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Palladium-Catalyzed Allyl Oxime from Allyloxycarbonyl Oxime

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Abstract

Oximes, which are important classes of nitrogen compounds, are ubiquitous in natural products, drugs as well as materials, and are important intermediates in organic synthesis. We have developed a mild and convenient protocol for the synthesis of allyl oximes. In the presence of $Pd(PPh_3)_4$ and DCM, allyloxycarbonyl oximes successfully underwent decaboxylate reaction at room temperature to afford the corresponding allyl oximes in moderate good yields in eight minutes. And the possible mechanism of the reaction was discussed.

Keywords

Palladium, Decarboxylation, Allyl Oxime

钯催化烯丙基碳酸肟脱羧合成烯丙基肟

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摘　要

肟类化合物是一类重要的含氮化合物，广泛存在于天然产物、药物和活性物质的一种单元结构，是一种

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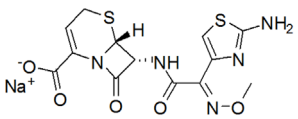
重要的有机合成中间体。研究了在钯催化条件下烯丙基碳酸肟脱羧反应，发展了一种反应条件温和，原料便宜易得，对环境友好的合成烯丙基肟方法，在常温下，以$Pd(PPh_3)_4$为催化剂，DCM为溶剂的反应体系中，反应8分钟就可以得到较高收率的烯丙基肟。并对该反应可能的机理进行了探讨。

关键词

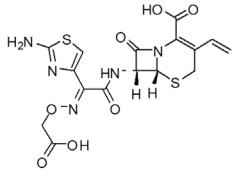
钯，脱羧，烯丙基肟

1. 引言

钯催化脱羧反应是构建 C-C 键，C-X 键的高效合成手段[1] [2]，这类反应可以避免经典偶联反应中常用的强酸、强碱和有毒的金属有机试剂，副产物只有二氧化碳，没有对环境不友好卤化物的生成[3]-[5]，并且反应条件温和，原料易得，肟类化合物是广泛存在于天然产物和活性物质的一种单元结构，具有广谱的杀菌消炎作用[6]。所以经常利用肟来修饰一些药物，一些广泛使用的药物如头孢唑肟钠，头孢噻肟钠，头孢特仑酯，头孢克肟等胺噻肟类头孢菌素[7] [8]。目前，实验室通常使用醛肟或酮肟在强碱性条件下和烯丙基卤反应合成烯丙基肟，或者用烯丙基醇胺和醛反应合成烯丙基肟[9] [10]。这两种方法虽然非常成熟，并应用于工业生产中，但需要在强碱性条件下才能反应，其他基团对碱性的耐受性抑制这种方法在药物合成中的应用[11]-[14]。



Ceftizoxime



Cefixime

2. 实验部分

2.1. 仪器与试剂

本实验所用的溶剂和试剂均为分析纯，购自国药集团化学试剂有限公司百灵威、Acros、Tci 等公司，未进一步处理，层析柱使用 300~400 目硅胶。核磁共振氢、碳谱采用 Bruker AV 500 型核磁共振仪，TMS(四甲基硅烷)为内标，$CDCl_3$ (氘代氯仿)为溶剂；气质由岛津 GC/MS QP2010 PLUS 测定。

2.2. 实验方法

干燥的 Schlenk 管中加入烯丙基碳酸肟酯(0.2 mmol)，$Pd(PPh_3)_4$ (5 % mol)，DCM (二氯甲烷，2 mL)，Ar 保护，常温下反应 8 min，反应结束后，加入乙醚，转移至圆底烧瓶，旋转蒸发仪蒸干溶剂，得到粘稠液体，以 300~400 目硅胶为固定相，以石油醚/乙酸乙酯为流动相分离提纯得到目标产物。

2.3. 产物结构表征

Benzaldehyde O-cinnamyloxime (2a)

黄色油状液体，^{1}HNMR (500 MHz, $CDCl_3$) δ: 8.14(s, 1H), 7.60 -7 .59 (m, 2H), 7.42 - 7.36 (m, 5H), 7.32 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 6.69 (dd, J = 15.5 Hz, 1H), 6.45 - 6.40 (m, 1H), 4.85 - 4.83 (m, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ: 148.9, 136.6, 133.5, 132.2, 129.8, 128.5, 127.8, 127.1, 126.6, 125.1; (EI, 70 eV)

m/z (%): 161 (M+, 49), 131 (35), 117 (22), 77 (77), 41 (100).

Acetophenone O-allyl oxime (2b)

无色油状液体, ^{1}HNMR (500 MHz, $CDCl_3$) δ: 7.65 - 7.64 (m, J = 7.5 Hz, 1H), 7.36 - 7.35 (m, 3H), 6.11 - 6.03 (m, 1H), 5.36 (dd, J = 1.5 Hz 1H), 5.33 (t, J = 5 Hz, 1H), 4.71 (d, J = 5.5 Hz, 1H), 5.44 (d, J = 1.5 Hz, 1H), 2.61 (s, 3H); 13CNMR (125 MHz, $CDCl_3$ δ: 154.8, 136.7, 134.5, 129.0, 128.4, 126.0, 117.3, 75.0, 12.8; LRMS (EI, 70 eV) *m/z* (%): 174 (M+, 100), 103 (20), 77 (73).

3,4-dihydro-1(2H)-one O-allyl oxime (2c)

无色油状液体, ^{1}HNMR (500 MHz, $CDCl_3$) δ: 7.70 (d, J = 8.0 Hz, 1H), 7.33 - 7.26 (m, H), 7.24 - 7.22 (m, 2H), 6.10 - 6.03 (m, 1H), 5.37 - 5.36 (m, 1H), 5.33 - 5.22 (m, 1H), 4.70 - 4.68 (m, 2H), 3.05 - 2.93 (m, 2H), 2.92 - 2.91 (m, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ: 162.9, 148.2, 136.1, 134.6, 130.2, 126.9, 125.5, 121.6, 117.2, 75.0, 28.6, 26.5; LRMS (EI, 70 eV) *m/z* (%): 201 (M+, 100), 184 (35), 129 (43), 41 (100).

3,4-dihydronaphthalen-1(2H)-one-O-allyl oxime (2d)

无色油状液体, ^{1}HNMR (500 MHz, $CDCl_3$) δ: 7.97 (d, J = 7.5, 1H), 7.25 - 7.11 (m, 3H), 6.10 - 6.03 (m, 1H), 5.35 (dd, J = 1.5, 1H), 5.32 - 5.21 (m, 1H), 4.70-4.69 (m, 2H), 2.78 - 2.72 (m, 4H), 1.87 - 182 (2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ: 154.2, 139.5, 134.6, 130.7, 128.9, 128.5, 126.3, 124.2, 117.2, 75.1, 29.7, 24.4, 21.4; LRMS (EI, 70 eV) *m/z* (%): 201 (M+, 59), 184 (35), 129 (43), 41 (100).

Benzaldehyde O-allyl oxime (2e)

无色油状液体, ^{1}HNMR (500 MHz, $CDCl_3$) δ: 8.12 (s, 1H), 7.59 - 7.57 (m, 2H), 7.36 (t, J = 3.5 Hz, 3H), 6.10 - 6.01 (m, 1H), 5.34 (d, J = 15.5 Hz, 1H), 5.25 (d, J = 9.0 Hz, 1H), 4.67 (d, J = 4.5 Hz, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ: 148.8, 134.0, 132.2, 129.8, 128.6, 127.0, 117.9, 75.1.LRMS (EI, 70 eV) *m/z* (%): 161 (M+, 50), 131 (35), 91 (39), 41 (100).

3-methoxybenzaldehyde O-allyl oxime (2f)

无色油状液体, ^{1}HNMR (500 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.29-7.25 (m, 1H), 7.16 (d, J = 2.5 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.93-6.91 (m, 1H), 6.09-6.01 (m, 1H), 5.37 (t, J = 1.5, 1H), 5.34-5.24 (m, 1H), 4.68 (t, J = 4.5 Hz, 2H), 3.83 (s, 3H); ^{13}CNMR (125 MHz,$CDCl_3$) δ: 159.8, 148.8, 133.9, 133.5, 129.7, 120.1, 118.0, 116.2, 111.1, 75.2, 55.3; LRMS (EI, 70 eV) *m/z* (%): 191(M+, 48), 131 (56), 91 (48), 41 (100).

4-methoxybenzaldehyde O-allyl oxime (2g)

无色油状液体, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.07 (s, 1H), 7.52 (t, J = 7, 2H), 6,89 (d, J = 8.5, 2H), 6.09-6.01 (m, 1H), 5.36 (d, J = 2.0, 1H), 5.33 (d, J = 1.5, 1H), 4.65 (d, J = 5.5, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 160.9, 148.5, 134.1, 128.5, 124.8, 117.8, 114.1, 75.0, 55.3, 29.7; LRMS (EI, 70 eV) *m/z* (%): 191(M+, 73), 134 (19), 77 (56), 41 (100).

4-chlorobenzaldehyde O-allyl oxime (2h)

无色油状液体, ^{1}HNMR (500 MHz, $CDCl_3$) δ: 8.07 (s, 1H), 7.51 (d, J = 8.5, 2H), 7.33 (d, J = 9.0, 2H), 6.08-6.00 (m, 1H), 5.37 (d, J = 1.5, 1H), 5.33 (d, J = 1.5, 1H), 4.67 (d, J = 5.5, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ: 147.6, 135.6, 133.8, 130.7, 128.9, 128.2, 118.1, 75.3; LRMS (EI, 70 eV) *m/z* (%): 195 (M+, 35), 165 (14), 111 (26), 41 (100).

benzaldehyde O-3-methylbut-2-enyl oxime (2i)

无色油状液体, ^{1}HNMR (500 MHz, $CDCl_3$) δ: 8.33 (s, 1H), 7.72 (t, J = 1.5, 2H), 7.48 - 7.43 (m, 1H), 7.14 (t, J = 7.5, 2H), 5.46 - 5.43 (m, 1H), 4.78 (d, J = 7.5, 2H), 1.78 (s, 3H), 1,76 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$) δ: 155.6, 153.7, 140.9, 131.6, 129.8, 128.8, 128.3, 117.5, 69.3, 25.7, 18.0; LRMS (EI, 70 eV) *m/z* (%): 18 9(M+,

52), 147 (23), 120 (57), 41 (100).

benzaldehyde O-2-methylallyl oxime (2j)

无色油状液体, ^{1}HNMR (500 MHz, $CDCl_3$) δ: 8.37 (s, 1H), 7.71 (t, J = 6.5, 2H), 7.45 - 7.39 (m, 3H), 4.85 (s, 1H), 4.80 (s, 1H), 4.39 (t, J = 7.0, 2H), 2.45 (t, J = 7.0, 2H), 1.79 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$) δ: 155.6, 153.6, 140.7, 131.6, 129.7, 128.7, 128.2, 112.7, 66.6, 36.5, 22.3; LRMS (EI, 70 eV) *m/z* (%): 175(M+, 34), 161 (47), 120 (59), 41 (100).

3. 结果与讨论

3.1. 钯催化烯丙基碳酸肟脱羧反应条件优化

以苯甲醛肟碳酸肉桂酯为模板，对钯催化剂、溶剂和反应温度进行筛选，探索反应最佳条件(如表 1 所示)。首先以零价 $Pd(PPh_3)_4$ 为催化剂，考察各种溶剂对反应的影响，在一系列溶剂中都能得到中等收率，在 PhMe 和 DME 的反应体系中产率分别为 76%和 69% (表 1，Entry 1 和 2)，THF，MeCN 和 DMSO 为溶剂时产率稍有降低，以 DCM 为溶剂时反应 8 min，产率达到 88% (表 1，Entry 5)，值得一提的是在水中该反应也能达到 47%的收率，以水为溶剂经济价值和环保效益都是最理想的，遗憾的是产率太低。接下来我们以 DCM 为溶剂考察钯催化剂对反应的影响，分别尝试了 $Pd(dba)_2$，$Pd(dppf)Cl_2$，$Pd(OAc)_2$，$PdCl_2/PPh_3$ 和 $Pd(PPh_3)Cl_2$，发现二价钯催化剂得到较高收率，但比零价 $Pd(PPh_3)_4$ 产率低(表 1，Entry 8 - 13)。同时还考察了温度对反应的影响，发现升高温度到 40℃时产率变化不大，当温度升到 80℃时，原料分解副产物增加，产率反而降低(表 1，Entry 15)。但当温度降至 0℃时，反应 45 分钟，产率只有 60%。因此，我们发现该反应的最佳条件：在常温下以 $Pd(PPh_3)_4$ 为催化剂，DCM 为溶剂，反应 8 分钟产率达到 88%。

3.2. 烯丙基碳酸肟脱羧反应适应性研究

在最佳反应条件下，对一系列的烯丙基碳酸肟脱羧反应进行研究(如表 2 所示)，该反应条件对酮肟的适应性较好，其中苯乙酮肟脱羧的产率达到 90% (Entry 2)，环酮肟脱羧反应产率也较高，但 2,3-二氢-1-茚酮肟的产率只有 74% (Entry 3)，当醛肟苯环上带有不同的取代基团时，对产率的影响较小(Entry 6 - 8)，当带有较弱的吸电子基时产率几乎不受影响(Entry 8)。并且在该反应条件下末端烯烃和中间烯烃都能得到较高的收率(9 - 10)。

3.3. 钯催化烯丙基碳酸肟脱羧反应可能机理

基于实验结果和相关文献报道[15]，探讨了钯催化烯丙基碳酸肟酯脱羧合成烯丙基肟的可能机理，零价钯和反应物 1 加成生成 Pd-π-烯丙基金属物种 A，A 随后脱去二氧化碳，生产金属物种 B，中间体 B 还原消除可能存在两条途径，生成产物 2 或 3，但实验结果显示只有产物 2，这可能是因为中间烯烃比末端烯烃的稳定性要好，从而得到单一产物。

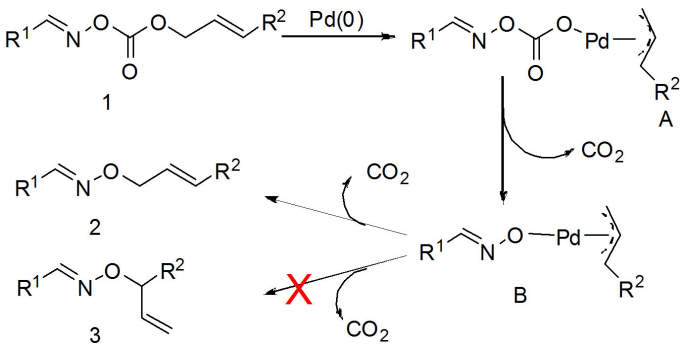
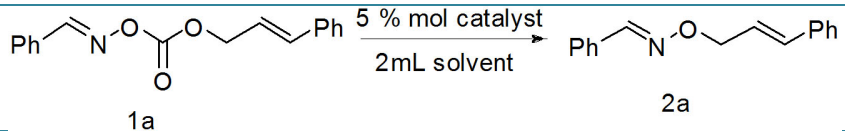


Table 1. Reaction conditions optimization
表 1. 反应条件优化 [a]

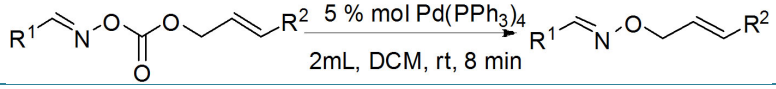


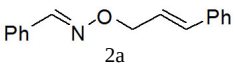
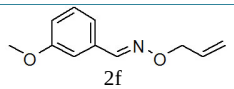
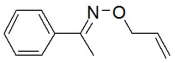
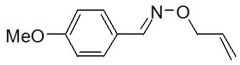
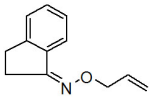
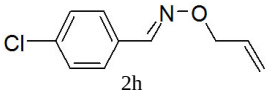
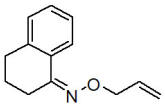
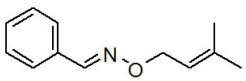
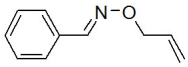
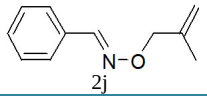
1a 2a

Entry	Pd/L	Solvent	T (℃)	T (min)	Yield (%)[b]
1	$Pd(PPh_3)_4$	PhMe	rt	50	76
2	$Pd(PPh_3)_4$	DME	rt	50	69
3	$Pd(PPh_3)_4$	THF	rt	4	58
4	$Pd(PPh_3)_4$	MeCN	rt	35	60
5	$Pd(PPh_3)_4$	DCM	rt	8	88
6	$Pd(PPh_3)_4$	DMSO	rt	30	57
7	$Pd(PPh_3)_4$	H_2O	rt	10	47
8	$Pd(dba)_2$	DCM	rt	20	65
9	$Pd(dppf)Cl_2$	DCM	rt	28	70
10	$Pd(OAc)_2$	DCM	rt	16	46
11[c]	$PdCl_2/PPh_3$	DCM	rt	20	75
12[d]	$Pd(dba)_2/PPh_3$	DCM	rt	20	77
13	$Pd(PPh_3)Cl_2$	DCM	rt	30	73
14	$Pd(PPh_3)_4$	DCM	40	8	85
15	$Pd(PPh_3)_4$	DCM	80	8	80
16	$Pd(PPh_3)_4$	DCM	0	45	60

[a]Reaction conditions: **1a** (0.2 mmol), catalyst (5 mol %) in solvent (2 mL) at room temperature; [b]Isolated yield; [c,d]10 mol % PPh_3 was used.

Table 2. Palladium-catalyzed allyl oxime from allyloxycarbonyl oxime
表 2. 钯催化烯丙基碳酸肟脱羧合成烯丙基肟 [a]



Entry	Product	Yield (%)[b]	Entry	Product	Yield (%)[b]
1	 2a	85	6	 2f	84
2	 2b	90	7	 2g	83
3	 2c	74	8	 2h	87
4	 2d	85	9	 2i	78
5	 2e	80	10	 2j	85

[a]Reaction conditions: **1a** (0.2 mmol), $Pd(PPh_3)_4$ (5 mol %) in solvent (2 mL) at room temperature; [b]Isolated yield.

4. 结论

我们发展了一种新型的快速合成烯丙基肟的方法，在常温下以 $Pd(PPh_3)_4$ 为催化剂，DCM 为溶剂的

反应体系中，反应 8 分钟就可以得到较高收率的烯丙基肟。该反应条件温和，对环境友好，反应底物适应范围广，反应速度快，为烯丙基肟的合成提供了一种经济、高效的途径。

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