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低价钛促进的苯并咪唑并[1,2-*c*]喹唑啉衍生物的合成

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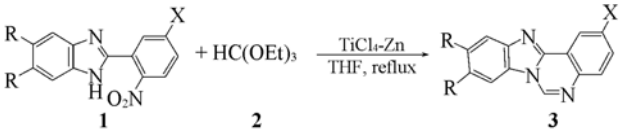
摘要 利用低价钛试剂促进的2-邻硝基苯基苯并咪唑与原甲酸酯或丙酮或固体光气的反应, 合成了一系列苯并咪唑并[1,2-*c*]喹唑啉衍生物, 化合物的结构经 IR, ^{1}H NMR, MS 和元素分析确定, 化合物 **4**c 的结构经单晶 X 射线衍射分析进一步确证. 该方法具有原料易得、操作简便和产率高等优点.

关键词 低价钛; 苯并咪唑并[1,2-*c*]喹唑啉; 2-邻硝基苯并咪唑
中图分类号 O626.416 **文献标识码** A **文章编号** 0251-0790(2007)10-1889-04

喹唑啉是一类具有广泛生理和药理活性的杂环化合物, 它具有抗癌、抗菌、抗疟疾、抗痉挛和抗炎等活性[1~6], 苯并咪唑并[1,2-*c*]喹唑啉具有很强的抗肿瘤活性[7], 因此该类化合物已受到人们的广泛关注. 这类化合物通常采用2-(邻氨基苯基)苯并咪唑与芳腈在微波辐射下反应制得, 收率中等[8]. 最近, 文献[9~11]报道了喹唑啉衍生物的合成方法. 但这些方法存在合成操作复杂、条件不易控制、原料来源困难和使用有毒物质等不足. 低价钛试剂是一种还原偶联试剂, 已广泛用于天然产物、碳环化合物和杂环化合物的合成[12,13]. 本文报道低价钛促进下苯并咪唑并[1,2-*c*]喹唑啉衍生物的合成.

1 结果与讨论

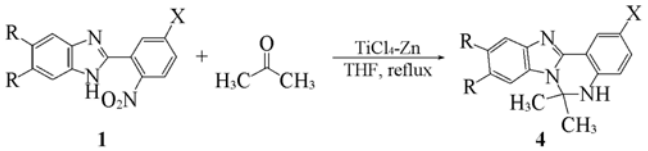
在氮气保护下, 用金属锌粉还原四氯化钛得低价钛试剂. 将2-邻硝基苯基咪唑(**1**)及原甲酸三乙酯(**2**)与低价钛试剂回流反应2 h, 得到还原环化产物苯并咪唑并[1,2-*c*]喹唑啉(**3**), 反应式如下:



1 **2** **3**

a. R=X=H; b. R=H, X=Cl; c. R=Cl, X=H; d. R=X=Cl; e. R=CH_3, X=H

化合物 **1** 与丙酮在室温反应, 可得到5,6-二氢化苯并咪唑并[1,2-*c*]喹唑啉(**4**), 反应式如下:

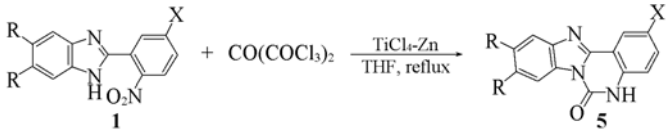


1 **4**

a. R=X=H; b. R=CH_3, X=Cl; c. R=X=Cl

2-邻硝基苯基苯并咪唑与其它酮(如丁酮、环戊酮、苯乙酮)反应时, 没有得到还原成环产物.

在低价钛试剂中, 2-邻硝基苯基苯并咪唑(**1**)与固体光气回流反应1 h, 即可得到产率较高的苯并咪唑并[1,2-*c*]喹唑啉-5-酮(**5**), 反应式如下:



1 **5**

a. R=X=H; b. R=H, X=Cl; c. R=Cl, X=H; d. R=X=Cl; e. R=CH_3, X=H; f. R=CH_3, X=Cl

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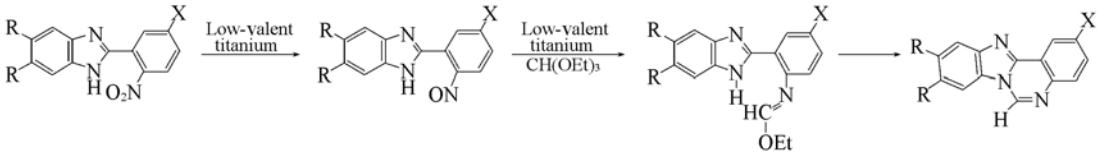
该反应为苯并咪唑并[1,2-*c*]喹唑啉衍生物的合成提供了一种方便的合成方法(未见文献报道).

根据低价钛作用下的硝基化合物的反应机理[14], 推测化合物**1**和**2**与低价钛试剂作用的反应可能经过下列过程: 化合物**1**中的硝基被低价钛还原成亚硝基, 亚硝基进一步被低价钛试剂还原后与原甲酸三乙酯反应形成亚胺, 咪唑环上的NH与亚胺发生加成-消除反应, 形成最终产物**3**(见Scheme 1).



Scheme 1 Possible mechanism in the formation of compound 3

为进一步确证产物的结构, 培养了化合物**4**c的单晶, 并进行了单晶X射线衍射分析. 化合物**4**c的分子结构见图1. 晶体属三斜晶系, 空间群*P*1, 晶胞参数: a = 0.8810(3) nm, b = 1.0507(4) nm, c = 1.1088(4) nm, α = 103.960(5)°, β = 91.066(5)°, γ = 110.304(5)°, V = 0.9283(6) nm^3, Z = 2, D_c = 1.426 g/cm^3, μ = 0.505 mm^{-1}, F(000) = 412.

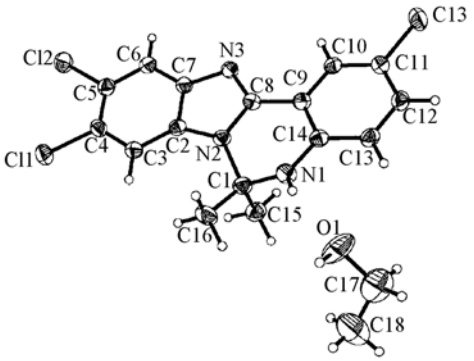


Fig. 1 Structure of compound 4c

在晶体结构中, 嘧啶环(N2—C8—C9—C14—N1—C1)为新形成的环, 由N1—C1的键长0.1452(4) nm和N2—C1的键长0.1491(4) nm可知, N1—C1和N2—C1为单键. 由于共轭效应的存在, 使得N1—C14[0.1374(4) nm]和N2—C18[0.1383(4) nm]的键长明显比典型的C_{sp^2}—N键长(0.1426 nm)短. 在嘧啶环中, 原子N2, C8, C9, C14和N1共平面, 而原子C1偏离该平面的距离为0.05176 nm, 这说明嘧啶环采取半椅式构象. 而咪唑环(N2—C2—C7—N3—C8)中五个原子共平面. 两个苯环(C2 ~ C7, C9 ~ C14)之间的二面角为6.41(6)°. 在晶体中存在溶剂(乙醇)分子, 并和目标分子之间形成N—H···O和O—H···N分子间氢键.

2 实验部分

2.1 仪器与试剂

XT-5显微熔点仪; Bruker Tensor 27红外光谱仪; Bruker DPX-400 MHz核磁共振仪(DMSO-d_6为溶剂, TMS为内标); Perkin-Elmer 2400 Ⅱ型元素分析仪; Bruker Smart-1000 CCD单晶X射线衍射仪.

四氢呋喃用固体KOH浸泡后, 再用金属钠加二苯甲酮回流后重新蒸馏, 其它试剂均为分析纯.

2.2 低价钛促进下苯并咪唑并[1,2-*c*]喹唑啉衍生物的合成

在100 mL三颈烧瓶中加入锌粉(1.3 g, 20 mmol)及THF 20 mL, 通入N_2气, 在搅拌下, 用针筒慢慢注入$TiCl_4$(1.1 mL, 10 mmol), 回流反应2 h, 冷却至室温. 滴加2-邻硝基苯基苯并咪唑(2 mmol)和原甲酸三乙酯(4 mmol)或丙酮(4 mmol)或固体光气(3 mmol)的THF溶液10 mL, 加毕, 在一定温度下反应一定时间, 用TLC跟踪至反应完毕. 反应混合物用100 mL质量分数为2%的盐酸水溶液分解, 用二氯乙烷萃取(50 mL×3), 用水洗涤. 无水硫酸钠干燥, 蒸除二氯乙烷, 残留物用体积分数为95%的乙醇重结晶, 得产物**3**或**4**或**5**.

2.3 产物4c的单晶X射线衍射分析

将化合物**4**c用体积分数为95%的乙醇重结晶, 得无色透明块状单晶. 选取大小为0.42 mm×0.39 mm×0.31 mm的单晶, 在X射线单晶衍射仪上, 采用石墨单色器, Mo $K\alpha$(λ = 0.071073 nm)辐射源, 以ω扫描方式, 在25 ℃和1.90° < θ < 25.00°范围内共收集3243个衍射数据, 其中1930个为可观察数据[$I > 2\sigma(I)$]. 全部数据均经LP因子和经验吸收校正, 结构用直接法(SHELXS97程序)解出, 经多轮Fourier合成获得全部非氢原子, 对全部非氢原子的坐标及各向异性热参数进行全矩阵最小二乘法

修正，最终的偏离因子 $R=0.0529$，$wR=0.1285$，最终差值电子云密度的最高峰为 373 e/nm^3，最低峰为 −311 e/nm^3.

产物 **3**，**4** 和 **5** 的结构经元素分析，IR，^{1}H NMR 和 MS 确证(表 1 和表 2).

Table 1　Physical data and elemental analyses of compounds 3, 4 and 5

Compd.	m. p./℃	Yield(%)	Elemental analysis(%, Calcd.)		
			C	H	N
3a	228—229	84	76.84(76.70)	4.09(4.14)	19.34(19.17)
3b	257—259	81	66.41(66.28)	3.23(3.18)	16.47(16.56)
3c	282—284	78	58.19(58.36)	2.40(2.45)	14.73(14.58)
3d	>300	74	52.26(52.13)	1.84(1.87)	13.15(13.03)
3e	247—248	76	77.87(77.71)	5.24(5.30)	17.05(16.99)
4a	244—245	71	77.15(77.08)	6.03(6.06)	16.92(16.85)
4b	212—214	65	69.51(69.34)	5.76(5.82)	13.55(13.48)
4c	202—204	78	54.58(54.49)	3.39(3.43)	12.03(11.92)
5a	>300	90	71.61(71.48)	3.93(3.86)	17.77(17.86)
5b	>300	92	62.53(62.35)	3.02(2.99)	15.64(15.58)
5c	>300	84	73.07(72.99)	4.93(4.98)	16.04(15.96)
5d	>300	88	64.63(64.54)	4.01(4.06)	14.22(14.11)

Table 2　IR, ^{1}H NMR and MS data of compounds 3, 4 and 5

Compd.	IR, $\tilde{\nu}$/cm^{-1}	^{1}H NMR(DMSO-d$_6$), δ	MS, *m/z*
3a	3025, 1602, 1520, 1476, 1360, 1264, 942, 762	7.51—7.60(2H, m, ArH), 7.77(1H, t, *J* = 8.00 Hz, ArH), 7.88(1H, t, *J* = 8.00 Hz, ArH), 7.95(1H, d, *J* = 8.00 Hz, ArH), 7.99(1H, d, *J* = 8.00 Hz, ArH), 8.41(1H, d, *J* = 8.40 Hz, ArH), 8.58(1H, d, *J* = 8.40 Hz, ArH), 9.76(1H, s, ArH)	219 (M$^+$, 100%)
3b	3052, 1602, 1523, 1472, 1453, 833	7.52—7.61(2H, m, ArH), 7.89(1H, dd, *J* = 8.80, 2.44 Hz, ArH), 7.95—8.01(2H, m, ArH), 8.42(1H, d, *J* = 8.04 Hz, ArH), 8.50(1H, d, *J* = 2.44 Hz, ArH), 9.78(1H, s, ArH)	255(M+2, 100%)
3c	3014, 1616, 1515, 1366, 861, 747	7.77—7.81(1H, m, ArH), 7.89—7.94(1H, m, ArH), 7.99(1H, d, *J* = 7.64 Hz, ArH), 8.23(1H, s, ArH), 8.54(1H, dd, *J* = 8.00, 1.24 Hz, ArH), 8.82(1H, s, ArH), 9.72(1H, s, ArH)	289(M+2, 100%)
3d	3053, 1605, 1469, 1353, 1281, 798	7.90—7.99(2H, m, ArH), 8.20(1H, s, ArH), 8.43(1H, s, ArH), 8.79(1H, s, ArH), 9.70(1H, s, ArH)	323(M+2, 100%)
3e	3046, 1608, 1525, 1473, 840, 780	2.45(3H, s, CH$_3$), 2.51(3H, s, CH$_3$), 7.72—7.76(2H, m, ArH), 7.84(1H, t, *J* = 8.04 Hz, ArH), 7.96(1H, d, *J* = 8.04 Hz, ArH), 8.18(1H, s, ArH), 8.53(1H, d, *J* = 8.04 Hz, ArH), 9.65(1H, s, ArH)	247(M$^+$, 100%)
4a	3323, 1612, 1519, 1452, 814, 738	1.85(6H, s, 2CH$_3$), 6.78—7.82(2H, m, ArH), 6.92(1H, s, NH), 7.19—7.28(3H, m, ArH), 7.63—7.65(1H, m, ArH), 7.73—7.75(1H, m, ArH), 7.91(1H, dd, *J* = 7.60, 1.24 Hz, ArH)	250(M+1, 100%)
4b	3212, 1618, 1508, 1437, 972, 899	1.94(6H, s, 2CH$_3$), 2.37(3H, s, CH$_3$), 2.40(3H, s, CH$_3$), 6.91(1H, s, NH), 7.40—7.43(1H, m, ArH), 7.56(1H, s, ArH), 7.69(1H, s, ArH), 7.80(1H, s, ArH), 8.04(1H, d, *J* = 2.40 Hz, ArH)	311(M$^+$, 100%)
4c	3216, 1618, 1513, 1369, 972, 859, 768	1.85(6H, s, 2CH$_3$), 6.85(1H, s, NH), 7.24(1H, s, ArH), 7.32(1H, dd, *J* = 8.80, 2.40 Hz, ArH), 7.81(1H, d, *J* = 2.40 Hz, ArH), 7.92(1H, m, ArH), 8.04(1H, s, ArH)	353(M+2, 100%)
5a	3150, 1722, 1614, 1382, 1330, 756	7.36—7.52(4H, m, ArH), 7.64—7.68(1H, m, ArH), 7.87(1H, d, *J* = 7.02 Hz, ArH), 8.32(1H, d, *J* = 8.00 Hz, ArH), 8.37(1H, d, *J* = 8.40 Hz, ArH), 11.98(1H, s, NH)	235(M$^+$, 100%)
5b	3204, 1712, 1611, 1385, 1238, 758	7.63(1H, d, *J* = 8.80 Hz, ArH), 7.43—7.50(2H, m, ArH), 7.65(1H, dd, *J* = 2.40, 8.40 Hz, ArH), 7.84(1H, d, *J* = 7.60 Hz, ArH), 8.18(1H, d, *J* = 2.40 Hz, ArH), 8.32(1H, d, *J* = 7.60 Hz, ArH), 12.05(1H, s, NH)	269(M$^+$, 100%)

Continued

Compd.	IR, $\tilde{\nu}$/cm^{-1}	^{1}H NMR(DMSO-d$_6$), δ	MS, m/z
5c	3156, 1720, 1596, 1551, 1344, 744	2.35(3H, s, CH_3), 2.37(3H, s, CH_3), 7.31—7.37(2H, m, ArH), 7.58—7.62(2H, m, ArH), 8.09(1H, s, ArH), 8.24(1H, d, J=7.60 Hz, ArH), 11.86(1H, s, NH)	264(M+1, 100%)
5d	3161, 1727, 1543, 1457, 1368, 750	2.35(3H, s, CH_3), 2.37(3H, s, CH_3), 7.34(1H, d, J=8.40 Hz, ArH), 7.56(1H, s, ArH), 7.62(1H, d, J=8.40 Hz, ArH), 8.06(1H, s, ArH), 8.13(1H, s, ArH), 11.95(1H, s, NH)	297(M^+, 100%)

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Synthesis of Benzoimidazo[1,2-*c*]quinazoline Derivatives Promoted by Low-valent Titanium

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Abstract Quinazoline is an important heterocyclic compound which has potential biological and pharmaceutical activities. It was reported that benzimidazo[1,2-*c*]quinazoline derivatives have a high anticancer activity. In this paper, a series of benzimidazo[1,2-*c*]quinazoline derivatives such as benzimidazo[1,2-*c*]quinazoline, 5,6-dihydrobenzimidazo[1,2-*c*]quinazoline and benzimidazo[1,2-*c*]quinazolin-5-one were synthesized *via* the reaction of 2-(*o*-nitrophenyl)benzimidazoles with triethyl orthoformate or acetone or triphosgene promoted by the low-valent titanium reagent($TiCl_4$-Zn system). The products were characterized *via* IR, ^{1}H NMR, MS and elemental analysis. The structure of compound **4**c was confirmed by X-ray single crystal diffraction. A possible reaction mechanism was put forward in this paper. This new method possesses the advantages of easily accessible starting materials, convenient manipulation and high yields.

Keywords Low-valent titanium; Benzimidazo[1,2-*c*]quinazoine; 2-(*o*-Nitrophenyl)benzimidazole

(Ed.: H, J, Z)