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CuCl/I₂ 催化末端烯烃与磺酰氯反应合成 烯基砜类化合物研究

曾祥华^{1,2}, 苗成霞¹, 王寿峰¹, 夏春谷¹, 孙 伟¹

(1. 中国科学院兰州化学物理研究所 羰基合成与选择氧化国家重点实验室, 甘肃兰州 730000;

2. 中国科学院大学, 北京 10039)

摘要: 研究了用 CuCl/I₂ 催化一系列末端烯烃和磺酰氯反应合成烯基砜类化合物, 反应体系中添加催化剂量的分子碘, 可以大幅度提高该反应的产率, 最高可获得 97% 的产率. 同时, 考察了各种铜盐的催化活性以及反应介质对反应的影响.

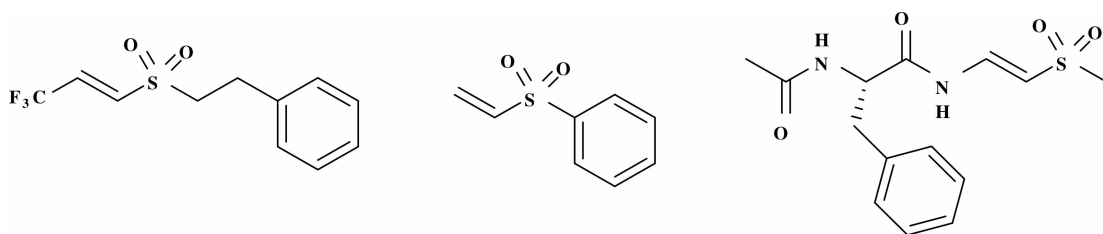
关键词: 苯乙烯; 氯化亚铜; 磺酰氯; 碘

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烯基砜类化合物是一种具有潜在生物活性的重要有机中间体, 在医药^[1-2] 和有机合成^[3-5] 领域得到广泛的关注. 烯基砜类化合物是许多药物分子中的重要结构单元, 例如: 半胱氨酸蛋白酶^[6] 和 VCAM-I^[7] 表达抑制剂 (图 1). 在有机合成方法中, 烯基砜基团是 Michael 加成反应的受体, 也可以作为 D-A 反应的重要原料^[8]. 同时, 烯基砜类化合物经 cine-取代反应, 可合成众多烯烃衍生物^[9]. 至今, 合成烯基砜类化合物的方法可以分为 3 种: (1) 烯烃与磺酰氯加成-消去法; (2) 烯化反应 ((Wittig 反应、Horner-Emmons-Wadsworth 反应和 Peterson 反应)^[9-12]; (3) 钯、铜盐催化砜盐和溴乙烯基、三氟甲磺酸乙烯基、硼酸二烯基或者烯烃偶联^[13-16]. 1964 年, Asscher 等人报道了氯化铜和氯

化亚铁催化苯乙烯或者脂肪烯烃与对甲苯磺酰氯或甲磺酰氯的加成反应, 并探讨了反应机理^[17]. 1971 年, Amiel 等人报道了氯化铜和氯化亚铜催化苯乙炔与苯磺酰氯的加成反应^[18]. Goralski 报道了一例氯化铜催化苯乙烯与噻吩磺酰氯生成反式的烯基砜类化合物^[19]. Kamigata 等人报道了钌催化苯乙烯与各种苯磺酰氯生成反式的烯基砜类化合物, 并研究了反应机理^[20]. 我们研究了催化剂量的碘对 CuCl 促进的末端烯烃与对甲苯磺酰氯或甲磺酰氯在无机碱的存在下一步合成烯基砜类化合物的影响, 在优化的条件下, 研究了一系列末端烯烃与对甲基苯磺酰氯、甲磺酰氯的反应, 以高达 97% 的产率获得相应的烯基砜类化合物.



图示 1 酶抑制剂中含有乙烯砜结构单元的化合物

Scheme 1 Examples of enzyme inhibitors containing vinyl sulfone

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作者简介: 曾祥华 (1983-), 男, 博士生.

* 通讯联系人, E-mail: wsun@licp.cas.cn.

1 实验部分

1.1 仪器和试剂

气相色谱-质谱联用仪: Agilent 公司 7890A/5975C, 核磁共振仪: Bruker Avance III TM-400MHz, 熔点测定仪: 北京泰克仪器有限公司, 所用试剂均从 Alfa Aesar 或国内试剂公司购买后直接使用。

1.2 氯化亚铜催化合成苯乙烯磺的反应

在 25 mL 的密封反应管中, 加入烯烃 (0.2 mmol), 对甲苯磺酰氯或甲磺酰氯 (0.2 mmol), 氯化亚铜 (0.002 mmol), 碘 (0.01 mmol), 碳酸钾 (0.3 mmol), 乙腈 (1.0 mL), 然后在 105 °C 或 115 °C 反应 12 h. 反应结束后冷却至室温, 减压抽干溶剂, 然后用石油醚/乙酸乙酯 (V : V = 3 : 1) 为洗脱剂柱分离得到目标产物。

1.3 产物的数据表征

(*E*)-1-methyl-4-(styrylsulfonyl) benzene (**2a**)^[21]: Yellow solid, (50.1 mg, 97%); mp: 117 ~ 118 °C (lit. mp: 118-15119 °C).

(*E*)-1-methyl-4-(4-methylstyrylsulfonyl) benzene (**2b**)^[21]: Yellow solid, (49.6 mg, 91%); mp: 154 ~ 156 °C (lit. mp: 152 ~ 154 °C).

(*E*)-1-methyl-3-(2-tosylvinyl) benzene (**2c**)^[22]: Yellow solid, (49.0 mg, 90%); mp: 80 ~ 82 °C (lit. mp: 82 ~ 83 °C).

(*E*)-1-methoxy-4-(2-tosylvinyl) benzene (**2d**)^[21]: Yellow solid, (50.2 mg, 87%); mp: 99 ~ 101 °C (lit. mp: 98 ~ 100 °C).

(*E*)-1-chloro-4-(2-tosylvinyl) benzene (**2e**)^[20]: Yellow solid, (42.6 mg, 73%); mp: 125 ~ 127 °C (lit. mp: 126 ~ 127 °C).

(*E*)-1-methyl-4-(4-(trifluoromethyl) styrylsulfonyl) benzene (**2f**): Yellow solid, (52.9 mg, 81%); mp: 147 ~ 149 °C. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) = 7.83 (d, *J* = 8.0 Hz, 2H), 7.60-7.65 (m, 5H), 7.35-7.37 (m, 2H), 6.94 (d, *J* = 15.2 Hz, 1H), 2.44 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) = 144.9, 139.9, 136.1 (d, *J* = 126 Hz), 130.4, 130.1, 129.8, 129.3, 128.7, 128.6, 126.0 (d, *J* = 3 Hz), 21.7. GC/MS *m/z*: 326.0.

(*E*)-2-(2-tosylvinyl) naphthalene (**2g**)^[23]: Yellow solid, (43.2 mg, 70%); mp: 158 ~ 160 °C

(lit. mp: 160 ~ 161 °C).

2-tosylethene-1, 1-diyl) dibenzene (**2h**)^[20]: Yellow solid, (46.8 mg, 70%); mp: 106 ~ 108 °C (lit. mp: 106 ~ 107 °C).

(*E*)-1-methyl-4-(2-phenylprop-1-enylsulfonyl) benzene (**2i**)^[20]: Yellow solid, (27.8 mg, 51%); mp: 99 ~ 101 °C (lit. mp: 102 ~ 103 °C).

(*E*)-(2-(methylsulfonyl) vinyl) benzene (**2j**)^[21]: Yellow oil, (34.6 mg, 95%). (*E*)-1-methyl-4-(2-(methylsulfonyl) vinyl) benzene (**2k**)^[21]: Yellow oil, (35.3 mg, 90%).

(*E*)-1-methyl-3-(2-(methylsulfonyl) vinyl) benzene (**2l**): Yellow oil, (34.2 mg, 87%). ¹H NMR (CDCl₃, 400 MHz) δ (ppm) = 7.59 (d, *J* = 15.2 Hz, 1H), 7.26-7.32 (m, 4H), 6.90 (d, *J* = 15.6 Hz, 1H), 3.03 (s, 3H), 2.38 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) = 144.2, 139.0, 132.3, 132.0, 129.2, 129.1, 125.9, 125.8, 43.3, 21.3. GC/MS *m/z*: 196.0.

(*E*)-1-chloro-4-(2-(methylsulfonyl) vinyl) benzene (**2m**)^[24]: Yellow oil, (30.3 mg, 70%).

(*E*)-1-(2-(methylsulfonyl) vinyl)-4-(trifluoromethyl) benzene (**2n**)^[25]: Yellow oil, (39.0 mg, 78%).

(*E*)-(2-(methylsulfonyl) ethene-1, 1-diyl) dibenzene (**2o**)^[26]: Yellow oil, (44.9 mg, 87%).

2 结果与讨论

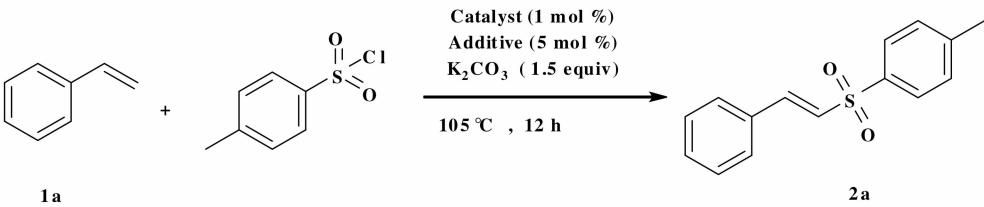
2.1 反应条件的优化

首先, 选取苯乙烯为底物, 在无催化剂的条件下, 添加碳酸钾作为碱, 105 °C 反应 12 h, 用 GC-MS 只检测到少量的 **2a** 产物 (表 1 中 Entry 1). 接下来, 我们考察了各种金属盐的催化活性, 如 CuI、CuBr 和 CuCl (Entries 2-4). 发现用 1% 一价铜盐作为催化剂时均可获得 80% 以上收率. 对比一价铜盐催化剂的反应结果, CuI 是最佳催化剂, 碘在反应中可能起到重要作用. 为了进一步提高反应产率, 我们研究了催化剂量的碘对反应的影响; 发现, 添加 5% 的碘, 以 CuCl 作为催化剂, 反应收率可提高至 97% (Entry 5); 而添加四乙基碘化铵时, 产率为 89% (Entry 6). 当用 CuCl₂ · 2H₂O 作为催化剂时 (Entry 7), 产率为 75%. 然后, 考察了溶剂对反应的影响 (Entries 8-11), 如二氯甲烷、四氢呋喃、1,

2-二氯乙烷和 *N,N*-二甲基甲酰胺. 结果表明, 乙腈是最佳溶剂. 筛选的最佳反应条件是 1% 氯化亚铜为催化剂, 5% 碘为添加剂, 1.5 当量 K₂CO₃ 为碱,

乙腈为反应介质, 回流反应 12 h. 此外, 该体系可适用于克级规模的反应, 在相同反应条件下仍可获得 90% 的产率(Entry 12).

表 1 合成烯基磺类化合物的反应条件筛选^a
Table 1 Optimization of reaction conditions for synthesis of vinyl sulfones^a



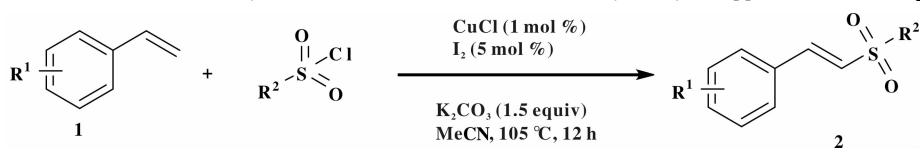
Entry	Catalyst	Additive	Solvent	Yield/% ^b
1	—	—	MeCN	trace
2	CuI	—	MeCN	85
3	CuBr	—	MeCN	82
4	CuCl	—	MeCN	80
5	CuCl	I ₂	MeCN	97
6	CuCl	Et ₄ NI	MeCN	89
7	CuCl ₂ · 2H ₂ O	I ₂	MeCN	75
8	CuCl	I ₂	CH ₂ Cl ₂	91
9	CuCl	I ₂	THF	85
10	CuCl	I ₂	ClCH ₂ CH ₂ Cl	87
11	CuCl	I ₂	DMF	78
12 ^c	CuCl	I ₂	MeCN	90

a. Reaction conditions: **1a** (0.2 mmol), catalyst (0.002 mmol), additive (0.01 mmol), TsCl (0.2 mmol), K₂CO₃ (0.3 mmol) and solvent (1.0 mL) at 105 °C for 12 h;
b. Isolated yield;
c. The reaction was carried out in 20 mmol scale.

2.2 反应底物的拓展

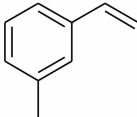
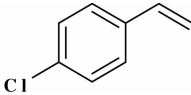
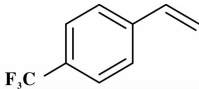
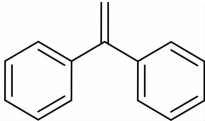
在优化的反应条件下, 我们考察了一系列端基烯烃与对甲基苯磺酰氯或甲基磺酰氯的反应(表 2). 研究发现, 当选取对甲苯磺酰氯为底物时, 烯烃苯环上的电子效应和烯烃双键的空间位阻均对反应活性有一定影响. 当苯环上取代基为供电子基团时, 如甲基和甲氧基等, 可获得 87% ~ 91% 的产率(Entries 2-4); 而当苯环上取代基为吸电子基团或烯烃双键为

多取代时, 产率仅为 51% ~ 81% (Entries 5-9). 此外, 我们又考察了甲磺酰氯为底物时, 与不同末端烯烃的反应活性, 该反应需要升高温度至 115 °C. 发现电子效应的影响与前类似, 当为供电子取代的苯环时, 可以得到 87% ~ 95% 的产率(Entries 10-12); 而为吸电子取代基时, 产率大约仅为 70% (Entries 13-14). 不同的是, 选取多取代的末端烯烃为底物时, 仍可获得 87% 的产率(Entry 15).

表 2 CuCl/I₂ 催化末端烯烃与磺酰氯的反应^aTable 2 Reactions of sulfonyl chlorides with terminal olefins catalyzed by a copper(I) chloride/I₂^a

Entry	Substrate	Sulfonyl Chloride	Product	Yield/% ^b
1		R ² = <i>p</i> -CH ₃ -C ₆ H ₄	2a	97
2		R ² = <i>p</i> -CH ₃ -C ₆ H ₄	2b	91
3		R ² = <i>p</i> -CH ₃ -C ₆ H ₄	2c	90
4		R ² = <i>p</i> -CH ₃ -C ₆ H ₄	2d	87
5		R ² = <i>p</i> -CH ₃ -C ₆ H ₄	2e	73
6		R ² = <i>p</i> -CH ₃ -C ₆ H ₄	2f	81
7		R ² = <i>p</i> -CH ₃ -C ₆ H ₄	2g	70
8		R ² = <i>p</i> -CH ₃ -C ₆ H ₄	2h	70
9		R ² = <i>p</i> -CH ₃ -C ₆ H ₄	2i	51
10 ^c		R ² = CH ₃	2j	95
11 ^c		R ² = CH ₃	2k	90

续表

Entry	Substrate	Sulfonyl Chloride	Product	Yield/% ^b
12 ^c		R ² = CH ₃	2l	87
13 ^c		R ² = CH ₃	2m	70
14 ^c		R ² = CH ₃	2n	78
15 ^c		R ² = CH ₃	2o	87

a. Unless otherwise noted, all reactions were carried out with **1** (0.2 mmol), sulfonyl chloride (0.2 mmol), CuCl (0.002 mmol), I₂ (0.01 mmol), K₂CO₃ (0.3 mmol) and MeCN (1.0 mL) at 105 °C for 12 h;
b. Isolated yield; c. The mixture was performed at 115 °C.

3 结 论

我们以氯化亚铜为催化剂，催化剂量的分子碘为添加剂，在 1.5 当量的 K₂CO₃ 存在下催化末端烯烃与磺酰氯生成一系列烯基砜类化合物，产率高达 97%。考察了末端烯烃苯环上取代基的电子效应以及双键的空间位阻等对反应活性的影响，结果表明苯环上供电子基团更有利于反应的进行。目前，我们课题组仍在继续开发新的、更绿色环保的催化体系实现更多烯基砜类化合物的催化合成。

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Synthesis of Vinyl Sulfones from Terminal Olefins and Sulfonyl Chloride Derivatives Catalyzed by Copper(I) Chloride/I₂

ZENG Xiang-hua^{1,2}, MIAO Cheng-xia¹, WANG Shou-feng¹, XIA Chun-gu¹, SUN Wei^{1,*}

(1 State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Lanzhou 730000, China;

2 The University of Chinese Academy of Sciences, Beijing 100039, China)

Abstract: A series of vinyl sulfones were synthesized from terminal olefins and sulfonyl chloride derivatives catalyzed by CuCl/I₂. Interestingly, addition of catalytic amount of I₂ was benefit for improving the yield greatly and the yield of vinyl sulfone was up to 97%. Besides, the activities of several kinds of copper salts and the effect of solvents were investigated.

Key words: styrene; copper(I) chloride; sulfonyl chloride; iodine