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Study on the Condensation Reaction of Hydrazide with Benzylideneacetophenone Catalyzed by Phosphotungstic Acid

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Abstract

The condensation of hydrazide with benzylideneacetophenone was studied by using phosphotungstic acid as catalyst. After a series of reaction conditions, the optimal reaction conditions were established, and the universality of the substrate was investigated. A series of acylhydrazones were obtained with the high yields, up to 99%. The reaction was simple and mild, which provided a new method for the synthesis of chalcone hydrazone.

Keywords

Heteropoly Acid, Condensation Reaction, Acylhydrazone

磷钨酸促进的酰肼与查尔酮缩合反应的研究

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摘　要

本文以杂多酸－磷钨酸为催化剂，对酰肼与查尔酮的缩合反应进行了研究。经过一系列反应条件的筛选，确立了最佳反应条件，并对底物的普适性进行了考察，得到了一系列高产率的酰腙类目标产物，最高产率达到99%。本反应操作简单，条件温和，为查尔酮酰腙合成提供了一种新的方法。

关键词

杂多酸，缩合反应，酰腙

1. 引言

酰腙是一类含有−CONHN = CH−基团的人工合成的化合物，通过酰肼与醛或酮缩合反应制得。因其分子结构中含有亚胺基(−CH = N−)故又属于席夫碱。在生物活性体系中体现出突出的抗菌、抗真菌、抗癌、脲酶抑制、抗氧化和抗糖化等良好的生理活性[1]-[7]。另外，酰腙类化合物与过渡金属、稀土金属等有着很强的配位能力，可以衍生出很多具有较高生物活性的金属配合物[8] [9] [10]。所以，在农药、医药、催化、分析和材料等方面有着广泛应用[11] [12] [13] [14] [15]，多年来一直备受人们的广泛关注。也引起了很多化学和生物学工作者们的极大兴趣，成为越来越活跃的研究领域之一。

本文以苯甲酰肼和查尔酮为原料，通过条件筛选得到最佳反应条件。在最佳条件下，合成了一系列收率较好的查尔酮苯甲酰腙衍生物。为合成酰腙的衍生物寻找一种简单的合成方法。

2. 实验部分

2.1. 试剂与仪器

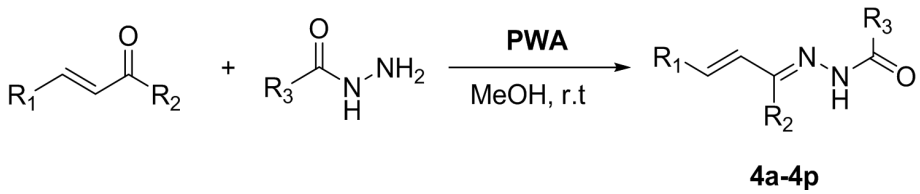
薄层层析硅胶用 GF254 硅胶和 300-400 目柱层析硅胶(青岛海洋化工厂)。常见的显色方式有：ZF-2 型三用紫外仪，碘缸，酸性溶液，茚三酮等，熔点是由 X-4 数字显示显微熔点仪测定。元素分析用 EA-1110 元素分析仪测定。核磁共振是有 VARIAN INOVA-400 型核磁共振波谱仪测定，核磁氢谱的内标为 TMS (δ = 0.00)，核磁碳谱的内标为 $CDCl_3$ (δ = 77.00)。常用试剂：石油醚、乙酸乙酯、甲醇、无水乙醇和二氯甲烷等分析纯试剂是由市售购买而来，未经处理直接使用。苯甲醛、苯乙酮、取代芳香醛、取代芳香酮和芳香胺等是购买于阿拉丁化学厂家，其中对有些不纯的底物在做反应时经过了纯化。

2.2. *α*,*β*-不饱和酮的合成

α,*β*-不饱和酮的合成参照文献[16]。

2.3. 目标化合物 4a~4q 的合成及结构分析

化合物 **4a~4q** 的合成反应如图 1 所示。以化合物 **4a** 为例，向反应管中依次加入查尔酮 0.0208 g (0.10 mmol)，



4a-4p

Figure 1. Synthesis of hydrazone derivatives of 1,3-diphenylallylidene)benzohydrazide (**4a-4p**)
图 1. 查尔酮苯甲酰腙衍生物(**4a~4p**)的合成

苯甲酰肼 0.0204 g (0.15 mmol)，磷钨酸 0.0042 g (0.15 mmol%)，0.5 mL 甲醇，在室温反应 24 h，TLC 跟踪反应情况，反应完毕后减压浓缩，得粗产物，经柱层析分离纯化，得到白色固体(洗脱液为 V1(石油醚):V2(乙酸乙酯) = 1:30，1:20，1:10，1:5)。目标化合物的表征如下：

4a: (Z)-N′-((E)-1,3-diphenylallylidene) benzohydrazide, White solid; 96% yield; m.p. 154~157˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (s, 1H), 7.66~7.27 (m, 15H), 6.42 (d, *J* = 16.4 Hz, 1 H). Anal. Calcd. (%) for $C_{22}H_{18}N_2O$:C, 80.96; H, 5.56; N, 8.59. Found (%): C, 81.07; H, 5.52; N, 8.49.

4b: (*Z*)-*N*′-((*E*)-1-(4-chlorophenyl)-3-phenylallylidene)benzohydrazide, Yellow solid; 92% yield; m.p. 161-163˚C; ^{1}H NMR (400 MHz, $CDCl_3$):δ 8.89(s, 1 H), 7.58~7.26 (m, 14 H), 6.38 (d, *J* = 16.4 Hz, 1 H). Anal. Calcd. (%) for $C_{22}H_{17}ClN_2O$:C, 73.23; H, 4.75; N, 7.76. Found (%): C, 73.44; H, 4.71; N, 7.69.

4c: (*Z*)-*N*′-((*E*)-1-(4-bromophenyl)-3-phenylallylidene) benzohydrazide, White solid; 94% yield; m.p. 173-175˚C; ^{1}H NMR (400 MHz, $CDCl_3$):δ 8.89 (s, 1 H), 7.87~7.19 (m, 14 H), 6.37 (d, 1 H, *J* = 16.8 Hz). Anal. Calcd. (%) for $C_{22}H_{17}BrN_2O$: C, 65.20; H, 4.23; N, 6.91. Found (%): C, 65.37; H, 4.19; N, 6.84.

4d: (*Z*)-*N*′-((*E*)-3-phenyl-1-(*p*-tolyl) allylidene) benzohydrazide, Yellow oil; 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (s, 1 H), 7.56 (d, *J* = 7.2 Hz, 1 H), 7.48~7.38 (m, 10 H), 7.34~7.27 (m, 2 H), 6.44 (d, *J* = 16.2 Hz, 1H), 2.49 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.16, 156.79, 140.25, 138.26, 136.13, 133.21, 131.99, 130.59, 129.16, 129.06, 128.95, 128.79, 128.67, 128.41, 128.10, 127.52, 1227.12, 21.52. Anal. Calcd. (%) for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found (%): C, 81.29; H, 5.83; N, 8.11.

4e: (*Z*)-*N*′-((*E*)-1-(4-methoxyphenyl)-3-phenylallylidene) benzohydrazide, Yellow oil; 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (s, 1 H), 7.59-7.57 (m, 2 H), 7.52-7.25 (m, 10 H), 7.15-7.13 (m, 2 H), 6.46 (d, *J* = 16.4 Hz, 1 H), 3.90 (s, 3 H). Anal. Calcd. (%) for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found (%): C, 77.75; H, 5.57; N, 7.73.

4f: (*Z*)-*N*′-((*E*)-1-(3-chlorophenyl)-3-phenylallylidene) benzohydrazide, White solid; 75% yield; m.p. 122-124˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (s, 1 H), 7.99~7.83 (m, 2 H), 7.74~7. 57 (m, 3 H), 7.53~7.26 (m, 8 H), 7.28~7.26 (m, 1 H), 6.40 (d, *J* = 16 Hz, 1 H). Anal. Calcd. (%) for $C_{22}H_{17}ClN_2O$: C, 73.23; H, 4.75; N, 7.76. Found (%): C, 73.38; H, 4.74; N, 7.71.

4g: (*Z*)-*N*′-((*E*)-3-phenyl-1-(*m*-tolyl)allylidene) benzohydrazide, Yellow oil; 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1 H), 7.59 (d, *J* = 7.2 Hz, 1 H), 7.42-7.38 (m, 10 H), 7.30~7.24 (m, 2 H), 6.42 (d, *J* = 16.6 Hz, 1 H), 2.42 (s, 3 H). Anal. Calcd. (%) for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found(%): C, 81.26; H, 5.85; N, 8.17.

4h: (*Z*)-*N*′-((*E*)-3-(4-fluorophenyl)-1-phenylallylidene) benzohydrazide, White solid; 85% yield; m.p. 114~116˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (s, 1 H), 7.98~7.88 (m, 1 H), 7.74~7.27 (m, 9 H), 7.12~6.99 (m, 2 H), 6.38 (d, J = 16.4 Hz, 1 H), 2.42 (s, 3 H). Anal. Calcd.(%) for $C_{22}H_{17}FN_2O$: C, 76.73; H, 4.98; N, 8.13. Found (%):C, 76.88; H, 4.74; N, 8.21.

4i: (*Z*)-*N*′-((*E*)-3-(4-chlorophenyl)-1-phenylallylidene)benzohydrazide A White solid; 87% yield; m.p. 118~121˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1 H), 8.01~7.94 (m, 1 H), 7.74~7.58 (m, 2 H), 7.53~7.52 (m, 9 H), 6.37 (d, *J* = 16.4 Hz, 1 H). Anal. Calcd.(%) for $C_{22}H_{17}ClN_2O$: C, 73.23; H, 4.75; N, 7.76. Found(%): C, 73.41; H, 4.66; N, 7.62.

4j: (*Z*)-*N*′-((*E*)-3-(4-bromophenyl)-1-phenylallylidene) benzohydrazide, Yellow solid; 65% yield; m.p. 112~114˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1 H), 7.65-7.62 (m, 3 H), 7.55~7.53 (m, 2 H), 7.50~7.44 (m, 3 H), 7.39-7.33 (m, 4 H), 7.27~7.25 (m, 2 H), 6.35 (d, *J* = 16.8 Hz, 1 H). Anal. Calcd. (%) for $C_{22}H_{17}BrN_2O$: C,

65.20; H, 4.23; N, 6.91. Found (%): C, 65.34; H, 4.12; N, 6.88.

4k: (*Z*)-*N*′-((*E*)-3-(4-methoxyphenyl)-1-phenylallylidene) benzohydrazide, Yellow solid; 88% yield; m.p. 106~109˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1 H), 7.65~7.46 (m, 6 H), 7.38~7.27 (m, 6 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.37 (d, *J* = 16 Hz, 1 H), 3.86 (s, 3H). Anal. Calcd. (%) for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found (%): C, 77.68; H, 5.59; N, 7.78.

4l: (*E*)-*N*′-((*E*)-4-(4-methoxyphenyl)but-3-en-2-ylidene)benzohydrazide, White solid; 92% yield; m.p. 202~204˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.01 (s, 1 H), 7.85 (s, 2 H), 7.55-7.36 (m, 5 H), 7.16-7.01 (m, 2 H), 6.99~6.88 (m, 2 H), 3.84 (s, 3 H), 2.18 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.21, 161.20, 153.58, 134.42, 133.04, 129.90, 127.87, 128.49, 127.53, 126.76, 114.47, 55.36, 29.34. MS (ESI m/z) 317.1 [(M + Na^+, 100%)]. Anal. Calcd. (%) for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found (%): C, 73.52; H, 6.09; N, 9.39.

4m: (*Z*)-4-chloro-*N*′-((*E*)-1,3-diphenylallylidene)benzohydrazide, Yellow solid; 99% yield; m.p. 175~176˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (s, 1 H), 8.02 (s, 1 H), 7.65~7.60 (m, 3 H), 7.46-7.39 (m, 5 H), 9.34~7.26 (m, 5 H), 7.23 (s, 1 H), 7.43 (d, *J* = 16 Hz, 1 H). Anal. Calcd. (%) for $C_{22}H_{17}ClN_2O$: C, 73.23; H, 4.75; N, 7.76. Found (%): C, 73.36; H, 4.68; N, 7.65.

4n: (*Z*)-4-bromo-*N*′-((*E*)-1,3-diphenylallylidene) benzohydrazide, Yellow solid; 98% yield; m.p. 124~126˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (s, 1 H), 8.02 (s, 1 H), 7.71~7.55 (m, 3 H), 7.53~7.50 (m, 2 H), 7.44~7.27 (m, 8 H), 6.43 (d, *J* = 16.4 Hz, 1 H). Anal. Calcd. (%) for $C_{22}H_{17}BrN_2O$: C, 65.20; H, 4.23; N, 6.91. Found (%): C, 65.33; H, 4.18; N, 6.82.

4o: (*Z*)-*N*′-((*E*)-1,3-diphenylallylidene)-4-methoxybenzohydrazide, Yellow solid; 78% yield; m.p. 204~207˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.92 (s, 1 H), 7.66-7.57 (m, 3 H), 7.52-7.49 (m, 2 H), 7.44-7.39 (m, 3 H), 7.35~7.27 (m, 4 H), 6.86 (d, *J* = 6 Hz, 2 H), 6.40 (d, *J* = 16.4 Hz, 1 H). Anal. Calcd. (%) for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found (%): C, 77.61; H, 5.53; N, 7.69.

4p: (*Z*)-2-chloro-*N*′-((*E*)-1,3-diphenylallylidene) benzohydrazide, White solid; 86% yield; m.p. 163~165˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.26 (s, 1 H), 7.87~7.84 (m, 1 H), 7.60~7.52 (m, 4 H), 7.47~7.36 (m, 3 H), 7.32-7.29 (m, 6 H), 6.91 (d, *J* = 16.4 Hz, 1 H). Anal. Calcd.(%) for $C_{22}H_{17}ClN_2O$: C, 73.23; H, 4.75; N, 7.76. Found(%): C, 73.41; H, 4.57; N, 7.59.

4q: (Z)-N′-((E)-1,3-diphenylallylidene)-2-methylbenzohydrazide, Yellow oil; 85% yield; ^{1}H NMR (400 MHz, CDCl3) δ:8.57 (s, 1 H), 7.60~7.51 (m, 3 H), 7.46~7.24 (m, 9 H), 7.21~7.13 (m, 2 H), 6.40 (d, *J* = 16.4 Hz, 1 H). Anal. Calcd. (%) for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found (%): C, 81.31; H, 5.79; N, 8.12.

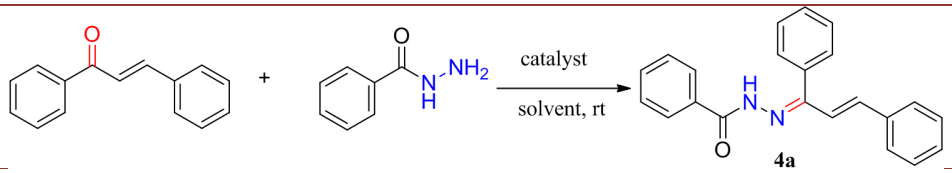
3. 结果与讨论

3.1. 最优反应条件的筛选

以查尔酮与苯甲酰肼反应为标准反应，分别进行了催化剂种类和用量、反应溶剂种类和用量、底物配比和反应时间等条件进行了优化，结果见表 1。

从表 1 中可以看出，在没有加入催化剂时，反应不发生(表 1，Entry 1)；用杂多酸磷钨酸和磷钼酸分别催化时，磷钨酸表现出了较好的产率(表 1，Entry 2)；当用 MCM-41 固载的磷钨酸(磷钼酸)催化反应时，产率有所降低，所以我们选定磷钨酸作为催化剂。然后进行了催化剂的量筛选，实验结果表明磷钨酸量为 0.15 mmol%产率最高。在对反应溶剂筛选时，发现甲醇作为溶剂，反应产率最高，89%。为了得到更高的产率，随后考察了其它溶剂对产率的影响。结果表明其它溶剂没有醇类溶剂的效果好，而在醇类溶剂中，反应产率依然在甲醇中得到最高。确定上述反应条件后，我们对底物比例进行了考察，分别对底物查尔酮：苯甲

Table 1. Optimization of reaction conditions[a]
表 1. 反应条件的优化[a]



4a

Entry	Catalyst	Solvent	(n) chalcone/(n) hydrazide	Temperature	Time	Yield(%)[b]
1	-	CH_3OH	1:1.2	R.T.	24	N.R.[c]
2	PWA (0.15 mmol%)	CH_3OH	1:1.2	R.T.	24	89
3	PMA (0.15 mmol%)	CH_3OH	1:1.2	R.T.	24	78
4	50 wt% PWA/MCM-41 (0.15 mmol%)	CH_3OH	1:1.2	R.T.	24	55
5	50 wt% PMA/MCM-41 (0.15 mmol%)	CH_3OH	1:1.2	R.T.	24	65
6	PWA (0.10 mmol%)	CH_3OH	1:1.2	R.T.	24	52
7	PWA (0.05 mmol%)	CH_3OH	1:1.2	R.T.	24	60
8	PWA (0.20 mmol%)	CH_3OH	1:1.2	R.T.	24	88
9	PWA (0.15 mmol%)	CH_2Cl_2	1:1.2	R.T.	24	60
10	PWA (0.15 mmol%)	CH_3CN	1:1.2	R.T.	24	52
11	PWA (0.15 mmol%)	$CH_3C_6H_5$	1:1.2	R.T.	24	58
12	PWA (0.15 mmol%)	CH_3COOEt	1:1.2	R.T.	24	64
13	PWA (0.15 mmol%)	THF	1:1.2	R.T.	24	43
14	PWA (0.15 mmol%)	C_2H_5OH	1:1.2	R.T.	24	75
15	PWA (0.15 mmol%)	CH_3OH	1:1	R.T.	24	75
16	PWA (0.15 mmol%)	CH_3OH	1:1.5	R.T.	24	96
17	PWA (0.15 mmol%)	CH_3OH	1:2	R.T.	24	80
18	PWA (0.15 mmol%)	CH_3OH	1:1.5	R.T.	12	73
19	PWA (0.15 mmol%)	CH_3OH	1:1.5	R.T.	18	82
20	PWA (0.15 mmol%)	CH_3OH	1:1.5	R.T.	36	83

[a]反应条件：查尔酮 0.1 mmol，酰肼 0.15 mmol 催化剂量为 0.15 mmol%在 0.5 mL 甲醇中室温反应 24 h。[b]柱层析产率。[c]N.R = No Reaction。

酰肼为 1:1，1:1.2，1:1.5，1:2 等比例下进行了筛选，结果见表 1 的 Entries 14-17。从表中可以看到，随着酰肼量的增加，产率有所上升，在 1:1.5 时，达到 96%的产率，当继续增加酰肼的量(比例为 1:2)时，产率有所下降，所以最有底物比例为 1:1.5。实验在常温条件下进行，这属于理想反应条件范畴。最后对反应时间进行了考察，结果列于表 1 的 Entries 17-20。反应中，当反应时间延长到 24 h 时，反应产率得到最高值 96%，继续延长反应时间，产率处于下降趋势。通过对实验条件的筛选，最佳反应条件为：室温下以 0.15 mmol%的磷钨酸为催化剂，0.5 mL 甲醇为溶剂，底物配比(查尔酮:苯甲酰肼)为 1:1.5，反应 24 h。

3.2. 底物结构对反应的影响

在最佳反应条件下，对底物进行了普适性的研究，结果详见表 1。

从表 2 中，可以看到 R_2 上的取代基无论是吸电子基团还是供电子基团，都能够很好地得到相应的目

Table 2. Substrate scope[a]
表 2. 底物结构的拓展 [a]

Entry	R_1	R_2	R_3	Product	Yield(%)[b]
1	Ph	Ph	Ph	**4a**	96
2	Ph	*p*-ClPh	Ph	**4b**	92
3	Ph	*p*-BrPh	Ph	**4c**	94
4	Ph	*p*-CH_3Ph	Ph	**4d**	83
5	Ph	*p*-OCH_3Ph	Ph	**4e**	90
6	Ph	*m*-ClPh	Ph	**4f**	75
7	Ph	*m*-CH_3Ph	Ph	**4g**	67
8	*p*-FPh	Ph	Ph	**4h**	85
9	*p*-ClPh	Ph	Ph	**4i**	87
10	*p*-BrPh	Ph	Ph	**4j**	65
11	*p*-OCH_3Ph	Ph	Ph	**4k**	88
12	*p*-OCH_3Ph	CH_3	Ph	**4l**	92
13	Ph	Ph	p-ClPh	**4m**	99
14	Ph	Ph	p-BrPh	**4n**	98
15	Ph	Ph	p-OCH_3Ph	**4o**	78
16	Ph	Ph	o-ClPh	**4p**	86
17	Ph	Ph	o-CH_3Ph	**4q**	85

[a]反应条件：查尔酮 0.1 mmol，酰肼 0.15 mmol 催化剂量为 0.004 g 在 0.5 mL 甲醇中室温反应 24 h。[b]柱层析产率。

标产物；当同种取代基苯环上的位置不同时，其产率也有很大的变化，而且对位取代的产率要高于间位取代，如 R_2，氯取代对位时的产率要高于其间位取代(Entries 2, 6)，对甲基比间甲基的产率高(Entries 4, 7)。对于 R_1 苯环上的取代基，除了 Br 取代产率较低外，其它产率都能达到 85%以上。在酰肼 R_3 取代基的改变中，从表中可以看出，对位和邻位取代的酰肼都获得了较高的产率。

4. 结论

本文研究了查尔酮和酰肼的缩合反应。通过优化实验，最终得出了最优反应条件：0.004 g 磷钨酸为催化剂、底物配比为 1:1.5(查尔酮:酰肼)，甲醇为溶剂，室温下反应 24 h。在该反应条件下，获得了一系列高产率的酰腙类目标产物，最高产率达到 99%。本反应具有反应条件温和，催化剂廉价易得等优点。

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