

# 酰胺催化脱水制备腈的研究进展

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## 摘要

氰基官能团因广泛存在于药物、农用化学品、染料和精细化学品中,且可方便地转化为其他重要官能团如醛基、羧基、酰胺、伯胺、亚胺等或构建杂环体系而受到化学家的大量关注。传统的腈类制备方法如烷基、芳基(拟)卤代物与氰化物反应、酰胺或醛肟脱水等存在剧毒氰源的使用、剧烈反应条件和原子经济性差等问题。而温和条件下酰胺的催化脱水是制备腈类的理想途径。本文将重点讨论近年来酰胺催化脱水制备腈的研究进展。

## 关键词

腈, 酰胺, 催化脱水

# Research Progress of Catalytic Dehydration of Amides to Nitriles

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## Abstract

The cyano functional group widely exists in pharmaceuticals, agrochemicals, dyes and fine chemicals. As it can be easily converted into other functional groups such as aldehyde, ester, amide, primary amine, and imine, its preparation has attracted numerous attention from organic chemists. Traditional methods for nitrile synthesis including reactions of alkyl- or aryl (pseudo)halides with cyanides and dehydration of amides or aldoximes often require highly toxic reagents, harsh conditions and suffer from poor atom economy. Catalytic amide dehydration under mild condi-

tions is an ideal approach to nitriles. This article focuses on recent advances in catalytic dehydration of amides to nitriles.

## Keywords

Nitrile, Amide, Catalytic Dehydration

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## 1. 引言

腈类化合物，天然存在于各种细菌、真菌和动植物中，并被广泛用作生产各种药物、农用化学品、聚合物和材料等的原料[1] [2]。大量的药物分子结构中包含氰基[3]，如维格列汀(Vildagliptin，一种糖尿病药物) [4]、来曲唑(Letrozole) [5]和阿那曲唑(Anastrozole，用于治疗乳腺癌的药物) [6]等(图 1(a))。此外，氰基官能团作为有机合成中的通用中间体，可以方便地转化为其他重要的官能团(如醛、羧酸、酯、酰胺、伯胺、亚胺等) [7]或构建杂环体系(如咪唑、嘧啶、三唑等) [8] [9] [10] [11]。然而传统的腈类制备方法如烷基、芳基(拟)卤代物与氰化物反应、酰胺或醛肟脱水(图 1(b))以及工业上常用的氨氧化、氢氰化反应等仍存在各种问题[12]，如剧毒氰源的使用、剧烈反应条件、原子经济性差等。相比之下，温和条件下金属或非金属催化的酰胺脱水是制备腈类的理想途径。本文将重点讨论近年来酰胺催化脱水的研究进展。

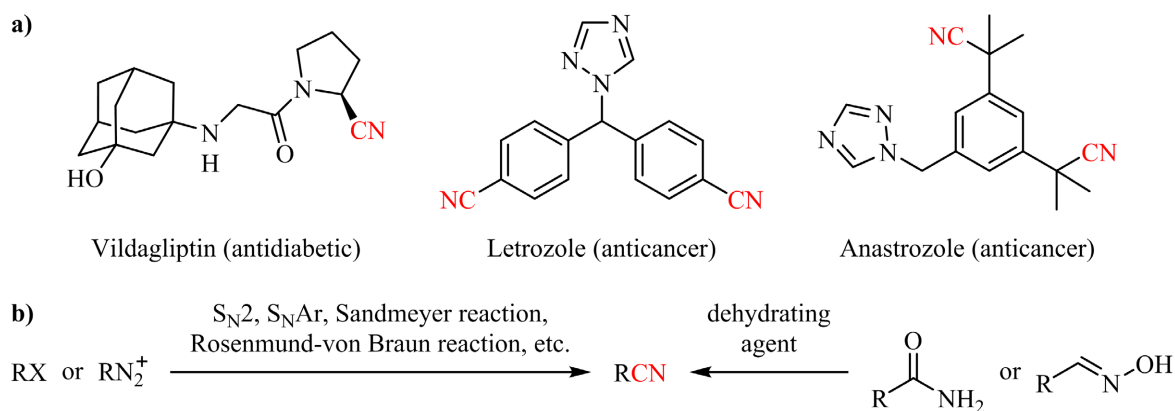


Figure 1. Representative cyano-containing pharmaceuticals (a) and traditional methods for nitrile synthesis (b)

图 1. 代表性含氰基药物(a)与传统腈类合成方法(b)

## 2. 金属催化酰胺脱水

### 2.1. 高温下金属催化酰胺脱水

早期的金属催化酰胺脱水条件[13]-[20]如 Yamamoto 等人报道的高铈酸共沸去水体系(图 2(a)) [18]，Kaneda 等人发展的钒氧化物/水滑石(Hydrotalcite, Mg<sub>6</sub>Al<sub>2</sub>(OH)<sub>16</sub>CO<sub>3</sub>)固相负载催化剂(图 2(b)) [19]，以及 Bergman 和 Ruck 报道的钨催化体系(图 2(c)) [20]等尽管在底物适用范围和官能团兼容性方面取得了一定进展，但普遍还需较高温度或在封管(高压釜)中进行。

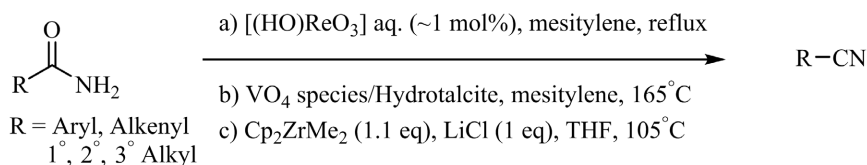


Figure 2. Metal-catalyzed amide dehydration at high temperature

图 2. 高温下金属催化酰胺脱水

## 2.2. (取代)乙腈作为脱水剂的金属催化酰胺脱水

Marazzi 小组于 2005 年首次报道了用乙腈作为脱水剂, 在二氯化钯催化下酰胺脱水生成腈的可逆过程[21]。随后, 若干催化体系成功实现了酰胺向腈的这一完全转化[22] [23] [24] [25]。其中, 代明骥小组报道了二(三苯基膦基)二氯化钯/醋酸铜和氯化钯/醋酸银两个互补的催化体系[23], 脂肪族、芳香族伯酰胺以及  $\alpha,\beta$ -不饱和酰胺特别是各种官能团取代的肉桂酰胺均取得了中等到优异的收率(图 3)。尤其前一催化体系对敏感官能团如氯、溴、碘、硝基等表现出较好的兼容性。此外, Croatt 小组发现 Pd(OAc)<sub>2</sub>/Selectfluor 体系同样可用于酰胺到腈的转化并取得较好的收率[25], 该体系对于大位阻叔烷基伯酰胺尤其有效(图 4)。

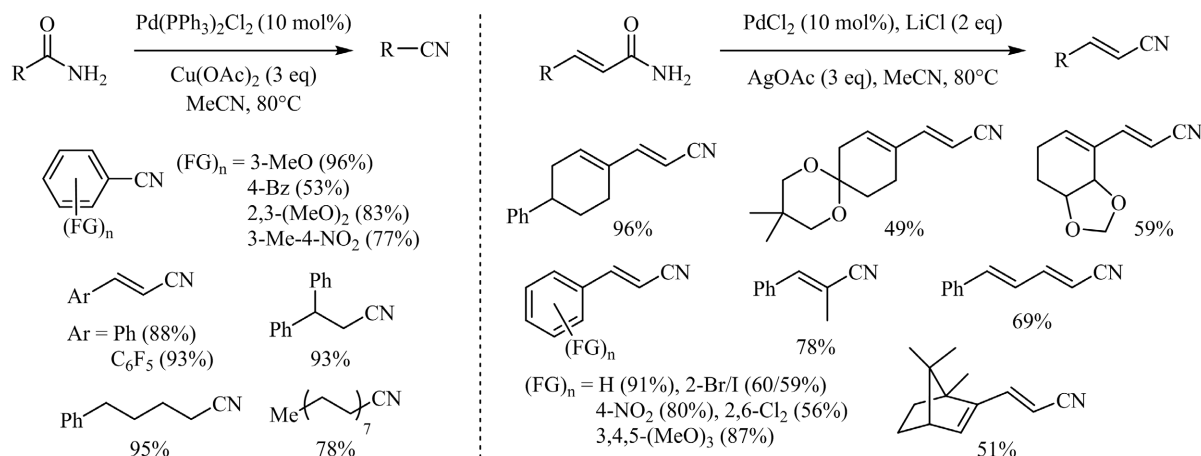


Figure 3. Cu(OAc)<sub>2</sub>/AgOAc participated palladium catalyzed amide dehydration

图 3. 醋酸铜/醋酸银参与的钯催化酰胺脱水

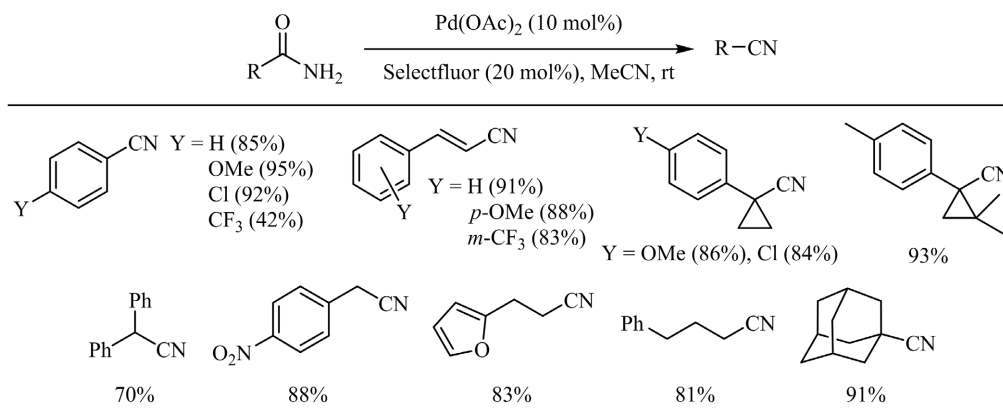


Figure 4. Selectfluor participated palladium catalyzed amide dehydration

图 4. Selectfluor 参与的钯催化酰胺脱水

2019年, Naka 等人发现改用二氯乙腈作为水分子受体对于水分子从酰胺到腈的转移过程在能量上更为有利[26]。在三氟乙酸钯催化下, 一系列天然氨基酸衍生的伯酰胺以中等到优秀的收率得到相应的  $\alpha$ -氨基腈, Cbz、Fmoc、Ac 和 Bz 等保护基团、醇羟基、酚羟基、羧基以及酰胺  $\alpha$ 、 $\beta$  位手性中心均不受影响(图 5)。

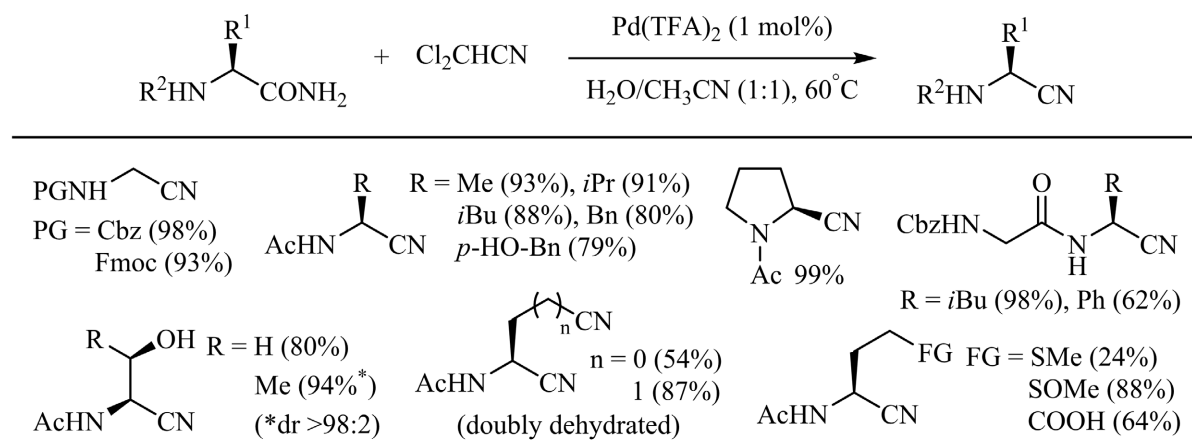


Figure 5. Palladium catalyzed amide dehydration using dichloroacetonitrile as dehydrating agent  
图 5. 二氯乙腈作脱水剂的钯催化酰胺脱水

### 2.3. 硅试剂参与的金催化脱水

近年来, 硅试剂参与的金催化酰胺脱水反应不断见诸报道[27]-[47]。Nagashima 小组于 2008 年报道了羰基三钌簇合物催化下硅试剂参与的酰胺脱水反应[27]。反应最初生成的  $N,N$ -双硅基酰胺通过硅基迁移得到  $N,O$ -双硅基亚胺酸酯, 后者顺式消除得到相应的腈和硅氧化物。在上述反应条件下, 芳香族和脂肪族伯酰胺均取得了良好到优秀的收率, 芳香酰胺邻位位阻和对位强供电子基对收率影响不大, 氯、溴和碳碳双键等官能团亦表现出较好的兼容性(图 6)。Beller 小组随后报道了羰基铁配合物催化的酰胺脱水[28]。相比于上述钌催化体系, 底物范围扩展到杂芳基-2-甲酰胺(中等收率), 而烟酰胺在此条件下无反应(图 7)。值得注意的是, 肉桂酰胺的双键大部分被还原(33%收率)。

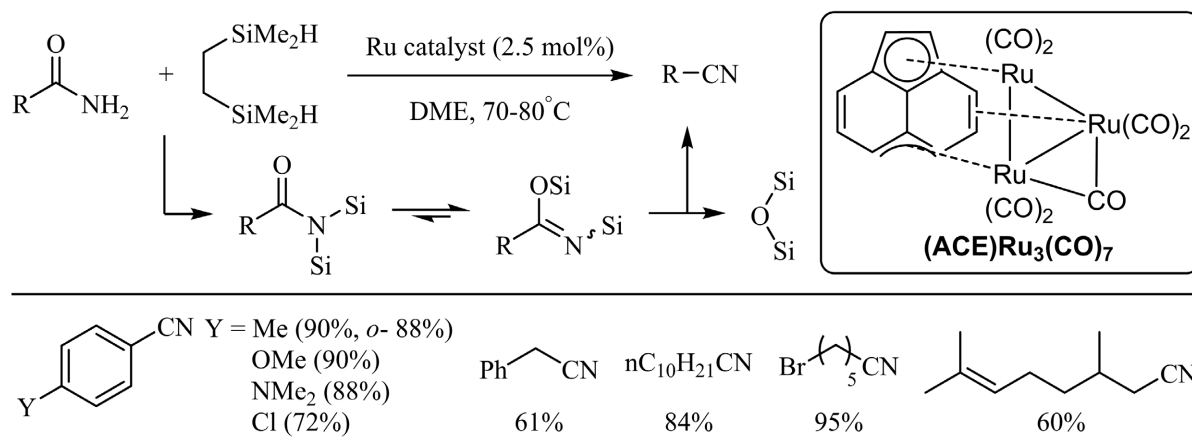
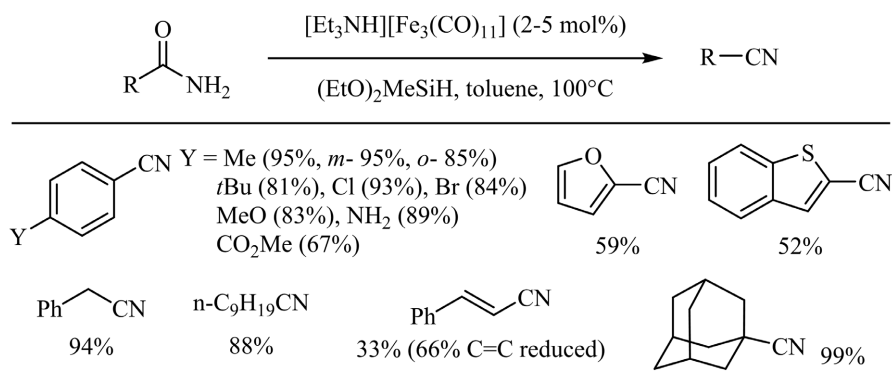
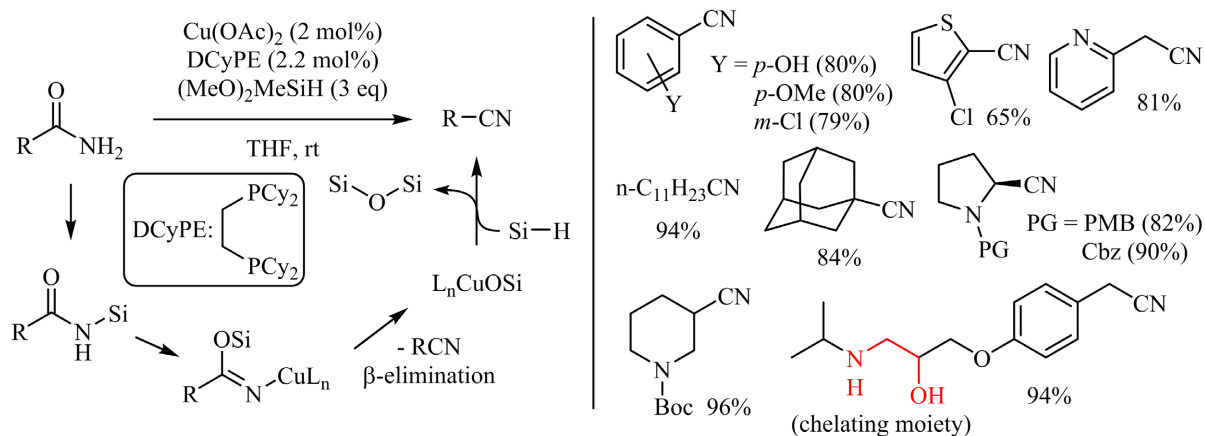


Figure 6. Ruthenium catalyzed silylative dehydration of amides  
图 6. 硅试剂参与的钌催化酰胺脱水



**Figure 7.** Iron catalyzed silylative dehydration of amides  
**图 7.** 硅试剂参与的铁催化酰胺脱水

2018年, Buchwald 等人通过密度泛函理论(DFT)计算发现上述反应历程中硅氧化物顺式热消除一步能垒较高( $\Delta G > 35$  kcal/mol), 针对这一问题, 他们发展出更加温和且高效的铜催化体系[38], 通过低能垒的 $\beta$ -消除极大地促进了脱水过程, 使反应在室温下顺利进行并大大拓展了官能团兼容性和底物适用范围(图8)。此外, 黄正及其同事们于2019年报道了三乙基硼烷/醋酸钾催化下苯基硅烷或聚甲基氢硅烷(PMHS)参与的酰胺脱水[43], 这一简单实用的催化体系同样可在温和条件下(室温或 $50^\circ\text{C}$ )以良好到优秀的收率将一系列脂肪族、芳香族伯酰胺转化为相应的腈。



**Figure 8.** Iron catalyzed silylative dehydration of amides  
**图 8.** 硅试剂参与的铜催化酰胺脱水

### 3. 非金属及有机催化的酰胺脱水

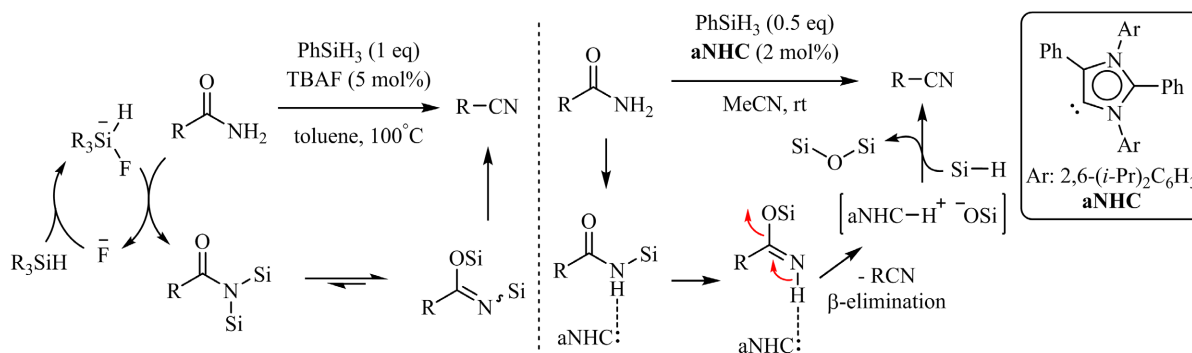
#### 3.1. 四丁基氟化铵(TBAF)和氮杂环卡宾(NHC)催化的酰胺脱水

Beller 小组和 Mandal 小组分别报道了四丁基氟化铵(TBAF) [48]和氮杂环卡宾(NHC) [49]催化的酰胺脱水反应(图9), 后者同样通过低能垒的 $\beta$ -消除得到相应的腈, 因而具有广泛的底物适用范围, 且对羟基、氨基、杂芳基如(吡啶、噻吩)等配位性基团有较好的兼容性。

#### 3.2. 三苯氧磷、DMSO 和环丙烯酮催化的酰胺脱水

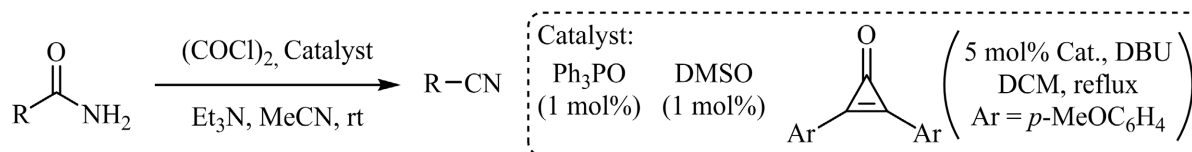
2018年, Malkov 等人报道了三苯氧磷催化的 Appel 型酰胺脱水[50], 脂肪族、芳香族酰胺(包括吡啶、

噻吩等杂芳基酰胺)以及  $\alpha$ -羟基(氨基)酰胺衍生物等均以优秀的收率转化为相应的氰基化合物,但 *N*-Boc 保护基在此条件下不兼容。DMSO 催化的 Swern 型酰胺脱水[51]和环丙烯酮催化脱水[52]也已见诸报道(图 10)。



**Figure 9.** TBAF and a NHC catalyzed amide dehydration

**图 9.** 四丁基氟化铵和氮杂环卡宾催化的酰胺脱水



**Figure 10.**  $\text{Ph}_3\text{PO}$ , DMSO and cyclopropanone catalyzed amide dehydration

**图 10.** 三苯氧磷、DMSO 和环丙烯酮催化的酰胺脱水

## 4. 总结

本文系统介绍了近年来发展的金属、非金属和有机催化的酰胺脱水制备腈的方法,并初步探讨了各种方法的反应机理、底物适用范围、官能团兼容性问题。相比于金属催化的酰胺脱水体系,非金属和有机小分子催化的相关报道仍然较少。对比 Buchwald 等人发展的铜催化体系和 Mandal 小组的氮杂环卡宾体系,二者在产率、底物范围和官能团兼容性等方面不相上下。因此,有机催化在这一领域有望取得更多的应用。此外,更加温和、高效、高选择性和原子经济性的催化脱水策略和相关机理也有待进一步探索。

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