有机化学 DOI: 10.6023/cjoc202108015 研究论文
Chinese Journal of Organic Chemistry ARTICLE

布朗斯特酸催化合成亚砜亚胺基二氢吡喃酮类衍生物

孙鑫浩 段学伦 宋汪泽* 姜文凤*
(大连理工大学化工学院 辽宁大连 116024)

摘要 亚砜亚胺基团和二氢吡喃酮结构均具有潜在的生物活性, 但目前尚无制备亚砜亚胺基取代的二氢吡喃酮类衍生物的方法. 开发了一种使用磷酸二苯酯作为布朗斯特酸催化剂, 通过亚砜亚胺和二氢吡喃酮的亲核取代反应, 合成亚砜亚胺基取代的二氢吡喃酮类衍生物的新方法, 收率为 44%～78%. 该方法条件温和、操作简单且官能团兼容性好, 无需传统方法中使用的贵金属催化剂, 为糖苷类化合物的合成提供了一种新颖高效的策略.
关键词 布朗斯特酸; 亚砜亚胺; 二氢吡喃酮; 糖苷类化合物

Brønsted Acid-Catalyzed the Synthesis of Sulfoximide Substituted Dihydropyranone Derivatives

Sun, Xinhao Duan, Xuelun Song, Wangze* Jiang, Wenfeng*
(*School of Chemical Engineering*, *Dalian University of Technology*, *Dalian*, *Liaoning 116024*)

Abstract Both sulfoximide and dihydropyranone derivatives have potential bioactivities. However, it is still undisclosed to prepare sulfoximide-substituted dihydropyranone derivatives. Herein, diphenyl phosphate, as Brønsted acid was used to catalyze the nucleophilic substitution reactions of sulfoximides and dihydropyranones to afford sulfoximide substituted dihydropyranone derivatives in 44%～78% yields. This method features mild conditions, simple operation and good functional group compatibility, which avoids using noble metals in traditional manners and provides a novel and effective strategy for the synthesis of glycosides.
Keywords Brønsted acid; sulfoximidie; dihydropyranone; glycoside

亚砜亚胺类化合物是砜基的一种含氮类似物, 由于其独特的结构与性质, 自从被发现以来一直备受关注, 并展示出广泛的生物活性[1]: PYK2 抑制剂**I**被用于治疗骨质疏松[2], 化合物**II**具有平喘作用[3], Pan-CDK 抑制剂**III**和 EphB4 抑制剂**IV**具有抗肿瘤活性[4-5], Fxa 抑制剂**V**可用于治疗血栓[6], 化合物氟啶虫胺腈(**VI**)是一种杀虫剂[7](图 1). 此外, 亚砜亚胺也被用作试剂[8]、手性助剂[9]、手性配体[10]或有机催化剂[11]等. 通过亚砜亚胺能够实现各种转化反应, 亚砜亚胺可以与芳基卤化物或芳基硼酸发生偶联反应实现芳基化[12], 亚砜亚胺可以与烷基溴化物和烯基溴化物发生取代反应实现烷基化[13]和乙烯基化[14], 亚砜亚胺可以与炔烃或炔丙酸等发生偶联反应实现炔基化[15], 此外亚砜亚胺还可发生酰化等其他类型的反应[16]. 但是, 目前还没有关于亚砜亚胺与二氢吡喃酮的反应被报道出来.

含有 *N*-糖苷键结构的氮苷糖具有广泛的药理作用, 是一些抗生素、抗肿瘤药物和抗病毒药物等的重要母环结构[17]. 使用 Achmatowicz 重排反应的产物二氢吡喃酮为糖基供体的“*de novo*”从头合成糖的策略, 已成为合成糖苷化合物的重要方法之一[18]. 2006 年, O'Doherty 等[19]以 6-氯嘌呤和 Boc 保护的二氢吡喃酮为原料, 通过形成 π-烯丙基钯中间体, 实现了氮苷糖类衍生物的高对映选择性及非对映选择性合成(Scheme 1, a). 2020 年, 我们课题组[20]以 Boc 保护的二氢吡喃酮为供体, 甲基香豆素为受体, 通过钯催化烯丙基-烯丙基偶联反应, 在温和条件下实现了碳苷糖类衍生物的高对映选择性及非对映选择性合成. 除了钯催化剂外, 铱也能够催化类似的反应. 2018 年, 我们课题组[21]在温和的条件下, 以

* Corresponding authors. E-mail: wzsong@dlut.edu.cn; jiangwf@dlut.edu.cn
Received August 12, 2021; revised October 8, 2021; published online October 28, 2021.
Project supported by the National Natural Science Foundation of China (Nos. 21571027, 21978039) and the Fundamental Research Funds for the Central Universities (No. DUT20YG120).
国家自然科学基金(Nos. 21571027, 21978039)和中央高校基本科研业务费(No. DUT20YG120)资助项目.

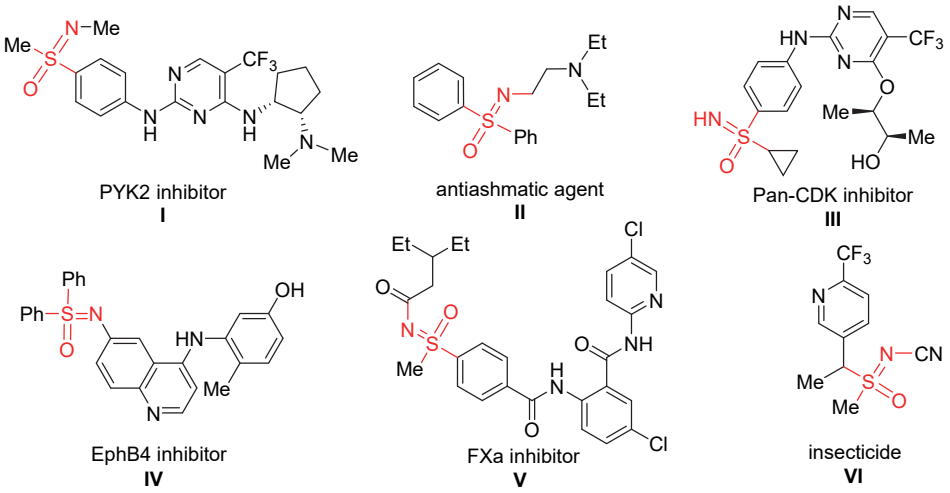
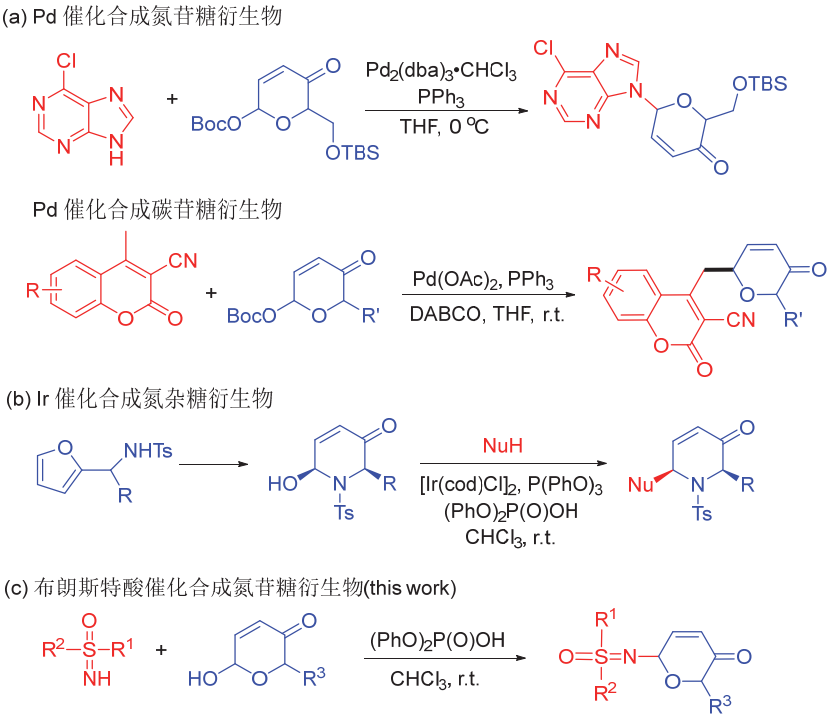


图 1 几种具有生物活性的亚砜亚胺类化合物

Figure 1 Selected examples of bioactive sulfoximines



图式 1 通过二氢吡喃酮合成糖苷类化合物

Scheme 1 Synthesis of glycosides using 2*H*-pyranone derivatives

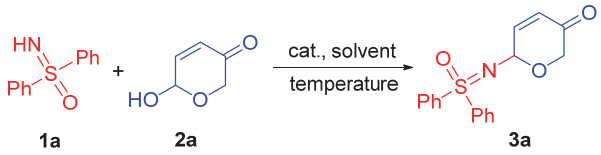
羟基无保护的二氢吡啶酮为供体，通过形成 π-烯丙基铱中间体实现了氮杂糖类衍生物的高区域选择性和非对映选择性合成(Scheme 1, b). 在上述研究工作的基础上，我们希望能够发展一种无金属催化的 *de novo* 合成糖苷类化合物的新方法，以避免使用贵金属催化剂(如钯、铱等)，以节约资源、降低成本，并解决产物中金属残留等问题. 本工作以亚砜亚胺类化合物和二氢吡喃酮为原料，在温和条件下使用布朗斯特酸(磷酸二苯酯)作为催化剂，通过亲核取代反应合成了亚砜亚胺基取代的二氢吡喃酮类衍生物(Scheme 1, c).

1 结果与讨论

首先，以二苯基亚砜亚胺(**1a**)为原料，使用 $Pd(OAc)_2$ 或 $[Ir(cod)Cl]_2$ 为催化剂，分别与 5,6-二氢-2*H*-吡喃-5-酮-2-碳酸叔丁酯(**2a'**)或 6-羟基-2*H*-吡喃-3-酮(**2a**)反应，并未取得良好的反应结果(表 1, Entries 1, 2). 当使用磷酸二苯酯作为催化剂时，**1a** 与 **2a** 发生反应，以中等产率得到亚砜亚胺基取代的二氢吡喃酮产物 **3a**(表 1, Entry 3). 随后对一系列布朗斯特酸如盐酸、对甲苯磺酸、三氟甲磺酸、三氟乙酸、樟脑磺酸和苯甲酸进行了筛选(表 1,

表 1 反应条件优化 [a]

Table 1 Optimization of reaction conditions



1a 2a 3a

Entry	Catalyst (mol%)	Temp./℃	Solvent	Yield[b]/%
1[c]	$[Ir(cod)Cl]_2$ (2.5)	r.t.	$CHCl_3$	0
2[d]	$Pd(OAc)_2$ (5)	r.t.	THF	33
3	$(PhO)_2P(O)OH$ (50)	r.t.	$CHCl_3$	43
4	HCl (50)	r.t.	$CHCl_3$	26
5	TsOH (50)	r.t.	$CHCl_3$	15
6	TfOH (50)	r.t.	$CHCl_3$	18
7	TFA (50)	r.t.	$CHCl_3$	25
8	CsA (50)	r.t.	$CHCl_3$	38
9	PhCOOH (50)	r.t.	$CHCl_3$	0
10	$(PhO)_2P(O)OH$ (50)	r.t.	DCM	41
11	$(PhO)_2P(O)OH$ (50)	r.t.	DCE	38
12	$(PhO)_2P(O)OH$ (50)	r.t.	Hexane	0
13	$(PhO)_2P(O)OH$ (50)	r.t.	Toluene	33
14	$(PhO)_2P(O)OH$ (50)	r.t.	THF	Trace
15	$(PhO)_2P(O)OH$ (50)	r.t.	Acetone	24
16	$(PhO)_2P(O)OH$ (50)	r.t.	MeCN	20
17	$(PhO)_2P(O)OH$ (50)	r.t.	DMF	0
18	$(PhO)_2P(O)OH$ (20)	r.t.	$CHCl_3$	43
19	$(PhO)_2P(O)OH$ (10)	r.t.	$CHCl_3$	38
20[e]	$(PhO)_2P(O)OH$ (20)	r.t.	$CHCl_3$	57
21[f]	$(PhO)_2P(O)OH$ (20)	r.t.	$CHCl_3$	58
22[f,g]	$(PhO)_2P(O)OH$ (20)	r.t.	$CHCl_3$	68
23[f,h]	$(PhO)_2P(O)OH$ (20)	r.t.	$CHCl_3$	64

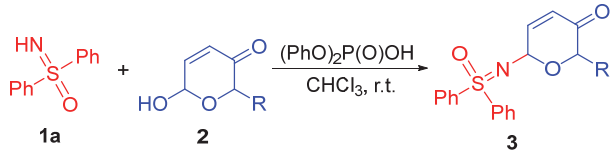
[a] Reaction condition: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst, solvent (0.2 mmol), room temperature for 12 h; [b] Isolated yield; [c] 10 mol% $P(OPh)_3$ was used as ligand. [d] *tert*-butyl(5-*oxo*-5,6-dihydro-2*H*-pyran-2-yl)carbonate (**2a'**) was used instead of **2a**, 7.5 mol% PPh_3 was used as ligand and 1.5 equiv. of DABCO was used as base. [e] **1a** (0.2 mmol), **2a** (0.4 mmol); [f] **1a** (0.4 mmol), **2a** (0.2 mmol); [g] Reaction time was 18 h; [h] Reaction time was 24 h.

Entries 4～9), 结果表明磷酸二苯酯是该反应的最佳催化剂. 然后对反应溶剂进行筛选(表 1, Entries 10～17). 当使用与氯仿相似的二氯甲烷和 1,2-二氯乙烷时, 反应也可以顺利进行(表 1, Entries 10, 11). 但使用正己烷、甲苯、四氢呋喃(THF)、丙酮、乙腈或 *N*,*N*-二甲基甲酰胺(DMF)为溶剂时, 反应的收率降低或者无法进行(表 1, Entries 12～17). 当催化剂磷酸二苯酯的用量降至 20 mol%, 催化效果并没有受到影响(表 1, Entry 18), 但当磷酸二苯酯的用量低于 20 mol%, 产率有所下降(表 1, Entry 19). 接着对反应底物的投料量进行考察(表 1, Entries 20～23). 提高反应物 **1a** 或 **2a** 任意一个的投料量都会提高产率, 最终我们选取 **1a** (0.4 mmol)和 **2a** (0.2 mmol)为最佳反应投料量(表 1, Entry 21). 随后将反应时间延长至 18 h, 以 68%的产率得到化合物 **3a**(表 1, Entry 22), 但进一步延长反应时间, 产率下降(表 1, Entry 23), 可能是因为亚砜亚胺取代的二氢吡喃酮产物不稳定, 在酸性条件下长时间搅拌发生了一定程度的分解.

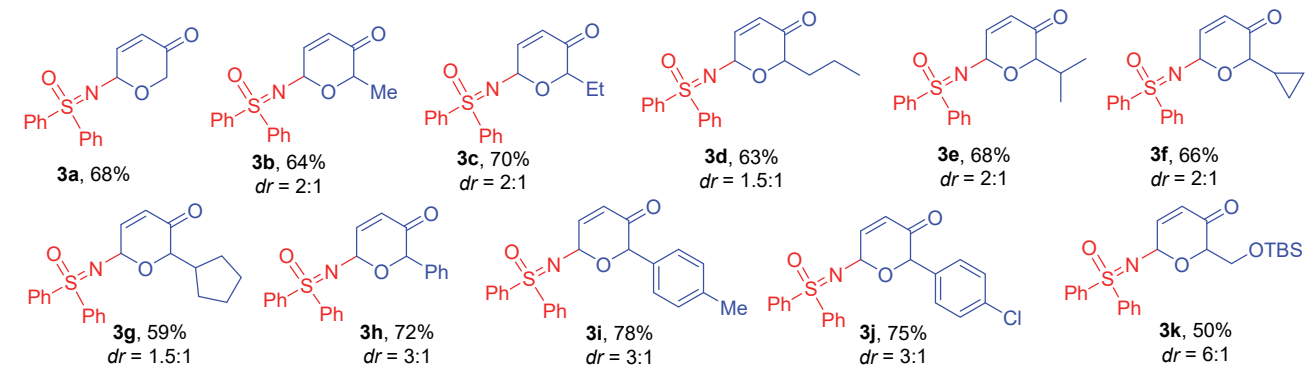
在确定了最佳的反应条件以后(表 1, Entry 22), 对二氢吡喃酮(**2**)的底物范围进行了研究. 如表 2 所示, 该方法适用于带有不同取代基的各类二氢吡喃酮类化合物, 以中等至良好的产率(50%～78%)生成结构多样的亚砜亚胺基取代的二氢吡喃酮类衍生物 **3** (*dr* 1.5∶1～6∶1). 随着二氢吡喃酮上取代基位阻的增加, 产率并不会明显下降(**3a**～**3g**), 因此该转化过程没有明显的位阻效应. 对于芳香基团(**3h**～**3j**)取代的二氢吡喃酮, 其产率优于脂肪基团取代的二氢吡喃酮(**3a**～**3g**, **3k**), 其中以对甲基苯基取代的二氢吡喃酮作为底物时的产率最高, 达到 78%(**3i**). 当使用位阻较大的底物时, 能够以中等的 *dr* 值(6∶1)得到相应的二氢吡喃酮类衍生物(**3k**).

表 2 二氢吡喃酮的底物范围 [a,b]

Table 2 Substrates scope of the 2*H*-pyranones



1a 2 3

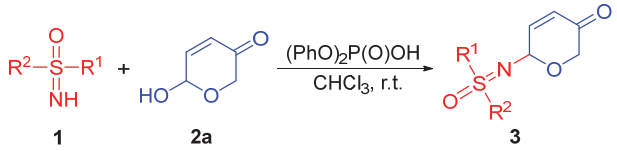


[a] Reaction condition: **1a** (0.4 mmol), **2** (0.2 mmol), $(PhO)_2P(O)OH$ (20 mol%), $CHCl_3$ (0.1 mol/L), room temperature for 18 h; [b] Isolated yield.

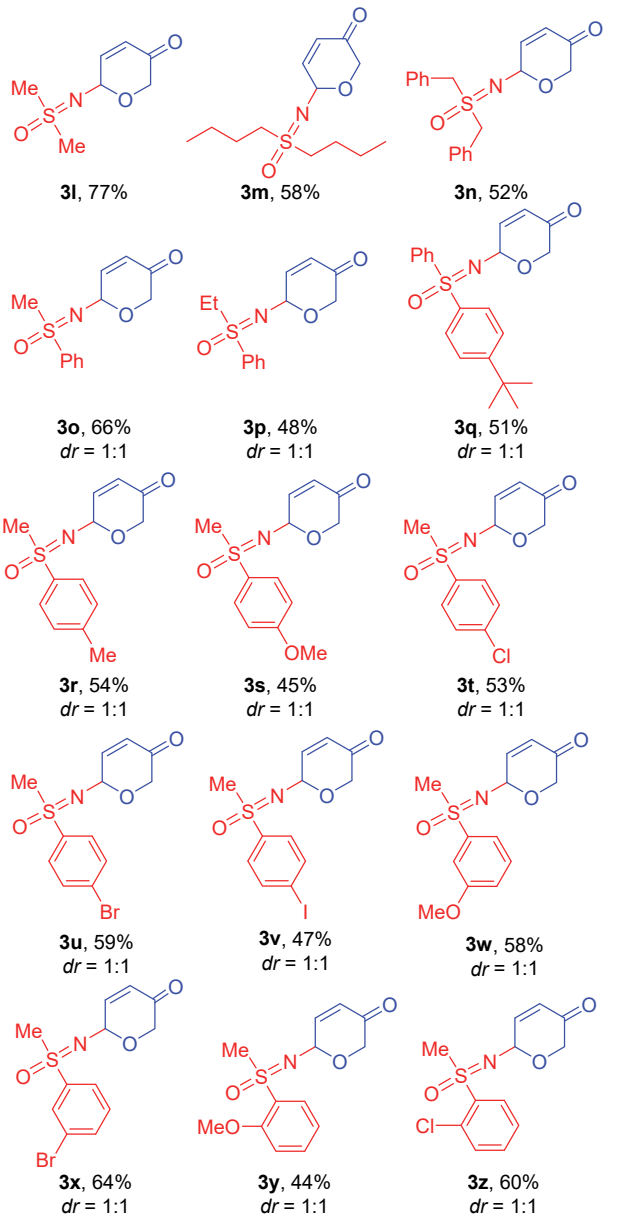
接下来，考察不同种类的亚砜亚胺化合物 **1** 与 6-羟基-*2H*-吡喃-3-酮(**2a**)的反应(表 3). 当 R^1 和 R^2 基团均为烷基时，二甲基亚砜亚胺取代的产物(**3l**)收率优于二正丁基(**3m**)和二苄基(**3n**)取代的产物. 当 R^1 和 R^2 基团不同时，将以 1∶1 的 *dr* 值得到各种亚砜亚胺基取代的二氢吡喃酮类衍生物，产率为 44%～66%. 当使用芳香基团代替脂肪基团时，产率有所下降. 甲基芳基亚砜亚胺取代的产物(**3o**)收率高于乙基芳基亚砜亚胺(**3p**). 有位阻的二芳基取代的亚砜亚胺也能够与二氢吡喃酮发生反应(**3q**). 当 R^1 为甲基，R^2 为芳基时，R^2 苯环的对位为甲基、甲氧基、氯、溴或碘等取代基团的底物均可参与反应，没有明显的电子效应(**3r**～**3v**)，其中以对溴取代亚砜亚胺的产率最高，达到 59% (**3u**). 当 R^1 为甲基，R^2 为芳基时，R^2 苯环上为间位或邻位取代基时，反应也可顺利进行(**3w**～**3z**)，其中间溴取代的亚砜亚胺的反应效果最好，产率达到 64% (**3x**).

表 3 亚砜亚胺的底物范围 [a,b]

Table 3 Substrate scope of the sulfoximines



1 **2a** **3**

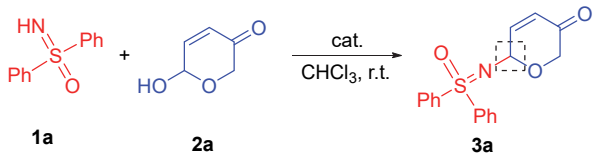


[a] Reaction condition: **1** (0.4 mmol), **2a** (0.2 mmol), $(PhO)_2P(O)OH$ (20 mol%), $CHCl_3$ (0.1 mol/L), room temperature for 18 h; [b] Isolated yield.

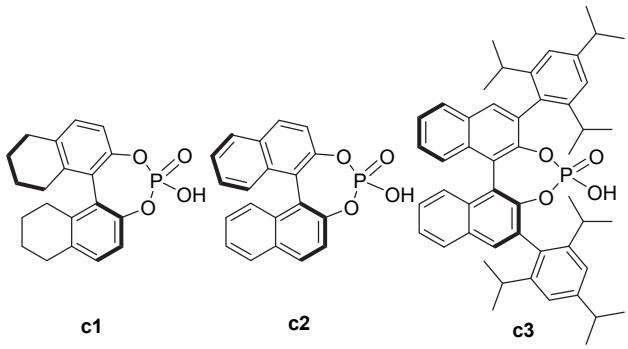
尝试通过不对称催化的方法合成手性亚砜亚胺基二氢吡喃酮类衍生物[22](表 4). 三种手性磷酸催化剂: *R*-(5,5',6,6',7,7',8,8')-八氢联萘酚膦酸酯(**c1**)、*S*-联萘酚磷酸酯(**c2**)和 *S*-3,3'-双(2,4,6-三异丙基苯基)-1,1'-二-2-萘酚环磷酸酯(**c3**)被用于催化二苯基亚砜亚胺(**1a**)和 6-羟基-2*H*-吡喃-3-酮(**2a**)的反应，分别以 41%、47%和 54%的分离产率得到了化合物 **3a**，但遗憾的是它们的对映选择性不高. 可能是由于反应时脱除的水分子影响了催化剂对底物的控制.

表 4 不对称催化条件筛选 [a]

Table 4 Screening of asymmetric catalytic conditions



1a **2a** **3a**



c1 **c2** **c3**

Entry	Catalyst	Yield[b]/%	*er*
1[c]	**c1**	41	48:52
2	**c2**	47	46:54
3	**c3**	54	49:51

[a] Reaction condition: **1a** (1.0 equiv.), **2a** (1.0 equiv.), catalyst (20 mol%), $CHCl_3$ (0.1 mol/L), room temperature for 12 h; [b] Isolated yield. [c] *er* values were determined by HPLC.

根据实验结果并结合已有文献报道[23]，推测出 Scheme 2 所示的可能的反应机理. 首先，磷酸二苯酯作为布朗斯特酸类型的催化剂，促进二氢吡喃酮类化合物 **2** 的羟基脱水形成碳正离子中间体 **A** 或氧鎓离子中间体 **B**. 磷酰基通过氢键作用活化亚砜亚胺类化合物 **1**，促进

亚砜亚胺类化合物 **1** 的氮原子亲核进攻氧鎓离子中间体，生成中间体 **C**. 随后脱除质子得到亚砜亚胺基取代的二氢吡喃酮类衍生物 **3**.

为了进一步证明产物的潜在应用价值，以对碘苯基取代的亚砜亚胺基二氢吡喃酮衍生物 **3v** 为原料进行两种转化反应[24](Scheme 3). 化合物 **3v** 与苯硼酸通过 Suzuki 反应合成联苯取代的亚砜亚胺基二氢吡喃酮衍生物，但该产物可能在碱性水溶液中分解，最终以 42% 的产率得到了联苯取代的亚砜亚胺 **4** (Scheme 3, a). 化合物 **3v** 在 $PdCl_2(PPh_3)_2$ 和 CuI 的共同催化下，与三甲基乙炔基硅烷通过 Sonogashira 反应制备化合物 **5**，产率 83%，*dr* 值 1∶1 (Scheme 3, b).

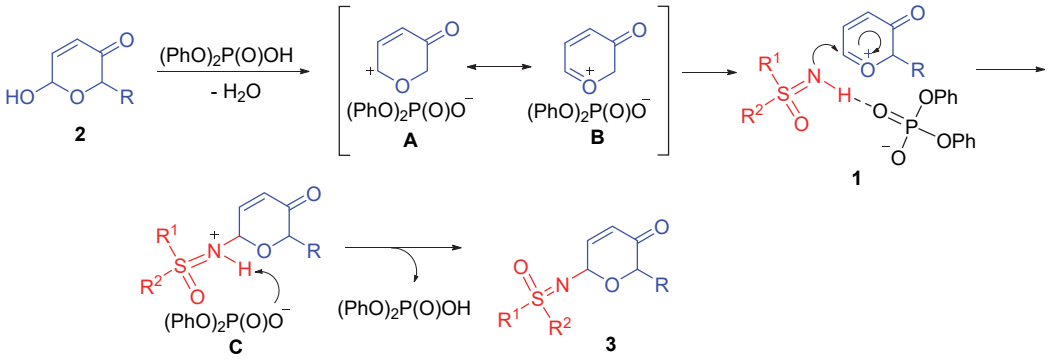
2 结论

发展了一种以Achmatowicz重排产物二氢吡喃酮为原料，通过布朗斯特酸催化合成亚砜亚胺取代的二氢吡喃酮类衍生物的新方法. 该方法的原料简单易得，底物范围广，条件温和，反应易操作，产率中等到良好. 该方法避免了传统上使用的贵金属钯、铱等催化剂，进一步丰富了“*de novo*”从头合成糖苷类化合物的策略，可为设计与合成氮苷糖类化合物提供方法学基础和指导.

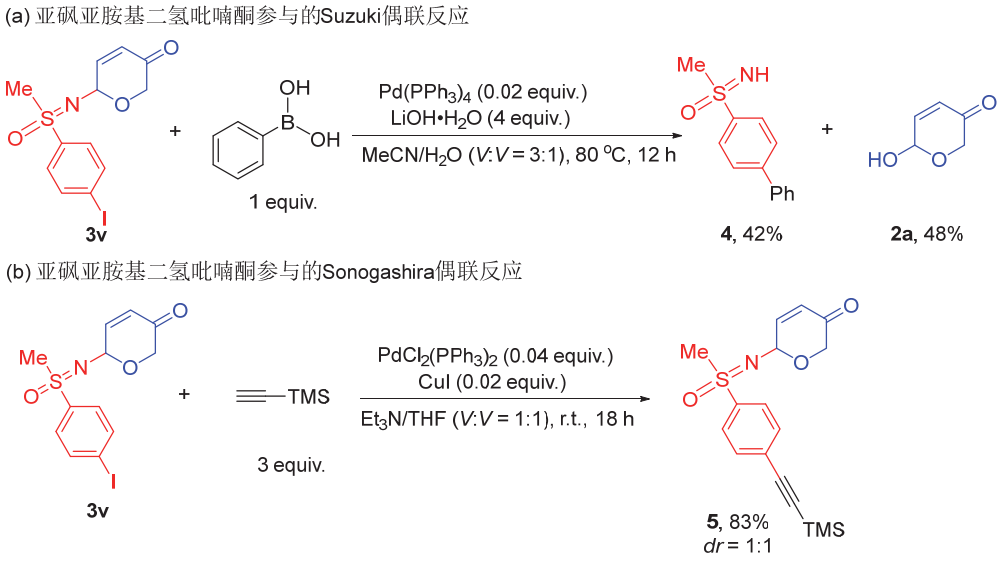
3 实验部分

3.1 仪器与试剂

所用试剂均为市售分析纯；薄层色谱使用预涂硅胶板，在 254 nm 处用紫外光检测；色谱柱为硅胶(40～60 μm)；^{1}H NMR 和 ^{13}C NMR 由 Bruker Avance II 400 MHz、Vaian DLG 400MHz 和 Bruker Avance NEO 600 MHz 核磁共振仪测定，其中 TMS 作为内标，$CDCl_3$ 作为溶剂；高分辨质谱(HRMS)采用 Agilent 仪器(TOF 质谱分析仪型)和电子喷雾注射质谱(ESI)测定. 熔点由 XP-4 熔点仪



图式 2 可能的反应机理
Scheme 2 Proposed reaction mechanism



图式 3 亚砜亚胺基二氢吡喃酮衍生物的应用
Scheme 3 Application of sulfoximide substituted dihydropyranone derivatives

测定.

3.2 实验方法

3.2.1 化合物 **3** 的合成

以 **3a** 的合成为例. 向反应瓶中加入二苯基亚砜亚胺(**1a**) (87 mg, 0.4 mmol)、6-羟基-*2H*-吡喃-3-酮(**2a**) (23 mg, 0.2 mmol)、磷酸二苯酯(10 mg, 0.04 mmol)以及氯仿(2 mL), 在室温下搅拌 18 h, 薄层色谱(TLC)监测, 反应结束后, 反应混合物通过硅胶薄层层析直接纯化得到化合物 **3a**. 化合物 **3b**～**3z** 以相同的方法制备.

6-(氧代(二苯基-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3a**): 无色液体, 43 mg, 产率 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (dd, J=9.7, 7.8 Hz, 4H), 7.58～7.48 (m, 6H), 7.00 (dd, J=10.2, 3.3 Hz, 1H), 6.09 (d, J=10.3 Hz, 1H), 5.46 (d, J=2.8 Hz, 1H), 4.69 (d, J=16.6 Hz, 1H), 4.05 (d, J=16.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 195.40, 150.50, 140.34, 139.97, 133.06, 133.03, 129.38, 129.33, 128.62, 128.18, 125.80, 78.35, 67.52; HRMS (ESI) calcd for $C_{17}H_{16}NSO_3$ $[M+H]^+$ 314.0845, found 314.0849.

2-甲基-6-(氧代(二苯基-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3b**): 无色液体, 42 mg, 产率 64%, *dr*=2∶1. *trans*-isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.00～7.97 (m, 4H), 7.52～7.47 (m, 6H), 6.93 (dd, J=10.1, 3.7 Hz, 1H), 6.01 (d, J=10.1 Hz, 1H), 5.51 (d, J=3.1 Hz, 1H), 4.83 (q, J=6.7 Hz, 1H), 1.24 (d, J=6.8 Hz, 3H); *cis*-isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.07～8.02 (m, 4H), 7.57～7.52 (m, 6H), 7.04 (dd, J=10.1, 1.2 Hz, 1H), 6.08 (dd, J=10.1, 1.7 Hz, 1H), 5.54 (d, J=1.3 Hz, 1H), 4.04～3.99 (m, 1H), 1.31 (d, J=6.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 197.89, 196.85, 152.65, 149.17, 140.86, 140.09, 132.96, 132.91, 132.89, 129.31, 129.26, 129.21, 129.07, 128.89, 128.49, 128.10, 126.94, 125.04, 124.79, 80.65, 77.58, 75.92, 70.65, 15.65, 15.14; HRMS (ESI) calcd for $C_{18}H_{18}NO_3S$ $[M+H]^+$ 328.1001, found 328.0999.

2-乙基-6-(氧代(二苯基-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3c**): 黄色液体, 48 mg, 产率 70%, *dr*=2∶1. *trans*-isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.08～7.96 (m, 4H), 7.56～7.45 (m, 6H), 6.94 (dd, J=10.1, 3.6 Hz, 1H), 6.01 (d, J=10.1 Hz, 1H), 5.51 (d, J=2.9 Hz, 1H), 4.64 (dd, J=8.0, 3.9 Hz, 1H), 1.92～1.59 (m, 2H), 0.90 (t, J=7.4 Hz, 3H); *cis*-isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.08～7.96 (m, 4H), 7.56～7.45 (m, 6H), 7.05 (dd, J=10.1, 1.2 Hz, 1H), 6.08 (dd, J=10.1, 1.8 Hz, 1H), 5.56 (d, J=1.3 Hz, 1H), 3.78～3.76 (m, 1H), 1.92～1.59 (m, 2H), 0.78 (t, J=7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 197.58, 196.46, 152.75, 149.36, 140.65, 140.10, 132.93, 132.85, 129.31, 129.27, 129.18, 129.07, 128.93, 128.69, 128.11, 127.96, 127.38, 125.43, 80.83, 80.70, 77.30, 75.73, 22.98, 22.89, 9.62; HRMS (ESI) calcd for $C_{19}H_{20}NO_3S$ $[M+H]^+$ 342.1158, found 342.1162.

2-丙基-6-(氧代(二苯基-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3d**): 黄色液体, 45 mg, 产率 63%, *dr*=1.5∶1. *trans*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07～7.96 (m, 4H), 7.57～7.43 (m, 6H), 6.93 (dd, J=10.1, 3.6 Hz, 1H), 6.01 (d, J=10.1 Hz, 1H), 5.49 (d, J=3.6 Hz, 1H), 4.70 (dd, J=8.7, 3.7 Hz, 1H), 1.89～1.52 (m, 2H), 1.43～1.12 (m, 2H), 0.91 (t, J=7.4 Hz, 3H); *cis*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07～7.96 (m, 4H), 7.57～7.43 (m, 6H), 7.05 (d, J=10.2 Hz, 1H), 6.08 (dd, J=10.1, 1.8 Hz, 1H), 5.55 (s, 1H), 3.83 (dd, J=9.1, 2.0 Hz, 1H), 1.89～1.52 (m, 2H), 1.43～1.12 (m, 2H), 0.78 (t, J=7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 197.71, 196.67, 152.71, 149.33, 141.07, 140.55, 140.05, 132.93, 132.85, 132.78, 129.32, 129.27, 129.17, 129.05, 128.92, 128.72, 128.14, 127.97, 127.36, 125.37, 124.79, 80.66, 79.26, 77.30, 74.56, 31.62, 31.59, 18.46, 18.19, 13.93, 13.67; HRMS (ESI) calcd for $C_{20}H_{22}NO_3S$ $[M+H]^+$ 356.1314, found 356.1319.

2-异丙基-6-(氧代(二苯基-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3e**): 黄色液体, 48 mg, 产率 68%, *dr*=2∶1. *trans*-isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.07～7.95 (m, 4H), 7.55～7.45 (m, 6H), 6.94 (dd, J=10.1, 3.7 Hz, 1H), 6.01 (d, J=10.0 Hz, 1H), 5.52 (d, J=3.1 Hz, 1H), 4.56 (d, J=3.4 Hz, 1H), 2.35 (dddd, J=16.5, 9.6, 8.5, 4.8 Hz, 1H), 1.00～0.63 (m, 6H); *cis*-isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.07～7.95 (m, 4H), 7.55～7.45 (m, 6H), 7.11～7.05 (m, 1H), 6.08 (dd, J=10.1, 1.6 Hz, 1H), 5.61 (d, J=1.0 Hz, 1H), 3.68 (s, 1H), 2.35 (dddd, J=16.5, 9.6, 8.5, 4.8 Hz, 1H), 1.00～0.63 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 197.69, 196.55, 152.87, 149.29, 141.86, 141.06, 140.62, 140.20, 132.93, 132.90, 132.75, 132.68, 129.29, 129.27, 129.14, 129.03, 128.87, 128.81, 128.10, 127.80, 125.83, 83.83, 80.93, 78.89, 77.19, 28.51, 28.09, 19.09, 16.54, 16.08; HRMS (ESI) calcd for $C_{20}H_{22}NO_3S$ $[M+H]^+$ 356.1314, found 356.1317.

2-环丙基-6-(氧代(二苯基-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3f**): 黄色液体, 47 mg, 产率 66%, *dr*=2∶1. *trans*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06～7.91 (m, 4H), 7.58～7.42 (m, 6H), 6.93 (dd, J=10.1, 3.5 Hz,

1H), 6.02 (dd, *J*=10.1, 1.0 Hz, 1H), 5.53～5.50 (m, 1H), 4.14 (d, *J*=7.6 Hz, 1H), 1.33～1.07 (m, 1H), 0.64～0.10 (m, 4H); *cis*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.06～7.91 (m, 4H), 7.58～7.42 (m, 6H), 7.02 (dd, *J*=10.1, 1.5 Hz, 1H), 6.09 (dd, *J*=10.1, 2.0 Hz, 1H), 5.53～5.50 (m, 1H), 4.14 (d, *J*=7.6 Hz, 1H), 1.33～1.07 (m, 1H), 0.64～0.10 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 195.82, 195.04, 151.32, 148.25, 139.95, 139.50, 139.43, 138.69, 131.91, 131.84, 131.78, 128.26, 128.19, 128.09, 128.01, 127.86, 127.57, 127.06, 126.84, 126.81, 126.21, 124.46, 80.71, 79.46, 76.73, 76.69, 10.07, 9.82, 1.99, 1.46, 0.03, −0.01; HRMS (ESI) calcd for $C_{20}H_{20}NO_3S$ $[M+H]^+$ 354.1158, found 354.1161.

2-环戊基-6-(氧代(二苯基-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3g**): 黄色液体, 45 mg, 产率 59%, *dr*=1.5∶1. *trans*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.06～7.95 (m, 4H), 7.56～7.46 (m, 6H), 6.92 (dd, *J*=10.1, 3.5 Hz, 1H), 6.00 (dd, *J*=10.1, 1.0 Hz, 1H), 5.51 (dd, *J*=3.5, 0.9 Hz, 1H), 4.61 (d, *J*=5.5 Hz, 1H), 2.54～2.38 (m, 1H), 1.74～1.17 (m, 8H); *cis*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.06～7.95 (m, 4H), 7.56～7.46 (m, 6H), 7.05 (dd, *J*=10.1, 1.3 Hz, 1H), 6.07 (dd, *J*=10.1, 2.0 Hz, 1H), 5.61 (dd, *J*=3.3, 1.6 Hz, 1H), 3.81 (dd, *J*=4.7, 1.5 Hz, 1H), 2.54～2.38 (m, 1H), 1.74～1.17 (m, 8H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 197.72, 196.70, 152.55, 149.20, 141.64, 140.91, 140.52, 140.06, 132.94, 132.90, 132.76, 132.65, 129.30, 129.27, 129.14, 129.04, 128.86, 128.81, 128.14, 127.81, 125.78, 124.79, 81.84, 80.96, 77.48, 77.39, 39.32, 39.27, 28.71, 28.55, 27.23, 26.68, 25.83, 25.67, 25.53, 25.50; HRMS (ESI) calcd for $C_{22}H_{24}NO_3S$ $[M+H]^+$ 382.1471, found 382.1473.

2-苯基-6-(氧代(二苯基-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3h**): 黄色液体, 56 mg, 产率 72%, *dr*=3∶1. *trans*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.05～7.95 (m, 4H), 7.56～7.40 (m, 6H), 7.29～7.22 (m, 5H), 7.03 (dd, *J*=10.2, 3.4 Hz, 1H), 6.15 (dd, *J*=10.2, 1.1 Hz, 1H), 5.71 (s, 1H), 5.59 (dd, *J*=3.3, 1.0 Hz, 1H); *cis*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.05～7.95 (m, 4H), 7.56～7.40 (m, 6H), 7.29～7.22 (m, 5H), 7.19 (dd, *J*=10.2, 1.4 Hz, 1H), 6.21 (dd, *J*=10.2, 1.9 Hz, 1H), 5.80 (dd, *J*=3.3, 1.6 Hz, 1H), 4.94 (d, *J*=1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 195.28, 194.28, 152.70, 150.06, 141.19, 140.92, 140.37, 140.00, 135.69, 135.57, 133.03, 132.95, 132.85, 132.78, 129.34, 129.27, 129.20, 129.11, 128.72, 128.19, 128.14, 128.09, 127.99, 127.93, 127.91, 127.84, 127.66, 127.58, 125.77, 124.81, 81.50, 81.49, 77.72, 77.52; HRMS (ESI) calcd for $C_{23}H_{20}NO_3S$ $[M+H]^+$ 390.1158, found 390.1158.

2-(对甲苯基)-6-(氧代(二苯基-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3i**): 黄色液体, 63 mg, 产率 78%, *dr*=3∶1. *trans*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.06～7.99 (m, 4H), 7.56～7.42 (m, 6H), 7.16～7.07 (m, 4H), 7.03 (dd, *J*=10.2, 3.4 Hz, 1H), 6.15 (dd, *J*=10.1, 1.1 Hz, 1H), 5.69 (s, 1H), 5.58 (dd, *J*=3.3, 1.1 Hz, 1H), 2.33 (d, *J*=3.6 Hz, 3H); *cis*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.05～7.98 (m, 4H), 7.56～7.42 (m, 6H), 7.21～7.18 (m, 1H), 7.16～7.07 (m, 4H), 6.21 (dd, *J*=10.2, 1.9 Hz, 1H), 5.79 (dd, *J*=3.3, 1.6 Hz, 1H), 4.93 (d, *J*=1.1 Hz, 1H), 2.33 (d, *J*=3.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 195.54, 194.56, 152.67, 150.09, 141.10, 140.94, 140.36, 140.06, 137.82, 137.62, 133.00, 132.95, 132.84, 132.79, 132.61, 129.33, 129.28, 129.18, 129.13, 128.95, 128.79, 128.66, 128.14, 128.01, 127.93, 127.79, 127.61, 127.58, 125.79, 81.51, 81.48, 77.65, 77.53, 21.24, 21.21; HRMS (ESI) calcd for $C_{24}H_{22}NO_3S$ $[M+H]^+$ 404.1314, found 404.1311.

2-(4-氯苯基)-6-(氧代(二苯基-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3j**): 黄色液体, 63 mg, 产率 75%, *dr*=3∶1. *trans*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.04～7.95 (m, 4H), 7.55～7.40 (m, 6H), 7.29～7.17 (m, 4H), 7.09～7.00 (m, 1H), 6.13 (dd, *J*=10.2, 1.0 Hz, 1H), 5.69 (s, 1H), 5.60 (dd, *J*=3.5, 1.0 Hz, 1H); *cis*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.04～7.95 (m, 4H), 7.55～7.40 (m, 6H), 7.29～7.17 (m, 4H), 7.09～7.00 (m, 1H), 6.20 (dd, *J*=10.2, 1.9 Hz, 1H), 5.82 (dd, *J*=3.3, 1.7 Hz, 1H), 4.92 (d, *J*=1.0 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 194.80, 193.72, 152.80, 149.93, 141.39, 140.86, 140.42, 139.79, 134.15, 134.09, 133.90, 133.74, 133.09, 133.00, 132.91, 132.80, 129.39, 129.29, 129.21, 129.14, 128.88, 128.64, 128.59, 128.29, 128.13, 128.03, 127.93, 127.39, 125.59, 124.81, 81.56, 80.56, 77.92, 76.41; HRMS (ESI) calcd for $C_{23}H_{19}ClNO_3S$ $[M+H]^+$ 424.0768, found 424.0755.

2-((叔丁基二甲基硅基)氧基)甲基)-6-(氧代(二苯基-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3k**): 无色液体, 46 mg, 产率 50%, *dr*=6∶1. *trans*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.07～8.00 (m, 4H), 7.56～7.47 (m, 6H), 6.96 (dd, *J*=10.2, 3.4 Hz, 1H), 6.05 (dd, *J*=10.2, 0.9 Hz, 1H), 5.65 (dd, *J*=3.4, 1.0 Hz, 1H), 4.72 (dd, *J*=4.6, 2.6 Hz, 1H), 4.03～3.91 (m, 2H), 0.87～0.82 (m, 9H), 0.05～

0.03 (m, 6H); *cis*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07～8.00 (m, 4H), 7.56～7.47 (m, 6H), 7.03 (dd, J=10.2, 1.7 Hz, 1H), 6.11 (dd, J=16.6, 6.1 Hz, 1H), 5.79 (d, J=2.9 Hz, 1H), 4.38 (t, J=2.2 Hz, 1H), 4.03～3.91 (m, 2H), 0.87～0.82 (m, 9H), 0.05～0.03 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 195.63, 150.17, 140.28, 140.15, 132.96, 132.92, 132.59, 129.29, 129.26, 129.15, 128.94, 128.22, 127.92, 125.98, 77.89, 63.38, 25.98, 25.86, 25.64, 18.29, －5.42; HRMS (ESI) calcd for $C_{24}H_{32}NO_4SSi$ $[M+H]^+$ 458.1816, found 458.1815.

6-((二甲基(氧代)-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3l**): 无色液体, 29 mg, 产率 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.94 (dd, J=10.3, 2.9 Hz, 1H), 6.08 (dd, J=10.3, 1.5 Hz, 1H), 5.64 (dd, J=2.8, 1.4 Hz, 1H), 4.45 (d, J=16.4 Hz, 1H), 4.08 (d, J=16.4 Hz, 1H), 3.15 (d, J=0.7 Hz, 3H), 3.08 (d, J=0.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 194.90, 150.80, 126.37, 78.04, 67.58, 44.61, 43.69; HRMS (ESI) calcd for $C_7H_{12}NO_3S$ $[M+H]^+$ 190.0532, found 190.0535.

6-((二丁基(氧代)-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3m**): 黄色液体, 32 mg, 产率 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.94 (dd, J=10.3, 2.9 Hz, 1H), 6.08 (dd, J=10.3, 1.4 Hz, 1H), 5.61 (dd, J=2.6, 1.3 Hz, 1H), 4.47 (d, J=16.4 Hz, 1H), 4.07 (d, J=16.4 Hz, 1H), 3.25～2.96 (m, 4H), 1.88～1.73 (m, 4H), 1.52～1.41 (m, 4H), 0.97 (dd, J=7.4, 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 195.20, 151.41, 126.16, 77.74, 67.72, 54.86, 52.11, 25.55, 23.62, 21.85, 21.67, 13.60, 13.57; HRMS (ESI) calcd for $C_{13}H_{23}NO_3SNa$ $[M+Na]^+$ 296.1291, found 296.1295.

6-((二苄基(氧代)-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3n**): 无色液体, 35 mg, 产率 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47～7.32 (m, 10H), 6.74 (dd, J=10.3, 2.8 Hz, 1H), 6.03 (dd, J=10.3, 0.9 Hz, 1H), 5.44 (s, 1H), 4.47 (d, J=13.9 Hz, 1H), 4.39 (dd, J=18.7, 15.2 Hz, 2H), 4.15 (s, 2H), 4.02 (d, J=16.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 195.27, 151.36, 131.49, 131.03, 129.18, 129.05, 128.96, 128.65, 128.60, 126.79, 126.04, 78.05, 67.94, 62.11, 58.53; HRMS (ESI) calcd for $C_{19}H_{19}NO_3SNa$ $[M+Na]^+$ 364.0978, found 364.0980.

6-((甲基(氧代)(苯基)-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3o**): 无色液体, 33 mg, 产率 66%, dr=1∶1. First isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00～7.96 (m, 2H), 7.69～7.56 (m, 3H), 6.93 (ddd, J=11.6, 10.4, 3.1 Hz, 1H), 6.10～6.05 (m, 1H), 5.45～5.40 (m, 1H), 4.64 (d, J=16.6 Hz, 1H), 3.91 (d, J=16.5 Hz, 1H), 3.20 (s, 3H); Second isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00～7.96 (m, 2H), 7.69～7.56 (m, 3H), 6.93 (ddd, J=11.6, 10.4, 3.1 Hz, 1H), 6.10～6.05 (m, 1H), 5.45～5.40 (m, 1H), 4.46 (d, J=16.5 Hz, 1H), 4.13～4.07 (m, 1H), 3.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 195.22, 195.15, 150.87, 150.12, 140.11, 138.82, 133.61, 133.46, 129.65, 129.46, 128.24, 127.97, 126.24, 125.80, 78.53, 77.83, 67.59, 67.50, 45.95, 45.62; HRMS (ESI) calcd for $C_{12}H_{14}NO_3S$ $[M+H]^+$ 252.0688, found 252.0694.

6-((乙基(氧代)(苯基)-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3p**): 无色液体, 25 mg, 产率 48%, dr=1∶1. First isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99～7.91 (m, 2H), 7.70～7.56 (m, 3H), 6.95 (ddd, J=11.9, 10.3, 3.1 Hz, 1H), 6.07 (ddd, J=10.3, 2.2, 1.3 Hz, 1H), 5.44 (ddd, J=12.0, 3.1, 1.1 Hz, 1H), 4.66 (d, J=16.6 Hz, 1H), 3.93 (d, J=16.5 Hz, 1H), 3.42～3.19 (m, 2H), 1.32～1.21 (m, 3H); Second isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99～7.91 (m, 2H), 7.70～7.56 (m, 3H), 6.95 (ddd, J=11.9, 10.3, 3.1 Hz, 1H), 6.07 (ddd, J=10.3, 2.2, 1.3 Hz, 1H), 5.44 (ddd, J=12.0, 3.1, 1.1 Hz, 1H), 4.48 (d, J=16.5 Hz, 1H), 4.09 (d, J=16.6 Hz, 1H), 3.42～3.19 (m, 2H), 1.32～1.21 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 195.41, 195.29, 151.21, 150.34, 138.13, 136.67, 133.55, 133.42, 129.55, 129.35, 129.03, 128.82, 126.09, 125.67, 78.49, 77.84, 67.62, 67.52, 51.79, 51.44, 7.58, 7.01; HRMS (ESI) calcd for $C_{13}H_{15}NO_3SNa$ $[M+Na]^+$ 288.0665, found 288.0670.

6-((4-(叔丁基)苯基)(氧代)(苯基)-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3q**): 黄色液体, 38 mg, 产率 51%, dr=1∶1. First isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05～7.89 (m, 4H), 7.56～7.49 (m, 5H), 7.02 (t, J=3.2 Hz, 1H), 6.10 (s, 1H), 5.46 (td, J=3.3, 1.1 Hz, 1H), 4.74 (d, J=9.0 Hz, 1H), 4.05 (d, J=7.0 Hz, 1H), 1.30 (t, J=2.3 Hz, 9H); Second isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05～7.89 (m, 4H), 7.56～7.49 (m, 5H), 7.00 (t, J=3.2 Hz, 1H), 6.07 (s, 1H), 5.46 (td, J=3.3, 1.1 Hz, 1H), 4.70 (d, J=9.1 Hz, 1H), 4.09 (d, J=7.0 Hz, 1H), 1.30 (t, J=2.3 Hz, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 195.50, 157.00, 156.96, 150.64, 140.59, 140.24, 136.91, 132.91, 132.87, 129.31, 129.26, 128.56, 128.53, 128.14, 128.05, 126.45, 126.42, 125.72, 125.67, 78.39, 78.36, 67.49, 67.47, 35.16, 31.03; HRMS (ESI) calcd for $C_{21}H_{24}NO_4S$ $[M+H]^+$ 370.1471, found 370.1469.

6-((甲基(氧代)(对甲苯基)-λ^6-亚砜基)氨基)-2*H*-吡

嗪-3(6*H*)-酮(**3r**): 黄色液体, 29 mg, 产率 54%, *dr*=1∶1. First isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.91～7.83 (m, 2H), 7.40 (t, *J*=8.1 Hz, 2H), 6.99～6.90 (m, 1H), 6.09 (dd, *J*=4.7, 1.2 Hz, 1H), 5.41 (dd, *J*=3.1, 1.1 Hz, 1H), 4.65 (d, *J*=16.6 Hz, 1H), 3.93 (d, *J*=16.5 Hz, 1H), 3.20 (s, 3H), 2.46 (t, *J*=3.9 Hz, 3H); Second isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.91～7.83 (m, 2H), 7.40 (t, *J*=8.1 Hz, 2H), 6.99～6.90 (m, 1H), 6.06 (dd, *J*=4.7, 1.2 Hz, 1H), 5.41 (dd, *J*=3.1, 1.1 Hz, 1H), 4.49 (d, *J*=16.5 Hz, 1H), 4.09 (d, *J*=16.6 Hz, 1H), 3.15 (s, 3H), 2.46 (t, *J*=3.9 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 195.31, 195.23, 151.01, 150.22, 144.67, 144.48, 136.78, 135.54, 130.29, 130.10, 128.31, 128.04, 126.16, 125.69, 78.56, 77.81, 77.30, 77.09, 76.88, 67.55, 67.45, 45.94, 45.68, 21.56; HRMS (ESI) calcd for $C_{13}H_{15}NO_3SNa$ $[M+Na]^+$ 288.0665, found 288.0670.

6-((4-甲氧基苯基)(甲基)(氧代)-*λ*^{6}-亚砜基)氨基)-2*H*-吡嗪-3(6*H*)-酮(**3s**): 黄色液体, 25 mg, 产率 45%, *dr*=1∶1. First isomer: ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 7.88 (dd, *J*=11.3, 9.0 Hz, 2H), 7.03 (dd, *J*=10.1, 9.1 Hz, 2H), 6.94～6.89 (m, 1H), 6.08～6.03 (m, 1H), 5.38 (dd, *J*=9.4, 1.7 Hz, 1H), 4.62 (d, *J*=16.6 Hz, 1H), 3.92 (d, *J*=16.5 Hz, 1H), 3.87 (d, *J*=2.4 Hz, 3H), 3.17 (s, 3H); Second isomer: ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 7.88 (dd, *J*=11.3, 9.0 Hz, 2H), 7.03 (dd, *J*=10.1, 9.1 Hz, 2H), 6.94～6.89 (m, 1H), 6.08～6.03 (m, 1H), 5.38 (dd, *J*=9.4, 1.7 Hz, 1H), 4.47 (d, *J*=16.5 Hz, 1H), 4.09～4.05 (m, 1H), 3.87 (d, *J*=2.4 Hz, 3H), 3.12 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 195.35, 195.25, 163.75, 163.67, 151.15, 150.27, 130.54, 130.20, 126.18, 125.68, 114.88, 114.67, 78.53, 77.84, 67.63, 67.46, 55.77, 55.72, 46.16, 45.94; HRMS (ESI) calcd for $C_{13}H_{16}NO_4S$ $[M+H]^+$ 282.0794, found 282.0802.

6-((4-氯苯基)(甲基)(氧代)-*λ*^{6}-亚砜基)氨基)-2*H*-吡嗪-3(6*H*)-酮(**3t**): 黄色液体, 30 mg, 产率 53%, *dr*=1∶1. First isomer: ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 7.90 (dd, *J*=8.5, 3.0 Hz, 2H), 7.55 (dd, *J*=13.9, 8.6 Hz, 2H), 6.90 (ddd, *J*=15.5, 10.3, 3.0 Hz, 1H), 6.08～6.05 (m, 1H), 5.40 (dd, *J*=10.8, 1.5 Hz, 1H), 4.59 (d, *J*=16.6 Hz, 1H), 3.91 (d, *J*=16.5 Hz, 1H), 3.19 (s, 3H); Second isomer: ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 7.90 (dd, *J*=8.5, 3.0 Hz, 2H), 7.55 (dd, *J*=13.9, 8.6 Hz, 2H), 6.90 (ddd, *J*=15.5, 10.3, 3.0 Hz, 1H), 6.08～6.05 (m, 1H), 5.40 (dd, *J*=10.8, 1.5 Hz, 1H), 4.41 (d, *J*=16.5 Hz, 1H), 4.08 (d, *J*=16.6 Hz, 1H), 3.13 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 195.02, 194.91, 150.67, 149.93, 140.41, 140.23, 138.70, 137.42, 129.94, 129.77, 129.74, 129.45, 126.30, 125.94, 78.47, 77.72, 67.65, 67.54, 46.05, 45.64; HRMS (ESI) calcd for $C_{12}H_{12}ClNO_3SNa$ $[M+Na]^+$ 308.0118, found 308.0121.

6-((4-溴苯基)(甲基)(氧代)-*λ*^{6}-亚砜基)氨基)-2*H*-吡嗪-3(6*H*)-酮(**3u**): 黄色液体, 39 mg, 产率 59%, *dr*=1∶1. First isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.84 (dd, *J*=8.6, 2.4 Hz, 2H), 7.73 (t, *J*=8.7 Hz, 2H), 6.91 (td, *J*=10.7, 3.0 Hz, 1H), 6.09 (d, *J*=2.4 Hz, 1H), 5.43 (d, *J*=2.7 Hz, 1H), 4.60 (d, *J*=16.6 Hz, 1H), 3.92 (d, *J*=16.5 Hz, 1H), 3.20 (s, 3H); Second isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.84 (dd, *J*=8.6, 2.4 Hz, 2H), 7.73 (t, *J*=8.7 Hz, 2H), 6.91 (td, *J*=10.7, 3.0 Hz, 1H), 6.07 (d, *J*=2.3 Hz, 1H), 5.41 (d, *J*=2.5 Hz, 1H), 4.42 (d, *J*=16.5 Hz, 1H), 4.12～4.07 (m, 1H), 3.14 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 195.03, 194.92, 150.68, 149.93, 139.29, 138.01, 132.95, 132.75, 129.86, 129.52, 128.96, 128.80, 126.33, 125.97, 78.49, 77.74, 67.69, 67.57, 46.05, 45.65; HRMS (ESI) calcd for $C_{12}H_{12}BrNO_3SNa$ $[M+Na]^+$ 351.9613, found 351.9620.

6-((4-碘苯基)(甲基)(氧代)-*λ*^{6}-亚砜基)氨基)-2*H*-吡嗪-3(6*H*)-酮(**3v**): 黄色液体, 35 mg, 产率 47%, *dr*=1∶1. First isomer: ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 7.96～7.91 (m, 2H), 7.67 (dd, *J*=8.4, 5.3 Hz, 2H), 6.92 (dd, *J*=10.3, 3.0 Hz, 1H), 6.08 (dd, *J*=4.2, 1.0 Hz, 1H), 5.40～5.39 (m, 1H), 4.41 (d, *J*=16.5 Hz, 1H), 4.10～4.07 (m, 1H), 3.13 (s, 3H); Second isomer: ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 7.94 (d, 2H), 7.67 (dd, *J*=8.4, 5.3 Hz, 2H), 6.89 (dd, *J*=10.3, 3.1 Hz, 1H), 6.06 (dd, *J*=4.2, 1.0 Hz, 1H), 5.41～5.40 (m, 1H), 4.59 (d, *J*=16.6 Hz, 1H), 3.91 (d, *J*=16.5 Hz, 1H), 3.18 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 195.01, 194.90, 150.64, 149.91, 139.98, 138.92, 138.73, 138.68, 129.69, 129.36, 126.32, 125.96, 101.48, 101.37, 78.49, 77.72, 67.67, 67.57, 45.98, 45.59; HRMS (ESI) calcd for $C_{12}H_{13}INO_3S$ $[M+H]^+$ 377.9655, found 377.9662.

6-((3-甲氧基苯基)(甲基)(氧代)-*λ*^{6}-亚砜基)氨基)-2*H*-吡嗪-3(6*H*)-酮(**3w**): 黄色液体, 33 mg, 产率 58%, *dr*=1∶1. First isomer: ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 7.55～7.45 (m, 3H), 7.20～7.12 (m, 1H), 6.93 (dd, *J*=10.3, 3.0 Hz, 1H), 6.08～6.06 (m, 1H), 5.41 (d, *J*=1.7 Hz, 1H), 4.62 (d, *J*=16.6 Hz, 1H), 3.92 (d, *J*=16.5 Hz, 1H), 3.87 (s, 3H), 3.19 (s, 3H); Second isomer: ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 7.55～7.45 (m, 3H), 7.20～7.12 (m, 1H), 6.90 (dd, *J*=10.3, 3.1 Hz, 1H), 6.05 (dd, *J*=4.6, 0.9 Hz,

1H), 5.39 (d, *J*=1.8 Hz, 1H), 4.46 (d, *J*=16.5 Hz, 1H), 4.08 (d, *J*=16.6 Hz, 1H), 3.86 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 195.24, 195.24, 195.14, 160.41, 160.21, 150.88, 150.09, 141.24, 139.90, 130.71, 130.49, 126.22, 125.76, 120.26, 119.85, 119.82, 112.93, 112.87, 78.61, 77.78, 67.59, 67.49, 55.78, 55.72, 45.86, 45.60; HRMS (ESI) calcd for $C_{13}H_{15}NO_4SNa$ $[M+Na]^+$ 304.0614, found 304.0619.

6-((3-溴苯基)(甲基)(氧代)-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3x**): 黄色液体, 42 mg, 产率 64%, *dr*=1∶1. First isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.11 (dt, *J*=3.6, 1.8 Hz, 1H), 7.90 (ddd, *J*=7.9, 3.3, 1.8 Hz, 1H), 7.77 (dddd, *J*=9.0, 8.0, 1.8, 0.9 Hz, 1H), 7.46 (dt, *J*=9.7, 7.9 Hz, 1H), 6.95～6.88 (m, 1H), 6.09 (dd, *J*=4.5, 1.3 Hz, 1H), 5.42 (dt, *J*=2.9, 1.4 Hz, 1H), 4.59 (d, *J*=16.6 Hz, 1H), 4.09 (d, *J*=16.6 Hz, 1H), 3.20 (s, 3H); Second isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.11 (dt, *J*=3.6, 1.8 Hz, 1H), 7.90 (ddd, *J*=7.9, 3.3, 1.8 Hz, 1H), 7.77 (dddd, *J*=9.0, 8.0, 1.8, 0.9 Hz, 1H), 7.46 (dt, *J*=9.7, 7.9 Hz, 1H), 6.95～6.88 (m, 1H), 6.06 (dd, *J*=4.5, 1.3 Hz, 1H), 5.42 (dt, *J*=2.9, 1.4 Hz, 1H), 4.42 (d, *J*=16.5 Hz, 1H), 3.92 (d, *J*=16.5 Hz, 1H), 3.15 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 195.00, 194.92, 150.51, 149.86, 142.38, 140.96, 136.68, 136.49, 131.21, 131.10, 130.92, 130.90, 126.68, 126.44, 126.33, 125.97, 123.66, 123.40, 78.48, 77.65, 67.56, 46.03, 45.56; HRMS (ESI) calcd for $C_{12}H_{12}BrNO_3SNa$ $[M+Na]^+$ 351.9613, found 351.9620.

6-((2-甲氧基苯基)(甲基)(氧代)-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3y**): 黄色液体, 25 mg, 产率 44%, *dr*=1∶1. First isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.11～7.99 (m, 1H), 7.68～7.57 (m, 1H), 7.21～7.04 (m, 2H), 6.94 (dd, *J*=10.2, 3.5 Hz, 1H), 6.03 (s, 1H), 5.41 (d, *J*=3.3 Hz, 1H), 4.67 (d, *J*=16.6 Hz, 1H), 3.99 (s, 3H), 3.75 (d, *J*=16.4 Hz, 1H), 3.35 (s, 3H); Second isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.11～7.99 (m, 1H), 7.68～7.57 (m, 1H), 7.21～7.04 (m, 2H), 6.83 (dd, *J*=10.2, 3.3 Hz, 1H), 6.01 (s, 1H), 5.19 (d, *J*=3.0 Hz, 1H), 4.45 (d, *J*=16.4 Hz, 1H), 4.04 (d, *J*=16.6 Hz, 1H), 3.98 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 195.70, 195.58, 156.90, 156.63, 150.62, 150.08, 135.70, 135.30, 131.97, 130.75, 126.03, 125.55, 121.25, 120.96, 112.20, 112.07, 79.04, 76.90, 67.20, 66.70, 56.10, 56.06, 43.69, 43.43; HRMS (ESI) calcd for $C_{13}H_{16}NO_4S$ $[M+H]^+$ 282.0794, found 282.0798.

6-((2-氯苯基)(甲基)(氧代)-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**3z**): 黄色液体, 34 mg, 产率 60%, *dr*=1∶1. First isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.22 (dt, *J*=16.8, 5.0 Hz, 1H), 7.65～7.43 (m, 3H), 6.90 (d, *J*=3.4 Hz, 1H), 6.04 (s, 1H), 5.42 (d, *J*=3.4 Hz, 1H), 4.63 (d, *J*=16.7 Hz, 1H), 3.83 (d, *J*=16.6 Hz, 1H), 3.38 (s, 3H); Second isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.22 (dt, *J*=16.8, 5.0 Hz, 1H), 7.65～7.43 (m, 3H), 6.88 (d, *J*=3.4 Hz, 1H), 6.01 (s, 1H), 5.12 (d, *J*=3.2 Hz, 1H), 4.51 (d, *J*=16.6 Hz, 1H), 4.02 (d, *J*=16.7 Hz, 1H), 3.38 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 195.27, 195.19, 150.01, 149.51, 138.14, 134.89, 134.85, 134.43, 133.24, 132.31, 132.15, 132.08, 131.97, 131.73, 128.11, 127.67, 126.18, 125.73, 79.16, 77.00, 67.37, 67.36, 43.44, 43.23; HRMS (ESI) calcd for $C_{12}H_{12}ClNO_3SNa$ $[M+Na]^+$ 308.0118, found 308.0119.

3.2.2 [1,1'-联苯]-4-(亚氨基)(甲基)-λ^6-亚砜(**4**)的合成

向反应瓶中加入化合物 **3v** (38 mg, 0.1 mmol)、苯硼酸(12 mg, 0.1mmol)、$Pd(PPh_3)_4$ (2.3 mg, 0.002 mmol)、$LiOH•H_2O$ (9.6 mg, 0.4 mmol)以及乙腈/水(1 mL, *V*∶*V*=3∶1), 在 80 ℃下搅拌 12 h, 反应结束后通过柱层析纯化产物 **4**. 白色固体, 10 mg, 产率 42%. m.p. 133～135 ℃ (lit.[25] 133～135 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.10～8.07 (m, 2H), 7.79～7.75 (m, 2H), 7.64～7.60 (m, 2H), 7.51～7.47 (m, 2H), 7.46～7.42 (m, 1H), 3.20 (s, 3H), 2.29 (s, 1H). 与已报道的谱图相符合[25].

3.2.3 6-((甲基(氧代)(4-((三甲基硅基)乙炔基)苯基)-λ^6-亚砜基)氨基)-2*H*-吡喃-3(6*H*)-酮(**5**)的合成

向反应瓶中加入化合物 **3v** (38 mg, 0.1 mmol)、三甲基乙炔基硅烷(43 μL, 0.3 mmol)、$PdCl_2(PPh_3)_2$ (2.8 mg, 0.004 mmol)、CuI (0.4 mg, 0.002 mmol)以及 Et_3N/THF (1 mL, *V*∶*V*=1∶1), 在室温下搅拌 12 h, 反应结束后通过柱层析纯化产物 **5**. 黄色液体, 29 mg, 产率 83%, *dr*=1∶1. First isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.90 (dd, *J*=8.5, 3.2 Hz, 2H), 7.64 (t, *J*=7.7 Hz, 2H), 6.92 (ddd, *J*=13.7, 10.3, 3.1 Hz, 1H), 6.10～6.08 (m, 1H), 5.41 (s, 1H), 4.42 (d, *J*=16.5 Hz, 1H), 4.10 (d, *J*=16.6 Hz, 1H), 3.15 (s, 3H), 0.26 (s, 9H); Second isomer: ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.90 (dd, *J*=8.5, 3.2 Hz, 2H), 7.64 (t, *J*=7.7 Hz, 2H), 6.92 (ddd, *J*=13.7, 10.3, 3.1 Hz, 1H), 6.08～6.06 (m, 1H), 5.41 (s, 1H), 4.62 (d, *J*=16.6 Hz, 1H), 3.90 (d, *J*=16.5 Hz, 1H), 3.20 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 195.36, 195.25, 150.87, 150.19, 139.72, 133.17, 133.00, 129.21, 129.02, 128.35, 128.11, 126.59, 126.26, 103.18, 103.01, 99.78, 99.52,

78.76, 77.98, 67.91, 67.81, 46.17, 45.76, −0.01; HRMS (ESI) calcd for $C_{17}H_{22}NO_3SSi$ $[M+H]^+$ 348.1084, found 348.1086.

辅助材料(Supporting Information) 原料 **1** 和 **2** 的合成方法和化合物 **3**, **5** 和 **6** 的核磁共振谱图. 这些材料可以免费从本刊网站(http://sioc-journal.cn/)上下载.

References

[1] (a) Bentley, H. R.; Mcdermott, E. E.; Pace, J.; Whitehead, J. K.; Moran, T. *Nature* **1949**, *163*, 675.
(b) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1.
(c) Wang, Y. Y.; Hong, X.; Deng, Z. *Chin. J. Org. Chem.* **2012**, *32*, 825 (in Chinese).
(王娅娅, 洪学传, 邓子新, 有机化学, **2012**, *32*, 825.)
(d) Bizet, V.; Kowalczyk, R.; Bolm, C. *Chem. Soc. Rev.* **2014**, *43*, 2426.
(e) Frings, M.; Bolm, C.; Blum, A.; Gnamm, C. *Eur. J. Med. Chem.* **2017**, *126*, 225.

[2] Walker, D. P.; Zawistoski, M. P.; McGlynn, M. A.; Li, J.-C.; Kung, D. W.; Bonnette, P. C.; Baumann, A.; Buckbinder, L.; Houser, J. A.; Boer, J.; Mistry, A.; Han, S.; Xing, L.; Guzman-Perez, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3253.

[3] (a) Satzinger, G. *Drug News Perspect*. **2001**, *14*, 197.
(b) Satzinger, G.; Stoss, P. *Arzneim. Forsch*. **1970**, *20*, 1214.

[4] (a) Siemeister, G.; Lücking, U.; Wengner, A. M.; Lienau, P.; Steinke, W.; Schatz, C.; Mumberg, D.; Ziegelbauer, K. *Mol. Cancer Ther.* **2012**, *11*, 2265.
(b) Lücking, U.; Jautelat, R.; Krüger, M.; Brumby, T.; Lienau, P.; Schäfer, M.; Briem, H.; Schulze, J.; Hillisch, A.; Reichel, A.; Wengner, A. M.; Siemeister, G. *ChemMedChem* **2013**, *8*, 1067.

[5] Chen, X. Y.; Bohmann, R. A.; Bolm, C. *Synlett* **2012**, 2808.

[6] Zhou, H.; Chen, Z. *Chin. J. Org. Chem.* **2018**, *38*, 719 (in Chinese).
(周豪, 陈知远, 有机化学, **2018**, *38*, 719.)

[7] Zhu, Y.; Loso, M. R.; Watson, G. B.; Sparks, T. C.; Rogers, R. B.; Huang, J. X.; Gerwick, B. C.; Babcock, J. M.; Kelley, D.; Hegde, V. B.; Nugent, B. M.; Renga, J. M.; Denholm, I.; Gorman, K.; DeBoer, G. J.; Hasler, J.; Meade, T.; Thomas, J. D. *J. Agric. Food Chem.* **2011**, *59*, 2950.

[8] Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341.

[9] Gais, H. J.; Mueller, H.; Bund, J.; Scommoda, M.; Brandt, J.; Raabe, G. *J. Am. Chem. Soc.* **1995**, *117*, 2453.

[10] Bolm, C.; Simic, O. *J. Am. Chem. Soc.* **2001**, *123*, 3830.

[11] Frings, M.; Thomé, I.; Bolm, C. *Beilstein J. Org. Chem*. **2012**, *8*, 1443.

[12] (a) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169.
(b) Sedelmeier, J.; Bolm, C. *J. Org. Chem.* **2005**, *70*, 6904.
(c) Cho, G. Y.; Remy, P.; Jansson, J.; Moessner, C.; Bolm, C. *Org. Lett.* **2004**, *16*, 2000.

[13] (a) Johnson, C. R.; Lavergne, O. M. *J. Org. Chem*. **1993**, *58*, 1922.
(b) Cheng, Y.; Dong, W.; Wang, L.; Parthasarathy, K.; Bolm, C. *Org. Lett.* **2014**, *16*, 2000.

[14] Dehli, J. R.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 8518.

[15] (a) Wang, L.; Huang, H.; Priebbenow, D, L.; Pan, F. F.; Bolm, C. *Angew. Chem., Int. Ed*. **2013**, *52*, 3478.
(b) Priebbenow, D. L.; Becker, P.; Bolm, C. *Org. Lett.* **2013**, *15*, 6155.
(c) Chen, X. Y.; Bohmann, R. A.; Wang, L.; Dong, S.; Räuber, C.; Bolm, C. *Org. Lett*. **2014**, *16*, 3796.

[16] Chen, X. Y.; Bohmann, R. A.; Wang, L.; Dong, S.; Räuber, C.; Bolm, C. *Chem.-Eur. J.* **2015**, *21*, 10330.

[17] (a) Dwek, R. A. *Chem. Rev*. **1996**, *96*, 683.
(b) Rodríguez, O. M.; Colinas, P. A.; Bravo, R. D. *Synlett* **2009**, 1154.
(c) Colinas, P. A.; Témpera, C. A.; Rodríguez, O. M.; Bravo, R. D. *Synthesis* **2009**, 4143.
(d) Di, H. M.; Liu, Y. T.; Ma, Y. R.; Yang, X. Y.; Jin, H.; Zhang, L. X. *Chin. J. Org. Chem*. **2021**, *41*, 2228 (in Chinese).
(底慧明, 刘云亭, 马艳榕, 杨鑫悦, 金辉, 唐果东, 张立新, 有机化学, **2021**, *41*, 2228.)

[18] Song, W.; Wang, S.; Tang, W. *Chem.-Asian J*. **2017**, *12*, 1027.

[19] Guppi, S. R.; Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 293.

[20] Li, J. H.; Zheng N.; Duan X. L.; Li, R.; Song, W. Z. *Adv. Synth. Catal.* **2021**, *363*, 846.

[21] Li, M.; Zheng, N.; Ullah, K.; Li, J. H.; Dong, K.; Zheng, Y. B.; Song, W. Z. *J. Org. Chem.* **2018**, *83*, 12822.

[22] Tan, B. *Chin. J. Org. Chem*. **2020**, *49*, 1404 (in Chinese).
(谭斌, 有机化学, **2020**, *49*, 1404.)

[23] (a) Mao, Y. J.; Lu, Y. N.; Li, T. Z.; Wu, Q.; Tan, W.; Shi, F. *Chin. J. Org. Chem*. **2020**, *40*, 3895 (in Chinese).
(毛雨佳, 陆一楠, 李天真, 吴琼, 谭伟, 石枫, 有机化学, **2020**, *40*, 3895.)
(b) Wang, X.; Chen, P.; Zhi, S. J.; Hu, H. Y.; Kan, Y. H.; Tang, G. D.; Zhang, Z. C. *Chin. J. Org. Chem*. **2021**, *41*, 1241 (in Chinese).
(王翔, 陈平, 支三军, 胡华友, 阚玉和, 唐果东, 张载超, 有机化学, **2021**, *41*, 1241.)
(c) Estopina-Duran, S.; Taylor, J. E. *Chem.-Eur. J*. **2021**, *27*, 106.
(d) Jiang, M. X.; Zhou, T.; Shi, B. F. *Chin. J. Org. Chem*. **2020**, *40*, 4364 (in Chinese).
(江梦雪, 周涛, 史炳锋, 有机化学, **2020**, *40*, 4364.)

[24] (a) Cho, G. Y.; Okamura, H.; Bolm, C. *J. Org. Chem.* **2005**, *70*, 2346.
(b) Hu, Z. F.; Peng, L. F.; Qiu, R. H.; Orita, A. *Chin. J. Org. Chem*. **2020**, *40*, 3112 (in Chinese).
(胡志芳, 彭丽芬, 邱仁华, 折田明浩, 有机化学, **2020**, *40*, 3112.)

[25] Steinkamp, A. D.; Wiezorek, S.; Brosge, F.; Bolm, C. *Org. Lett.* **2016**, *18*, 5348.

(Zhao, C.)

