doi:10.13582/j.cnki.1672-9102.2017.03.015

5-取代-4-羟基苯甲氨基-3-巯基-1,2,4-三唑的无溶剂合成

白珊[1],李尚儒[2],何晶晶[2],张金改[2],张慧霖[2],骆春香[2],谢文林[2,3]

(1.长沙环境保护职业技术学院,湖南 长沙 410004;2. 湖南科技大学 化学化工学院,湖南 湘潭 411201;
3. 湖南科技大学 理论有机化学与功能分子教育部重点实验室,湖南 湘潭 411201)

摘　要:在无溶剂条件下,由羟基苯甲醛,5-取代-3-巯基-4-氨基-1,2,4-三唑,对甲苯磺酸经过室温研磨合成了5-取代-4-羟基苯亚甲氨基-3-巯基-1,2,4-三唑,此化合物再经硼氢化钠还原得到5-取代-4-羟基苯甲氨基-3-巯基-1,2,4-三唑衍生物.其结构分别用 IR,NMR 和 MS 进行了表征.此方法具有反应条件温和,操作简单,产率高等优点,是一种有效合成5-取代-4-羟基苯甲氨基-3-巯基-1,2,4-三唑衍生物的新方法.

关键词:1,2,4-三唑; 羟基苯甲醛; 席夫碱; 无溶剂; 合成
中图分类号:0626　　**文献标志码:**A　　**文章编号:**1672-9102(2017)03-0086-05

Synthesis of 5-substituted-3-hydrosulfuryl-4-hydroxybenzylamino-1,2,4-triazole under solvent-free conditions

Bai Shan[1], Li Shangru[2], He Jingjing[2], Zhang Jingai[2], Zhang Huilin[2], Luo Chunxiang[2], Xie Wenlin[2,3]
(1. Changsha Enviromental Protection College, Changsha 410004, China;
2. School of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Xiangtan 411201, China;
3. Key Laboratory of Theoretical Organic Chemistry and Function Molecules Ministry of Education,
Hunan University of Science and Technology, Xiangtan 411201, China)

Abstract: 5-substituted-3-hydrosulfuryl-4-hydroxybenzmethyleneamino-1,2,4-triazole were synthesized by reaction of 5-substituted-3-hydrosulfuryl-4-amino-1,2,4-triazole and hydroxybenzaldehyde in the presence of p-toluenesulfonic acid under solvent-free conditions by grinding at room temperature, and then, the synthesized compounds were reduced to 5-substituted-3-hydrosulfuryl-4-hydroxybenzylamino-1,2,4-triazole, The structures of the products were characterized by IR, NMR and MS. The procedure offers several advantages including milder reaction conditions, easier work-up and higher yields, It is a novel synthesis method of 5-substituted-3-hydrosulfuryl-4-arylmethylamino-1,2,4-triazole.

Keywords: 1,2,4-triazole; hydroxybenzaldehyde; schiff base; solvent-free; synthesis

1,2,4-三唑是含3个氮原子的五元芳香杂环化合物,具有较强配位和形成氢键的能力,可与生物体内的酶和受体等形成氢键,与金属离子配位以及发生疏水作用,静电作用等[1].从而表现出广谱的生物活性和药理活性,如抗菌[2-3],抗癌[4],抗病毒[5],抗惊厥[6]等.研究发现,三唑类化合物能够选择性地与羊毛甾醇 C-14α-脱甲基化酶(CYP51)结合,从而抑制麦角甾醇的生物合成,显示出优异的抗真菌活性[7-8].其中以氟康唑和伊曲康唑为代表的三唑类抗真菌药物是目前临床上治疗深部真菌感染应用最广

收稿日期:2017-02-20
基金项目:国家自然科学基金资助项目(21571058);湖南省自然科学基金资助项目(2015JJ4026)
通信作者:谢文林(1967-),男,湖南邵东人,博士,教授,主要从事有机合成和多肽药物的研究.E-mail: xwl2000zsu@163.com

泛的药物,鉴于三唑类化合物在临床应用中表现出的优越性, 已成为抗真菌药物研究的热点[9].

近年来无溶剂合成法在有机合成中得到了较为广泛的应用,较传统合成方法而言,该方法不仅降低了成本,避免了使用有机溶剂带来的毒性和危险,对环境友好,而且还提供了与传统溶剂反应不同的分子环境,能增强反应选择性,提高反应收率. 因此,无溶剂有机合成已经成为绿色化学重要的组成部分[10-11].本文在无溶剂条件下,由羟基苯甲醛和 5-取代-3-巯基-4-氨基-1,2,4-三唑在对甲苯磺酸的催化下经过室温研磨合成了 5-取代-4-羟基苯亚甲氨基-3-巯基-1,2,4-三唑,此化合物再经硼氢化钠还原得到未见文献报道的 5-取代-4-羟基苯甲氨基-3-巯基-1,2,4-三唑新型衍生物,反应如图 1 所示.

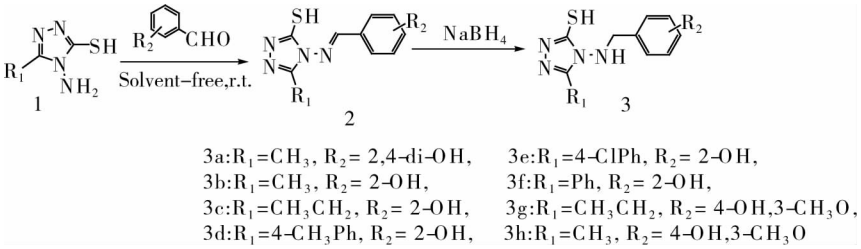

图 1　5-取代-4-羟基苯甲氨基-3-巯基-1,2,4-三唑衍生物的合成

1　实验部分

1.1　仪器和试剂

XT-4 型显微熔点仪(温度计未校正); PE-2000 型傅里叶变换红外光谱仪(KBr 压片); Waters Xevo QTOF 高分辨液相色谱/质谱联用仪; Bruker AV-II 500 MHz 核磁共振光谱仪($CDCl_3$ 作溶剂, TMS 为内标). 所用试剂均为分析纯或化学纯.

1.2　5-取代-4-羟基苯亚甲氨基-3-巯基-1,2,4-三唑(2)的合成

在室温下,取羟基苯甲醛类化合物(2.0 mmol),5-取代-3-巯基-4-氨基-1,2,4-三唑 1(2.2 mmol) 和对甲苯磺酸(0.4 mmol), 放置于研钵中,均匀研磨 25min,TLC 跟踪反应,反应结束后.用 50 ml 甲醇溶解,过滤.然后在有机相中加入 50 mL 蒸馏水,有固体析出,过滤,滤渣用蒸馏水洗涤 2~3 次,再经甲醇重结晶得到希夫碱 2.

1.3　5-取代-4-羟基苯甲氨基-3-巯基-1,2,4-三唑衍生物(3)的合成

称取上述得到的 5-取代-4-羟基苯亚甲氨基-3-巯基-1,2,4-三唑 2(1.0 mmol)放入反应瓶中,用 5 mL的甲醇溶解,在冰浴条件下分批加入 $NaBH_4$(1.3 mmol),待 $NaBH_4$ 加完后.然后在室温条件下反应,TLC 跟踪反应,待反应结束后,加入 50 mL 蒸馏水,析出固体,过滤,再经柱层析得到 5-取代-4-羟基苯甲氨基-3-巯基-1,2,4-三唑衍生物 3.

5-甲基-4-[2,4-二羟基苯甲氨基]-3-巯基-1,2,4-三唑(3a): 棕黄色晶体,产率:95%, m.p. 205~207℃.

^{1}H NMR (DMSO-d6, 500MHz) δ: 1.81 (s, 3H, CH_3), 4.06 (d, J = 3.5 Hz, 2H, CH_2), 6.11 (d, J = 8.0 Hz, 1H, PhH), 6.15 (t, J = 3.5, 1H, NH), 6.27 (s, 1H, PhH), 6.70 (d, J = 8.0 Hz, 1H, PhH), 9.24 (s, 1H, OH), 9.33 (s, 1H, OH), 13.42 (s, 1H, SH); ^{13}C NMR (DMSO-d6, 125 MHz) δ: 9.65, 47.01, 102.24, 106.01, 113.32, 131.88, 19.82, 157.03, 158.10, 165.14; IR (KBr) ν: 3229, 3011, 2923, 1620, 1463, 1429, 1314, 1257, 1194, 1110 cm^{-1}; HRMS (ESI, *m/z*) calcd for $[C_{10}H_{11}N_4O_2S]^-$(M-H)$^-$ 251.0608, found 251.0615

5-甲基-4-[2-羟基苯甲氨基]-3-巯基-1,2,4-三唑(3b): 灰色晶体,产率:89%,m.p. 196~197 ℃.

^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.87 (s, 3H, CH_3), 4.07 (d, J =3.5 Hz, 2H, CH_2), 6.20 (t, J = 4.5 Hz, 1H, NH), 6.71 (t, J = 7.5 Hz, 1H, PhH), 6.81 (d, J = 8.0 Hz, 1H, PhH), 7.05(d, J = 7.5 Hz, 1H, PhH), 7.08 (t, J = 7.5 Hz , 1H, PhH), 9.48 (s, 1H, OH), 13.47 (s, 1H, SH); ^{13}C NMR (DMSO-d_6,

125 MHz) δ:10.03, 47.32, 115.09, 118.75, 122.74, 128.92, 130.96, 153.82, 155.98, 165.47; IR (KBr) ν: IR (KBr) ν: 3414, 3010, 1595, 1556, 1479, 1418, 1369, 1200, 1012 cm^{-1}; HRMS (ESI, *m/z*) calcd for $[C_{10}H_{11}N_4OS]^-(M-H)^-$ 235.0659, found 235.0662

5-乙基-4-[2-羟基-苯甲氨基] -3-巯基-1,2,4-三唑(3c): 黄色晶体,产率:90%,m.p. 165~167 ℃.

^1H NMR (DMSO-d_6, 500 MHz) δ: 0.97 (t, J =7.5 Hz, 3H, CH_3), 2.24 (q, J =7.5 Hz, 2H, CH_2), 4.21 (d, J =4.5 Hz, 2H, N-CH_2), 6.27 (t, J = 4.5 Hz, 1H, NH), 6.71 (t, J = 7.5 Hz, 1H, PhH), 6.80 (d, J = 8.0 Hz, 1H, PhH), 7.00(d, J = 7.5 Hz, 1H, PhH), 7.10 (t, J = 7.5 Hz , 1H, PhH), 9.50 (s, 1H, OH), 13.47 (s, 1H, SH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 10.03, 17.20, 47.32, 115.09, 118.75, 122.74, 128.92, 130.96, 153.82, 155.98, 165.47; IR (KBr) ν: 3237, 3005, 2923, 2854, 1573, 1510, 1483, 1467, 1435, 1266, 1231, 1104 cm^{-1}; HRMS (ESI, *m/z*) calcd for $[C_{11}H_{13}N_4OS]^-(M-H)^-$ 249.0816, found 249.0812

5-(4-甲苯基)-4-[2-羟基苯甲氨基]-3-巯基-1,2,4-三唑(3d): 棕黄色晶体,产率:78%,m.p. 190~192 ℃.

^1H NMR (500 MHz-d_6, DMSO) δ: 2.35 (s, 3H, CH_3), 4.18 (d, *J* = 5.5 Hz, 2H, CH_2), 6.33 (t, *J* = 6.0 Hz, 1H, NH), 6.68 (t, *J* = 7.5 Hz, 1H, PhH), 6.73 (d, *J* = 8.0 Hz, 1H, PhH), 7.04 (d, *J* = 7.5 Hz, 1H, PhH), 7.08 (d, *J* = 8.0 Hz, 1H, PhH), 7.24 (d, *J* = 8.0 Hz, 2H, PhH), 7.91 (d, *J* = 8.0 Hz, 2H, PhH), 13.92 (s, 1H, SH), 9.52 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 31.15, 48.27, 115.49, 119.20, 122.51, 123.14, 127.92(2C), 129.31, 129.40(2C), 130.81, 140.60, 149.36, 156.28, 166.73; IR (KBr) ν: 3210, 3018, 2925, 1591, 1513, 1459, 1313, 1232, 1048 cm^{-1}; HRMS (ESI, *m/z*) calcd for $[C_{16}H_{15}N_4OS]^-(M-H)^-$ 311.0972, found 311.0979

5-(4-氯苯基)-4-[2-羟基苯甲氨基] -3-巯基-1,2,4-三唑(3e): 黄色晶体,产率:75%,m.p. 204~206 ℃.

^1H NMR (DMSO-d_6, 500 MHz) δ: 4.19 (d, J = 5.5 Hz, 2H, CH_2), 6.45 (t, J = 5.0 Hz, 1H, NH), 6.63 (m, 2H, PhH); 6.93 (d, J = 7.5 Hz, 1H, PhH), 6.97 (t, J = 7.5 Hz, 1H, PhH), 7.45 (d, J = 8.5 Hz, 2H, PhH), 7.94 (d, J=8.5 Hz, 2H, PhH), 9.50 (s, 1H, -OH), 14.04 (s, 1H, -SH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 60.14, 114.87, 118.46, 121,72, 124.16, 128.23, 128.91, 129.29, 130.58, 134.83, 148.25, 155.88, 166.45; IR (KBr) ν: 3207, 3006, 2930, 1597, 1506, 1462, 1416, 1385, 1314, 1233, 1094, 1052 cm^{-1}; HRMS (ESI, *m/z*) calcd for $[C_{15}H_{12}ClN_4OS]^-(M-H)^-$ 331.0426, found 331.0428

5-苯基-4-[2-羟基苯甲氨基]-3-巯基-1,2,4-三唑(3f): 棕黄色晶体,产率:81%,m.p. 197~198 ℃.

^1H NMR (500 MHz, DMSO) δ: 4.20 (d, *J* = 5.5 Hz, 2H, CH_2), 6.38 (t, *J* = 5.5 Hz, 1H, NH), 6.65 (t, *J* = 7.5 Hz, 1H, PhH), 6.70 (d, *J* = 8.0 Hz, 1H, PhH), 7.03 (t, *J* = 7.5 Hz, 2H, PhH), 7.42 (t, *J* = 7.5 Hz, 2H, PhH), 7.47 (t, *J* = 7.5 Hz, 1H, PhH), 7.98 (d, *J* = 7.5 Hz, 2H, PhH), 13.99 (s, 1H, SH), 9.52 (s, 1H, OH); ^{13}C NMR (125 MHz, DMSO) δ: 47.68, 114.96, 118.67, 121.96, 125.39, 127.55, 128.27, 128.80, 130.39, 130.28, 148.97, 155.80, 166.39; IR (KBr) ν: 3245, 3107, 2926, 2856, 1585, 1502, 1477,1451, 1406, 1347, 1282, 1219, 1156 cm^{-1}; HRMS (ESI, *m/z*) calcd for $[C_{15}H_{13}N_4OS]^-(M-H)^-$ 297.0816, found 297.0812

5-乙基-4-[3-甲氧基-4-羟基苯甲氨基]-3-巯基-1,2,4-三唑(3g):棕黄色晶体,产率:82%,m.p. 215~216 ℃.

^1H NMR (DMSO-d_6, 500 MHz) δ: 1.21 (t, J =7.5 Hz, 3H, CH_3), 2.71 (q, J =7.5 Hz, 2H, CH_2), 3.84 (s, 3H, OCH_3), 4.28 (d, J =3.5 Hz, 2H, CH_2), 6.35 (t, *J* = 5.5 Hz, 1H, NH), 6.92 (d, *J*=

8.0 Hz, 1H, NH), 7.32 (d, J = 8.5 Hz, 1H, PhH), 7.46(s, 1H, PhH), 9.98 (s, 1H, OH), 13.65 (s, 1H, SH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 11.03, 17.25, 47.22, 52.63, 116.09, 117.75, 121.71, 128.90, 130.56, 152.82, 155.88, 164.40; IR (KBr) ν: 3258, 3005, 2926, 1585, 1501, 1476, 1451, 1405, 1282, 1156, 1074 cm^{-1}; HRMS (ESI, *m/z*) calcd for $[C_{12}H_{15}N_4O_2S]^-$(M-H)$^-$ 279.0921, found 279.0925

5-甲基-4-[3-甲氧基-4-羟基苯甲氨基]-3-巯基-1,2,4-三唑(3h): 棕黄色晶体,产率:78%,m.p. 212~213 ℃.

^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.71 (t, J =7.5 Hz, 3H, CH_3), 3.89 (s, 3H, OCH_3), 4.58 (d, J = 3.5 Hz, 2H, CH_2), 6.39 (t, *J* = 5.5 Hz, 1H, NH), 6.90 (d, J = 8.0 Hz, 1H, NH), 7.22 (d, J = 8.5 Hz, 1H, PhH), 7.56(s, 1H, PhH), 9.55 (s, 1H, OH), 13.42 (s, 1H, SH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 11.63, 47.22, 56.14, 116.19, 117.76, 121.74, 129.90, 130.586, 152.48, 161.86, 165.23; IR (KBr) ν: 3254, 3006, 2926, 1584, 1194, 1410, 1275, 1153, 1096 cm^{-1}; HRMS (ESI, *m/z*) calcd for $[C_{11}H_{13}N_4O_2S]^-$(M-H)$^-$ 265.0765, found 265.0768.

2　结果与讨论

2.1　目标化合物的合成

首先在无溶剂条件下,对中间体 5-取代-4-羟基苯亚甲氨基-3-巯基-1,2,4-三唑(2)进行合成,在合成中发现酸的催化很重要,于是对不同的酸如硫酸, 盐酸, 醋酸和对甲苯磺酸进行了筛选,结果发现对甲苯磺酸的催化效果最好.因此,在这一类化合物的合成中选择对甲苯磺酸做催化剂.在目标产物 5-取代-4-羟基苯甲氨基-3-巯基-1,2,4-三唑(3)的合成时,采用硼氢化钠做为还原剂进行还原,还原时注意还原剂硼氢化钠需分批加入,而且首先需要在冰浴下进行,当硼氢化钠加完后再在室温下进行反应,否则还原效果较差.

2.2　目标化合物的波谱分析

目标化合物 5-取代-4-羟基苯甲氨基-3-巯基-1,2,4-三唑衍生物的结构经 IR,1H NMR 和 MS 进行了表征.以 5-甲基-4-[2,4-二羟基苯甲氨基]-3-巯基-1,2,4-三唑(3a)为例,在 IR 谱中,3229 cm^{-1}处有一强吸收峰,为氨基的 N-H 伸缩振动吸收峰;3011 cm^{-1}处有一吸收峰,为苯环的 C-H 伸缩振动吸收峰,2923 cm^{-1}处出现的吸收峰为甲基的伸缩振动吸收, 1429~11620 cm^{-1}处为苯环的骨架振动吸收峰; 在 ^{1}H NMR中,在 δ1.81 处出现一个单峰,为甲基的质子吸收峰,在 δ4.06 处出现一二重峰,为 CH_2 的质子吸收峰,在 δ9.24 和 δ9.33 处出现两个单峰,分别为两个羟基的质子吸收峰,在 δ13.42 处出现的单峰为巯基的质子吸收峰.高分辨质谱分析表明,化合物的分子离子峰 251.061 5[M-H]$^-$与预期相符(计算值为 251.060 8).由此可知,化合物 3a 具有预期的结构.

3　结论

在无溶剂条件下,以对甲苯磺酸催化剂利用羟基苯甲醛和 5-取代-3-巯基-4-氨基-1,2,4-三唑在室温下研磨合成了 5-取代-4-羟基苯亚甲氨基-3-巯基-1,2,4-三唑,此化合物再经硼氢化钠还原得到 5-取代-4-羟基苯甲氨基-3-巯基-1,2,4-三唑衍生物,利用 IR,NMR 和 HRMS 对所合成的化合物进行了结构表征.该方法与传统溶剂法相比,具有反应时间短,反应操作简单,收率高等特点,是一种有效合成 5-取代-4-羟基苯甲氨基-3-巯基-1,2,4-三唑衍生物的新方法.

参考文献:

[1] Zhang Y. Y,Zhou C H. Synthesis and activities of naphthalimide azoles as a new type of antibacterial and antifungal agents [J].

Bioorg Med Chem Lett, 2011, 21(14): 4349-4352.

[2] Mathew V, Keshavayyab J, Vaidya V P. Heterocyclic system containing bridgehead nitrogen atom: synthesis and pharmacological activities of some substituted 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles [J]. Eur J Med Chem, 2006, 41(9):1048-1058.

[3] Prasad D J,Ashok M, Karegoudar P, et al. Synthesis and antimicrobial activities of some new triazolothiadiazoles bearing 4-methylthiobenzyl moiety [J]. Eur J Med Chem, 2009, 44(2):551-557.

[4] Li X, Lin Y,Yuan Y, et al. Novel efficient anticancer agents and DNA-intercalators of 1,2,3-triazol-1,8-naphthalimides: design, synthesis, and biological activity [J]. Tetrahedron, 2011, 67(12): 2299-2304.

[5] Grandi M D,Olson M, Prashad A S, et al. Small molecule inhibitors of HIV RT Ribonuclease H [J]. Bioorg Med Chem Lett, 2010, 20(1): 398-402.

[6] Shalini M, Yogeeswari P, Sriram D. Cyclization of the semicarbazone template of aryl semicarbazones: synthesis and anticonvulsant activity of 4,5-diphenyl-2H-1,2,4-triazol-3(4H)-one [J]. Biochem Pharmacol, 2009, 63(3):187-193.

[7] Sheng C, Zhang W, Ji H, et al. Structure-Based Optimization of Azole Antifungal Agents by CoMFA, CoMSIA, and Molecular Docking [J]. J Med Chem, 2006, 49(8): 2512-2525.

[8] Xiao L, Madison V, Chau A S. Three-Dimensional Models of Wild-Type and Mutated Forms of Cytochrome P450 14α-Sterol Demethylases from *Aspergillus fumigatus* and*Candida albicans* Provide Insights into Posaconazole Binding [J]. Antimicrob Agents Chemother, 2004, 48(2): 568-574.

[9] Aoyama Y, Yoshida Y. Interaction of azole antifungal agents with cytochrome P-450_{14DM} purified from *Saccharomyces cerevisiae* microsomes [J]. Biochem Pharmacol, 1987, 36(2):229-235.

[10] Tanaka K, Toda F. Solvent-Free Organic Synthesis [J]. Chem Rev,2000,100 (3): 1025-1074.

[11] Lu Y Y, Ren Z J, Cao W G, et al. Solvent - Free Synthesis of Ethyl α-Cyanocinnamate in the Presence of CaO[J].Synth Commun, 2004, 35(41): 2047-2051.