·研究论文·

新型顺-1,3-二芳基螺[吡唑-4,2′-吡唑并[1,2-*a*]吡唑]衍生物的非对映选择性合成

朱美军[1], 张 瑜[2], 陆玉玲[2], 孙 晶[2], 颜朝国[2*]
(1. 江海职业技术学院,江苏 扬州 225101; 2. 扬州大学 化学化工学院,江苏 扬州 225002)

摘要: 在三乙胺催化下,环偶氮甲亚胺与 4-芳亚基-5-甲基-2-苯基吡唑-3-酮在乙腈中回流反应,经 1,3-偶极环加成反应合成了 13 个新型的 1,3-二芳基取代的螺[吡唑-4,2′-吡唑并[1,2-*a*]吡唑]衍生物(**3a ~ 3m**),其结构经 ^{1}H NMR, ^{13}C NMR, IR 和 HR-MS(ESI)表征。采用 X-射线单晶衍射研究了 **3d**, **3h**, **3j** 和 **3l** 的单晶结构。结果表明:**3** 为特殊的顺式-1,3-二芳基构型。

关 键 词: 偶氮甲亚胺; 吡唑酮; 螺环化合物; 1,3-偶极环加成; 非对映选择性合成
中图分类号: O626.2 **文献标志码**: A **DOI**: 10.15952/j.cnki.cjsc.1005-1511.2017.12.17214

Diastereoselective Synthesis of Novel *cis*-1,3-Diarylspiro[pyrazole-4,2′-pyrazolo[1,2-*a*]pyrazoles]

ZHU Mei-jun[1], ZHANG Yu[2], LU Yu-ling[2], SUN Jing[2], YAN Chao-guo[2*]

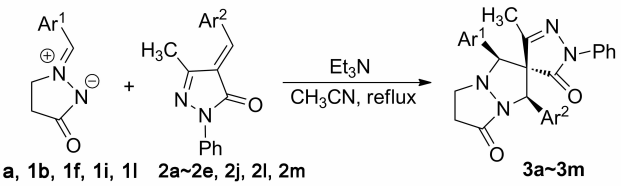
(1. Jianghai Polytechnic College, Yangzhou 225101, China;
2. College of Chemistry & Chemical Engineering, Yangzhou University, Yangzhou 225002, China)

Abstract: Thirteen novel 1,3-diaryl-substituted spiro[pyrazole-4,2′-pyrazolo[1,2-*a*]pyrazoles] derivatives(**3a ~ 3m**) were synthesized by triethylamine catalyzed 1,3-dipolar cycloaddition of cyclic azomethine imines with 4-arylidene-5-methyl-2-phenylpyrazol-3-ones in refluxing acetonitrile. The structures were characterized by ^{1}H NMR, ^{13}C NMR, IR and HR-MS(ESI). The single crystal structures of **3d**, **3h**, **3j** and **3l** were investigated by X-ray single diffraction. The results indicated that **3** have unusual *cis*-1,3-diaryl-configuration.

Keywords: azomethine imine; prazol-3-one; spiro compound; 1,3-dipolar cycloaddition; diastereoselective synthesis

吡唑及其衍生物是多种天然产物和合成化合物的重要结构单元。吡唑类化合物大多具有良好的生物活性,在新药和农药开发中有诸多应用[1]。其中,吡唑并[1,2-*a*]吡唑是应用最为广泛的吡唑类化合物之一[2-3]。如吡唑并[1,2-*a*]吡唑啉酮可用作除草剂,也可用作乙酰辅酶 A 羧化酶和肌醇(内肽)胞质 Ca^{2+}-ATPase 的抑制剂[4-5]。此外,还对有氧和厌氧细菌有显著的广谱杀灭活性[6]。γ-内酰胺类抗生素是基于肽模拟物的吡唑并[1,2-α]吡唑啉酮类化合物[7],药理

收稿日期: 2017-09-07; **修订日期**: 2017-11-07
基金项目: 国家自然科学基金资助项目(21572196)
作者简介: 朱美军(1975 -),女,汉族,江苏扬州人,硕士,主要从事有机合成的研究。E-mail: happyfengjunyang@126.com
通信联系人: 颜朝国,教授, E-mail: cgyan@yzu.edu.cn



1a, 1b, 1f, 1i, 1l　**2a~2e, 2j, 2l, 2m**　**3a~3m**

Comp	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
Ar^1	C_6H_5	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$
Ar^2	*p*-BrC_6H_4	C_6H_5	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	*p*-BrC_6H_4	*p*-$CH_3C_6H_4$	*m*-ClC_6H_4
Yield/%	56	60	68	70	75	68	64
Comp	**3h**	**3i**	**3j**	**3k**	**3l**	**3m**	
Ar^1	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4	*p*-ClC_6H_4	*p*-BrC_6H_4	*p*-BrC_6H_4	*p*-BrC_6H_4	
Ar^2	*p*-BrC_6H_4	C_6H_5	*p*-ClC_6H_4	*p*-BrC_6H_4	*m*-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$	
Yield/%	65	60	78	75	78	74	

Scheme 1

性质独特,药用价值较高,其合成方法的研究一直是该领域的热点之一[8-9]。

1,3-偶极子偶氮甲亚胺和含双键、三键的亲偶极体的1,3-偶极环加成反应,由于具有底物多样性,区域选择性和立体选择性,成为合成吡唑并[1,2-*a*]吡唑啉酮衍生物的高效方法之一[10-19]。本课题组持续开展了螺杂环化合物的高效合成方法的研究工作,取得诸多成果[20-23]。但使用环状偶氮甲亚胺进行1,3-偶极环加成反应合成螺吡唑并[1,2-*a*]吡唑啉酮衍生物的报道较少[24-26]。最近,我们成功地通过环状偶氮甲亚胺进行1,3-偶极环加成反应,合成了螺[茚-2,2′-吡唑并[1,2-*a*]吡唑]和螺[二氢吲哚-3,2′-吡唑并[1,2-*a*]吡唑]衍生物[27]。为进一步拓展环状偶氮甲亚胺在1,3-偶极环加成反应中的应用范围,我们继续展开了环状偶氮甲亚胺与4-亚芳基-5-甲基-2-苯基吡唑-3-酮的1,3-偶极环加成反应的研究。

本文在三乙胺催化下,环偶氮甲亚胺(**1a**, **1b**, **1f**, **1i**, **1l**)与4-芳亚基-5-甲基-2-苯基吡唑-3-酮(**2a~2e**, **2j**, **2l**, **2m**)在乙腈中回流反应,经1,3-偶极环加成反应合成了13个新型的1,3-二芳基取代的螺[吡唑-4,2′-吡唑并[1,2-*a*]吡唑]衍生物(**3a~3m**, Scheme 1),其结构经^{1}H NMR, ^{13}C NMR, IR和HR-MS(ESI)表征。采用X-射线单晶衍射研究了**3d**, **3h**, **3j**和**3l**的单晶结构。

1　实验部分

1.1　仪器与试剂

XT-4型显微熔点仪(温度未校正);Agilent DD2 400 MHz型核磁共振仪($CDCl_3$为溶剂,TMS为内标);Bruker Tensor 27型红外光谱仪(KBr压片);Bruker MaXis型超高分辨质谱仪;Bruker Smart APEX-2型X-射线单晶衍射仪。

1和**2a~2m**按文献[14]方法合成;其余所用试剂和溶剂均为分析纯。

1.2　**3a~3m**的合成通法

在反应瓶中依次加入**1** 0.5 mmol, **2** 0.5 mmol,三乙胺0.1 mmol和乙腈15.0 mL,回流反应6 h。旋蒸除溶,残余物经硅胶柱层析(洗脱剂:石油醚/乙酸乙酯=1/1, *V*/*V*)纯化得**3a~3m**。

3a:白色固体,产率56%, m. p. 160~162 ℃; ^{1}H NMR δ: 7.80~7.77 (m, 2H, ArH), 7.44~7.39 (m, 4H, ArH), 7.28~7.29 (m, 2H, ArH), 7.26~7.25 (m, 1H, ArH), 7.24~7.22 (m, 3H, ArH), 7.04~7.02 (m, 2H, ArH), 5.66 (s, 1H, CH), 4.41 (s, 1H, CH), 3.95~3.88 (m, 1H, CH), 3.27~3.19 (m, 1H, CH), 3.08~2.99 (m, 1H, CH), 2.97~2.90 (m, 1H, CH), 1.56 (s, 3H, CH_3); ^{13}C NMR δ: 173.9, 170.5, 159.1, 137.3, 134.5, 132.0, 131.6, 129.1, 129.0, 128.9, 126.0, 125.8, 122.2, 119.2, 77.3, 72.7, 63.5, 47.8, 31.8, 17.2; IR ν: 2 871, 1 702, 1 494, 1 397, 1 320, 1 246, 1 125, 1 081, 1 007, 854, 806, 725 cm^{-1}; HR-MS(ESI) *m*/*z*: Calcd for $C_{27}H_{24}N_4O_2Br$ {[M+H]$^+$} 515.107 7, found 515.108 4。

3b:白色固体,产率60%, m. p. 198~200

℃; ^{1}H NMR δ: 7.82 ~ 7.79(m, 2H, ArH), 7.41 (t, J = 8.0 Hz, 2H, ArH), 7.30 ~ 7.27(m, 2H, ArH), 7.26 ~ 7.22(m, 2H, ArH), 7.14 ~ 7.10 (m, 4H, ArH), 7.07 ~ 7.05(m, 2H, ArH), 5.74(s, 1H, CH), 4.38(s, 1H, CH), 3.93 ~ 3.86(m, 1H, CH), 3.24 ~ 3.16(m, 1H, CH), 3.07 ~ 3.00(m, 1H, CH), 2.96 ~ 2.90(m, 1H, CH), 2.27(s, 3H, CH_3), 1.57(s, 3H, CH_3); ^{13}C NMR δ: 173.4, 170.9, 159.6, 138.9, 137.4, 135.3, 129.6, 128.9, 128.8, 128.6, 128.2, 125.9, 125.6, 125.0, 119.3, 77.4, 77.2, 72.9, 63.8, 47.9, 32.1, 21.1, 17.1; IR ν: 3 020, 1 713, 1 594, 1 500, 1 455, 1 368, 1 327, 1 246, 1 187, 1 095, 1 016, 857, 816, 753 cm^{-1}; HR-MS(ESI) m/z: Calcd for $C_{28}H_{27}N_4O_2$ {[M + H]$^+$} 451.212 9, found 451.213 4。

3c: 白色固体, 产率 68%, m. p. 184 ~ 186 ℃; ^{1}H NMR δ: 7.81 ~ 7.79(m, 2H, ArH), 7.41 (t, J = 8.0 Hz, 2H, ArH), 7.23(t, J = 7.2 Hz, 1H, ArH), 7.13 ~ 7.05(m, 6H, ArH), 7.02 ~ 7.00(m, 2H, ArH), 5.70(s, 1H, CH), 4.37 (s, 1H, CH), 3.93 ~ 3.87 (m, 1H, CH), 3.22 ~ 3.15(m, 1H, CH), 3.08 ~ 3.02(m, 1H, CH), 2.95 ~ 2.88(m, 1H, CH), 2.28(s, 3H, CH_3), 2.27(s, 3H, CH_3), 1.56(s, 3H, CH_3); ^{13}C NMR δ: 172.9, 170.9, 159.7, 138.8, 137.9, 137.4, 132.2, 129.6, 129.5, 128.9, 128.7, 125.9, 125.6, 124.8, 119.2, 77.3, 72.9, 63.7, 48.2, 32.4, 21.1, 21.0, 17.2; IR ν: 1 714, 1 596, 1 502, 1 453, 1 365, 1 322, 1 242, 1 184, 1 090, 1 029, 859, 821, 755 cm^{-1}; HR-MS (ESI) m/z: Calcd for $C_{29}H_{29}N_4O_2$ {[M + H]$^+$} 465.228 5, found 465.229 3。

3d: 白色固体, 产率 70%, m. p. 178 ~ 180 ℃; ^{1}H NMR δ: 7.80(d, J = 8.0 Hz, 2H, ArH), 7.41 (t, J = 8.0 Hz, 2H, ArH), 7.23(t, J = 7.2 Hz, 1H, ArH), 7.13 ~ 7.11 (m, 2H, ArH), 7.07 ~ 7.00(m, 4H, ArH), 6.82 ~ 6.80(m, 2H, ArH), 5.69(s, 1H, CH), 4.37(s, 1H, CH), 3.93 ~ 3.87(m, 1H, CH), 3.76(s, 3H, OCH_3), 3.22 ~ 3.15(m, 1H, CH), 3.08 ~ 3.01(m, 1H, CH), 2.95 ~ 2.89(m, 1H, CH), 2.27(s, 3H, CH_3), 1.57(s, 3H, CH_3); ^{13}C NMR δ: 172.9, 170.9, 159.8, 159.3, 138.8, 137.4, 129.6, 128.9, 128.7, 127.2, 126.2, 125.9, 125.6, 119.2, 114.2, 77.2, 73.0, 63.5, 55.2, 48.2, 32.3, 21.1, 17.2; IR ν: 3 003, 2 834, 1 713, 1 599, 1 505, 1 455, 1 363, 1 318, 1 249, 1 184, 1 122, 1 087, 1 030, 923, 829, 758 cm^{-1}; HR-MS(ESI) m/z: Calcd for $C_{29}H_{29}N_4O_3$ {[M + H]$^+$} 481.223 4, found 481.224 0。

3e: 白色固体, 产率 75%, m. p. 190 ~ 192 ℃; ^{1}H NMR δ: 7.81 ~ 7.79 (m, 2H, ArH), 7.44 ~ 7.40(m, 4H, ArH), 7.24(t, J = 7.6 Hz, 1H, ArH), 7.11 ~ 7.01(m, 6H, ArH), 5.65(s, 1H, CH), 4.38(s, 1H, CH), 3.93 ~ 3.86(m, 1H, CH), 3.25 ~ 3.17(m, 1H, CH), 3.08 ~ 2.99(m, 1H, CH), 2.96 ~ 2.89(m, 1H, CH), 2.27 (s, 3H, CH_3), 1.57 (s, 3H, CH_3); ^{13}C NMR δ: 173.8, 170.6, 159.2, 139.0, 137.3, 134.6, 132.0, 129.6, 129.0, 128.4, 126.8, 125.9, 125.7, 122.1, 119.2, 77.3, 72.7, 63.4, 47.9, 31.9, 21.1, 17.3; IR ν: 3 037, 2 936, 2 886, 1 709, 1 598, 1 497, 1 406, 1 369, 1 335, 1 290, 1 235, 1 181, 1 083, 1 008, 859, 819, 754 cm^{-1}; HR-MS(ESI) m/z: Calcd for $C_{28}H_{26}N_4O_2Br$ {[M + H]$^+$} 529.123 4, found 529.123 2。

3f: 白色固体, 产率 68%, m. p. 154 ~ 156 ℃; ^{1}H NMR δ: 7.79 ~ 7.78 (m, 2H, ArH), 7.43 ~ 7.39(m, 2H, ArH), 7.24 ~ 7.22(m, 1H, ArH), 7.19 ~ 7.11(m, 3H, ArH), 7.06 ~ 7.02 (m, 1H, ArH), 6.98 ~ 6.87 (m, 2H, ArH), 6.83 ~ 6.78(m, 2H, ArH), 5.69(s, 1H, CH), 4.35(s, 1H, CH), 3.92 ~ 3.86(m, 1H, CH), 3.74(s, 3H, OCH_3), 3.22 ~ 3.15(m, 1H,CH), 3.08 ~ 3.00(m, 1H, CH), 2.96 ~ 2.89(m, 1H, CH), 2.27(s, 3H, CH_3), 1.55(s, 3H, CH_3); ^{13}C NMR δ: 170.9, 159.8, 159.6, 138.4, 137.4, 135.2, 128.9, 128.8, 128.7, 127.2, 125.6, 125.5, 123.4, 122.0, 119.3, 114.2, 72.8, 63.7, 55.1, 47.8, 32.0, 21.4, 17.2; IR ν: 2 945, 2 836, 1 714, 1 601, 1 504, 1 455, 1 362, 1 299, 1 246, 1 176, 1 124, 1 086, 1 030, 847, 757 cm^{-1}; HR-MS(ESI) m/z: Calcd for $C_{29}H_{28}N_4O_3Na$ {[M + Na]$^+$} 503.205 9, found

503.205 7。

3g: 白色固体,产率 64%, m. p. 156 ~ 158 ℃; ^{1}H NMR δ: 7.78(d, J = 7.6 Hz, 2H, ArH), 7.43 ~ 7.40(t, J = 6.4 Hz, 2H, ArH), 7.23 ~ 7.22(m, 2H, ArH), 7.21 ~ 7.17(m, 2H, ArH), 7.16 ~ 7.13(m, 2H, ArH), 6.92 ~ 6.90(m, 1H, ArH), 6.80 ~ 6.78(m, 2H, ArH), 5.66(s, 1H, CH), 4.35(s, 1H, CH), 3.90 ~ 3.88(m, 1H, CH), 3.74(s, 3H, OCH_3), 3.23 ~ 3.20(m, 1H, CH), 2.99 ~ 2.94(m, 2H, CH), 1.67 ~ 1.60(m, 1H, CH), 1.56(s, 3H, CH_3); ^{13}C NMR δ: 174.4, 170.6, 159.9, 159.1, 137.7, 134.9, 130.2, 128.9, 128.3, 127.2, 125.7, 125.3, 123.2, 123.2, 119.3, 114.3, 72.6, 63.2, 55.2, 47.3, 31.5, 17.2; IR ν: 3 063, 2 995, 2 944, 2 830, 1 713, 1 601, 1 505, 1 460, 1 412, 1 364, 1 302, 1 246, 1 182, 1 089, 1 032, 907, 848, 758 cm^{-1}; HR-MS(ESI) m/z: Calcd for $C_{28}H_{25}N_4O_3ClNa$ {[M + Na]$^+$} 523.151 3, found 523.151 8。

3h: 白色固体,产率 65%, m. p. 200 ~ 202 ℃; ^{1}H NMR δ: 7.81 ~ 7.79(m, 2H, ArH), 7.43 ~ 7.39(m, 4H, ArH), 7.25 ~ 7.22(m, 1H, ArH), 7.16 ~ 7.13(m, 2H, ArH), 7.03 ~ 7.01(m, 2H, ArH), 6.80 ~ 6.77(m, 2H, ArH), 5.64(s, 1H, CH), 4.36(s, 1H, CH), 3.93 ~ 3.86(m, 1H, CH), 3.74(s, 3H, OCH_3), 3.24 ~ 3.17(m, 1H, CH), 3.06 ~ 3.00(m, 1H, CH), 2.96 ~ 2.89(m, 1H, CH), 1.58(s, 3H, CH_3); ^{13}C NMR δ: 173.9, 170.6, 160.0, 159.2, 137.3, 134.6, 132.0, 129.0, 127.2, 126.8, 125.7, 123.2, 122.1, 119.1, 114.3, 77.3, 72.7, 63.3, 55.2, 47.8, 31.9, 17.3; IR ν: 2 945, 1 707, 1 607, 1 503, 1 408, 1 370, 1 303, 1 248, 1 178, 1 086, 1 041, 826, 771 cm^{-1}; HR-MS(ESI) m/z: Calcd for $C_{28}H_{26}N_4O_3Br$ {[M + H]$^+$} 545.118 3, found 545.118 6。

3i: 白色固体,产率 60%, m. p. 168 ~ 170 ℃; ^{1}H NMR δ: 7.81 ~ 7.79(m, 2H, ArH), 7.44 ~ 7.40(m, 2H, ArH), 7.29 ~ 7.27(m, 4H, ArH), 7.25 ~ 7.23(m, 2H, ArH), 7.18 ~ 7.16(m, 2H, ArH), 7.14 ~ 7.12(m, 2H, ArH), 5.74(s, 1H, CH), 4.37(s, 1H, CH), 3.94 ~ 3.87(m, 1H, CH), 3.22 ~ 3.15(m, 1H, CH), 3.07 ~ 3.01(m, 1H, CH), 2.97 ~ 2.89(m, 1H, CH), 1.58(s, 3H, CH_3); ^{13}C NMR δ: 173.5, 170.6, 159.2, 137.3, 135.2, 134.9, 130.4, 129.2, 129.0, 128.9, 128.3, 127.4, 125.8, 125.0, 119.2, 76.8, 72.8, 63.9, 47.9, 31.9, 17.1; IR ν: 2 928, 2 843, 1 706, 1 598, 1 496, 1 366, 1 319, 1 245, 1 179, 1 096, 1 017, 847, 782, 708 cm^{-1}; HR-MS(ESI) m/z: Calcd for $C_{27}H_{24}N_4O_2Cl$ {[M + H]$^+$} 471.158 2, found 471.158 6。

3j: 白色固体,产率 78%, m. p. 204 ~ 206 ℃; ^{1}H NMR δ: 7.81 ~ 7.79(m, 2H, ArH), 7.43(t, J = 8.0 Hz, 2H, ArH), 7.28 ~ 7.27(m, 3H, ArH), 7.25 ~ 7.23(m, 2H, ArH), 7.18 ~ 7.16(m, 2H, ArH), 7.09 ~ 7.07(m, 2H, ArH), 5.68(s, 1H, CH), 4.36(s, 1H, CH), 3.93 ~ 3.86(m, 1H, CH), 3.23 ~ 3.16(m, 1H, CH), 3.08 ~ 3.02(m, 1H, CH), 2.97 ~ 2.90(m, 1H, CH), 1.55(s, 3H, CH_3); ^{13}C NMR δ: 173.9, 170.3, 158.8, 137.2, 135.0, 134.2, 133.8, 130.1, 129.3, 129.1, 129.0, 127.3, 126.4, 125.9, 119.1, 72.7, 63.4, 47.8, 31.8, 17.2; IR ν: 2 942, 2 885, 1 704, 1 494, 1 407, 1 370, 1 336, 1 285, 1 234, 1 184, 1 092, 1 009, 824, 762, 733, 701 cm^{-1}; HR-MS(ESI) m/z: Calcd for $C_{27}H_{23}N_4O_2Cl_2$ {[M + H]$^+$} 505.119 3, found 505.119 8。

3k: 白色固体,产率 75%, m. p. 210 ~ 212 ℃; ^{1}H NMR δ: 7.79(d, J = 8.0 Hz, 2H, ArH), 7.44 ~ 7.40(m, 6H, ArH), 7.25 ~ 7.23(m, 1H, ArH), 7.10(d, J = 8.0 Hz, 2H, ArH), 7.01(d, J = 8.0 Hz, 2H, ArH), 5.65(s, 1H, CH), 4.34(s, 1H, CH), 3.93 ~ 3.86(m, 1H, CH), 3.22 ~ 3.15(m, 1H, CH), 3.09 ~ 2.99(m, 1H, CH), 2.96 ~ 2.89(m, 1H, CH), 1.55(s, 3H, CH_3); ^{13}C NMR δ: 173.9, 170.3, 158.8, 137.1, 134.1, 132.2, 132.0, 130.7, 129.0, 127.6, 126.7, 125.9, 123.2, 122.3, 119.9, 72.5, 63.5, 47.8, 31.8, 17.2; IR ν: 2 942, 1 740, 1 655, 1 600, 1 494, 1 406, 1 369, 1 336, 1 288, 1 238, 1 184, 1 082, 1 008, 823, 759 cm^{-1}; HR-MS(ESI) m/z: Calcd for $C_{27}H_{23}N_4O_2Br_2$ {[M + H]$^+$} 593.018 2, found 593.018 1。

3l: 白色固体,产率 78%, m. p. 193 ~ 195 ℃;

^{1}H NMR δ: 8.19 ~ 8.14(m, 2H, ArH), 7.78(d, J = 7.2 Hz, 2H, ArH), 7.48 ~ 7.42(m, 5H, ArH), 7.34 ~ 7.25(m, 2H, ArH), 7.12(d, J = 7.6 Hz, 2H, ArH), 5.75(s, 1H, CH), 4.39(s, 1H, CH), 3.99 ~ 3.92(m, 1H, CH), 3.28 ~ 3.21(m, 1H, CH), 3.07 ~ 2.93(m, 2H, CH), 1.51(s, 3H, CH_3); ^{13}C NMR δ: 175.3, 170.1, 158.2, 148.4, 137.9, 136.9, 132.2, 131.1, 130.4, 130.1, 129.0, 127.6, 126.1, 123.3, 120.3, 119.3, 72.3, 63.4, 47.2, 31.1, 17.2; IR ν: 3 072, 2 930, 1 712, 1 596, 1 534, 1 494, 1 403, 1 354, 1 240, 1 180, 1 088, 1 006, 822, 761, 718 cm^{-1}; HR-MS(ESI) m/z: Calcd for $C_{27}H_{22}N_5O_4BrNa$ {[M + Na]$^+$} 582.075 3, found 582.074 7。

3m: 白色固体,产率 74%, m. p. 158 ~ 160 ℃; ^{1}H NMR δ: 8.18 ~ 8.15(m, 2H, ArH), 7.80 ~ 7.78(m, 2H, ArH), 7.42 ~ 7.32(m, 7H, ArH), 7.09(d, J = 7.6 Hz, 2H, ArH), 5.74(s, 1H, CH), 4.37(s, 1H, CH), 3.94 ~ 3.89(m, 1H, CH), 3.25 ~ 3.19(m, 1H, CH), 3.01 ~ 2.95(m, 2H, CH), 1.25(s, 3H, CH_3); ^{13}C NMR δ: 174.7, 169.9, 158.1, 147.7, 142.6, 137.0, 132.2, 130.3, 129.1, 127.6, 126.2, 126.0, 124.1, 123.3, 119.0, 72.4, 63.5, 47.5, 31.3, 29.6, 17.2; IR ν: 3 072, 2 925, 2 854, 1 714, 1 599, 1 521, 1 495, 1 402, 1 344, 1 241, 1 181, 1 114, 1 011, 846, 757, 719 cm^{-1}; HR-MS(ESI) m/z: Calcd for $C_{27}H_{22}N_5O_4BrNa$ {[M + Na]$^+$} 582.075 3, found 582.075 6。

2 结果与讨论

2.1 合成

参考文献[27]方法合成 **3b**,反应不完全,产率仅 30% 左右。延长反应时间,仍然有部分原料不能反应。加入酸(或碱)催化剂可以改善反应结果。当加入催化量的三乙胺时,反应可快速完成,顺利的合成 **3b**,产率大幅提高(约 60%)。在此反应条件下,可以中等至良好的产率合成预期产物。初步的构效分析表明,两种反应底物上的取代基对产率影响较小。

2.2 表征

(1) ^{1}H NMR

由于产物的吡唑环中存在 3 个手性碳原子,反应中可能形成多种非对映异构体。化合物的^{1}H NMR 谱图中仅显示一组特征吸收峰,这表明产物中仅存在一种非对映异构体。如 **3d** 在 δ 3.76 处的特征峰为甲氧基的单峰,δ 2.27 和 δ 1.57处出现了两个甲基的单峰,δ 5.89 和 δ 4.33 处单峰为吡咯环 C—H 的特征吸收峰,δ 3.93 ~ 2.89处的多重峰为吡唑啉酮环中相邻的两个亚甲基由于非对映特性而出现的 4 个 H 的吸收峰。

(2) X-射线单晶衍射

图 1 ~ 图 4 为 **3d**, **3h**, **3j** 和 **3l** 的单晶结构图。由图 1 ~ 图 4 可见,4 个分子具有相同的相对构型。两个芳基在新形成的吡唑环中均位于顺式位置。5-甲基-2-苯基吡唑-3-酮单元中的羰基位于两个芳基的反式位置,甲基伸向两个芳基的同一侧。结合^{1}H NMR 的分析,我们确定 **3a ~ 3m** 均具有该相对构型,中间吡唑环中位于 1,3-位上的两个芳基以顺式构型存在,这与文献[24]报道不同。值得注意的是,我们之前合成的螺[茚-2,2′-吡唑并[1,2-*a*]吡唑]和螺[二氢吲哚-3,2′-吡唑并[1,2-*a*]吡唑]也具有顺式 1,3-二芳基的相对构型[27]。

综上可知,环状偶氮甲亚胺与环状亲 1,3-偶极子的环环加成反应具有非常高的非对映选择性。

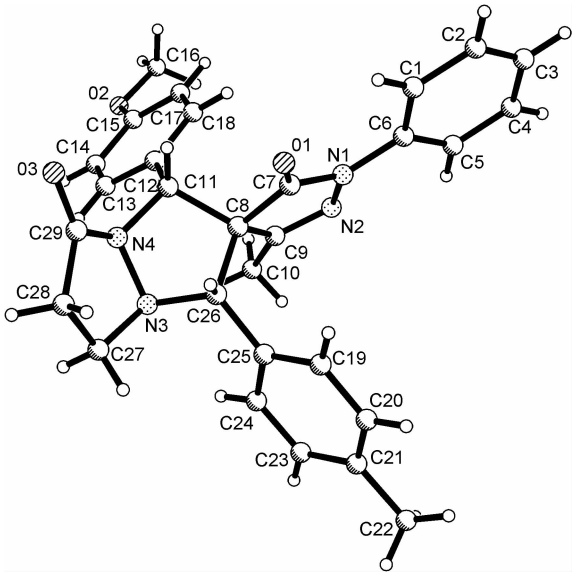


图 1 **3d**(CCDC: 1538806)的单晶分子结构

Figure 1 Single crystal structure of **3d**

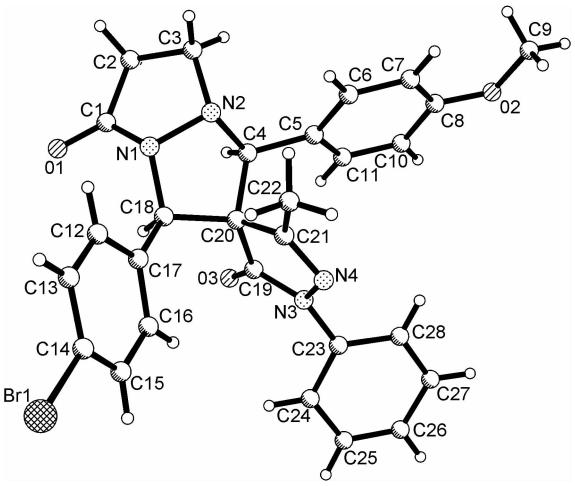


图 2　**3h**(CCDC: 1538807)的单晶分子结构

Figure 2　Single crystal structure of **3h**

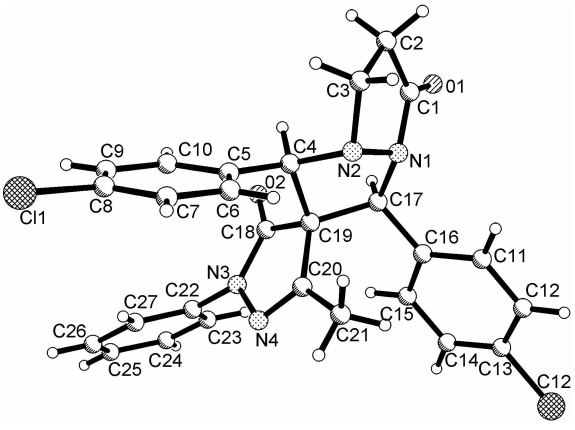


图 3　**3j**(CCDC: 1538808)的单晶分子结构

Figure 3　Single crystal structure of **3j**

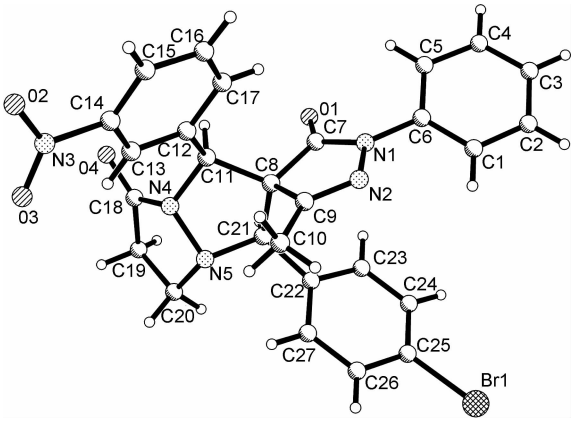


图 4　**3l**(CCDC: 1544352)的单晶分子结构

Figure 4　Single crystal structure of **3l**

3　结论

通过环状偶氮甲亚胺与 4-亚芳基-5-甲基-2-苯基吡唑-3-酮的 1,3-偶极环加成反应合成了一系列顺-1,3-二芳基取代的螺[吡唑-4,2′-吡唑并[1,2-*a*]吡唑]。该多环体系由 3 个吡唑环分别以并环和螺环方式连接,结构新颖。该反应具有反应条件简单、底物普适性强、反应产率高,非对映选择性好等优点。合成的新化合物在药物研发中具有潜在的应用价值。

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