

文章编号: 1001-3555(2013)03-0250-06

Pd₂dba₃ 高效催化碘代芳烃的双羰化反应合成 α-酮酰胺

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摘要: 以高效、廉价易得的 Pd₂dba₃ 作为催化剂, 成功实现了碘代芳烃的双羰化反应, 得到的 α-酮酰胺最高分离收率达 90%。该催化体系对于不同取代基的碘代芳烃和仲胺都具有广泛的底物适应性。

关键词: Pd₂dba₃; 双羰化反应; α-酮酰胺

中图分类号: O643.32 **文献标志码:** A

α-酮酰胺是一类双官能团化合物, 因反应中心多而显示出比一般化合物更为重要和特殊的化学性质, 在有机合成及生物进程中起着承上启下的重要中间体作用。如作为脂肪糖类、核糖、氨基酸及蛋白质的合成中间体, 作为酶抑制剂或酶作用底物等。他们是合成 α-氨基酸、α-羟基酸和杂环化合物的重要中间体, 在生物化学、农药及食品生产中也发挥着越来越重要的作用^[1-3]。因此, 近年来该类化合物的合成研究备受关注。

常规的有机合成方法合成 α-酮酰胺需经过多步复杂反应, 而且条件苛刻, 难以推广应用^[4-6]。因而, 探索环境友好的反应体系以高效合成 α-酮酰胺类化合物已经成为研究的热点。

双羰化反应为 α-酮酰胺的合成提供了一条极为便利的途径, 该反应可以从简单的化工原料出发一步合成 α-酮酰胺。所谓的双羰化反应是指卤代烃在过渡金属络合物催化剂作用下, 当有亲核试剂存在的情况时, 与两分子一氧化碳反应, 生成 α-酮酸及其衍生物, 当亲核试剂为胺时得到 α-酮酰胺^[7]。与传统合成方法^[8-10]相比双羰化反应步骤简单、原料易得, 在精细化学品合成中有巨大的潜在应用价值。因此, 本研究采用三(二亚苄基丙酮)(Pd₂dba₃)二钯为催化剂、三乙烯二胺(DABCO)作为碱, 探索碘代芳烃和脂肪仲胺高效合成 α-酮酰胺的双羰化反应。

1 实验部分

1.1 仪器与试剂

Bruker Avance III 400 MHz 核磁共振仪, 四甲基硅烷(TMS)为内标, 柱层析硅胶为 0.071~0.050 mm。

有机试剂没有经过处理直接使用。

1.2 Pd₂dba₃ 催化碘代芳烃与脂肪仲胺的双羰化

将碘代芳烃(1.0 mmol)、仲胺(4.0 mmol)、三乙烯二胺(DABCO)、三(二亚苄基丙酮)二钯(1.0% mmol)及 4.0 mL THF 依次加入 100 mL 带有磁子的不锈钢反应釜中, CO 置换 3 次, 充入 2.0 MPa CO, 置于 60 °C 油浴中反应 20 h。反应结束后, 冷却至室温, 放空未反应气体。反应液用 6890N/5973N 型 GC-MS 定性分析目标产物, 并经柱层析分离计算产物收率。

N,N-diethyl-2-oxo-2-phenylacetamide

Yellow oil, ¹H NMR (400 MHz, CDCl₃) δ 1.00 (t, *J* = 7.6 Hz, 3H), 1.22 (t, *J* = 7.6 Hz, 3H), 3.23 (q, *J* = 7.0 Hz, 3H), 3.50 (q, *J* = 7.0 Hz, 2H), 7.34-7.43 (m, 2H), 7.58 (t, *J* = 6.4 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 191.5, 166.7, 134.5, 133.1, 129.5, 128.9, 42.0, 38.7, 14.0, 12.8; EI-MS: *m/z* = 205 (M⁺)。

N,N-Di-*n*-propylphenylglyoxyamide

Yellow oil, ¹H NMR (400 MHz, CDCl₃) δ 7.91

收稿日期: 2013-04-17; 修回日期: 2013-05-14。

基金项目: 国家青年科学基金项目(21103044)和教育部博士点基金(201114104120003)。

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(d, $J = 8.8$ Hz, 2H), 7.59 (t, $J = 7.2$ Hz, 1H), 7.46 (t, $J = 7.8$ Hz, 2H), 3.43 (t, $J = 7.8$ Hz, 2H), 3.08 (t, $J = 7.6$ Hz, 2H), 1.73–1.67 (m, 2H), 1.61–1.61 (m, 2H), 0.96 (t, $J = 7.6$ Hz, 3H), 0.75 (t, $J = 7.6$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 191.5, 167.1, 134.4, 133.3, 129.6, 128.9, 49.3, 45.8, 21.8, 20.6, 11.4, 11.0; EI-MS m/z : 233 (M⁺).

N, N-Di-*n*-butylphenylglyoxyamide

Yellow oil, ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, $J = 8.4$ Hz, 2H), 7.61 (t, $J = 7.6$ Hz, 1H), 7.46 (t, $J = 7.6$ Hz, 2H), 3.45 (t, $J = 7.6$ Hz, 2H), 3.10 (t, $J = 7.6$ Hz, 2H), 1.68–1.61 (m, 2H), 1.55–1.47 (m, 2H), 1.44–1.34 (m, 2H), 1.20–1.11 (m, 2H), 0.95 (t, $J = 7.2$ Hz, 3H), 0.77 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 191.6, 167.0, 134.5, 133.3, 129.6, 128.9, 47.4, 44.0, 30.6, 29.4, 20.2, 19.7, 13.9, 13.5; EI-MS m/z : 261 (M⁺); HRMS, M+H: 262.1804; Found: 262.1802.

1-morpholino-2-phenylethane-1, 2-dione

Yellow oil, ¹H NMR (400 MHz, CDCl₃) δ 3.38–3.40 (m, 2H), 3.65–3.67 (m, 2H), 3.77–3.83 (m, 4H), 7.51–7.56 (m, 2H), 7.65–7.69 (m, 1H), 7.95 (dd, $J = 1.2$ Hz, $J = 8.4$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 191.2, 165.4, 135.0, 133.0, 129.7, 129.1, 66.7, 66.6, 46.3, 41.6; EI-MS: $m/z = 219$ (M⁺).

N, N-Diethyl-*p*-tolylglyoxyamide

Yellow oil, ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.4$ Hz, 2H), 3.51 (q, $J = 7.1$ Hz, 3H), 3.18 (q, $J = 7.1$ Hz, 3H), 2.41 (s, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.10 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 191.4, 166.9, 145.7, 130.8, 129.7, 129.6, 42.0, 38.7, 21.9, 14.1, 12.8; EI-MS m/z : 219 (M⁺).

N, N-Diethyl-*o*-tolylglyoxyamide

Yellow oil, ¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, $J = 8.8$ Hz, 1H), 7.43 (t, $J = 8.0$ Hz, 1H), 3.50 (q, $J = 7.1$ Hz, 2H), 3.21 (q, $J = 7.1$ Hz, 2H), 2.64 (s, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.13 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (100 MHz,

CDCl₃) δ 193.6, 167.4, 141.5, 133.5, 132.6, 132.5, 131.6, 42.1, 38.7, 21.8, 13.9, 12.7; EI-MS m/z : 219 (M⁺).

N, N-Diethyl-*p*-anisolphenyglyoxyamide

Yellow oil, ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, $J = 9.4$ Hz, 2H), 6.87 (d, $J = 9.4$ Hz, 2H), 3.79 (s, 3H), 3.43 (q, $J = 7.2$ Hz, 2H), 3.13 (q, $J = 7.0$ Hz, 2H), 1.17 (t, $J = 7.2$ Hz, 3H), 1.04 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 190.2, 166.9, 164.5, 131.8, 126.1, 114.1, 55.4, 41.9, 38.5, 13.9, 12.6; EI-MS m/z : 235 (M⁺).

N, N-Diethyl-4-chloro-phenylglyoxyamide

Yellow oil, ¹H NMR (400 MHz, CDCl₃) δ .85 (d, $J = 6.8$ Hz, 2H), 7.45 (d, $J = 6.8$ Hz, 2H), 3.51 (q, $J = 7.2$ Hz, 2H), 3.19 (q, $J = 7.1$ Hz, 2H), 1.22 (t, $J = 7.2$ Hz, 3H), 1.12 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 190.2, 166.2, 141.1, 131.6, 131.0, 129.3, 42.1, 38.9, 14.1, 12.8; EI-MS m/z : 240 (M⁺).

N, N-Diethyl-4-nitrophenylglyoxyamide

A light orange solid: m. p. 95–96 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, $J = 8.8$ Hz, 2H), 8.10 (d, $J = 8.8$ Hz, 2H), 3.54 (q, $J = 7.1$ Hz, 2H), 3.22 (q, $J = 7.1$ Hz, 2H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.15 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 189.1, 165.4, 151.0, 137.7, 130.7, 124.1, 42.2, 39.2, 14.3, 12.8. EI-MS m/z : 250 (M⁺).

N, N-Diethyl-4-acetylphenylglyoxyamide

A a red solid: m. p. 48–49 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.05–7.99 (m, 4H), 3.52 (q, $J = 7.1$ Hz, 2H), 3.20 (q, $J = 7.2$ Hz, 2H), 2.63 (s, 3H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.16 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 197.3, 190.6, 166.1, 141.1, 136.3, 129.8, 128.7, 42.1, 39.0, 27.0, 14.2, 12.8; EI-MS m/z : 247 (M⁺).

N, N-Diethyl-2-naphthylglyoxyamide

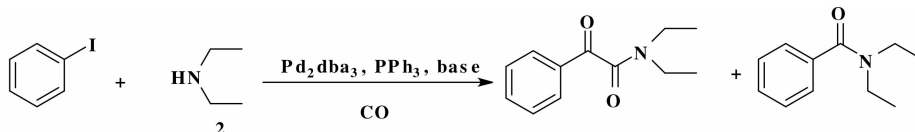
A white solid: m. p. 52–53 °C, ¹H NMR (400 MHz, CDCl₃) δ 9.23 (d, $J = 8.4$ Hz, 1H), 7.24–8.09 (m, 6H), 3.55 (q, $J = 7.1$ Hz, 2H), 3.26 (q, $J = 7.1$ Hz, 2H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.14 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ

194.1, 167.2, 135.7, 134.3, 134.0, 131.0, 129.2, 128.7, 128.5, 126.9, 125.8, 124.5, 42.2, 38.8, 13.9, 12.8; EI-MS m/z : 255 (M^+).

2 结果与讨论

2.1 不同催化条件的影响

为了研究合成 α -酮酰胺的新路线, 我们将三乙烯二乙胺(DABCO)作为碱, 在三苯基膦配体存在下, 实现了钯催化碘代芳烃和二乙胺的双羰化反应



图式1 Pd_2dba_3 催化碘苯与二乙胺的双羰化反应方程式

Scheme 1 Reaction equation of the double carbonylation of iodobenzene and diethylamine catalyzed by Pd_2dba_3

表1 不同配体对碘代芳烃双羰化的影响

Table 1 Effects of the different ligands on the double carbonylation of iodobenzene. ^a

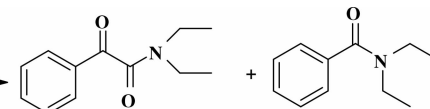
Entry	Ligand	Conv. /%	Yield/% ^b	
			Double	Single
1	PPh_3	>99	97	3.0
2	—	5.0	5.0	NR
3	dppm	13	11	2.0
4	dppe	8.5	2.0	6.5
5	dppp	17	14.0	3.0
6	TPPTS	9.0	7.0	2.0
7	$PPy_3 \cdot HBF_4$	>99	96	4.0
8	α -phos	32	27	5.0

a. Reaction conditions: iodobenzene (1.0 mmol), diethylamine (4.0 mmol); Pd_2dba_3 (0.01 mmol); ligand (0.02 mmol), DABCO (2.0 mmol), THF (4.0 mL), 60 °C for 20 h; b. GC yield

2.2 反应底物的拓展

在优化的反应条件下, 对反应底物进行了拓展, 显示了较好的底物适应性. 我们首先对不同的胺进行了考察: 对于不同链长的仲胺类都取得了较高收率的 α -酮酰胺 (表2中的实验1-4). 对于伯胺, 如正丁胺和环己基胺不发生双羰化反应 (实验5, 6). 随后我们对不同碘代芳烃底物进行了考察,

(图式1). 实验发现, 在这种条件下, α -酮酰胺作为主要产物生成, 气相色谱产率高达97%. 同时, 单羰化的产物产率为3%. 另外, 我们也考察了在相同条件下不加三苯基膦配体, 发现产率很低. 随后, 我们详细考察了不同有机膦配体对该反应的影响. 结果表明, 三苯基膦是最理想的膦配体 (表1). 上述结果显示反应的最优化条件为: 四氢呋喃作溶剂, 三乙烯二乙胺作碱, 在60 °C、2.0 MPa CO的压力下, 反应20 h.



图式1 Pd_2dba_3 催化碘苯与二乙胺的双羰化反应方程式

Scheme 1 Reaction equation of the double carbonylation of iodobenzene and diethylamine catalyzed by Pd_2dba_3

表1 不同配体对碘代芳烃双羰化的影响

Table 1 Effects of the different ligands on the double carbonylation of iodobenzene. ^a

Entry	Ligand	Conv. /%	Yield/% ^b	
			Double	Single
1	PPh_3	>99	97	3.0
2	—	5.0	5.0	NR
3	dppm	13	11	2.0
4	dppe	8.5	2.0	6.5
5	dppp	17	14.0	3.0
6	TPPTS	9.0	7.0	2.0
7	$PPy_3 \cdot HBF_4$	>99	96	4.0
8	α -phos	32	27	5.0

a. Reaction conditions: iodobenzene (1.0 mmol), diethylamine (4.0 mmol); Pd_2dba_3 (0.01 mmol); ligand (0.02 mmol), DABCO (2.0 mmol), THF (4.0 mL), 60 °C for 20 h; b. GC yield

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发现在三(二亚苄基丙酮)二钯和三苯基膦的作用下可以高效催化大多数碘代芳烃底物, 包括反应底物是富电子基和供电子基的碘苯, 除了4-硝基碘苯, 都得到了很高的收率, 可认为是双羰化反应最有利的底物 (实验7, 10-12). 然而, 邻位取代的碘苯收率较低, 分别为84%和62% (实验8, 10). 对于2-萘碘, 亦可得到84%的收率 (实验13).

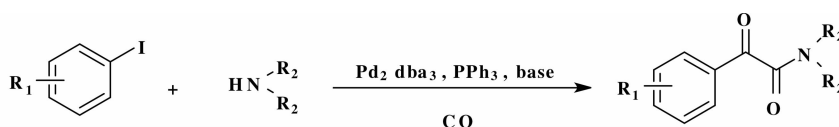
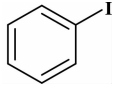
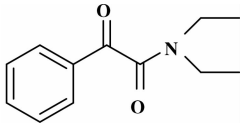
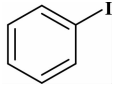
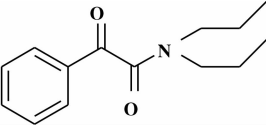
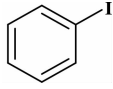
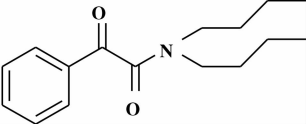
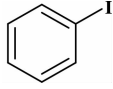

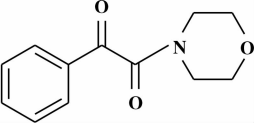
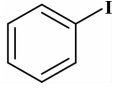
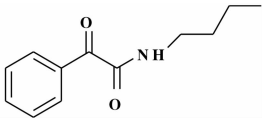
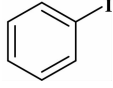
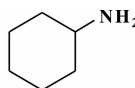
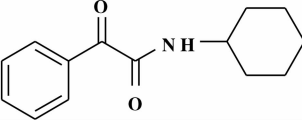
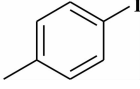
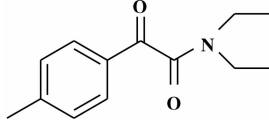
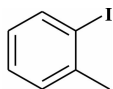
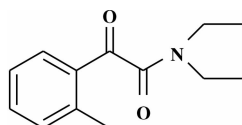
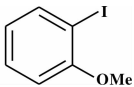
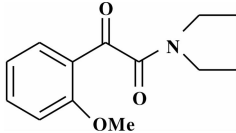
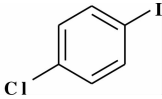
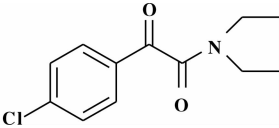
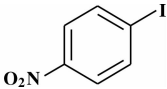
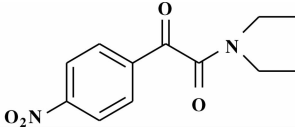
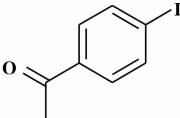
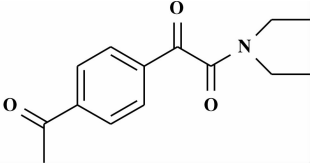
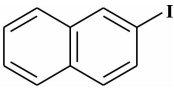
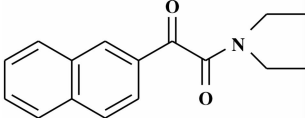


表 2 不同碘代芳烃双羰基化反应

Table 2 The double carbonylation of different aryl iodides and amines. ^a

Entry	Iodobenzene	Amine	Product	Yields/% ^b
1		(CH ₃ CH ₂) ₂ NH		90
2		(CH ₃ CH ₂ CH ₂) ₂ NH		87
3		(CH ₃ CH ₂ CH ₂ CH ₂) ₂ NH		90
4				74
5		<i>n</i> -CH ₃ CH ₂ CH ₂ CH ₂ NH ₂		NR
6				NR
7		(CH ₃ CH ₂) ₂ NH		87
8		(CH ₃ CH ₂) ₂ NH		84

续表 2

Entry	Iodobenzene	Amine	Product	Yields/% ^b
9		(CH ₃ CH ₂) ₂ NH		62
10		(CH ₃ CH ₂) ₂ NH		89
11		(CH ₃ CH ₂) ₂ NH		40
12		(CH ₃ CH ₂) ₂ NH		70
13		(CH ₃ CH ₂) ₂ NH		84

a. Reaction conditions: iodobenzene (1.0 mmol), diethylamine (4.0 mmol), Pd₂dba₃ (0.01 mmol), PPh₃ (0.02 mmol), DABCO (2.0 mmol); THF (4.0 mL), 60 °C for 20 h; b. Isolated yield

3 结 论

我们通过详细考察不同反应条件下碘代芳烃的双羰化反应, 拓展了不同取代碘苯和胺类底物的适应性, 发展了双羰化反应新催化体系, 高效合成了 α -酮酰胺类化合物. 在四氢呋喃体系中, 60 °C 和 2.0 MPa CO 压力下, 采用三(二亚苄基丙酮)二钯作催化剂, 以三乙烯二胺作碱, 多种取代碘苯及胺经双羰化反应只需一步即可得到目标产物, 最高收率达 90%.

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Pd₂dba₃ : A Highly Active Catalyst of Double Carbonylation Reaction for Synthesis of α-keto amide

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Abstract: An efficient double carbonylation reaction of aryl iodides were carried out in presence of a catalytic system *in situ* prepared from Pd₂dba₃, achieving the corresponding products α-keto amide with up to 90% of yield under mild conditions. This developed catalytic system demonstrates a broad tolerance of aryl iodides with various substituents during the double carbonylation reaction.

Key words: Pd₂dba₃; double carbonylation reaction; α-keto amide