

芳烃的氰甲基化反应

朱梦娇, 郑丁铭, 吉江涛

浙江师范大学化学与材料科学学院, 浙江 金华

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摘 要

腈类基团是一类广泛存在于一些具有药理学作用的化合物和一些天然产物中的重要官能团。芳基乙腈更是可以作为一些具有生物活性分子的起始原料, 而且腈基可以很容易地转化为各种其他官能团, 比如胺、酸、酰胺等。芳基乙腈本身也可以作为某些杂环结构的构建单元。本文将对这类官能团的合成, 即芳烃的氰甲基化进行总结和分析。通过文献调研发现, 目前这类反应主要通过金属催化实现。

关键词

芳基的氰甲基化, 腈, 金属催化

Cyanomethylation of Aromatic Hydrocarbons

Mengjiao Zhu, Dingming Zheng, Jiangtao Ji

College of Chemistry and Materials Science, Zhejiang Normal University, Jinhua Zhejiang

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Abstract

Nitrile groups are a kind of important functional groups widely existing in some compounds with pharmacological effects and some natural products. Aryl acetonitrile can be used as a starting material for some biologically active molecules, and the cyanide group can be easily converted into various other functional groups, such as amines, acids, amides, etc. Aryl acetonitrile itself can also be used as a building block for some heterocyclic structures. In this paper, the synthesis of these functional groups, that is, the cyanomethylation of aromatics, will be summarized and analyzed. Through the literature research, at present, this kind of reaction is mainly achieved by metal catalysis.

Keywords

Aryl Cyanomethylation, Nitrile, Metal Catalysis

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1. 引言

腈基团近年来在药物合成中发挥着越来越重要的作用[1][2],并且在许多农作物增强抗性方面和改变材料延展性方面也发挥着极其重要的作用[3]-[5]。基于芳基乙腈的特殊结构,既有亲电性又有酸性。芳基取代腈不仅是构建伯胺、内酯、吡啶、醛类、羧酸、双环脒和酯类等化合物的重要组成部分[6]-[11],也是合成具有生物活性化合物的重要组成部分[12]-[15]。然而,直接通过芳基来合成芳基腈是非常困难的,只有少数文献报道描述了腈碳离子与另一个未经活化的芳基氟化物或具有吸电子基团的芳基卤化物的非催化偶联。虽然反应过程丰富、便宜,但是他们的反应性极低,使得这种合成方法的发展受到了严重抑制[16]-[23]。鉴于以上调查结果,本文将着重介绍经由金属催化介导的芳烃的氰甲基化。

2. 芳烃的氰甲基化

2.1. 钯催化芳烃卤化物与硅烷或异恶唑偶联实现的氰甲基化

2005年, Hartwig 等人[24]对芳烃的氰甲基化反应条件进行了探索,发现在弱碱性条件下,锌介导钯催化芳基卤化物与腈偶联得到芳基乙腈,从而实现芳基的氰甲基化。如图1所示,首先,腈具有弱酸性,因此,必须使用强碱来生成氰烷基阴离子,生成的阴离子会更快地辅助催化反应的进程,涉及强碱的腈参与的反应会大大限制官能团的耐受性。因此开发出在反应中加入 ZnF_2 ,产生一种被激活进行金属转化的高价硅,但又不会强到过早地切断 Si-C 键或使单芳基化产物去质子化。

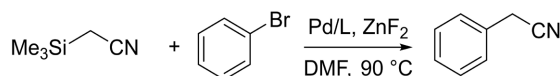


Figure 1. Coupling reaction of aromatic halide and silane catalyzed by zinc mediated palladium

图 1. 由锌介导钯催化的芳烃卤化物与硅烷的偶联反应

这种反应所生成中间体的碱性不如碱金属腈基试剂强,正是这种较低的碱性增大了官能团容忍度,与芳烃上的各种官能团,如氰基、酮基、硝基和酯取代基皆能兼容而且保证了选择性地产生单芳基化产物。目前这种合成方法已广泛地应用于药物开发,但成本昂贵,而且连接的芳基溴化钯配合物有些不稳定,因此该配合物的分解与硅腈的反应同时发生,增大了反应难度,以此需要更为简单易得的合成方法,如图2所示。

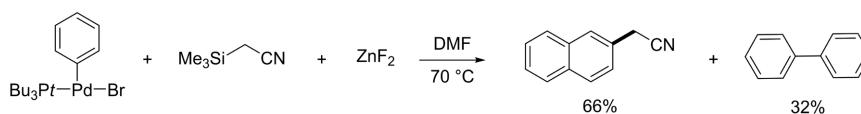


Figure 2. Decomposition reaction of aryl palladium bromide complexes

图 2. 芳基溴化钯配合物的分解反应

2011 年, Schmalz [25]发现了芳基卤化物与异恶唑硼酸在钯催化剂的参与下通过 Suzuki 偶联可以实现芳烃的氰甲基化。主要尝试通过 Pd 催化芳基溴 1 和 4-异恶唑硼酸 2 的 Suzuki 偶联, 将 4-异恶唑取代基连接到不同的芳烃上。后续通过碱性条件下加热或者碱诱导偶联产物(即异恶唑) 3 断裂, 生成甲酰基腈 4, 然后通过逆向克莱森反应将其转化为 5 (见图 3)。

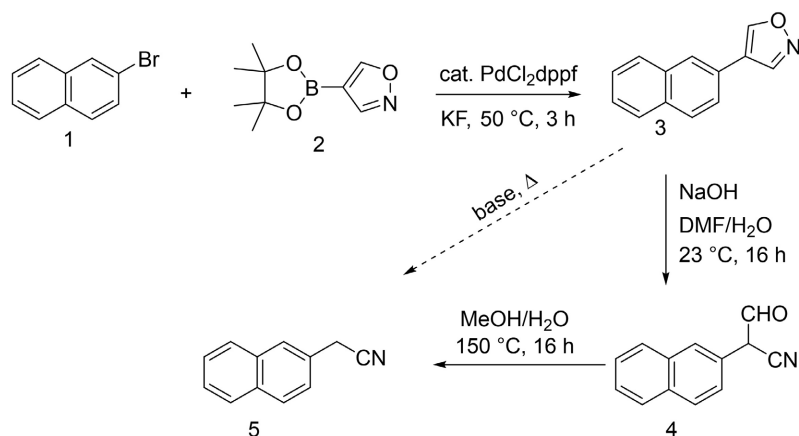


Figure 3. Process of palladium-catalyzed coupling reaction between aromatic halide and isoxazole boric acid
图 3. 芳烃卤化物与异恶唑硼酸经钯催化的偶联反应过程

该团队对于之前硼参与的反应机制(见图 4), 得出了上述反应模式所提出的反应机理, 皆做出了验证并表征了所有所提出的中间体, 得出了该反应的反应机制(见图 5)。

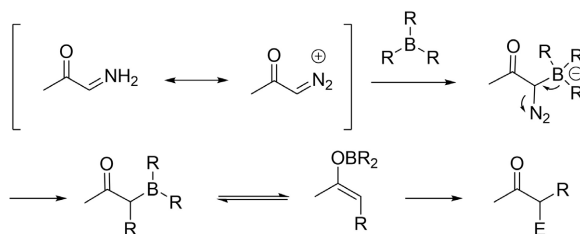


Figure 4. Reaction mechanism involving boron
图 4. 硼参与的反应机制

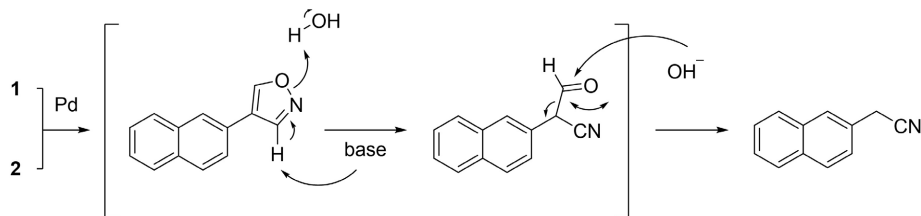


Figure 5. Mechanism of palladium-catalyzed coupling reaction between aromatic halide and isoxazole boric acid
图 5. 芳烃卤化物与异恶唑硼酸经钯催化的偶联反应机制

2.2. 钯催化并经由脱羧实现的氰甲基化

刘磊及其团队[26]在 2011 年通过钯催化芳基溴、氯化物甚至三氟酸盐与易得的氰乙酸盐脱羧偶联来合成芳基乙腈, 从而实现芳烃的氰甲基化。该反应过程研究了氯苯与氰乙酸钠或钾的偶联, 在加入合适的钯盐、膦配体和溶剂且不使用任何额外碱的情况下, 以较高收率选择性地获得了所需的单芳基化产物(如图 6)。

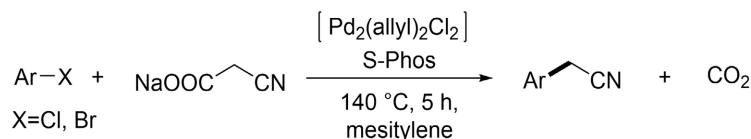


Figure 6. Decarboxyl-coupling reaction of aryl halides catalyzed by palladium
图 6. 钯催化芳基卤化物的脱羧偶联反应

该反应体系对于芳烃上所带有富电子或贫电子的官能团皆可兼容, 包括硫醚、醚、酮、酯、烯烃、硝基、甲酰基、酰胺、硅基、腈、和胺基。对于杂环卤化物也可以很好的兼容, 最重要的是, 碱基敏感的官能团(例如, 具有烯化氢原子的酮和酯)也可以在该反应中耐受, 可以进行 Heck 偶联反应的烯烃和具有自由质子官能团的胺同样可以在当前的反应条件下存活。对于具有某些合成目的反应, 脱羧偶联不仅提供了一种概念上的替代方法, 而且在试剂可及性和反应范围方面也可以得到实际的应用。

2.3. 铜催化介导的芳烃的氰甲基化

2021 年, 马大为等人[27]-[35]受到前人的启发, 报道了一种通过 Cu 催化实现芳烃的氰甲基化。其团队基于之前对于对草酸二胺促进 Cu 催化偶联反应的研究, 发现 Cu 催化的芳基化仅对芳基碘化物有效, 对于杂芳基卤化物和 α -烷基取代的氰乙酸乙酯仍然存在问题。其团队主要目的是开发出一个催化体系, 用于 Cu 催化氰乙酸乙酯及其衍生物的芳基化反应, 他们以 4-氯苯甲醚与氰乙酸乙酯偶联为反应模型(如图 7)。在最优反应条件下, 对于一系列(杂)芳基卤化物(Cl, Br)在对位和间位上具有给电子或吸电子基团, 反应良好(见图 8)。

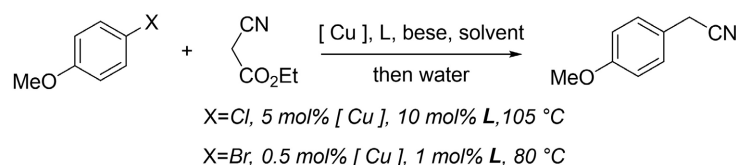


Figure 7. Reaction model of conjugation of aromatics and ethyl cyanoacetate
图 7. 芳烃与氰乙酸乙酯偶联的反应模型

筛选了一系列草酸酰胺配体, 最终确定吡啶化的草酸二胺(如图 9)是促进 Cu 催化(杂)芳基卤化物与氰乙酸乙酯及其单烷基化衍生物偶联反应的有效配体。

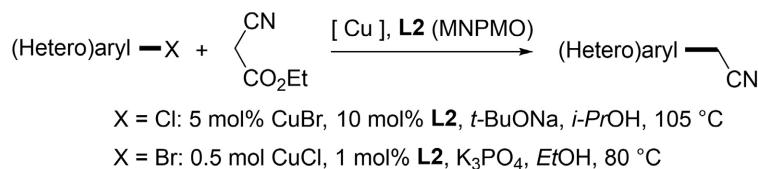


Figure 8. Coupling reactions of (hetero) aryl halides catalyzed by copper
图 8. 铜催化的(杂)芳基卤化物的偶联反应

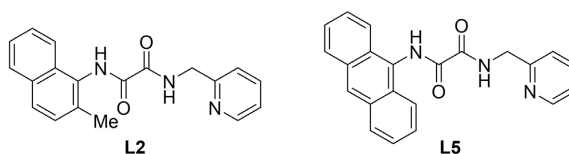


Figure 9. Pyridinated diamine oxalate ligand
图 9. 吡啶化的草酸二胺配体

2.4. 光诱导镍催化芳基卤化物的氰甲基化

2023 年, Rueping 小组[34]发现了一种通过光诱导、镍催化芳基卤化物, 同时通过氰乙酸铯脱羧来实现氰甲基化的方法。通过一系列条件优化, 筛选出了最优条件, $\text{Ni}(\text{cod})_2$ 作为镍源, L4 作为配体(图 10), 4CzIPN 作为光催化剂, 用 440 nm 蓝色 LED 的照射, 获得所需的芳基乙腈, 但产率较低, 当添加 1 当量 LiCl 后产率得到了显著提高(图 10)。作者推测 Li^+ 可能与羰基作用, 促进了氰乙酸铯的脱羧。调整 LiCl 添加浓度并不能提高产率, 用 NH_4Cl 取代也不能生成产物, 这也突出了 LiCl 的关键作用, 但是该方法的局限性是富电子的芳基溴化物在该方案中表现出较低的活性。



Figure 10. Decarboxylcyanomethylation of aryl halides catalyzed by photoinduced nickel
图 10. 光诱导镍催化芳基卤化物的脱羧氰甲基化反应

2.5. 芳基硼酸通过脱氨偶联实现氰甲基化

2014 年, 王剑波及其团队[28]-[36]发现了一种无需金属催化而是通过 α -氨基乙腈与芳基硼酸脱氨偶联来实现氰甲基化(如图 11 所示)。该反应体系可以兼容吸电子取代基和供电子取代基以及末端的烯基, 酯和酮在该条件下也是可耐受的。

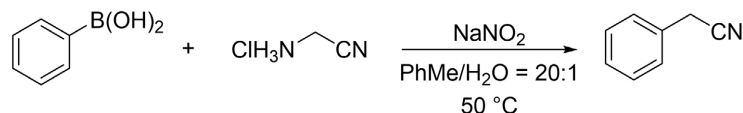


Figure 11. Deamination coupling reaction of arylboric acid
图 11. 芳基硼酸的脱氨偶联反应

王剑波等人[33]-[37]在 2013 年他们报道的一篇关于重氮化合物与有机硼化合物的反应中提到过, 这种类型的反应遵循一个简单的过程, 即富电子重氮碳原子与缺电子硼中心的配位, 随后发生 1,2-迁移形成碳-碳键。重氮碳本质上是富电子的, 它可以与硼试剂的缺电硼中心反应形成四配位硼中间体 6, 随后硼上的一个取代基通过 1,2-迁移转移到碳上, 同时释放二氮气体(图 12)。这个反应的转化是碳插入到 B-X 键中。根据该反应中使用的硼试剂(即四配位硼中间体中不同的迁移基团 X), 可以预期发生各种转变。

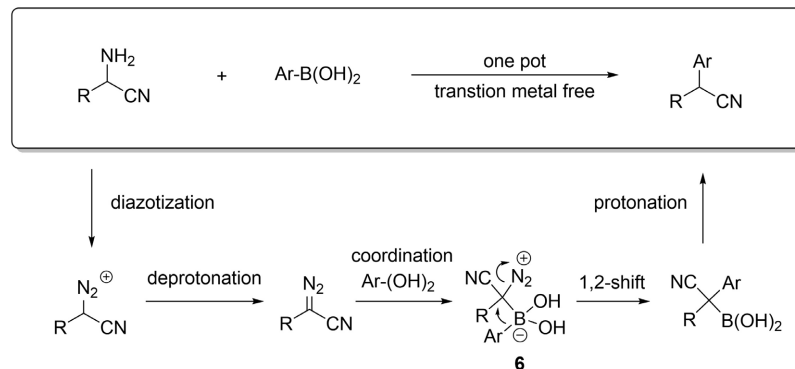


Figure 12. Arylboric acid deamination coupling process
图 12. 芳基硼酸脱氨偶联过程

2.6. 通过硫克萊森重排实现的芳烃氰甲基化

2018 年, 彭勃课题组[29]通过乙腈与芳基氟烷基亚砜的硫-克萊森型重排实现了芳烃的邻位氰甲基化(如图 13)。该反应可以将氰甲基与氟烷基引入芳烃中, 该反应依赖于过量的乙腈和氟烷基取代基的电负性作用, 这两者都促进了亚砜与乙腈的亲电组装。因此, 该反应耐受各种含氟烷基亚砜的官能团。

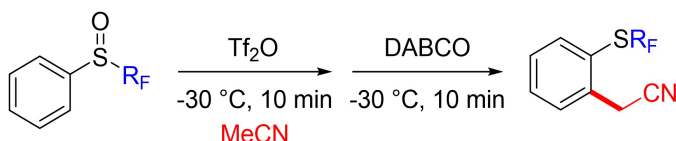


Figure 13. Rearrangement reaction of acetonitrile with aryl haloalkane sulfoxide

图 13. 乙腈与芳基氟烷基亚砜的重排反应

3. 芳烃的氰烷基化

Hartwig [30]和 Verkade [31]-[39]分别在 2002 年和 2003 年提出了, 在钯催化剂的存在下将腈与芳基卤化物偶联, 从而得到芳基的氰烷基化产物(图 14)。该反应可以发生在具有一系列电子性质的芳基卤化物上, 包括富电子、缺电子的底物。刘磊等人[26]-[28]在 2011 年也提出了一种通过钯催化脱羧偶联实现芳烃氰烷基化的反应模式(图 15), 该反应可以实现三级甚至四级(包括环)氰乙酸盐的脱羧偶联, 且收率很高。

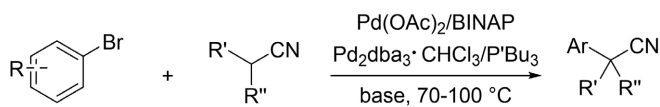


Figure 14. Palladium-catalyzed coupling of bromine aryl and nitrile

图 14. 钯催化的溴代芳基与腈的偶联

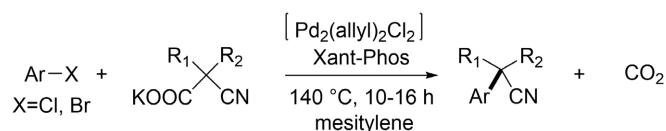


Figure 15. Palladium-catalyzed cyanoalkylation of aryl halides coupled with nitrile acetate decarboxylates

图 15. 钯催化芳基卤化物与腈乙酸盐脱羧偶联的氰烷基化反应

在 2018 年, 彭勃及其团队[32]报道了芳基高价碘与 α -有机锡取代腈在 TMSOTf 的辅助下偶联, 成功实现芳烃的氰烷基化(图 16)。与传统的芳基的氰烷基化相比, 该反应成功保留了可以进一步转化的碘官能团, 为进一步引入其他官能团提供了有利的条件。该反应首先形成烯酮亚胺中间体, 在经由[3,3]迁移重排得到目标产物(图 17), 该反应具有优异的官能团兼容性, 但是过程用到有机锡, 对环境不友好, 不符合绿色化学的理念。

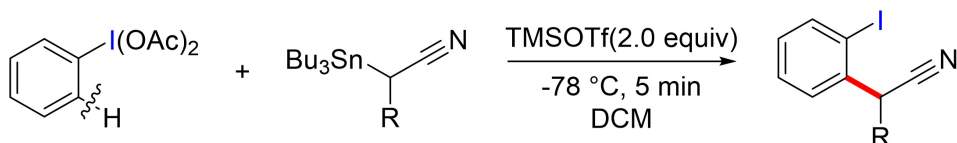


Figure 16. Coupling reaction between aryl hypervalent iodine and tin nitrile

图 16. 芳基高价碘与锡基腈的偶联反应

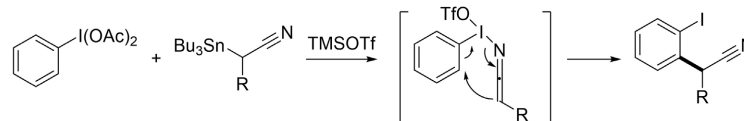


Figure 17. The coupling reaction process of hypervalent iodine and tin nitrile
图 17. 高价碘与锡基腈的偶联反应过程

4. 总结

本文介绍了近几年来芳烃的氰甲基化反应，该反应逐渐发展为具有反应成本低，反应条件温和、反应效率高、底物适用性好等优点的反应。相比于金属催化介导的芳烃的氰甲基化，无金属条件下的芳烃的氰甲基化反应的相关报道仍然较少，未来对于无金属催化的芳烃的氰甲基化反应，仍然是一个很大的挑战。

我们认为芳烃的氰甲基化反应还有以下发展空间：1) 解决反应成本过高的问题，非金属催化成为主要反应模式；2) 使该类反应成为对环境友好型的反应，即合成原料更为绿色环保，反应产生的废弃物更易处理；3) 该反应未来更具实用性，即可以工业化生产合成各种药物分子的前体；4) 探索更多合成芳烃氰甲基化的合成方法，为其未来的发展提供支持。我们相信在不久的将来，芳烃氰甲基化反应一定会得到更大的发展。

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