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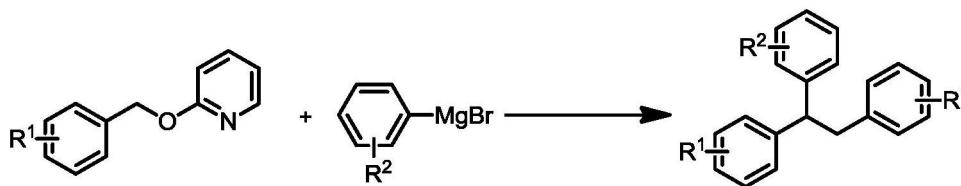
(54) 发明名称

一种合成1,1,2-三芳基乙烷的方法

(57) 摘要

本发明公开了一种铬催化合成1,1,2-三芳基乙烷化合物的方法,该方法以廉价易得的金属铬盐为催化剂,芳基格氏试剂为芳基供体,醚为溶剂,将苯基吡啶醚在0~100℃搅拌反应3~24小时,生成相应的1,1,2-三芳基乙烷化合物。本方法具有成本低、反应条件温和、底物适用范围广、选择性高、步骤经济、反应体系干净等优点,避免了大量添加剂的使用和副产物的生成。

1. 一种铬催化合成1,1,2-三芳基乙烷化合物的方法,其特征在于:将式中所示的苄基吡啶醚化合物、金属铬盐、芳基格氏试剂加入醚类溶剂中反应,反应完全后经分离得到1,1,2-三芳基乙烷化合物:



式中, R^1 代表氢、烷基、烷氧基、苯基、苯氧基、硅基、胺基、苯乙烯基,环氧基、呋喃基、噻吩基、氟、氯等任意一种或两种,或者 R^1 代表取代苯基,其取代基包括烷基、萘基、烷氧基、硅氧基、三氟甲氧基、羟基、氟、氯等任意一种或两种;

式中, R^2 代表烷基、甲硫基、三氟甲氧基、苯基、硅基、胺基、环氧基、氟等任意一种。

2. 根据权利要求1所述的合成1,1,2-三芳基乙烷的方法,其特征在于:催化剂铬盐的加入量为苄基吡啶醚化合物摩尔量的0.5~20%。

3. 根据权利要求1所述的合成1,1,2-三芳基乙烷的方法,其特征在于:芳基格氏试剂的加入量为苄基吡啶醚化合物摩尔量的1-4当量。

4. 根据权利要求1所述的合成1,1,2-三芳基乙烷的方法,其特征在于:在0~100℃下搅拌反应3~24小时。

5. 醚类溶剂包括但不限于:四氢呋喃、2-甲基四氢呋喃或乙醚。

6. 金属铬盐包括但不限于:二氯化铬、三氯化铬、乙酰丙酮铬或醋酸铬。

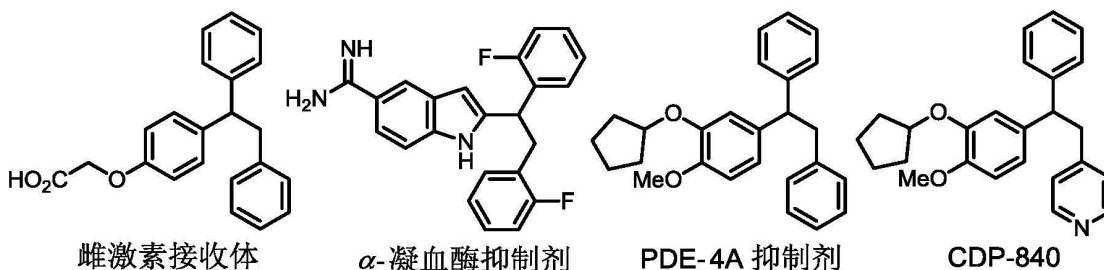
一种合成1,1,2-三芳基乙烷的方法

技术领域

[0001] 本发明属于1,1,2-三芳基乙烷化合物的制备技术领域,具体涉及一种以金属铬盐为催化剂,实现苄基吡啶醚与芳基格氏试剂反应得到相应的1,1,2-三芳基乙烷化合物的方法。

背景技术

[0002] 1,1,2-三芳基乙烷是一类重要的分子骨架,广泛存在于药物和生物活性分子中。因此,发展更为简单高效的合成1,1,2-三芳基乙烷的方法具有重要的研究意义和应用前景。目前,市场上许多畅销的药品含有1,1,2-三芳基乙烷骨架,例如结构式如下的:雌激素接收体、 α -凝血酶抑制剂、PDE-4A抑制剂、CDP-840等。

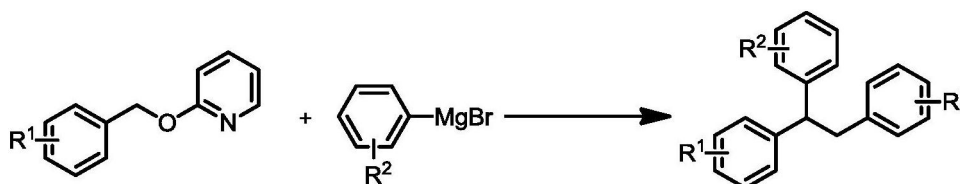


目前文献中主要有两种方法用于合成1,1,2-三芳基乙烷化合物:一种是以 β -酮砜类化合物为起始原料经三步反应制备(Tetrahedron 2017, 73, 1275-1282),另一种是镍催化芳基烯烃的1,2-双功能化反应制备(Angew.Chem.Int.Ed.2019, 58, 3198-3202)。其中以 β -酮砜类化合物为原料的反应中需要用到硼氢化钠、三氟化硼乙醚以及醋酸钯等多种试剂,实验步骤较繁琐,反应中环境不友好的硫化物的产生和贵金属钯的使用极大地增加了生产成本;另外在镍催化的芳基烯烃的反应中不仅需要引入配体对反应选择性进行调控,同时也需要加入添加剂和使用混合溶剂用于产率的进一步优化,反应体系较复杂,选择性问题的存在不利于后期产物分离提纯,添加剂和混合溶剂的使用不宜于扩大量生产。

发明内容

[0003] 本发明的目的是提供一种成本低、反应条件温和、底物适用范围广、选择性高、步骤经济、反应体系干净的制备1,1,2-三芳基乙烷化合物的方法。本发明方案是:将苄基吡啶醚化合物、金属铬盐、芳基格氏试剂加入醚类溶剂中反应,反应完全后经分离得到1,1,2-三芳基乙烷化合物。

[0004] 本发明合成1,1,2-三芳基乙烷化合物的反应通式:



式中,R¹代表氢、烷基、烷氧基、苯基、苯氧基、硅基、胺基、苯乙烯基,环氧基、咪喃

基、噻吩基、氟、氯等任意一种或两种,或者R¹代表取代苯基,其取代基包括烷基、萘基、烷氧基、硅氧基、三氟甲氧基、羟基、氟、氯等任意一种或两种;R²代表烷基、甲硫基、三氟甲氧基、苯基、硅基、胺基、环氧基、氟等任意一种。

[0005] 基于本发明所用催化剂包括二氯化铬、三氯化铬、乙酰丙酮铬或醋酸铬,优选为二氯化铬。

[0006] 基于本发明的催化剂的加入量为苄基吡啶醚化合物摩尔量的0.5~20%,优选为苄基吡啶醚化合物摩尔量的1%。

[0007] 基于本发明的芳基格氏试剂的加入量为苄基吡啶醚化合物摩尔量的1-4当量,优选为苄基吡啶醚化合物摩尔量的2~3当量。

[0008] 基于本发明所用醚类溶剂包括四氢呋喃、2-甲基四氢呋喃或乙醚,优选为四氢呋喃。

[0009] 基于本发明的反应温度为0~100℃,优选40℃。

[0010] 基于本发明的反应时间为3~24小时,优选12小时。

[0011] 本发明合成1,1,2-三芳基乙烷化合物的具体制备过程描述如下:

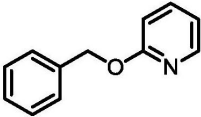
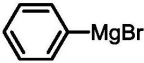
在反应管中加入苄基吡啶醚化合物与0.01倍摩尔量二氯化铬,在氮气保护下加入1毫升醚类溶剂,搅拌5分钟之后加入2-3倍摩尔量芳基格氏试剂。反应体系置于40℃条件下搅拌反应12小时。反应结束后,加入稀盐酸继续搅拌5分钟,随后用饱和碳酸氢钠水溶液中和至中性。反应液用乙酸乙酯萃取三次,合并有机相,有机相经无水硫酸钠干燥、抽滤和旋转蒸发除去溶剂得到粗产物,最后经硅胶柱层析得到相应的1,1,2-三芳基乙烷化合物。

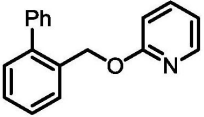
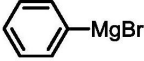
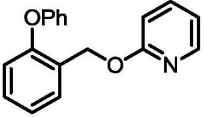
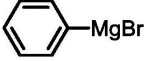
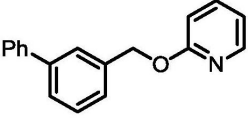
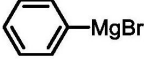
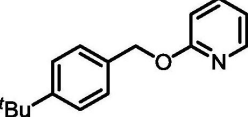
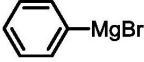
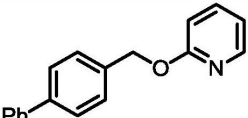
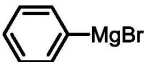
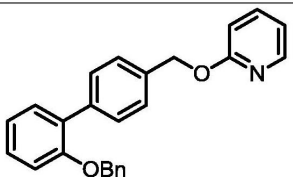
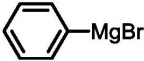
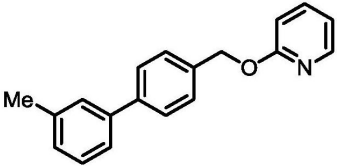
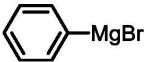
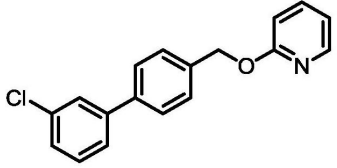
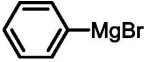
具体实施方式

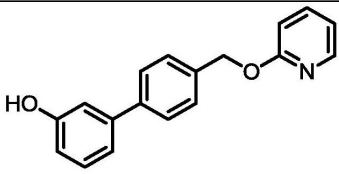
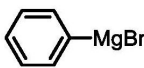
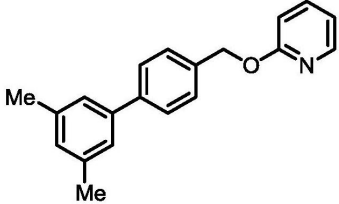
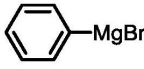
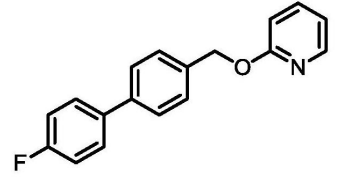
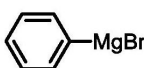
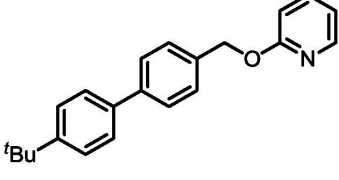
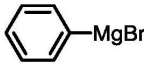
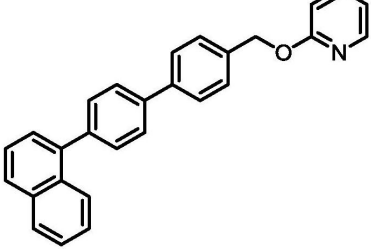
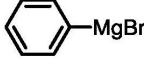
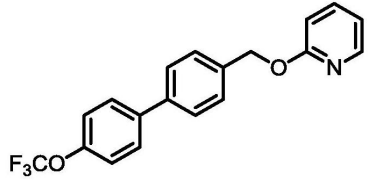
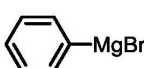
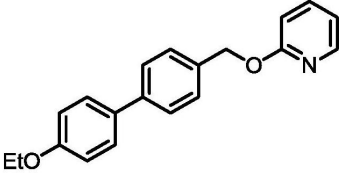
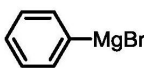
[0012] 以下的实施例,在于详细的说明本发明而非限制本发明。

[0013] 实施例(如表一所示)。

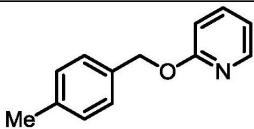
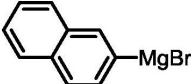
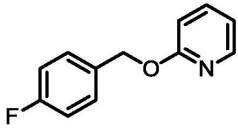
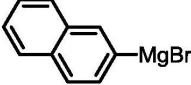
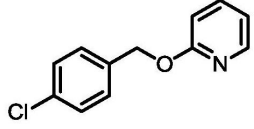
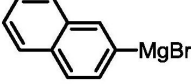
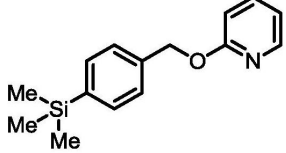
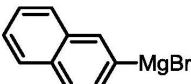
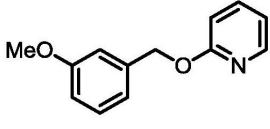
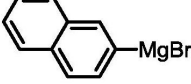
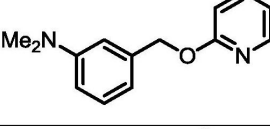
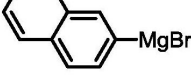
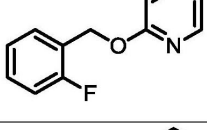
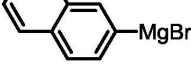
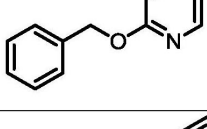
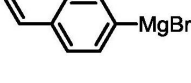
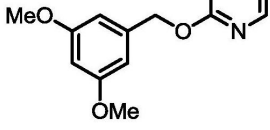
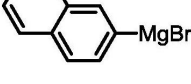
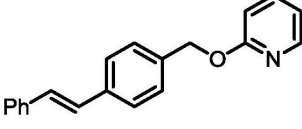
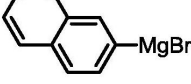
[0014] 表一

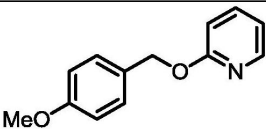
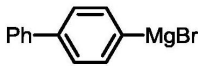
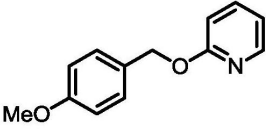
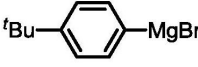
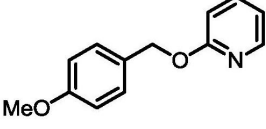
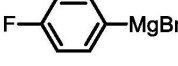
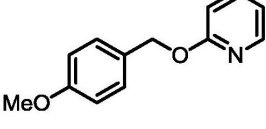
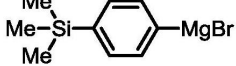
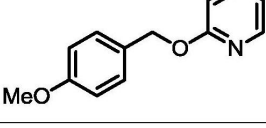
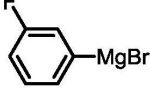
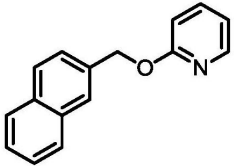
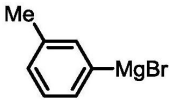
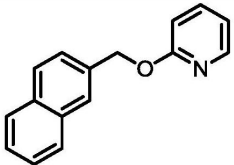

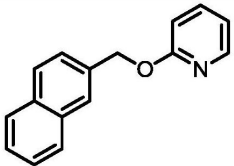

实施例	底物		条件	产量
1			二氯化铬(0.004 mmol), 2-苄氧基吡啶(0.4 mmol), 苯	81%

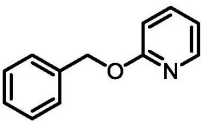
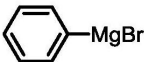
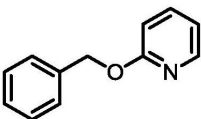
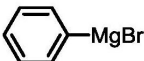
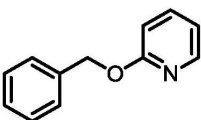
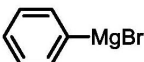
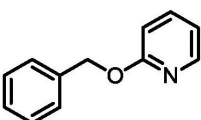
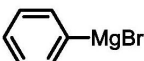
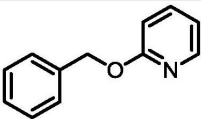
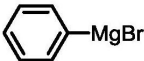
			基溴化镁 (0.8 mmol), 四氢呋喃 (1 mL), 40 °C, 12 h。	
2			参考实施例 1	83%
3			参考实施例 1	89%
4			参考实施例 1	94%
5			参考实施例 1	91%
6			参考实施例 1	82%
7			参考实施例 1	83%
8			参考实施例 1	90%
9			参考实施例 1	77%

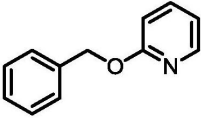
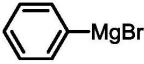
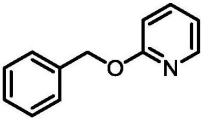
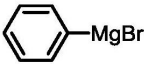
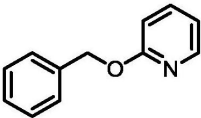
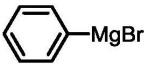
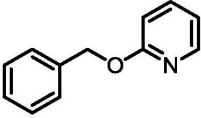
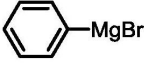
10			参考实施例 1	94%
11			参考实施例 1	93%
12			参考实施例 1	91%
13			参考实施例 1	92%
14			参考实施例 1	96%
15			参考实施例 1	95%
16			参考实施例 1	83%

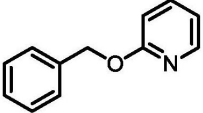
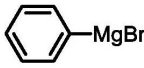
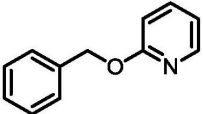
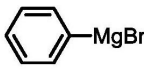
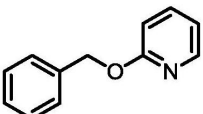
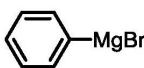
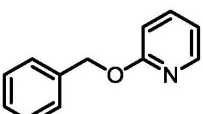
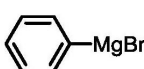
17			参考实施例 1	92%
18			参考实施例 1	96%
19			参考实施例 1	98%
20			参考实施例 1	82%
21			参考实施例 1	85%
22			参考实施例 1	92%
23			二氯化铬 (0.004 mmol), 2-(4-甲氧基)苯氧基吡啶(0.4 mmol), 2-萘基溴化镁(0.8 mmol), 四氢呋喃(1 mL), 40 °C, 12 h。	91%

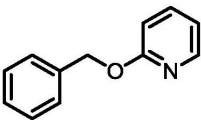
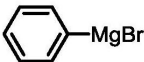
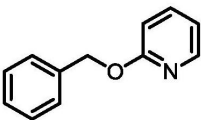
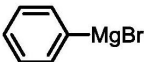
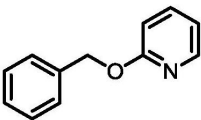
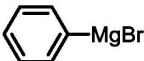
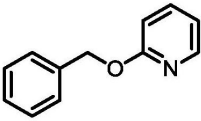
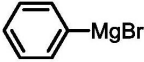
24			参考实施例 23	89%
25			参考实施例 23	94%
26			参考实施例 23	73%
27			参考实施例 23	89%
28			参考实施例 23	90%
29			参考实施例 23	57%
30			参考实施例 23	71%
31			参考实施例 23	89%
32			参考实施例 23	86%
33			参考实施例 23	80%

34			参考实施例 23	91%
35			参考实施例 23	86%
36			参考实施例 23	93%
37			参考实施例 23	62%
38			参考实施例 23	89%
39			二氯化铬 (0.004 mmol), 2-(2-萘)亚甲氧基吡啶 (0.4 mmol), (3-甲基)苯基溴化镁 (0.8 mmol), 四氢呋喃 (1 mL), 40 °C, 12 h。	64%
40			参考实施例 39	90%
41			参考实施例 39	81%

42			乙酰丙酮铬(0.004 mmol), 2-苄氧基吡啶(0.4 mmol), 苄基溴化镁(0.8 mmol), 四氢呋喃(1 mL), 40 °C, 12 h。	65%
43			三氯化铬(0.004 mmol), 2-苄氧基吡啶(0.4 mmol), 苄基溴化镁(0.8 mmol), 四氢呋喃(1 mL), 40 °C, 12 h。	78%
44			醋酸铬(0.04 mmol), 2-苄氧基吡啶(0.4 mmol), 苄基溴化镁(0.8 mmol), 四氢呋喃(1 mL), 40 °C, 12 h。	68%
45			二氯化铬(0.002 mmol), 2-苄氧基吡啶(0.4 mmol), 苄基溴化镁(0.8 mmol), 四氢呋喃(1 mL), 40 °C, 12 h。	27%
46			二氯化铬(0.003 mmol), 2-苄氧基	55%

			吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 四氢呋喃 (1 mL), 40 °C, 12 h。	
47			二氯化铬 (0.008 mmol), 2-苄氧基吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 四氢呋喃 (1 mL), 40 °C, 12 h。	82%
48			二氯化铬 (0.04 mmol), 2-苄氧基吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 四氢呋喃 (1 mL), 40 °C, 12 h。	83%
49			二氯化铬 (0.004 mmol), 2-苄氧基吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 四氢呋喃 (1 mL), 0 °C, 12 h。	35%
50			二氯化铬 (0.004 mmol), 2-苄氧基吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 四氢呋喃	74%

			(1 mL), 60 °C, 12 h。	
51			二氯化铬 (0.004 mmol), 2-苄氧基吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 四氢呋喃 (1 mL), 80 °C, 12 h。	64%
52			二氯化铬 (0.004 mmol), 2-苄氧基吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 四氢呋喃 (1 mL), 100 °C, 12 h。	49%
53			二氯化铬 (0.004 mmol), 2-苄氧基吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 2-甲基四氢呋喃(1 mL), 40 °C, 12 h。	76%
54			二氯化铬 (0.004 mmol), 2-苄氧基吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 乙醚 (1 mL), 40 °C, 12 h。	67%

55			二氯化铬 (0.004 mmol), 2-苄氧基吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 四氢呋喃 (1 mL), 40 °C, 10 h。	76%
56			二氯化铬 (0.004 mmol), 2-苄氧基吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 四氢呋喃 (1 mL), 40 °C, 6 h。	61%
57			二氯化铬 (0.004 mmol), 2-苄氧基吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 四氢呋喃 (1 mL), 40 °C, 3 h。	23%
对比例			2-苄氧基吡啶(0.4 mmol), 苯基溴化镁 (0.8 mmol), 四氢呋喃(1 mL), 40 °C, 12 h。	0