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含 1,3,4-噻二唑二氢嘧啶类衍生物的合成

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摘 要:二氢嘧啶类衍生物具有广泛的生物活性,因此对其新型衍生物的合成进行研究具有重要意义.文章以芳香醛、乙酰丙酮和硫脲为原料,通过 Biginelli 反应合成中间产物 4-甲基-6-芳基-5-乙酰基-2-巯基-1,6-二氢嘧啶(1),以浓盐酸为催化剂将中间体 1 与硫代卡巴肼反应得到化合物 1-(4-甲基-6-芳基-2-巯基-1,6-二氢嘧啶-5-基)乙酮硫代卡巴腙(2),以冰乙酸为催化剂将化合物 2 与原甲酸三乙酯进行缩合反应合成一系列新型含 1,3,4-噻二唑二氢嘧啶类的衍生物.经 IR, ^{1}H NMR, ^{13}C NMR 和 HRMS(ESI)对目标产物进行表征.结果表明:所合成化合物的结构与预期化合物的结构一致.

关键词:1,3,4-噻二唑;二氢嘧啶;硫代卡巴肼;合成

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Synthesis of Dihydropyrimidine Derivatives Containing 1,3,4-Thiadiazole

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Abstract: Dihydropyrimidine derivatives have a wide range of biological activities, so it is of great significance to study the synthesis of their new derivatives. Using aromatic aldehydes, acetylacetone, and thiourea as raw materials, the intermediate product (1) 4-methyl-6-aryl-5-acetyl-2-mercapto-1, 6-dihydropyrimidine is synthesized through the Biginelli reaction. The intermediate product (2) 1-(4-methyl-6-aryl-2-mercapto-1,6-dihydropyrimidin-5-yl) ethanone thiocarbazone is achieved via the reaction of compound 1 with thiocarbohydrazide in the presence of catalyst concentrated hydrochloric acid. A series of novel dihydropyrimidine derivatives containing 1,3,4-thiadiazole are synthesized by condensation reaction of compound 2 with triethyl orthoformate using acetic acid as a catalyst. The structures of the products are characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS(ESI). Results indicate that the structure of the synthesized compound is consistent with the expected structure of the compound.

Keywords: 1,3,4-thiadiazole; dihydropyrimidine; thiocarbohydrazide; synthesis

二氢嘧啶是含有 2 个氮原子的六元杂环化合物[1],它广泛存在于天然产物和药物分子中,其衍生物具

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有良好的生物活性,如抗菌[2]、抑制环氧化酶-2 (COX-2)[3]、抗高血糖[4]、抗 HIV[5]、抗惊厥[6]、抗肿瘤[7]、抗癌[8]、抗病毒[9]和抗抑郁[10]等.许多药物分子中都含有二氢嘧啶单元[11],如镇静催眠药巴比妥酸、抗甲状腺药物甲基硫氧嘧啶、抗病毒药物碘尿苷、抗癌药物 5-氟尿嘧啶、抗 HIV 药物艾诺韦林和维生素 B2 等.

1,3,4-噻二唑是一类含氮、含硫的五元杂环化合物[12],具有非常重要的杂环结构,广泛应用于医药和农药等领域.1,3,4-噻二唑也具有广泛的生物活性,如抗菌[13]、抗癌[14]、抗高血压[15]、杀虫[16]、抗氧化和抗癫痫等.现已有许多含有 1,3,4-噻二唑环的药物被应用于临床,如乙酰唑胺和醋甲唑胺等.

由于二氢嘧啶类衍生物和 1,3,4-噻二唑类衍生物具有显著的药用价值,开发高生物活性含 1,3,4-噻二唑二氢嘧啶类衍生物就显得尤为重要.因此,本文以二氢嘧啶为母核结构,根据药物设计中的拼合原理,将 1,3,4-噻二唑与二氢嘧啶结合起来合成一系列含 1,3,4-噻二唑二氢嘧啶类的新型衍生物,并采用红外、核磁、高分辨质谱对目标化合物进行表征.目标化合物 3 的合成反应式如图 1 所示.

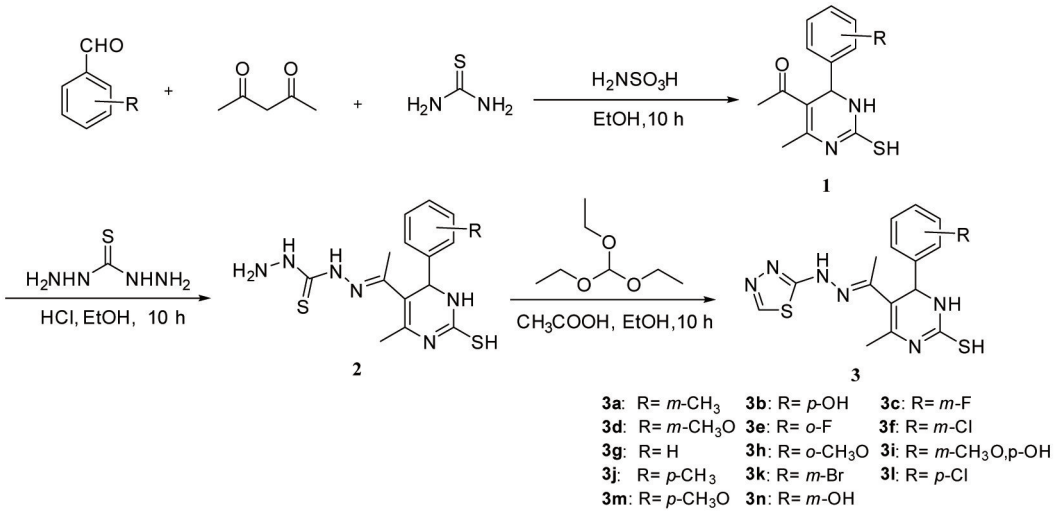

图 1 目标化合物 3 的合成

1 试验部分

1.1 仪器和试剂

试验所用仪器: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);Bruker ESQUIRE 型质谱仪(ESI); Bruker AV-II 500 MHz 核磁共振光谱仪(DMSO-d_6 为溶剂,TMS 为内标).试验所用试剂均购于阿拉丁和国药集团,均为分析纯或化学纯,柱层析硅胶使用青岛海洋化工有限公司的产品(60~80 μm).

1.2 中间体 4-甲基-6-芳基-5-乙酰基-2-巯基-1,6-二氢嘧啶(1)的合成

称取硫脲(1.52 g, 20 mmol)、氨基磺酸(1.65 g, 17 mmol)溶于装有 10 mL 无水乙醇的反应瓶中,逐滴加入乙酰丙酮(1.70 g, 17 mmol),当反应瓶中的固体完全溶解后,加入芳香醛(18 mmol),反应 10 min后将反应体系温度升至 80 ℃,回流反应约 10 h.反应结束后,反应液中析出大量固体,趁热过滤,滤渣用热乙醇洗涤 3~4 次,收集滤饼,经柱层析得到中间产物 4-甲基-6-芳基-5-乙酰基-2-巯基-1,6-二氢嘧啶(1).

1.3 中间体 1-(4-甲基-6-芳基-2-巯基-1,6-二氢嘧啶-5-基)乙酮硫代卡巴腙(2)的合成

将 N,N′-二氨基硫脲(1.06 g, 10 mmol)溶于无水乙醇(10 mL)中,再滴加 6 mol/L 的盐酸(1 mL),50 ℃下反应 10 min 后,加入中间产物 1(7 mmol),反应 10 min 后将反应体系升温至 80 ℃,回流反应 10 h.反应结束后,反应瓶中有固体出现,趁热过滤,滤饼用热乙醇洗涤 3~4 次,然后经柱层析得到中间产物 1-(4-甲基-6-芳基-2-巯基-1,6-二氢嘧啶-5-基)乙酮硫代卡巴腙(2).

1.4　目标化合物 5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-芳基-2-巯基-1,6-二氢嘧啶(3)的合成

将化合物 2(1.5 mmol)溶于无水乙醇(5 mL)中,再滴加冰乙酸(0.03 g,0.5 mmol),50 ℃下反应 15 min 后,加入原甲酸三乙酯(0.30 g, 2 mmol),在 80 ℃下反应约 10 h.反应结束后,反应液中析出大量固体,趁热过滤,滤饼用乙醇重结晶得到目标化合物 5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-芳基-2-巯基-1,6-二氢嘧啶(3).

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(3-甲苯基)-2-巯基-1,6-二氢嘧啶(3a):黄色固体. Yield: 85%, m.p. 243~245 ℃.

^{1}H NMR (500 MHz, DMSO-d_6):δ 9.24 (d, J = 3.5 Hz, 1H), 9.01 (s, 1H), 7.75 (s, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.21 (s, 1H), 7.14 (t, J = 6.6 Hz, 2H), 4.87 (s, 1H), 4.13 (s, 1H), 2.33 (s, 3H), 2.08 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 180.0, 166.5, 157.6, 147.2, 138.8, 138.2, 128.9, 128.7, 127.1, 123.5, 78.1, 59.3, 51.9, 25.2, 21.7, 14.3; IR(KBr):3 379, 1 517, 1 486, 1 437, 1 313, 1 224, 1 170, 895, 800, 717, 573; HRMS(ESI) calcd for $C_{16}H_{19}N_6S_2(M+H)^+$: 359.110 7, found:359.110 8.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(4-羟基苯基)-2-巯基-1,6-二氢嘧啶(3b):白色固体. Yield: 75%, m.p. 244~246 ℃.

^{1}H NMR (500 MHz, DMSO-d_6):δ 9.50 (s, 1H), 9.17 (d, J = 3.4 Hz, 1H), 9.01 (s, 1H), 7.71 (s, 1H), 7.15 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 2.0 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 4.79~4.76 (m, 1H), 4.01 (s, 1H), 2.04 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 179.7, 166.5, 157.8, 157.2, 147.2, 128.7, 127.7, 115.7, 78.2, 59.4,51.67, 25.0, 14.4; IR(KBr):3 360, 3 159, 1 511, 1 430, 1 312, 1 274, 1 271, 1 180, 1 128, 830, 646; HRMS(ESI) calcd for $C_{15}H_{17}N_6OS_2(M+H)^+$: 361.090 0, found: 361.090 4.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(3-氟苯基)-2-巯基-1,6-二氢嘧啶(3c): 白色固体. Yield: 70%, m.p. 241~243 ℃.

^{1}H NMR (500 MHz, DMSO-d_6):δ 9.31 (s, 1H), 9.01 (s, 1H), 7.87 (s, 1H), 7.49 (dd, J = 14.0, 8.0 Hz, 1H), 7.25~7.16 (m, 3H), 4.96 (s, 1H), 4.21 (s, 1H), 2.09 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 180.2, 166.4, 162.7 (d, J = 244.0 Hz), 157.4, 147.2, 141.9 (d, J = 6.9 Hz), 131.2 (d, J = 8.2 Hz), 122.6, 115.0 (d, J = 21.0 Hz), 113.6(d, J = 22.7 Hz), 78.0, 59.2, 51.5, 25.2, 14.2; IR(KBr):3 163, 1 562, 1 495, 1 444, 1 252, 1 198, 1 075, 796, 745, 700, 641; HRMS(ESI) calcd for $C_{15}H_{16}FN_6S_2(M+H)^+$: 363.085 6, found:363.086 0.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(3-甲氧基苯基)-2-巯基-1,6-二氢嘧啶(3d):红色固体.Yield: 77%, m.p. 278~280 ℃.

^{1}H NMR (500 MHz, DMSO-d_6):δ 9.27 (s, 1H), 9.01 (s, 1H), 7.70 (s, 1H), 7.26 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 4.84 (s, 1H), 4.09 (s, 1H), 3.74 (s, 3H), 2.05 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 174.0, 159.7, 145.0, 133.9, 130.0, 119.3, 113.4, 112.8, 110.1, 55.8, 55.4, 18.3, 17.8;IR(KBr):3 411, 2 968, 2 930, 1 611, 1 512, 1 251, 1 130, 840, 750, 636, 616; HRMS(ESI) calcd for $C_{16}H_{19}N_6OS_2(M+H)^+$: 375.105 6, found:375.105 4.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(2-氟苯基)-2-巯基-1,6-二氢嘧啶(3e):白色固体.Yield: 79%, m.p. 197~199 ℃.

^{1}H NMR (500 MHz, DMSO-d_6):δ 11.39 (s, 1H), 9.95 (s, 1H), 9.24 (s, 1H), 8.64 (s, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.22~7.13 (m, 3H), 5.50 (d, J = 3.5 Hz, 1H), 2.08 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 174.0, 160.6, 158.7, 134.2, 130.2 (d, J = 14.0 Hz), 130.1 (d, J = 8.2 Hz), 129.1, 125.0, 116.1, 116.0, 108.8, 50.1, 18.3, 17.6;IR(KBr):3 231, 2 970, 1 573, 1 479,

1 453, 1 252, 1 201, 1 138, 1 037, 756, 640; HRMS(ESI) calcd for $C_{15}H_{16}FN_6S_2(M+H)^+$: 363.085 6, found:363.086 2.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(3-氯苯基)-2-巯基-1,6-二氢嘧啶(3f):黄色固体.Yield: 56%, m.p. 243~245 ℃.

^{1}H NMR (500 MHz, DMSO-d_6):δ 9.30 (d, J = 3.8 Hz, 1H), 9.01 (s, 1H), 7.87 (s, 1H), 7.49~7.46 (m, 2H), 7.41 (d, J= 8.1 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 5.14~4.72 (m, 1H), 4.20 (s, 1H), 2.09 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 180.2, 166.4, 157.4, 147.2, 141.4, 133.9, 131.0, 128.2, 126.6, 125.2, 78.0, 59.2, 51.5, 25.2, 14.3; IR(KBr):3 368, 3 188, 2 952, 1 522, 1 476, 1 452, 1 202, 783, 696, 579, 539; HRMS(ESI) calcd for $C_{15}H_{16}ClN_6S_2(M+H)^+$: 379.056 1, found: 379.056 6.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-苯基-2-巯基-1,6-二氢嘧啶(3g):红色固体.Yield: 87%, m.p. 250~252 ℃.

^{1}H NMR (500 MHz, DMSO-d_6):δ 9.27 (d, J = 3.8 Hz, 1H), 9.01 (s, 1H), 7.77 (s, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.39~7.31 (m, 3H), 4.93 (s, 1H), 4.16 (s, 1H), 2.09 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 180.1, 166.5, 157.6, 147.2, 138.8, 129.1, 128.1, 126.5, 78.1, 59.4, 51.9, 25.2, 14.3; IR(KBr):3 432, 3 153, 2 971, 1 564, 1 500, 1 248, 1 189, 1 072, 744, 700, 644; HRMS(ESI) calcd for $C_{15}H_{17}N_6S_2(M+H)^+$: 345.095 1, found:345.095 7.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(2-甲氧基苯基)-2-巯基-1,6-二氢嘧啶(3h):灰色固体.Yield: 80%, m.p. 243~246 ℃.

^{1}H NMR (500 MHz, DMSO-d_6):δ 9.10 (d, J = 4.0 Hz, 1H), 9.01 (s, 1H), 7.83 (s, 1H), 7.36 (t, J = 8.6 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 7.08~6.99 (m, 2H), 4.96 (d, J = 6.1 Hz, 1H), 3.89 (s, 3H), 2.10 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 180.2, 166.3 157.2, 155.9, 147.1, 129.8, 126.4, 126.4, 120.7, 111.8, 77.7, 57.5, 56.2, 48.2, 25.7, 14.0; IR(KBr):3 347, 3 216, 2 930, 1 552, 1 497, 1 294, 1 243, 1 185, 1 111, 1 029, 749; HRMS(ESI) calcd for $C_{16}H_{19}N_6OS_2(M+H)^+$: 375.105 6, found:375.106 0.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(3-甲氧基-4-羟基苯基)-2-巯基-1,6-二氢嘧啶(3i):红色固体.Yield: 71%, m.p. 240~243 ℃.

^{1}H NMR (500 MHz, DMSO-d_6):δ 9.16 (d, J = 3.3 Hz, 1H), 9.06 (s, 1H), 9.01 (s, 1H), 7.74 (s, 1H), 6.99 (d, J = 1.9 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.71 (dd, J = 8.2, 1.8 Hz, 1H), 4.76 (t, J = 3.7 Hz, 1H), 4.04 (s, 1H), 3.78 (s, 3H), 2.04 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 179.2, 166.1, 157.3, 147.7, 146.7, 145.9, 128.8, 118.3, 115.2, 110.5, 77.8, 58.7, 55.7, 51.4, 24.5, 13.9; IR(KBr):3 458, 3 378, 1 520, 1 489, 1 430, 1 382, 1 277, 1 158, 812, 745, 608; HRMS(ESI) calcd for $C_{15}H_{16}N_7O_2S_2(M+H)^+$: 390.080 1, found:391.101 3.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(对甲苯基)-2-巯基-1,6-二氢嘧啶(3j):白色固体.Yield: 86%, m.p. 275~277 ℃.

^{1}H NMR (500 MHz, DMSO-d_6):δ 9.23 (d, J = 3.9 Hz, 1H), 9.01 (s, 1H), 7.73 (s, 1H), 7.24 (t, 4H), 4.87 (s, 1H), 4.12 (s, 1H), 2.31 (s, 3H), 2.08 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 180.0, 166.5, 157.7, 147.2, 137.3, 135.7, 129.6, 126.4, 78.1, 59.4, 51.7, 25.2, 21.1, 14.3; IR(KBr):3 156, 2 968, 1 562, 1 500, 1 442, 1 382, 1 249, 1 185, 1 074, 743, 644; HRMS(ESI) calcd for $C_{16}H_{19}N_6S_2(M+H)^+$: 359.110 7, found: 359.110 9.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(间溴苯基)-2-巯基-1,6-二氢嘧啶(3k):黄色固体.Yield: 55%, m.p. 251~253 ℃.

^{1}H NMR (500 MHz, DMSO-d_6):δ 9.30 (d, J = 2.7 Hz, 1H), 9.00 (s, 1H), 7.87 (s, 1H), 7.61 (s,

1H), 7.53 (d, J = 7.9 Hz, 1H), 7.42~7.31 (m, 2H), 4.94 (s, 1H), 4.18 (s, 1H), 2.07 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 180.1, 166.4, 157.4, 147.2, 141.6, 131.2, 131.0, 129.4, 125.5, 122.5, 78.0, 59.1, 51.3, 25.2 14.3; IR(KBr): 3 407, 3 193, 1 736, 1 546, 1 505, 1 311, 1 189, 1 072, 793, 745, 688; HRMS(ESI) calcd for $C_{15}H_{16}BrN_6S_2(M+H)^+$: 423.005 6, found: 422.952 0.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(对氯苯基)-2-巯基-1,6-二氢嘧啶(3l):红色固体.Yield: 60%, m.p. 254~256 ℃.

^{1}H NMR (500 MHz, DMSO-d_6): δ 9.30 (d, J = 4.1 Hz, 1H), 9.01 (s, 1H), 7.82 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 4.94 (s, 1H), 4.16 (s, 1H), 2.08 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 180.1, 166.4, 157.5, 147.3, 137.8, 132.7, 129.1, 128.5, 78.0, 59.3, 51.4, 25.2, 14.3; IR(KBr): 3 160, 2 967, 1 561, 1 496, 1 443, 1 248, 1 185, 1 089, 1 009, 827, 746; HRMS(ESI) calcd for $C_{15}H_{16}ClN_6S_2(M+H)^+$: 379.056 1, found: 379.056 9.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(4-甲氧基苯基)-2-巯基-1,6-二氢嘧啶(3m): 红色固体.Yield: 64%, m.p. 266~268 ℃.

^{1}H NMR (500 MHz, DMSO-d_6): δ 9.23 (d, J = 3.8 Hz, 1H), 9.01 (s, 1H), 7.73 (s, 1H), 7.28 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 4.84 (t, 1H), 4.08 (s, 1H), 3.76 (s, 3H), 2.06 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 179.9, 166.5, 159.1, 157.7, 147.2, 130.5, 127.7, 114.4, 78.2, 59.4, 55.6, 51.5, 25.1, 14.3; IR(KBr): 3 173, 2 964, 1 558, 1 502, 1 250, 1 180, 1 074, 1 030, 896, 747, 637; HRMS(ESI) calcd for $C_{16}H_{19}N_6OS_2(M+H)^+$: 375.105 6, found: 375.106 4.

5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-(3-羟基苯基)-2-巯基-1,6-二氢嘧啶(3n):黄色固体.Yield: 57%, m.p. 246~248 ℃.

^{1}H NMR (500 MHz, DMSO-d_6): δ 9.58 (s, 1H), 9.20 (s, 1H), 9.00 (s, 1H), 7.70 (s, 1H), 7.19 (t, J = 7.7 Hz, 1H), 6.79~6.68 (m, 3H), 4.81 (s, 1H), 4.08 (s, 1H), 2.06 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 179.7, 166.5, 166.2, 157.9, 157.6, 142.5, 140.1, 130.1, 117.0, 115.0, 113.3, 78.1, 59.3, 51.8, 25.2, 14.3; IR(KBr): 3 409, 2 923, 1 612, 1 492, 1 305, 1 227, 1 176, 997, 941, 787, 654; HRMS(ESI) calcd for $C_{15}H_{17}N_6OS_2(M+H)^+$: 361.090 0, found: 361.090 4.

2　结果与讨论

2.1　目标化合物的合成

按照文献[17]的方法,采用 Biginelli 反应在氨基磺酸的催化下合成中间体 4-甲基-6-芳基-5-乙酰基-2-巯基-1,6-二氢嘧啶(1),再将中间体 1 与 N,N′-二氨基硫脲在盐酸催化下得到中间体 1-(4-甲基-6-芳基-2-巯基-1,6-二氢嘧啶-5-基)乙酮硫代卡巴腙(2), 然后再将中间体 2 与原甲酸三乙酯在冰乙酸催化下合成得到目标化物 5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-芳基-2-巯基-1,6-二氢嘧啶(3).在目标化合物 3 的合成中发现酸的催化很重要,于是对不同的酸如磷酸、盐酸、醋酸、三氟乙酸和对甲苯磺酸进行筛选,结果发现醋酸的催化效果最好,因此,在这一类化合物的合成中选择醋酸为催化剂.催化剂对反应产率的影响如表 1 所示.

表 1　催化剂对反应产率的影响

序号	催化剂	产率/%
1	H_3PO_4	38
2	HCl	28
3	TsOH	43
4	CH_3COOH	66
5	CF_3COOH	54

2.2　目标化合物的波谱分析

通过 IR, ^{1}H NMR, ^{13}C NMR 和 HRMS(ESI)等表征手段对目标化合物 3 的化学结构进行表征,其中

以目标化合物 5-(1-(1,3,4-噻二唑-2-基)亚联氨基)乙基)-4-甲基-6-苯基-2-巯基-1,6-二氢嘧啶(3g)为例,在 IR 谱中(图 2),3 153, 3 214, 3 432 cm^{-1}处各有一吸收峰,为氨基的 N-H 和巯基 S-H 伸缩振动吸收峰;3 077 cm^{-1}处有一吸收峰,为苯环的 C-H 伸缩振动吸收峰,2 971, 2 931 cm^{-1}处出现的吸收峰为甲基的伸缩振动吸收, 1 500~1 624 cm^{-1}处为苯环的骨架振动吸收峰.在^{1}H NMR 中(图 3),在化学位移 1.44×10^{-6}, 2.09×10^{-6}处的 2 个 3 个氢的单峰,分别为分子中 2 个甲基的质子吸收峰;在化学位移 4.16×10^{-6}处的单峰为二氢嘧啶环中手性碳的质子吸收峰;在化学位移 4.98×10^{-6}处的单峰为 1,3,4-噻二唑环上-CH 的质子吸收峰;在化学位移 9.01×10^{-6}, 9.27×10^{-6}, 7.77×10^{-6}处的单峰为活泼氢-NH 和-SH 的质子吸收峰;在化学位移 7.32×10^{-6}~7.45×10^{-6}处的峰为苯环上的质子吸收峰.在^{13}C NMR 中(图 4),在化学位移 14.26×10^{-6}, 25.16×10^{-6}处的峰为 2 个甲基的碳吸收峰;在化学位移 51.90×10^{-6}处的峰为二氢嘧啶环上的手性碳吸收峰;在化学位移166.48×10^{-6}处的峰为二氢嘧啶环上 C=S 碳吸收峰;在化学位移 180.08×10^{-6}处的峰为与亚氨基相连噻二唑上的碳吸 收峰.高分辨质谱图显示(图 5),HRMS(ESI) calcd for $C_{15}H_{17}N_6S_2(M+H)^+$: 345.095 1, found:345.095 7,证明该化合物的理论分子量与高分辨质谱所测的分子量的数值相符.

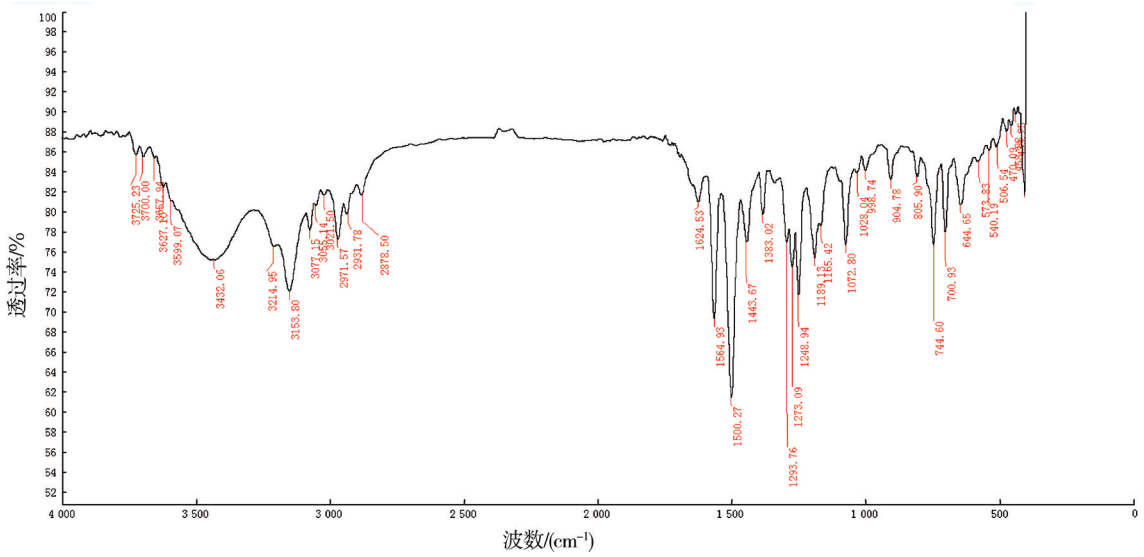

图 2 化合物 3g 的 IR 谱图

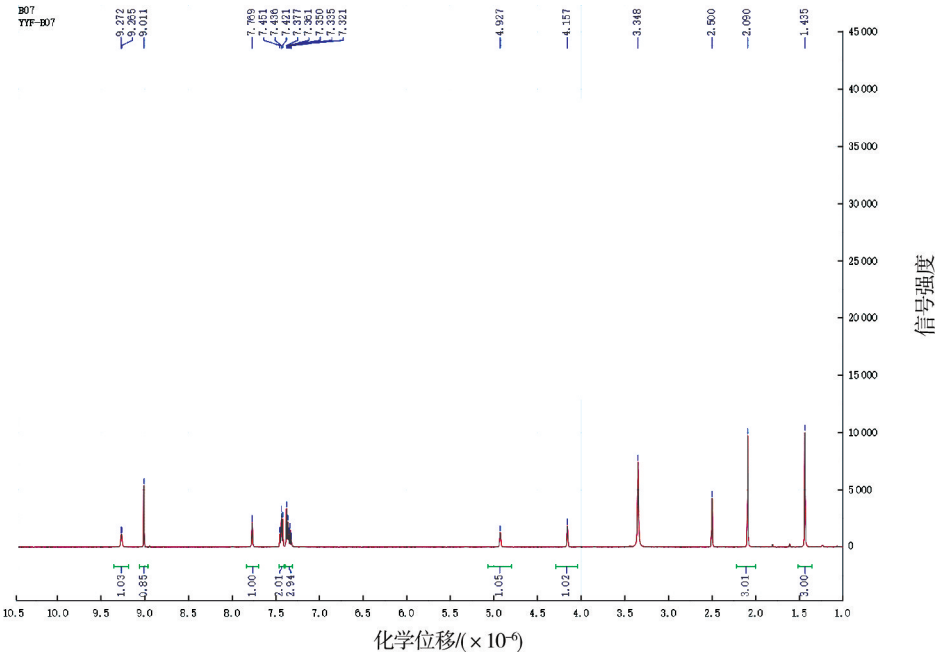

图 3 化合物 3g 的^{1}H NMR 谱图

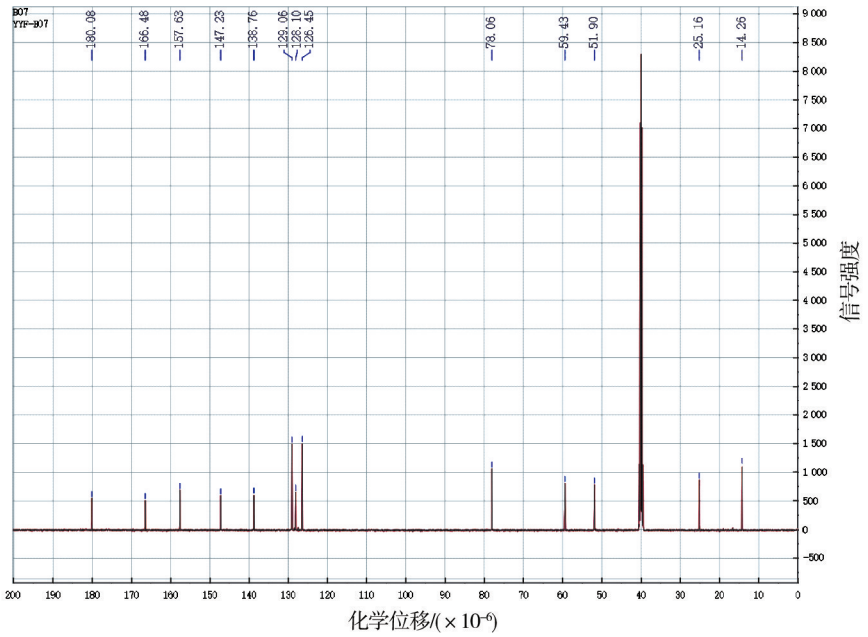

图 4　化合物 3g 的 ^{13}C NMR 谱图

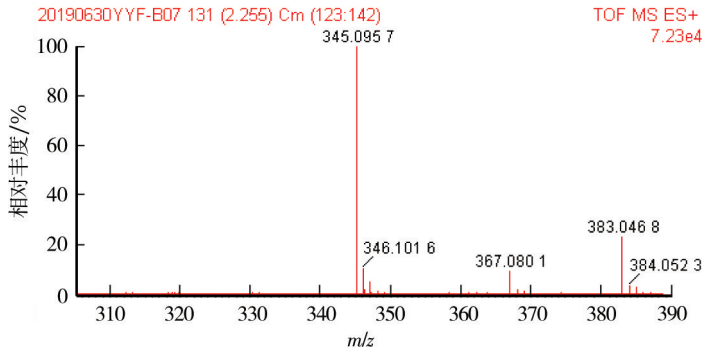

图 5　化合物 3g 的 HRMS(ESI)谱图

3　结论

1)通过 Biginelli 反应合成 4-甲基-6-芳基-5-乙酰基-2-巯基-1,6-二氢嘧啶,再以二氢嘧啶为母体经缩合、环化反应,合成 14 个新的含 1,3,4-噻二唑二氢嘧啶类的目标化合物,此合成方法的建立为二氢嘧啶衍生物的合成提供了借鉴.

2)鉴于二氢嘧啶和 1,3,4-噻二唑广泛的生物活性,后续可尝试在抑菌、抗癌、抗炎以及抗病毒等方面对这些化合物进行筛选,以期得到更有价值的应用.

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