Chem Sci Trans., 2012, **1(2),** 341-346
DOI:10.7598/cst2012.4585

Chemical Science Transactions
ISSN/E-ISSN: 2278-3458/2278-3318

RESEARCH ARTICLE

$Fe(HSO_4)_3$ Supported on Nano-TiO_2 : An Efficient Heterogeneous Catalyst for Intramolecular Cyclization of 3-Propaygylmercapto Triazoles to 6-Methyl-thiazolo[3,2-*B*][1,2,4]triazoles

MEHDI BAKAVOLI[a], VAHID R. HEDAYATI[a*], MAJID M. HERAVI[b], ABOLGHASEM DAVOODNIA[a] and HOSSEIN ESHGHI[c]

[a]Department of Chemistry, Islamic Azad University Mashhad Branch, Mashhad, Iran
[b]Department of Chemistry, School of Sciences, Azzahra University, Tehran, Iran
[c]Department of Chemistry, Ferdowsi University of Mashhad, Mashhad, Iran
hedayati660@yahoo.com

Received 22 May 2012 / Accepted 20 June 2012

Abstract: Intramolecular cyclization of 3-propargylmercapto-1,2,4-triazole derivatives (**2**) to their corresponding 6-methyl thiazolo[3,2-b][1,2,4]triazoles (**3**) was affected in the presence of nano catalyst, $Fe(HSO_4)_3/TiO_2$ as solid acid in high yields.

Keywords: Intramolecular cyclization, 3-Propargylmercapto-triazoles, Nano catalyst, Ferric hydrogen sulfate

Introduction

Thiazolo[3,2-b][1,2,4]triazoles are interesting compounds from the view point of chemical reactivity[1-5] and biological activity. Antibacterial[6,7], anti-inflammatory[8], antiviral[9,10], antitumor[11,12] and antifungal[13] activities of these compounds have encouraged the researchers over the years to look for milder and high yielding synthetic approaches.

Thiazolo[3,2-b][1,2,4]triazoles (**3**) were first synthesized by Potts and Hussain[14] via the reaction of 5-alkyle-3-mercapto-1,2,4-triazoles (**1**) with chloroacetone and subsequent dehydration of the corresponding ketone in the presence of $POCl_3$. In 1978, Srinvasan and co-workers reported the synthesis of 5-alkyl-3-propargylmercapto-1,2,4-triazole (**2**) in moderate yields, through the reaction of **1** with propargyl bromide, in the presence of sodium acetate. Further annulation of **2** to thiazolo[3,2-b][1,2,4] triazoles has been also reported under mercury(II) acetate catalysis in poor to moderate yields[15].

Regioselective cyclization of 3-propargylmercapto-1,2,4-triazoles to their corresponding thiazolo[3,2-b][1,2,4]triazoles in the presence of sodium hydroxide has been reported[16]. We have recently described the use of Pd-salt for catalyzed intramolecular cyclization and functionalization of acetylenes[17] and also we have used heteroployacids (HPA) to obtain triazolo thiadiazin and triazino thiadiazines[18].

There have been much attention towards the application of heterogeneous catalysts in organic synthesis and this subject has been reviewed[19]. Among the many solid acid catalysts ferric hydrogen sulfate has emerged as a promising solid acid catalyst for acid catalyzed reactions, such as Friedel–Crafts acylation[20], Schmidt reaction[21] and functional group protections[22,23] in homogenous and heterogeneous systems. For several years TiO_2-supported catalysts have attracted attention due to the possibility of obtaining highly active materials[24-26]. Along this line with these findings and due to our interest in catalyzed intramolecular cyclization and functionalization of acetylenes[17] we have examined the efficiency of nanostructure $Fe(HSO_4)_3/TiO_2$ as a heterogeneous catalyst for intramolecular cyclization of 3-propargylmercapto-1,2,4-triazoles **2** to obtain thiazolo [3,2-b][1,2,4]triazoles (**3**).

Experimental

$Fe(HSO_4)_3$ was obtained according to a literature procedure[19]. The $Fe(HSO_4)_3/TiO_2$ was prepared by ultrasonic method, as nano titanium dioxide (Degussa P25) (0.12 g, 1.5 mmol) was dispersed in ethanol (20 mL) for 15 min. The dispersion was continued and the ferric hydrogen sulfate (0.17 g, 0.5 mmol) was added slowly and was stirred for 2 h. Then the mixture was filtered and dried at 100 ^oC. EDAX Analysis (At %): Ti 85.44, Fe 4.78, S 9.78. IR (KBr disc), 3421, 1637, 1079, 802 and 652.

*Preparation of 5-alkyle-3-propargylmercapto-1,2,4-triazoles (**2**)*

An appropriate 5-alkyle-3-mercapto-1,2,4-triazole (5 mmol) and sodium methoxide (5 mmol) was dissolved in methanol (50 mL) to which was added propargyl bromide (5 mmol) drop wise. This mixture was stirred for 30 min. After evaporation of solvent and pouring the residue into crushed ice, the solid that separated was filtered and crystallized from a suitable solvent.

^1H NMR spectral data for **2a:** ($[^2H_6]$DMSO) 3.13 (1H, s) 3.72 (2H, s) 8.01 (1H, s). IR(KBr disc), 3250, 2830, 2500, 2100 cm^{-1}. ^1H NMR spectral data for **2b:** ($[^2H_6]$DMSO) 3.08 (3H, s) 3.33 (1H, s) 3.76 (2H, s). IR(KBr disc), 3240, 2860, 2490, 2050 cm^{-1}. ^1H NMR spectral data for **2c:** ($[^2H_6]$DMSO) 1.01 (3H, t) 2.43 (2H, q) 3.12 (1H, s) 3.70 (2H, s). IR(KBr disc), 3260, 2850, 2510, 2150 cm^{-1}.

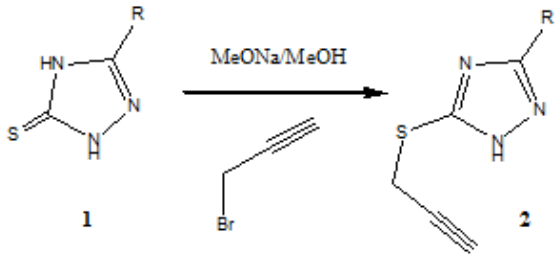
*Preparation of thiazolo[3,2-b][1,2,4]triazoles derivatives (**3**)*

A mixture of derivative **2** (1 mmol) and appropriate nano-catalyst $Fe(HSO_4)_3/TiO_2$ (0.15 mmol) in acetic acid (10 mL) was refluxed for 2-2.5 hours. The progress of the reaction was monitored by TLC using hexane/ethylacetat (3/2). The catalyst was removed by filtering and washed with warmed acetic acid (the catalyst is not soluble in acetic acid). The catalyst was washed with chloroform after filtration. The filtrate was cooled and the solid was collected by filtration, washed with water, dried and recrystallized from ethanol to give pure product **3** to excellent yields (Table 3).

^1H NMR spectral data for **3a:** ($CDCl_3$) 2.70 (3H, s) 6.51 (1H, s) 8.19 (1H, s). IR(KBr disc), 3220, 3050, 1470, 1400, 1190, 630 cm^{-1}. ^1H NMR spectral data for **3b:** ($CDCl_3$) 2.53 (3H, s) 2.75 (3H, s) 6.49 (1H, s). IR(KBr disc), 3290,1640,1470,1310, 1280 cm^{-1}. ^1H NMR spectral data for **3c:** ($CDCl_3$) 1.02 (3H, t) 2.08 (2H, q) 2.64 (3H, s) 6.41 (1H, s). IR(KBr disc), 3110, 3040, 3000, 1460, 1440, 1330, 1275, 680 cm^{-1}.

Results and Discussion

To prepare 5-alkyl-3-propargylmercapto-1,2,4-triazole **2**, 5-alkyle-3-mercapto-1,2,4-tri azole (**1**) was condensed with propargyl bromide in the presence of sodium methoxide to afford the corresponding derivative **2** (Scheme **1**).



1 2

Scheme 1. Condensation of 5-alkyl-3-mercapto-1,2,4-triazoles with propargyl bromide

Yields of the condensation are shown in Table 1.

Table 1. Preparation of 3-propargylmercapto-1,2,4-triazoles (**2a-2c**)

Product	R	Yield, %	M.P / ^{o}C	Rec. Solvent
2a	H	78	110	Ethanol
2b	Me	86	125	Ethanol
2c	Et	80	128	Ethanol

Ferric hydrogen sulfate is an acidic salt and probably can be used in cyclization of 5-alkyl-3-propargyl mercapto-1,2,4-triazole (**2**) as an effective catalyst. For this, compound **2** was refluxed in the presence of ferric hydrogen sulfate alone to obtain 6-methylthiazolo[3,2-b] [1,2,4]triazoles (**3**) for 24 hours, but the results were disappointed. Poor yield products from this reaction were separated by column chromatography. Obtained yields from this method are shown in Table 2.

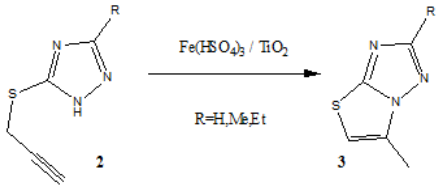
Table 2. Cyclization of 5-alkyl-3-propargylmercapto-1,2,4-triazoles using $Fe(HSO_4)_3$ alone

Compd.	R	Reaction time, h	Yield, %
3a	H	24	17
3b	Me	24	24
3c	Et	24	20

Nano metal oxides such as TiO_2 duo to high surface area can lead to more effective molecular contacts. In order to achieve higher yield of products, we prepared $Fe(HSO_4)_3$ /TiO_2 through dispersion of acidic salt of iron III and nano titanium dioxide by ultrasonic process for 2 hours in ethanol. Then the mixture was filtered and dried at 100 ^{o}C.

The advantages of $Fe(HSO_4)_3/TiO_2$ rather to other catalysts in previous researches are to be cheap, simple preparation. We also expected that because of high surface area of nano $Fe(HSO_4)_3/TiO_2$, the reaction can be completed by just a little amount of catalyst. In addition, separation and purification of product is simple. Therefore we decided to use nanostructure $Fe(HSO_4)_3/TiO_2$ for intramolecular cyclization of 5-alkyl-3-propargyl mercapto-1,2,4-triazole (**2**).

Compound **2** was refluxed in the presence of $Fe(HSO_4)_3/TiO_2$ to obtain 6-methyl thiazolo[3,2-b][1,2,4]triazoles **3** in acetic acid for about 2-2.5 hours, yields were excellent. Use of this nano-catalyst gave cleaner products and higher yields over a short time (Scheme 2).



Scheme 2. Cyclization of 5-alkyl-3-propargylmercapto-1,2,4-triazoles in the presence of $Fe(HSO_4)_3/TiO_2$

The reaction was monitored by TLC and the work up was the same as mentioned in the experimental section. Nano-catalysts were separated by filtration and the products were purified by recrystalizing from ethanol. The yields are shown in Table 3. The products were identified by ^{1}H NMR, IR spectroscopy and melting points were compared to those reported before[16]. In ^{1}H NMR spectrum of these compounds the methyl protons belong to 1,3-thiazole moiety and vinyl proton were appeared at 2.6-2.7 δ and 6.4-6.5 δ, which confirmed the structure.

Table 3. Cyclization of 5-alkyl-3-propargylmercapto-triazoles using nano $Fe(HSO_4)_3/TiO_2$

Compd.	R	Reaction time, h	M.P/°C	Yield, %	Rec. solvent
3a	H	2.5	66-68	89	Ethanol
3b	Me	2	69-71	90	Ethanol
3c	Et	2	70-72	92	Ethanol

Generally reactions catalyzed by ferric hydrogen sulfate may be represented by the conventional mechanisms of bronsted acid catalysis. The mechanism may include the protonation of substrate by conversion of the ionic intermediate to yield the reaction product[27-29].

Finally, the catalytic activity of the re-covered catalyst, ferric hydrogen sulfate supported on TiO_2, was examined and the same catalytic activity of fresh $Fe(HSO_4)_3/TiO_2$ was observed. In fact, one of the special advantages of the nano-catalyst is its insolubility in organic solvents which makes its recovery very convenient. Next, we investigated the reusability and recycling of catalyst. The best result was obtained, by using 5-alkyl-3-propargylmercapto-1,2,4-triazole (1 mmol) and $Fe(HSO_4)_3/TiO_2$ (0.15 mmol), including 0.015 mmol $Fe(HSO_4)_3$ refluxed in acetic acid. After completing the reaction, the catalyst was separated by simple filtration and air-dried. According to above, the reaction was completely carried out by using of 1.5mol% $Fe(HSO_4)_3$ supporting on nano-TiO_2. Re-covered catalyst was reused in subsequent reactions without significant decrease in activity even after five runs.

Catalyst characterization

SEM images related to the $Fe(HSO_4)_3/TiO_2$ are shown in Figure 1. It indicates that particles are fairly spherical and are about 46 nm in diameter. The results of EDAX analysis confirm the existence of Fe and S in this nanostructure (Figure 2).

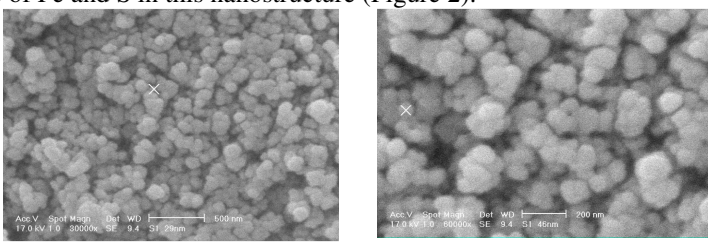


Figure 1. SEM related to $Fe(HSO_4)_3/TiO_2$

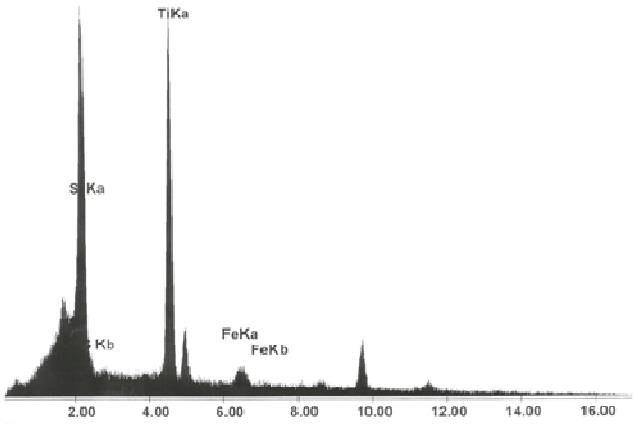


Figure 2. EDAX related to $Fe(HSO_4)_3/TiO_2$

In the IR spectrum of co-catalyst, S=O, S-O and O-H bands were appeared at ν=1637, ν=1079 and ν = 3421 cm^{-1}, respectively, which are related to HSO_4^-. According to above, it can be concluded that ferric hydrogen sulfate has been supported on the surface of nano TiO_2 particles. Although ferric hydrogen sulfate is the catalyst of choice, it seems likely that titanium dioxide is an essential co-catalyst.

Conclusion

As presented, this methodology offers significant improvements with regard to yield of products, simplicity in operation and green aspects by avoiding toxic catalysts and solvents. The cyclization of 3- propargylmercapto-1,2,4-triazoles was completely carried out by using of 1.5mol% $Fe(HSO_4)_3$ supporting on nano-TiO_2 over a short time. Re-covered catalyst was reused in subsequent reactions without significant decrease in activity even after five runs.

References

1. Invidiata F, Lampronti P, Furno G and Semoni D, *J Heterocycl Chem.,* 1997, **34**, 1255-1258.
2. Heindel N D and Reid J R, *Org Prep Proced Int.,* 1981, **13**, 123.
3. Chadha V K, *J Indian Chem Soc.,* 1978, **55**, 817.
4. Chadha V K and Sharma G R, *J Indian Chem Soc.,* 1980, **57**, 1112.
5. Claramunt and José Elguero, *J Chem Soc Perkin Trans 1,* 1987, 1853.
6. Omar A M M E and Aboulmafe O M, *J Heterocycl Chem.,* 1986, **23**, 1339.
7. Ghannoum M Eweiss N F, Bahajaj A A and Quereshi M, *Microbios.,* 1983, **37**, 151.
8. Rasad A R, Ramalengamat T, Ras A B, Drawn P W and Sattur P B, *Indian J Chem.,* 1986, **26B**, 556.
9. Falke D and Rada B, *Acta Virol*.,1970**, 14(2)**, 115.
10. Sidwell R W Dixon G J, Sellers S M and Schabel F M, *J Appl Microbiol.,* 1968, **16**, 370.
11. Creasey W A, Fink M E, Handschurnacker R E and Calabresi P, *Cancer Res.,* 1963, **23**, 444.
12. Walters T R, Aur R J, Hernandez K, Vietti T and Pinkel D, *Cancer Res.,* 1972, **29(4)**, 1057-1060.
13. Malolcsy G, Acta *Phympatėzol,* 1966, **1**, 245.
14. Potts K T and Hussain S, *J Org Chem.*, 1971, **36**, 10.

15. Upadhyaya P, Surendra Nath T G and Srinvasan V R, *Synthesis,* 1978, 288.
16. Heravi M M and Tajbakhsh M, *J Chem Res (S),* 1998, 488
17. Heravi M M and Bakavoli M, *J Chem Res.,* 1995, **11**, 480.
18. Motamedi R, Heravi M M, Bamohram F F and Haeri A**,** *J Heterocycl Chem.,* 2008, **45**, 1211.
19. Eshghi H Bakavoli M and Moradi H, *Chin Chem Lett.,* 2008, **19**, 1423.
20. Salehi P, Khodaei M M, Zolfigol M A and Zeinoldini S, *Synth Commun.,* 2003, **33**, 1367.
21. Eshghi H, *J Chin Chem Soc.,* 2006, **53**, 987-990.
22. Shirini F, Zolfigol M A, Salehi P and Abedini M, *Curr Org Chem.,* 2008, **12**, 183.
23. Eshghi H, Rahimizadeh M and Saberi S, *Catal Commun.,* 2008, **9**, 2460-2466.
24. Maity S K, Rana M S, Bej S K, Ancheyta-Juarez J, Murali Dhar G and Prasada Rao T S R, *Appl Catal A,* 2001, **205**, 215-225.
25. Dzwigaj S, Louis C, Breysse M, Cattenot M, Beliére V, Geantet C and Vrinat M, *Appl Catal B*, 2003, **41**, 181-191.
26. Ramirez J Cedeno L and Busca G, *J Catal.,* 1999, **184(1),** 59-67.
27. Heravi M M, Zadmard R, Bolourtchian S and Aghapoor K, *J Sci Tech.,* 1999*,* **23***,* 151.
28. Heravi M M, Aghapoor K and Nooshabadi M, *Monatshefte Fur Chemie.,* 1997, **128(11)**, 1143-1147.
29. Zadmard R, Heravi M M and Bolurchian S, *Indian J Heterocycl Chem.,* 1998, **7(3)**, 239-240.