

水相中微波辐射下芳基硫醚衍生物的铜催化合成

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摘要 开展了水相中硫脲与碘代芳烃反应生成芳基硫醚衍生物的微波辅助合成研究。高效地合成了一系列的芳基硫醚衍生物,最高收率达到90%。

关键词 微波辅助合成,硫脲,碘代芳烃,水相

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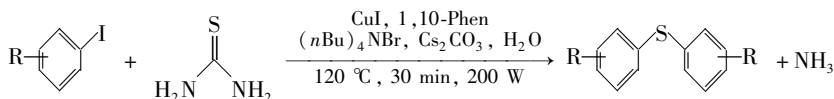
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过渡金属催化生成C—S键的偶联反应在有机合成研究中占据主要地位。经该偶联反应可形成系列芳基硫醚化合物,在染料、医药、农药以及聚合物的制备中均有广泛的应用。因糖尿病、炎症免疫、阿尔茨海默病及帕金森病等治疗药物中多为含有C—S键的芳基硫醚衍生物,因此构建C—S键在有机合成中有重要应用^[1-3]。近20年来许多过渡金属化合物催化剂已被广泛用于催化合成芳基硫醚衍生物。目前,已有钯、镍、钴、钛、铁、锆和钨等金属的化合物被用于催化偶联形成C—S键芳基硫醚衍生物。使用绿色低毒、可循环的催化剂来制备芳基硫醚衍生物已成为重要热点之一。虽然铜催化剂在化学反应中的应用可实现低成本和高适用性^[4-9],但催化反应一般都是在有机溶液中进行的,因而仍存在有机溶剂污染的弊端,为此,已开发了在水中的催化反应^[10]。微波辅助有机合成反应是近10年兴起的一项新技术^[11-12]。因此,在微波作用下开发高效铜催化体系在水相中芳基硫醚衍生物的合成有实际意义^[13-14]。

本文在前期研究基础上^[15],用碘代芳烃和硫脲为原料,在微波作用下合成了系列芳基硫醚衍生物。目标化合物的合成反应如Scheme 1所示。



Scheme 1 Synthesis of aryl halides

1 实验部分

1.1 仪器和试剂

DISCOVER-S型微电脑微波反应器(美国CEM公司);ZF-I型三用紫外线分析仪(上海顾村电光仪器厂);AVANCE III-400MHz型核磁共振仪(德国Bruker Biospin公司),CDCl₃为溶剂,TMS为内标;Agilent 6890N-Agilent 5973型气-质联用谱仪(美国Agilent公司)。

硫脲、碘代芳烃(分析纯,上海晶纯试剂有限公司),其余试剂均为国产分析纯。硅胶H和G为青岛海洋化工厂产品,未再活化。

1.2 合成反应操作

在10 mL干燥的长颈烧瓶内加入碘代芳烃、硫脲、铜盐、1,10-邻菲啰啉(1,10-phen)、碱和相转移催化剂((nBu)₄NBr),混合均匀再加入3 mL水作为溶剂。置微波反应器中在200 W功率下加热一定时间后,冷却至室温。经10 mL×3乙酸乙酯萃取,萃取物减压浓缩,上硅胶柱层析,用乙酸乙酯-石油醚(体积比1:10)洗脱得到目标产物。

1.3 合成硫醚化合物的 NMR 和 MS 表征

各化合物的¹H NMR(CDCl₃)、¹³C NMR(CDCl₃)谱和质谱数据基本与文献^[15]一致。

苯硫醚:¹H NMR(CDCl₃, 400 MHz), δ: 7.43 ~ 7.28 (m, 10H); ¹³C NMR(CDCl₃, 100 MHz), δ: 136.1, 131.4, 129.5, 127.5; MS(EI, *m/z*): 186[*M*⁺]。

对甲基苯硫醚:¹H NMR(CDCl₃, 400 MHz), δ: 7.28 (d, *J* = 8 Hz, 4H), 7.15 (d, *J* = 8 Hz, 4H), 2.37 (s, 6H); ¹³C NMR(CDCl₃, 100 MHz), δ: 136.9, 132.7, 131.1, 129.9, 21.1; MS(EI, *m/z*): 214[*M*⁺]。

邻甲基苯硫醚:¹H NMR(CDCl₃, 400 MHz), δ: 7.29 ~ 7.15 (m, 4H), 7.14 ~ 7.08 (m, 4H), 2.41 (s, 6H); ¹³C NMR(CDCl₃, 100 MHz), δ: 138.9, 134.4, 131.4, 130.5, 127.2, 126.7, 20.5; MS(EI, *m/z*): 214[*M*⁺]。

对硝基苯硫醚:¹H NMR(CDCl₃, 400 MHz), δ: 7.23 (d, *J* = 8.4 Hz, 4H), 7.52 (d, *J* = 8.4 Hz, 4H); ¹³C NMR(CDCl₃, 100 MHz), δ: 147.3, 142.8, 131.1, 124.6; MS(EI, *m/z*): 276[*M*⁺]。

邻硝基苯硫醚:¹H NMR(CDCl₃, 400 MHz), δ: 8.1 (d, *J* = 8.0 Hz, 2H), 7.59 ~ 7.48 (m, 4H), 7.31 (d, *J* = 8.0 Hz, 2H); ¹³C NMR(CDCl₃, 100 MHz), δ: 149.5, 133.8, 133.6, 131.6, 128.6, 125.5; MS(EI, *m/z*): 276[*M*⁺]。

对氯苯硫醚:¹H NMR(CDCl₃, 400 MHz), δ: 7.32 (d, *J* = 8.8 Hz, 4H), 7.28 (d, *J* = 8.8 Hz, 4H); ¹³C NMR(CDCl₃, 100 MHz), δ: 134.0, 133.6, 132.7, 129.5; MS(EI, *m/z*): 255[*M*⁺]。

对溴苯硫醚:¹H NMR(CDCl₃, 400 MHz), δ: 7.46 (d, *J* = 8.4 Hz, 4H), 7.24 (d, *J* = 8.4 Hz, 4H); ¹³C NMR(CDCl₃, 100 MHz), δ: 134.5, 132.8, 132.4, 121.1; MS(EI, *m/z*): 344[*M*⁺]。

对乙酰基苯硫醚:¹H NMR(CDCl₃, 400 MHz), δ: 7.92 (dd, *J* = 1.6, 6.8 Hz, 4H), 7.45 (dd, *J* = 1.6, 6.8 Hz, 4H), 2.62 (s, 6H); ¹³C NMR(CDCl₃, 100 MHz), δ: 197.3, 141.0, 135.9, 130.8, 129.2, 26.6; MS(EI, *m/z*): 270[*M*⁺]。

对甲氧基苯硫醚:¹H NMR(CDCl₃, 400 MHz), δ: 7.31 (d, *J* = 7.2 Hz, 4H), 6.87 (d, *J* = 7.2 Hz, 4H), 3.82 (s, 6H); ¹³C NMR(CDCl₃, 100 MHz), δ: 159.3, 132.8, 127.8, 114.9, 55.4; MS(EI, *m/z*): 246[*M*⁺]。

间甲氧基苯硫醚:¹H NMR(CDCl₃, 400 MHz), δ: 7.25 (t, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.93 (s, 2H), 6.80 ~ 6.83 (m, 2H), 3.79 (s, 6H); ¹³C NMR(CDCl₃, 100 MHz), δ: 160.2, 136.8, 130.0, 123.4, 116.3, 113.0, 55.3; MS(EI, *m/z*): 246[*M*⁺]。

间吡啶硫醚:¹H NMR(CDCl₃, 400 MHz), δ: 8.56 (s, 2H), 8.48 ~ 8.46 (m, 2H), 7.62 ~ 7.59 (m, 2H), 7.23 ~ 7.20 (m, 2H); ¹³C NMR(CDCl₃, 100 MHz), δ: 151.7, 148.6, 138.8, 131.8, 124.2; MS(EI, *m/z*): 188[*M*⁺]。

2 结果与讨论

2.1 反应条件的选择

首先以硫脲与碘苯的偶联硫醚化反应为模型,考察了铜盐对反应收率的影响,结果列于表1。从表1可以看出,在其它条件相同的情况下,5种铜源中,CuI的催化效果最好,而CuSO₄·5H₂O、Cu(OAc)₂·H₂O、CuCl₂·2H₂O和CuO的效果均不理想。其次又考察了碱对反应的影响,从表1数据可见,用Cs₂CO₃的收率高达87%,而其它无机碱与Cs₂CO₃相比均不太理想。因此,对其它条件的考察均以CuI为催化剂,Cs₂CO₃在碱条件下进行。温度和微波辐射时间对反应收率的影响,表明温度对该反应起重要作用,高温更有利于反应;120℃下反应30min收率最高。据此,确定适宜反应条件为:卤代芳烃(2.0 mmol),硫脲(1.2 mmol),CuI(0.1 mmol),1,10-phen(0.1 mmol),Cs₂CO₃(1.0 mmol),四丁基溴化铵(0.1 mmol),水3 mL,200 W微波辐射下120℃反应30min。

2.2 与其它碘代芳烃的反应

在上述选定条件下,考察了不同碘代芳烃与硫脲的偶联反应,结果列于表2。从表2可以看出,上述催化体系对于各种碘代芳烃与硫脲的偶联反应均具有较高的催化活性,大部分底物均能以相对较高的

表 1 铜催化下碘苯与硫脲适宜反应条件的优化^a

Table 1 Optimization of the copper-catalyzed coupling reaction between iodobenzene and thiourea^a


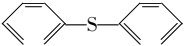
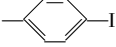
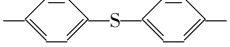

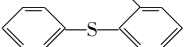
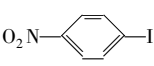
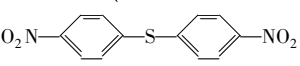

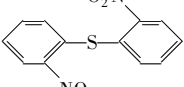
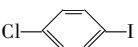
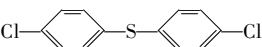
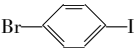
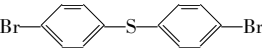
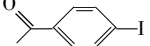
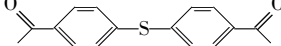
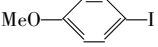
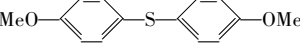

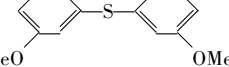

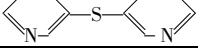
Entry	[Cu] source	Base	Time/min	Temperature/℃	Yield/% ^b
1	Cu(OAc) ₂ · H ₂ O	NaOH	30	110	39
2	CuSO ₄ · 5H ₂ O	NaOH	30	110	42
3	CuCl ₂ · 2H ₂ O	NaOH	30	110	70
4	CuI	NaOH	30	110	80
5	CuO	NaOH	30	110	17
6	CuI	Cs ₂ CO ₃	30	110	87
7	CuI	Na ₂ CO ₃	30	110	26
8	CuI	KOH	30	110	58
9	CuI	K ₂ CO ₃	30	110	63
10	CuI	Cs ₂ CO ₃	30	100	78
11	CuI	Cs ₂ CO ₃	30	120	85
12	CuI	Cs ₂ CO ₃	20	110	67
13	CuI	Cs ₂ CO ₃	40	110	84

a. Reaction conditions: iodobenzene(2.0 mmol), thiourea(1.2 mmol), Cu source(0.1 mmol), 1,10-phen(0.1 mmol), base(1.0 mmol), (*n*Bu)₄NBr(0.1 mmol), water(3 mL), 200 W; *b.* determined by GC using 1,4-dichrobenzene as internal standard.

收率生成相应的硫醚目标产物,表 2 数据还显示,带吸电子基团取代基芳烃的硫醚偶联反应比供电子的芳烃效果好,对位是硝基的碘苯收率高达 90%,除对甲基碘苯外有强供电子基的甲氧基碘苯的反应收率则仅为 73%。催化体系对同时有 Cl、Br 取代基的碘代芳烃的硫代反应表现出很好的选择性,反应几乎是专一性的发生在碘取代位。该体系对惰性杂环卤代芳烃的硫代反应也具有较好的催化活性。其它取代基位置对促进偶联活性顺序为对位取代基 > 邻位取代基 > 间位取代基。

表 2 铜-1,10-邻菲罗啉催化的碘代芳烃与硫脲反应^a

Table 2 Copper/1,10-phen coupling reactions between different aryl iodide and thiourea^a

Entry	Aryl halides	Products	Yield/% ^b
1			87
2			80
3			76
4			90
5			82
6			80
7			75
8			88
9			73
10			67
11			68

a. Reaction conditions: aryl halides(2.0 mmol), thiourea(1.2 mmol), CuI(0.1 mmol), 1,10-phen(0.1 mmol), Cs₂ CO₃(1.0 mmol), (*n*Bu)₄NBr(0.1 mmol), water(3 mL), 200 W, 110 ℃, 30 min; *b.* isolated yield.

3 结 论

在微波辐射下,以环境友好的 CuI 为催化剂,在水相中,相转移剂存在下,由碘代芳烃和硫脲的偶联反应合成了系列芳基硫醚衍生物。避免了使用有毒且易于造成环境污染的有机溶剂,微波辐射下可快速偶联生成相应的硫醚化物,该催化体系不同取代基碘代芳烃与硫脲的偶联反应有很好的适应性,收率普遍达到约 90%,合成工艺具有普适性。

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Microwave-assisted Copper-catalyzed Synthesis of Aryl Sulfides Derivatives in Water

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Abstract In aqueous solution, the synthesis of aryl sulfides derivatives from the reaction between thiourea and aryl iodides using copper as catalyst under microwave irradiation was investigated. A variety of aryl sulfides can be synthesized with yields up to 90%.

Keywords microwave irradiation synthesis, thiourea, aryl halides, aqueous solution