*Journal of the Korean Chemical Society*
**2012**, *Vol. 56, No. 1*
Printed in the Republic of Korea
http://dx.doi.org/10.5012/jkcs.2012.56.1.078

# New Synthesis of Perhydrotriazolotriazoles Catalyzed by $TiCl_4$ under Ambient Conditions

**J. Safari*, S. Gandomi-Ravandi, and M. Ghotbinejad**

*Laboratory of Organic Compound Research, Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan, P.O.Box: 87317-51167, I.R. Iran.*
**E-mail: safari@kashanu.ac.ir*

(Received July 27, 2011; Accepted December 9, 2011)

**ABSTRACT.** Aromatic 2,3-diazabuta-1,3-dienes in glacial acetic acid with isothiocyanate in the presence of catalyst $TiCl_4$ at room temperature produced via criss-cross cycloaddition reactions the corresponding perhydro[1,2,4]triazolo[1,2-a][1,2,4] triazole-1,5-dithiones in relatively high yields and short reaction time.

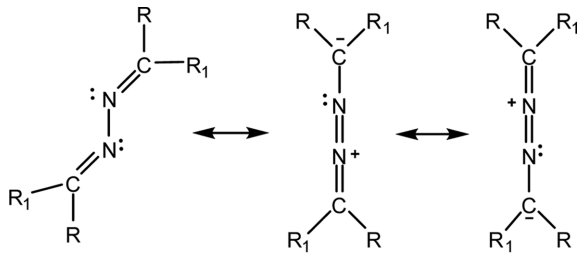
**Key words:** Criss cross cycloaddition, Azine, Catalyst, Perhydrotriazolotriazole

## INTRODUCTION

1, 3-Dipolar cycloaddition reactions are fundamental processes in organic chemistry,[1] and their asymmetric version offers a powerful and reliable synthetic methodology to access five-membered heterocyclic rings in regio-and stereocontrolled fashion.[2-5] Criss-cross cycloaddition was described in 1917 as intermolecular reaction of benzaldazine with 2 equiv of thiocyanate affording a heterocyclic compound having two fused five-membered ring.[6] Criss-cross cycloaddition may be classified as a special type of [3+2] cycloaddition[7] or 1, 3-Dipolar cycloaddition, respectively. The formation of their products was explained in 1963 by Huisgen[8] as a success of two successive 1, 3-Dipolar cycloadditions. This assumption was proved in 1973 when as *Table* 1, 3-Dipole was identified by X-ray crystallographic analysis.[9] The 1, 3-Dipolar aldazine or ketazine are actually 1, 3-Heterodienes and have double 1, 3-Dipolar sites (*Scheme* 1).

These acyclic 1, 3-Heterodienes adopt the s-trans conformation due to steric interactions of the alkyl or aryl substations. This conformation dose not undergoes the [4+2] cycloaddition known as the Diels-Alder reaction. Azines as heterodiene reacted with two eqiv of dipolarophiles, such as thiocyanate, in [3+2] cycloaddition reactions and gave Perhydrotriazolotriazole derivatives.[10-12]

Meantime, it was found that this kind of compounds possesses many kinds of biological activities such as fungicidal,[13,14] bactericidal,[13,14] analgesics,[15-17] anxiolytic[17] and anti-inflammatory.[18]




***Scheme* 1.** Heterodienes containing double 1, 3-Dipolar sites.

## RESULTS AND DISCUSSION

Main recent papers describing synthesis of perhydrotriazolotriazoles by classical method,[19,20] but this method has defects such as long reaction times and low yield. Herein we report a facial and efficient method for the synthesis perhydrotriazolotriazoles catalyzed by $TiCl_4$. In an initial study, for examination of the catalytic activity of different catalysts such as $BF_3$, $VCl_3$, $WCl_6$, $AlCl_3$, $ZrCl_4$, $SbCl_3$, $Al_2O_3$-$P_2O_5$ and $TiCl_4$ in this cycloaddition reaction, benzaldazine was first reacted with potassium isothiocyanate in $CH_3CN$ (10 mL) in the presence of each catalysts (0.2 eqiv.) separately. In the course of this study we found that $TiCl_4$ was the most effective catalyst in term of yield of the perhydrotriazolotriazoles (98%) while other catalysts formed the product with the yields of 46-88% (*Table* 1). In the absence of catalyst, the yield of the product was found to be very low (*Table* 2). All the products were char-

***Table* 1.** Synthesis of perhydrotriazolotriazole **(3a)** in the presence of different catalysts

| Entry | Catalyst | Yield (%)[a] |
|---|---|---|
| 1 | $BF_3$ | 85 |
| 2 | $VCl_3$ | 47 |
| 3 | $WCl_6$ | 51 |
| 4 | $AlCl_3$ | 78 |
| 5 | $ZrCl_4$ | 82 |
| 6 | $SbCl_3$ | 88 |
| 7 | $TiCl_4$ | 98 |
| 8 | $Al_2O_3$-$P_2O_5$ | - |

[a]Yields refer to the pure isolated product.

acterized by NMR, IR and elemental alanalyses. The presence of signal at 1247-1293 $cm^{-1}$ in IR spectra and 10.21-11.51 ppm in $^1H$ NMR spectra, due to NH related to the fused five membered rings.

## CONCLUSION

This work demonstrates a novel and highly efficient methodology for the synthesis of perhydrotriazolotriazoles from two successive 1, 3-Dipolar cycloadditon of azine derivatives and potassium isothiocyanate through $TiCl_4$ catalyzed at room temperature. In addition of efficiency and simplicity, this protocol provides a fast and low cost procedure for the synthesis of these products.

## EXPERIMENTAL

### Instrumentation

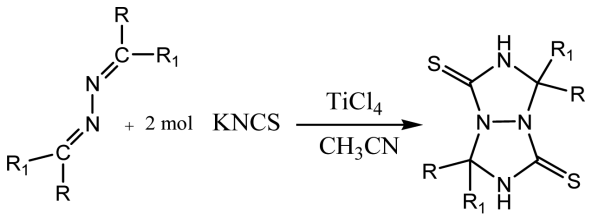
Thin layer chromatography (TLC) was performed to monitor the reaction progress and purity of products. Melting points were measured using an electro thermal MK3 apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer FT-IR 550 spectrometer in KBr pellets and reported in $cm^{-1}$. NMR spectra were measured on a Bruker DRX 400 MHz spectrometer in DMSO-d6 with chemical shift (δ) given in ppm relative to TMS as internal standard. The element analysis (C, H, N) were obtained from a Carlo ERBA model EA 1108 analyzer carried out on Perkin- Elmer 240 c analyzers.

### Reagents

All reactions were carried out at room temperature. Solvents and chemicals were purchased from Merck and used without prior purification. The compounds were prepared following reported procedure.

### Recommended procedure

To mixture of KSCN (2.5 g, 0.0257 mol), $CH_3CN$ (10 mL) and aldazine (0.0128 mol) was added $TiCl_4$ and the reaction mixture was stirred at room temperature for 20 min. the progress of the reaction was followed by TLC. After completion of the reaction, the suspension was poured in $H_2O$ (200 mL) and the mixture was concentrated in vacuo to remove the solvent. The resulting solid was washed successively with water. After dried in vacuum the product was obtained with enough purity for spectral analysis (*Scheme* 2).




(1) (2) (3)

R=Aryl
$R_1$=H, $CH_3$,...

***Scheme* 2.** Preparation of perhydrotriazolotriazole derivatives catalyzed by $TiCl_4$.

***Table* 2.** Synthesis of perhydrotriazolotriazoles in $CH_3CN$ in the presence of catalyst $TiCl_4$ at room temperature (Method A) and in the absence of catalyst $TiCl_4$ (Method B)

| Product[a] | R | R1 | Min(time)/Yield%[b] (Method A) | Min(time)/Yield%[b] (Method B) |
|---|---|---|---|---|
| 3a | $C_6H_5$ | H | 21/97 | 105/91 |
| 3b | 4-Cl $C_6H_5$ | H | 15/91 | 60/79 |
| 3c | 3-Cl $C_6H_5$ | H | 20/89 | 120/75 |
| N.R | 4-OMe $C_6H_5$ | H | - | - |
| 3d | 3-Br $C_6H_5$ | H | 20/90 | 100/80 |
| 3e | $C_6H_5$ | Me | 38/76 | 120/65 |
| N.R | 4-OH $C_6H_5$ | Me | - | - |
| 3f | 3-Me $C_6H_5$ | Me | 40/79 | 180/68 |

[a]All products were characterized by $^1H$ NMR, $^{13}C$ NMR, IR and element analysis.
[b]Isolated yields

***Tetrahydro-3, 7-diphenyl-[1,2,4] triazolo [1,2-a][1,2,4] triazole-1,5-dithione* (3a, $C_{16}H_{14}N_4S_2$)**

Yield: (97%) **3a**. M.p.: 187-188 °C; $R_F$/(ethyl acetate/n-Hexane) (3/7)=0.51, $^1$H NMR (400 MHz, DMSO): $\delta$= 6.82 (s, 2H, CH), 7.39 (t, 2H, CH), 7.41 (t, 2H, CH), 7.45 (t, 2H, CH), 11.42 (s, 2H, NH) ppm; $^{13}$C NMR (100 MHz, DMSO): $\delta$=73.02 (CH), 126.25 (CH), 127.76 (CH), 128.31 (CH), 129.73 (CH), 184.10 (C) ppm; IR (KBr): $\bar{\nu}$=3391, 1500, 1251 cm$^{-1}$, Anal. Calcd. For $C_{16}H_{14}N_4S_2$ (326.433): C, 58.89%; H, 4.29%; N, 17.18%; S, 19.63%; Found: C, 58.82%; H, 4.39%; N, 17.34%; S, 19.73%.

***3,7-Bis(4-chlorophenyl)-tetrahydro-[1,2,4]triazolo [1,2-a][1,2,4]triazole-1,5-dithione* (3b, $C_{16}H_{12}N_4S_2Cl_2$)**

Yield: (91%) **3b**. M.p.: 198-200 °C; $R_F$/(ethyl acetate/ n-Hexane) (3/7)=0.32; $^1$H NMR (400 MHz, DMSO): $\delta$= 6.85 (s, 1H, CH), 7.39 (dd, 1H, CH), 7.51 (dd, 1H, CH), 11.48 (s, 1H, NH) ppm; $^{13}$C NMR (100 MHz, DMSO): $\delta$=75.50 (CH), 128.41 (CH), 130.45 (CH), 133.20 (CH), 133.81 (CH), 184.11 (C), ppm; IR (KBr): $\bar{\nu}$=3410, 1490, 1248 cm$^{-1}$, Anal. Calcd. For $C_{16}H_{12}N_4S_2Cl_2$ (395.323): C, 48.60%; H, 3.04%; N, 14.18%; S, 16.20%; Cl, 17.72% Found: C, 48.32%; H, 3.13%; N, 14.31%; S, 16.29%; Cl, 17.81%

***3,7-Bis(3-chlorophenyl)-tetrahydro-[1,2,4]triazolo [1,2-a][1,2,4]triazole-1,5-dithione* (3c, $C_{16}H_{12}N_4S_2Cl_2$)**

Yield: (89%) **3c**. M.p.: 194-195 °C; $R_F$/(ethyl acetate/n-Hexane) (3/7)=0.31; $^1$H NMR (400 MHz, DMSO): $\delta$= 6.89 (s, 2H, CH), 7.16 (dd, 2H, CH), 7.37 (dd, 2H, CH), 7.42 (dd, 2H, CH), 7.49 (dd, 2H, CH), 11.50 (s, 2H, NH) ppm; $^{13}$C NMR (100 MHz, DMSO): $\delta$=76.62 (CH), 124.88 (CH), 126.39 (CH), 128.12 (CH), 134.15 (C), 184.47 (C), ppm; IR (KBr): $\bar{\nu}$=3415, 1500, 1252 cm$^{-1}$, Anal. Calcd. For $C_{16}H_{12}N_4S_2Cl_2$ (395.323): C, 48.60%; H, 3.04%; N, 14.18%; S, 16.20%; Cl, 17.72% Found: C, 48.32%; H, 3.13%; N, 14.31%; S, 16.29%.; Cl, 17.81%.

***3,7-Bis(3-bromophenyl)-tetrahydro-[1,2,4]triazolo [1,2-a][1,2,4]triazole-1,5-dithione* (3d, $C_{16}H_{12}N_4S_2Br_2$)**

Yield: (90%) **3d**. M.p.: 158-159 °C; $R_F$/(ethyl acetate/n-Hexane) (3/7)=0.38; $^1$H NMR (400 MHz, DMSO): $\delta$= 6.89 (s, 2H, CH), 7.41 (dd, 2H, CH), 7.42 (t, 2H, CH), 7.56 (t, 2H, CH), 7.62 (dd, 2H, CH), 11.51 (s, 2H, NH) ppm; $^{13}$C NMR (100 MHz, DMSO): $\delta$=74.01 (CH), 125.27 (C), 127.45 (CH), 127.79 (CH), 131.22 (CH), 132.61 (CH), 136.45 (C), 184.00 (C), ppm; IR (KBr): $\bar{\nu}$=3393, 1489, 1247 cm$^{-1}$, Anal. Calcd. For $C_{16}H_{12}N_4S_2Br_2$ (482.226): C, 39.85%; H, 2.51%; N, 11.62%; S, 13.30%; Br, 33.14% Found: C, 39.80%; H, 2.56%; N, 11.74%; S, 13.39%.; Br, 33.16%.

***Tetrahydro-3,7-dimethyl-3,7-diphenyl-[1,2,4] triazolo [1,2-a][1,2,4]triazole-1,5-dithione* (3e, $C_{18}H_{18}N_4S_2$)**

Yield: (76%) **3e**. M.p.: 118-119 °C; $R_F$/(ethyl acetate/n-Hexane) (3/7)=0.42 $^1$H NMR (400 MHz, DMSO): $\delta$=2.29 (s, 6H, $CH_3$), 7.38 (t, 2H, CH), 7.91 (t, 2H, CH), 8.27 (t, 2H, CH), 10.21 (s, 2H, NH) ppm; $^{13}$C NMR (100 MHz, DMSO): $\delta$=14.48 ($CH_3$), 70.37 (C), 127.02 (CH), 128.71 (CH), 129.68 (CH), 138.08 (C), 179.41 (C), ppm; IR (KBr): $\bar{\nu}$=3405, 1588, 1291 cm$^{-1}$, Anal. Calcd. For $C_{18}H_{18}N_4S_2$ (354.487): C, 61.02%; H, 5.08%; N, 15.82%; S, 18.08%; Found: C, 60.87%; H, 5.13%; N, 15.91%; S, 18.15%.

***Tetrahydro-3,7-dimethyl-3,7-di(*m*-tolyl)-[1,2,4] triazolo [1,2-a][1,2,4]triazole-1,5-dithione* (3f, $C_{20}H_{22}N_4S_2$)**

Yield: (79%) **3f**. M.p.: 159-160 °C; $R_F$/(ethyl acetate/n-Hexane) (3/7)=0.45; $^1$H NMR (400 MHz, DMSO): $\delta$= 2.27 (s, 6H, CH3), 2.33 (s, 6H, CH3), 7.19 (dd, 2H, CH), 7.68 (dd, 2H, CH), 7.76 (t, 2H, CH), 7.91 (t, 2H, CH), 10.18 (s, 2H, NH) ppm; $^{13}$C NMR (100 MHz, DMSO): $\delta$=24.6 ($CH_3$), 28.9 ($CH_3$), 76.2 (C), 124.01 (CH), 127.01 (CH), 128.51 (CH), 128.80 (CH), 138.21 (C), 142.42 (C), 183.51 (C), ppm; IR (KBr): $\bar{\nu}$=3386, 15878, 1293 cm$^{-1}$, Anal. Calcd. For $C_{20}H_{22}N_4S_2$ (382.540): C, 62.83%; H, 5.67%; N, 14.66%; S, 16.75%; Found: C, 62.77%; H, 5.84%; N, 14.81%; S, 16.87%.

**Acknowledgements.** We express our appreciation to the University of Kashan Research Council for financial support of this work.

## REFERENCES

1. Padwa, A. Vol. 2; Wiley: New York, 1984; p 277.
2. Harwood, L. M.; Vickers, R. J. Wiley: New York, 2002, p 169.
3. Gothelf, K. V.; Jorgensen, K. A.; Kobayashi, S. Wiley-VCH: Weinheim, 2002; p 211.
4. Karlsson, S.; Hogberg, H. E. *Org. Prep. Proceed. Int.* **2001**, *33*, 103.
5. Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105.
6. Bailey, J. R.; Moor, N. H. *J. Am. Chem. Soc.* **1917**, *39*, 279.
7. Bailey, J. R.; McPherson, A. T. *J. Am. Chem. Soc.* **1917**, *39*, 1322.
8. Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565.
9. Gieren, A.; Narayana, P. P.; Burger, K.; Thenn, W. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 475.

10. Burger, K.; Thenn, W.; Rauh, R.; Schickaneder, H. *Angew. Chem., Int. Ed. Engl*. **1974**, *13*, 477.
11. Burger, K.; Schickaneder, H.; Thenn, W. *Tetrahedron Lett.* **1975**, *16*, 1125.
12. Evans, S.; Gearhart, R. C.; Schweizer, E. E. *J. Org. Chem.* **1977**, *42*, 452.
13. Deshpande, D. S. *Chem. Abstr.* **1985**, *94*, 65568.
14. Paget, C. J.; Wikl, J. H. *Chem. Abstr.* **1976**, *84*, 44070.
15. Kamal, A.; Sattur, P. B. *Chem. Abstr.* **1985**, *102*, 166690.
16. Morogues, J.; Vega, A.; Prieto, J.; Marquez, M. Roberts, D. J. *Chem. Abstr.* **1976**, *84*, 180138.
17. Prasad, A. R.; Ramalingam,T.; Rao, A. B. Diwan, P. V.; Sattur, P. B. *Chem. Abstr.* **1987**, *106*, 84500.
18. Moran, D. B.; Dusza, J. P. Albright, J. D. *Chem. Abstr.* **1981**, *95*, 97829.
19. Zachova, H.; Man, S.; Taraba, J.; Potacek, M. *Tetrahedron* **2009**, *65*, 792.
20. Verner, J.; Potacek, M. *Molecules* **2006**, *11*, 34.