 3.29, and 3.20, respectively. The H-4′ multiplet resonated at δ3.42–3.45.

A possible mechanism for the deamination and dethiolation process could be due to the formation of the N-nitroso intermediate, which undergoes a [3.3] sigmatropic rearrangement followed by the loss of a molecule of nitrogen to form intermediate **I**, which tautomerize to **II** and loses a molecule of sulfur monoxide under the basic conditions. Subsequent acetylation of triazole **6** gave the respective *seco C*-nucleoside **7** (Scheme 3).



SCHEME 3

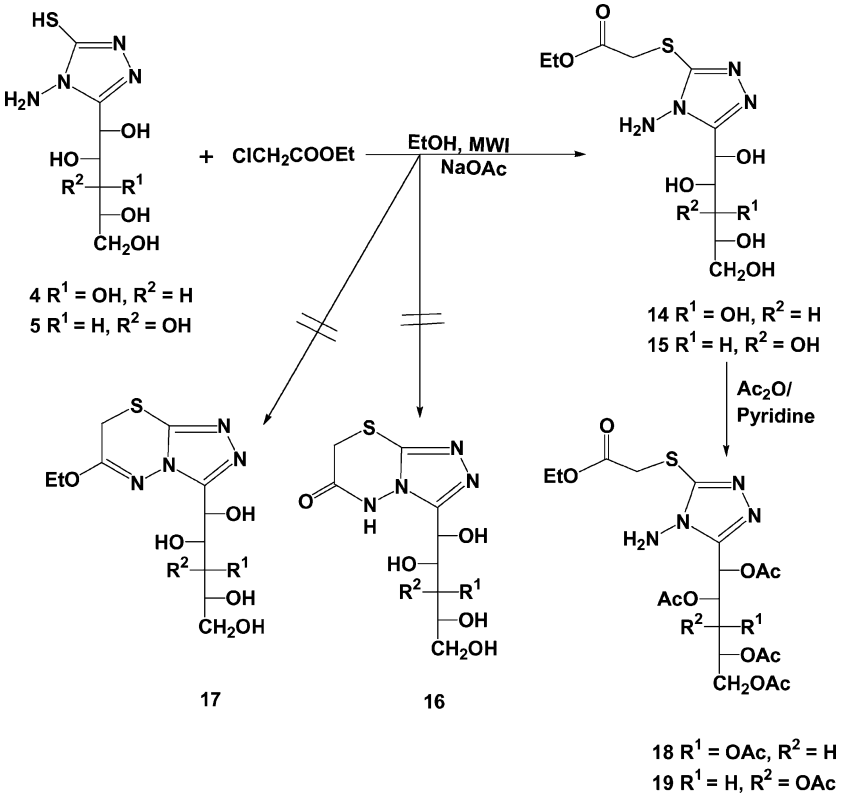


SCHEME 4

The 4-amino-5-mercapto-1,2,4-triazole ring system is a versatile key intermediate for the synthesis of N- and S-bridged heterocyclic derivatives. We were interested in studying the effect of MWI on the 4-amino-mercapto-1,2,4-triazole system found in compounds **4** and **5** (Scheme 4). Condensation of a mixture of **4** or **5** with *p*-NO_2benzaldehyde in DMF in the presence of a catalytic amount of PTSA provided **8** and **9** in moderate yields (61–63%) under conventional heating conditions, whereas the yields were improved to 80–82% using MWI. Surprisingly, no 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole (**10**) was formed during either of the reaction conditions. The uncyclized nature of **8** and **9** was confirmed from the study of their ^{1}H NMR spectra as well as those of their acetylated derivatives **11** and **12**, which were obtained by conventional acetylation of **8** and **9** with acetic anhydride in pyridine. The existence of a characteristic exchangeable singlet for the SH proton at the downfield region at δ 13.90–14.00 and 11.01–11.05 for **8**, **9** and **11**, **12**, respectively, ruled out their existence either in the thione structure **13** or

the cyclized form 1,2,4-triazolo[3,4-b]1,3,4-thiadiazole structure **10**. Moreover, the assigned azomethine proton at δ 10.15–10.37 and 10.21–10.93 for **8**, **9** and **11**, **12**, respectively, was also in agreement with the assigned acyclic structures **8** and **9** rather than the cyclized one **10**.

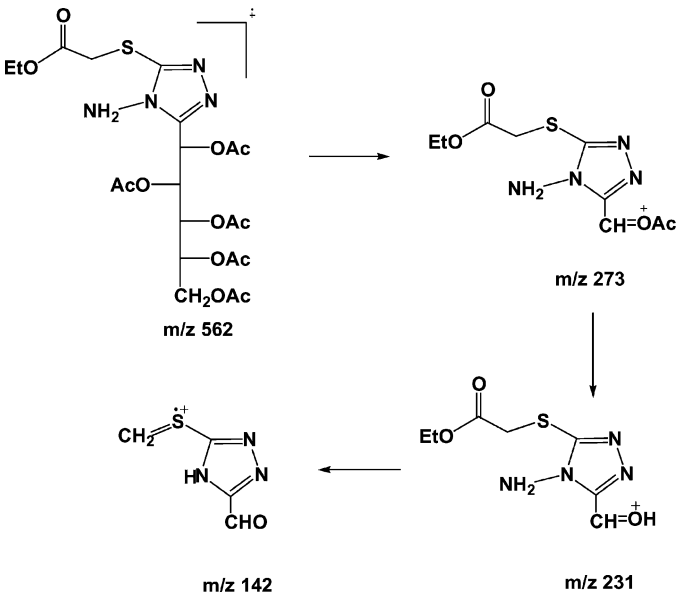
Three possible structures could be expected from the carboxymethylation of **4** and **5** with ethyl chloroacetate in the presence of sodium acetate under microwave irradiation. One of these expected products is a S-alkyl derivatives such as **14** and **15**. Compounds **14** and **15** could provide two additional products **16** and **17** after ring closure with loss of ethanol or water, respectively. Acetylation of **14** and **15** with acetic anhydride in pyridine gave 4-amino-3-(1,2,3,4,5-penta-*O*-acetyl-D-*gluco* and D-*galacto*-pentitol-1-yl)-5-(ethoxycarbonylmethy)thio-1,2,4-triazoles **18** and **19**. Spectral data ruled out the formation of the cyclized products **16** and **17** (Scheme 5).



SCHEME 5

Moreover, verification of the uncyclized structure was confirmed from the mass spectrum of **18**, which showed a molecular ion peak at m/z 562 in agreement with the molecular formula $C_{21}H_{30}N_4O_{12}S$. A C-1-C-2 bond fission of the alditolyl moiety followed by loss of ketene afforded a base peak at m/z 231 (100%), which reflects the stability of the 1,2,4-triazole ring towards

electron bombardment.[17,19] A loss of EtO_2C and NH_2 radicals from the base peak afforded a fragment at *m/z* 142 (Scheme 6).



SCHEME 6

In addition to the other expected sugar protons in the ^1H NMR spectra of **18** and **19,** two exchangeable protons corresponding to the NH_2 protons resonated at δ 5.32 and 5.25, respectively. Two doublets of the AB type spin system with J_{gem} 16.8 and 17.6 Hz, respectively, were attributed to the SCH_2 protons, which indicated that these two protons are not equivalent.[21] The ^1H-^1H DQFCOSY technique facilitated the correlation of protons with each other. Thus, the higher frequency region H-2′ of compound **18** was assigned as doublet of doublets at δ 6.18 and coupled with H-1′ (d, δ 5.69) and H-3′ (dd, δ 4.98), which in turn was correlated with H-4′ (m, δ 5.03–5.05). H-5′ was assigned to a doublet of doublets at δ 4.15 coupled with H-5″ and H-4′. The signals corresponding to the ethyl moiety were assigned to a triplet at δ 1.28 corresponding to CH_3 group and correlated with the quartet signal due to CH_2 at δ 4.23.

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