HETEROCYCLES, Vol. 68, No. 9, 2006, pp. 1901 - 1907. © The Japan Institute of Heterocyclic Chemistry
Received, 6th June, 2006, Accepted, 25th July, 2006, Published online, 28th July, 2006. COM-06-10802

ACCELERATED SYNTHESIS OF NOVEL 1,2,4-TRIAZOLO[3,4-*b*][1,3,4]-THIADIAZEPINES UNDER MICROWAVE IRRADIATION

Ahmet Çetin

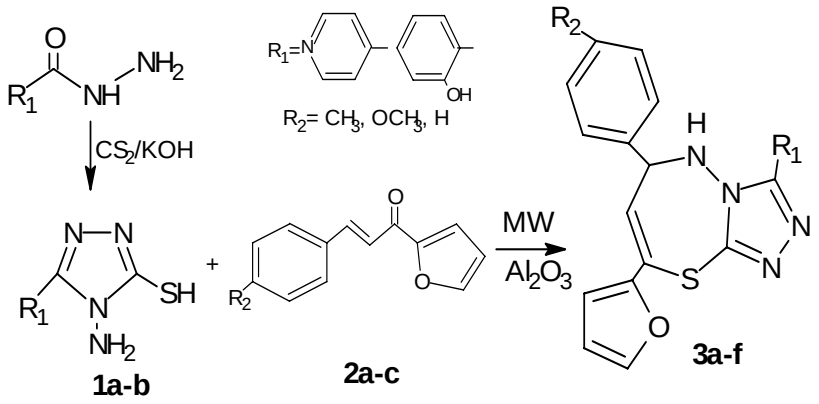
Firat University, Graduate School of Natural and Applied Sciences, Department of Chemistry, Elazig, Turkey. acetin74@hotmail.com

Abstract- A convenient and efficient one step, base catalyzed synthesis of 3,5-disubstituted-4-amino-1,2,4-triazoles by condensation of thiol and hydrazide is presented. An environmentally benign and economic synthesis for the title compounds is described from readily accessible substituted 4-amino-5-mercapto-1,2,4-triazoles and substituted chalcones on basic alumina that are accelerated by exposure to microwave irradiation.

INTRODUCTION

During the last decade, microwave (MW) dielectric heating has developed into a convenient and widely used tool in organic synthesis.[1] Microwave heating has taken an incontestable place in analytical and organic laboratory practice as a very effective and non-polluting method of activation.[2] Microwave irradiation is a powerful technique which is increasingly used to accelerate thermal organic reactions.[3] The advantage of MW heating over conventional heating is that the reaction mixtures absorb the energy directly. Thus, the temperature gradient rises steeply, to lead to an acceleration of the reaction, an essential condition in a flow-through system. Another important advantage of MW heating in such system is the “on/off condition,” i.e. the possibility to turning the MW source on or off instantaneously.[4,5]

In general, most of these methods involve multiple synthetic steps, which often require harsh reaction conditions or reagents that are not readily available, making these methods unsuitable for use in the synthesis of 1,2,4-triazole derivatives libraries. Thus, there exists a need for a simpler synthesis of 1,3,4-thiadiazepine derivatives that can be accessed under milder conditions from readily available starting materials and can be automated.[6] Various 1,2,4-triazole derivatives are associated with diverse pharmacologial activities, such as anti-microbial, bactericidal, anti-inflammatory, anti-viral, anti-hypertensive, anti-depressant, anthelmintic, and analgesic effects.[3,7,8] 3,5-Disubstituted 4-amino-1,2,4-triazoles are potentially good corrosion inhibitors.[9] 3,5-Disubstituted 1,2,4-triazoles have also been actively studied as bridging ligands coordinating through their vicinal N atoms and some have special structure with interesting magnetic properties.[10] Substituted thiadiazepines have been tested for their *in vitro* antibacterial and antifungal activity.[11]



Scheme1

Triazoles fused with six-membered ring systems are found to possess diverse applications in the field of medicine, agriculture and industry. The commonly known systems are triazoles fused with pyridines, pyridazines, pyrimidines, pyrazines, and triazines. The literature survey reveals that there are not so many examples of triazoles fused with thiadiazines.[12] Moreover, a large number of triazolothiadiazines has been shown to exhibit antidepressant and photographic couplers.[13]

RESULTS AND DISCUSSION

From the result shown in Scheme1, it is clear that the basic alumina is the most adaptable support for synthesizing **3a-f**, since a comparatively higher yield was achieved in a shorter time. The reaction of 3,5-disubstituted 4-amino-1,2,4-triazoles (**1a,b)** with substituted chalcones **(2a-c)** on basic alumina under microwave irradiation afforded the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepine derivatives **(3a-f**) within 2-5 min. On the other hand, reaction under some conditions was also carried out in solution phase (8-12 min). The results obtained from these conditions showed that the product was obtained in a lower yield (42-54%)

after prolonged heating (54-60 h) using Na_2CO_3 as a base in dioxane (Table 1). Solvents for recrystallization and melting points of the compounds are given experimental section.

Table 1: Comparative study on the synthesis of **3a-f** under microwave irradiation and conventional method.

Com-pound	Reaction period (min[a])/(min[b])/(h[c])	Yield (%) a/b/c
3a	2/8/54	85/80/42
3b	3/12/60	80/80/40
3c	5/12/60	95/85/48
3d	3/8/54	84/75 /45
3e	4/12/60	90/83/ 47
3f	5/12/60	98/ 85/54

[a]Solid phase MWI, [b]Solution phase MWI, [c]Conventional heating

The structure of all synthesized compounds was established on the basis of their spectroscopic data. The disappearance of the signal at δ 14.02 of –SH proton of mercapto triazoles and the appearance of the signal at δ 10.02-9.76 due to –NH of the thiadiazepine ring in the ^{1}H NMR spectrum also confirmed their structures formation. Likewise, the ^{13}C NMR spectra of condensed products displayed disappearance of signal at δ 185-190 ppm due to of chalcones (C=O) and also the appearance of the signals at δ 40-45, and δ 93-98 due to signals of the thiadiazepine ring in the ^{13}C NMR spectrum confirmed product formation. In the X-Ray single crystallographic analysis of compound (**2b**), the intramolecular hydrogen bonds (O–H....N, N–H....S, and C–H....N) and intermolecular hydrogen bonds N–H....S, N–H....O indicated by dashed lines.

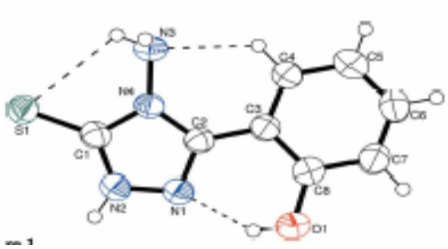


Figure 1. The molecular structure of **2b**, showing the atomic numbering scheme.

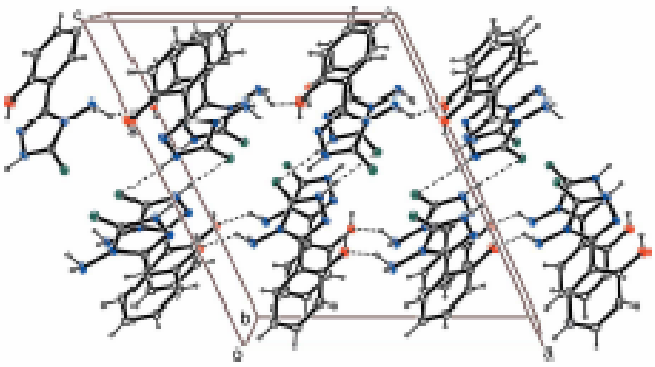


Figure 2. A projection of the crystal structure of **1b** along the b axis. Crystallographic data (excluding structure factors) for the structure in this paper have been publication in the Acta Cryst.,[14] or [e-mail: acetin74@hotmail.com].

In conclusion, we have developed and facile rapid and the economic methodology for various synthesis of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepine derivatives

on a solid support using MWI keeping modernization and simplication of classical procedure. The results shown in Table 1 demonstrate that the versatility of the process as considerable reaction rate enhancement has been observed by shortening the reaction time from hours to seconds with improved yield as compared to conventional heating method.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a digital Gallenkamp melting point apparatus and are uncorrected. Elemental analyses (C, H, N) were carried out using LECO-932 CHNSO by Technical and Scientific Research Council of Turkey, TUBITAK. The IR spectra were recorded for KBr disks with a Mattson 1000 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian-Mercury-Plus 400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR spectrometer in DMSO-d_6 with TMS as an internal standard. Starting materials was obtained from Fluka or Aldrich.

General procedure for the synthesis of 5-substituted 4-amino-2,4-dihydro-4*H*-1,2,4-triazole-3-thione (**1a-b**)**:** A solution of KOH (0.015 mole, 8.40 g), 100 mL of absolute EtOH and substituted hydrazide (0.01 mole) was treated to the addition of carbon disulfide (0.015 mole, 0.91 mL). This mixture was diluted with 50 mL of absolute EtOH and agitated for 14 h. It was then diluted with 200 mL of dry Et_2O and vacuum dried at 70 ^{0}C. A suspension of potassium salts, 0.03 mole of 98 % hydrazine hydrate (15 mL) and 2 mL of water was refluxed with stirring for 2-3 h. The color of reaction mixture changed to green, hydrogen sulfide was evolved, and a homogeneous solution resulted. Dilution with 100 mL of cold water and acidification with concentrated hydrochloric acid precipitated a white solid. The product was filtered, washed with 5x10 mL portions of cold water, and recrystallized from EtOH to analytical purity.

4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiol (**1a**): mp 250 ^{0}C, IR (KBr): υ 3380-3200 (NH_2), 3090-3000 (Ar. CH), 2925-2762-2560 (S-H); ^{1}H NMR (DMSO-*d6*): δ 14.02 (br, 1H, SH), 8.74 (dd, *J*=6.23, 1.47, 2H, pyridyl H_3, H_5), 7.99 (dd, *J*=6.23, 1.47, 2H, pyridyl H_2, H_6), 5.84 (br, 2H, NH_2); ^{13}C NMR (DMSO-d*6*): δ 168.4, 150.9, 148.1, 133.6, 122.3; *Anal.* Calcd for $C_7H_7N_5S$: C 43.51, H 3.65, N 36.24. Found: C 43.56, H 3.69, N 36.22.

4-amino-5-(2-hydroxyphenyl)-4*H*-1,2,4-triazole-3-thiol (**1b**): mp 216-218 ^{0}C; IR (KBr): υ 3460-3180 (OH, NH_2), 3080-3020 (Ar. CH), 2925-2762-2560 (S-H); ^{1}H NMR (DMSO-*d6*): δ 14.02 (br, 1H, SH), 8.84 (br, 1H, OH), 7.42 (dd, *J*=7.70, 1.83, 1H), δ 7.35 (t, *J*=7.70, 1H), 6.98 (d, *J*=7.70, 1H), 6.90 (dt, *J*=7.70, 1.83, 1H), 5.61 (br, 2H, NH_2); ^{3}C NMR (DMSO-*d6*): δ 165.7, 156.7, 149.8, 132.8, 131.5, 119.8,

116.9, 113.7; *Anal.* Calcd for $C_8H_8N_4OS$: C 46.14, H 3.87, N 26.90. Found: C 46.09, H 3.89, N 26.94.

General procedure for the synthesis of chalcones (**2a-c**): prepared according to our method reported earlier.[15]

General procedure for the synthesis of 1,3,4-thiadiazepin derivatives (**3a-e**)

Method A: An equimolar mixture of 5-substituted 4-amino-3-mercapto-1,2,4-triazole (**1a,b**) and chalcones (**2a-c**) (10 mmole) in CH_2CI_2 (10mL) was mixed with solid support (10g) (basic alumina[16]). The reaction mixture was evaporated and the adsorbed material was dried and placed in an alimuna bath.[17] The microwave oven then irradiated until the completion of reaction (TLC). The mixture was cooled and product was extracted into CH_2CI_2 (20 mL). The product was obtained by evaporating the solvent and recrystallized from a mixture of CH_2CI_2 / EtOH.

Method B: To a solution of 5-substituted 4-amino-1,2,4-triazole-3-thiol (10 mmole) (**1a,b**) in dioxane (10 mL) taken an Erlenmeyer flask were added 10 mmole of chalcones (**2a-c**) and K_2CO_3. The reaction mixture was subjected to microwave irradiation for 8-12 min with an interval after every 20-30 s. The reaction mixture was cooled, inorganic salt was filtered off and solvent was evaporated. The solid obtained was recrystallised from a mixture of CH_2CI_2 / EtOH.

Method C: An equimolar mixture of 4-amino-1,2,4-triazole-3-thiol (**1a,b**) and chalcones (**2a-c**) (10 mmole) was solubilized in dry toluene (30 mL). Trifluoroacetic acid (8 drops) as acidic catalyst, or piperidine (10 drops) as a basic catalyst, was then added to the reaction mixture and refluxed with azeotropical removal of water formed for an appropriate time (40-54 h) until the reactants disappeared as followed by TLC. The excess of solvent was removed under reduced pressure and the residue left was recrystallized from dry MeOH to give the respective product **3a-f**.

8-(2-Furyl)-5,6-dihydro-6-phenyl-3-(pyridin-4-yl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepine (**3a**). mp 220-222 ^{0}C, IR (KBr): υ 3306 (NH), 3140-2980 (Ar/Al. CH), 1586 (C=N); ^{1}H NMR (DMSO-d*6*): δ 4.92 (dd, 1H, J= 1.30, 0.65, thiadiazepine HN-CH-CH), 5.21 (d, 1H, J= 1.30, thiadiazepine C-C=CH), 6.84-7.00 (m, 2H, furyl H_3, H_4), 7.68 (d, *J*=1.73, 1H, Furyl H_5), 7.18-7.20-7.23 (m, 5H, Ph CH), 7.98 (dd, *J*=6.23, 1.47, 2H, pyridyl H_3, H_5), 8.80 (dd, *J*=6.22, 1.47, 2H, pyridyl H_2, H_6), 9.75 (br, 1H, NH); ^{13}C NMR (DMSO-d*6*): δ 165.7, 153.6, 151.8, 149.5, 149.4, 146.8, 142.0, 133.2, 130.1, 129.1, 127.3, 119.3, 117.6, 103.8, 96.6, 41.7; *Anal.* Calcd for $C_{21}H_{17}N_5OS$: C 65.10, H 4.42, N 18.08. Found: C 64.97, H 4.46, N 18.05.

8-(2-Furyl)-5,6-dihydro-6-(4-methylphenyl)-3-(pyridin-4-yl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepine (**3b**): mp 240-241 ^{0}C, IR (KBr): υ 3296 (NH), 3100-2940 (Ar/Al. CH), 1580 (C=N); ^{1}H NMR (DMSO-d6): δ 2.24 (s, 3H, CH_3), 4.94 (dd, 1H, J= 1.30, 0.65, thiadiazepine HN-CH-CH), 5.26 (d, 1H, J= 1.30, thiadiazepine C-C=CH), 6.86-6.89 (m, 2H, furyl H_3, H_4), 7.17 (d, *J*=6.23, 2H, Ph CH, m-CH_3), 7.08 (d, *J*=6.23, 2H, Ph CH, o-CH_3), 7.76 (d, *J*=1.74, 1H, furyl H_5), 7.97 (dd, *J*=6.23, 1.46, 2H, pyridyl H_3, H_5), 8.79 (dd, *J*=6.23, 1.47, 2H, pyridyl H_2, H_6), 9.76 (br, 1H, NH); ^{13}C NMR (DMSO-d*6*): δ 165.7, 153.4, 151.9, 149.5, 149.3, 146.8, 142.1, 136.1, 130.1, 129.1, 120.3, 119.4, 117.6, 103.8, 97.2, 41.7, 21.9; *Anal.* Calcd for $C_{22}H_{19}N_5OS$: C 65.81, H 4.77, N 17.44. Found: C 65.87, H 4.79, N 17.39.

8-(2-Furyl)-5,6-dihydro-6-(4-methoxyphenyl)-3-(pyridin-4-yl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepine (**3c**): mp 78 ^{0}C, IR (KBr): υ 3340 (NH), 3120-2960 (Ar/Al. CH), 1586 (C=N); ^{1}H NMR (DMSO-d*6*): δ 3.83 (s, 3H, OCH_3), 4.93 (dd, 1H, J= 1.30, 0.65, thiadiazepine HN-CH-CH), 5.27 (d, 1H, J= 1.30, thiadiazepine C-C=CH), 6.80-6.84 (m, 2H, furyl H_3, H_4), 6.90 (d, *J*=6.23, 2H, Ph CH, o-OCH_3), 7.18 (d, *J*=6.23, 2H, Ph CH, m-OCH_3), 7.80 (d, *J*=1.73, 1H, furyl H_5), 7.93 (dd, *J*=6.23, 1.47, 2H, pyridyl H_3, H_5), 8.78 (dd, *J*=6.22, 1.47, 2H, pyridyl H_2, H_6), 10.01 (br, 1H, NH); ^{13}C NMR (DMSO-d*6*): δ 165.7, 160.1, 153.6, 151.9, 149.5, 149.3, 146.8, 142.1, 130.1, 127.1, 119.3, 117.4, 117.6, 103.8, 97.6, 56.2, 41.7; *Anal.* Calcd for $C_{22}H_{19}N_5O_2S$: C 63.29, H 4.59, N 16.78. Found: C 63.23, H 4.65, N 16.83.

8-(2-Furyl)-5,6-dihydro-6-phenyl-3-(2-hydroxyphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepine (**3d**): mp 147-149 ^{0}C, IR (KBr): υ 3290-3180 (NH, OH), 3100-2880 (Ar/Al. CH), 1588 (C=N); ^{1}H NMR (DMSO-d*6*): δ 4.94 (dd, 1H, J= 1.32, 0.66, thiadiazepine HN-CH-CH), 5.21 (d, 1H, J= 1.32, thiadiazepine C-C=CH), 6.70-7.98 (m, 13H, Ar. CH, NH), 8.58 (br, 1H, OH); ^{13}C NMR (DMSO-d*6*): δ 160.8, 153.4, 151.9, 149.4, 149.1, 143.8, 137.0, 134.1, 130.0, 129.9, 129.3, 127.1, 123.9, 119.6, 116.7, 104.8, 111.1, 96.9, 42.3; *Anal.* Calcd for $C_{22}H_{18}N_4O_2S$: C 65.65, H 4.51, N 13.92. Found: C 65.60, H 4.57, N 13.90.

8-(2-Furyl)-5,6-dihydro-6-(4-methylphenyl)-3-(2-hydroxyphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepine (**3e**): mp >350 ^{0}C, IR (KBr): υ 3320-3242 (NH, OH), 3140-2910 (Ar/Al. CH), 1588 (C=N); ^{1}H NMR (DMSO-d*6*): δ 2.25 (s, 3H, CH_3), 4.98 (dd, 1H, J= 1.32, 0.66, thiadiazepine HN-CH-CH), 5.28 (d, 1H, J= 1.32, thiadiazepine C-C=CH), 6.66-8.06 (m, 12H, Ar. CH, NH), 8.77 (br, 1H, OH); ^{13}C NMR (DMSO-d*6*): δ 160.8, 153.4, 151.9, 149.3, 148.9, 143.7, 137.8, 133.6, 130.8, 129.0, 129.2, 126.0, 123.2, 119.6, 116.7, 104.8, 111.1, 97.1, 43.1; *Anal.* Calcd for $C_{23}H_{20}N_4O_2S$: C 66.33, H 4.84, N 13.45. Found: C 66.37, H 4.88, N 13.41.

8-(2-Furyl)-5,6-dihydro-6-(4-methoxyphenyl)-3-(2-hydroxyphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepine (**3f**): mp >350 ^{0}C; IR (KBr): υ 3328-3220 (NH, OH), 3140-2900 (Ar/Al. CH), 1582 (C=N); ^{1}H NMR (DMSO-d*6*): δ 3.83 (s, 3H, OCH_3), 4.94 (dd, 1H, J= 1.31, 0.66, thiadiazepine HN-CH-CH), 5.29 (d, 1H, J= 1.31, thiadiazepine C-C=CH), 6.72-7.96 (m, 12H, Ar. CH, NH), 8.72 (br, 1H, OH); ^{13}C NMR (DMSO-d*6*): δ 161.3, 160.8, 153.4, 151.9, 149.4, 149.1, 143.8, 133.8, 128.9, 128.0, 127.9, 19.7, 123.2, 116.7, 114.2, 104.8, 111.1, 96.8, 42.6; *Anal.* Calcd for $C_{23}H_{20}N_4O_3S$: C 63.87, H 4.66, N 12.95. Found: C 63.83, H 4.71, N 12.91.

REFERENCES

1. A. Loupy, 'Microwaves in Organic Synthesis,' Wiley-VCH: Weinheim, 2002.
2. K. Bougrin, A. Loupy, and M. Soufiaoui, *J. Photochem. Photobiol.*, 2005, **6**, 139.
3. A. Dandia, R. Singh, and S. Khaturia, *Bioorg. Med. Chem*., 2006, **14**, 1303.
4. N. Leadsbeqter and M. Marco, *J. Org. Chem*., 2005, **68**, 888.
5. A. Caceres, M. Jaimes, G. Chavez, B. Bravo, F. Ysambertt, and N. Marquez, *Talanta*, 2005, **68**, 359.
6. T. Sriram and K. C. Prasun, *Tetrahedron Lett.*, 2005, **46**, 7889.
7. F. Fülöp, E. Semega, C. Dombi, and G. Bernath, *J. Heterocycl. Chem*., 1990, **27**, 951.
8. A. Cansız, M. Koparır, and A. Demirdağ, *Molecules*, 2004, **9**, 204.
9. F. Bentis, M. Lagrenee, M. Traisnel, and J. C. Hornez, *Corros. Sci*., 1999, **41**, 789.
10. O. Kahn and C. Martinez, *Science*, 1998, **279**, 44.
11. M. Kidwai, P. Sapra, P. Misra, R. K. Saxena, and M. Singh, *Bioorg. Med. Chem*., 2001, **9**, 217.
12. B. S. Holla, P. M. Akrabeli, and M. K. Shivananda, *Il Farmaco*, 2001, **56**, 919.
13. Y. Kawashima, Y. H. Ishikawa, S. Kida, T. Tanaka, and K. Masuda, *Chem. Abstr*., 1987, **106**, 138475.
14. M. Dinçer, N. Özdemir, A. Çetin, A. Cansız, and M. Şekerci, *Acta Cryst.*, 2005, **E61**, o17.
15. A. Çetin, A. Cansız, and M. Dığrak, *Heteroatom Chem*., 2003, **14**, 345.
16. Aluminium Oxide, Basic, Brockmann I (Aldrich Chem. Co. Cat. No:19, 944-3,150 mesh, 58Å, Surface area 155m^2/g) were used as received.
17. G. Bram, A. Loupy, and M. Majdoub, *Tetrahedron*, 1990, **46**, 5167.