

从悉尼酮、慕尼黑酮到蒙特利尔酮: 用城市命名的有机化合物

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2015-03-06 收稿, 2015-03-27 接受, 2015-06-18 网络版发表

摘要 有机化学中用城市命名的化合物非常罕见, 悉尼酮、慕尼黑酮和蒙特利尔酮是3个有趣的例子. 它们分别发现于1935, 1964和2007年. 这3种化合物都是五元杂环介离子化合物, 而非简单的酮类结构. 它们都可作为1,3-偶极体与烯烃和炔烃等不饱和化合物发生偶极环加成反应. 近年来, 特别是由于蒙特利尔酮的发现, 这几种类型的化合物受到了人们越来越多的关注. 本文将简要介绍这3类重要化合物的发现历史以及结构和反应特性, 特别是在偶极环加成反应中的应用.

关键词

悉尼酮
慕尼黑酮
蒙特利尔酮
介离子化合物
偶极环加成
杂环化合物

众所周知, 有机化学中有许多人名反应^[1,2], 但用城市命名的化合物在有机化学中并不多见. 悉尼酮、慕尼黑酮和蒙特利尔酮是3个用城市命名化合物的有趣例子^[3]. 那么, 这些化合物是如何发现及为何用这些城市来命名呢? 它们有什么样的结构和反应特性? 以下将分别予以讨论.

1 悉尼酮

悉尼酮(sydnones), 全名为1,2,3-噁二唑-5-氧化物(1,2,3-oxadiazolium-5-olate), 其结构如图1所示. 但它不是一般的内盐或两性离子(zwitterions), 而是属于介离子化合物(mesoionic compounds)^[4-8]. 顾名思义, 所谓介离子化合物是指其极性介于两性离子和共价化合物之间的一类化合物. 后面将对这类化合物作详细介绍.

早在1935年, Earl和Mackney^[9]在用乙酸酐处理由*N*-苯基甘氨酸**2**与亚硝酸反应得到的*N*-亚硝基-*N*-苯基甘氨酸**3**时, 意外得到一种稳定的晶体化合物. 该化合物在酸性条件下可水解成肼、甲酸和二氧化

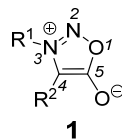
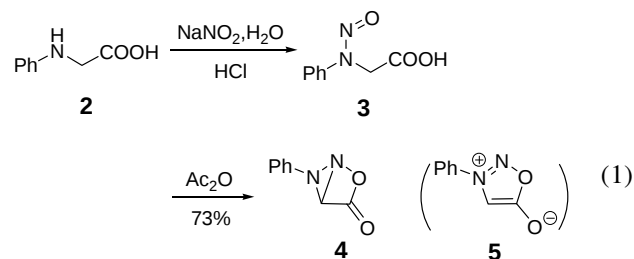


图1 悉尼酮的结构

Figure 1 The structure of sydnones

化碳; 同时, 它又有类似内酯的性质, 在氢氧化钠水溶液中加热会水解重新生成*N*-亚硝基氨基酸. 依据当时有限的鉴定手段, 他们推断该化合物具有**4**的稠环结构(但后来证明, 该化合物的结构实际上为**5**), 见式(1).



后续的研究发现^[10], 利用这种方法可以很容易

引用格式: 苗群, 孙怀林. 从悉尼酮、慕尼黑酮到蒙特利尔酮: 用城市命名的有机化合物. 科学通报, 2015, 60: 2003-2013

Miao Q, Sun H L. Sydnones, münchenones and montréalones: Organic compounds named after cities (in Chinese). Chin Sci Bull, 2015, 60: 2003-2013, doi: 10.1360/N972015-00209

得到一大批这类结构的化合物. 由于采用系统命名比较麻烦, 加上其结构尚有不确定性, Earl等人用他们所在的悉尼大学(University of Sydney)所坐落的城市, 即悉尼市的名字将这类化合物命名为悉尼酮(sydnone). 之所以称其为酮, 即采用“-ones”为后缀, 是因为结构4上带有的羰基.

这类化合物很快引起其他研究者的重视. 然而, Baker和Ollis^[11]对该化合物的稠环结构4却提出了异议. 他们参照Schönberg^[12]对一些三唑类化合物结构的研究结果, 提出悉尼酮应该是几种内盐式结构的共振杂化体(式(2)).

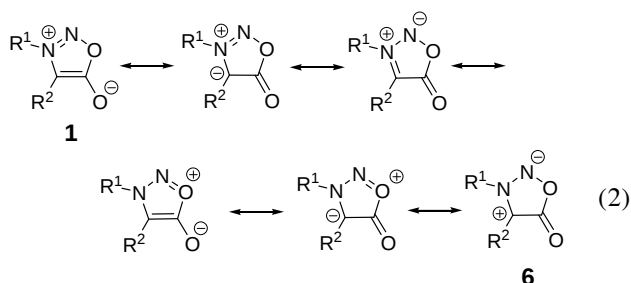
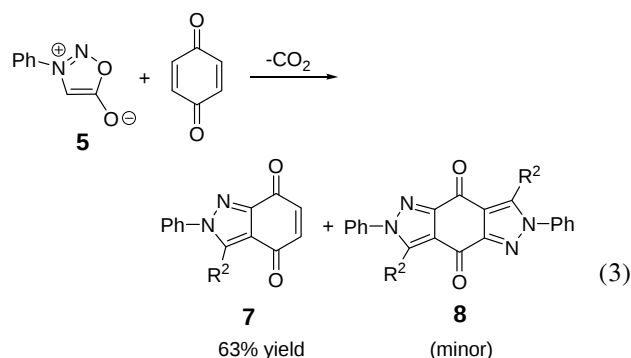


图2 悉尼酮环上的亲电取代反应

Figure 2 The electrophilic substitution of sydnone ring

Hammick和Voaden^[23]发现悉尼酮可以与醌的环上双键发生反应生成7和8, 同时失去1分子二氧化碳(式(3)). 但该反应只被视为悉尼酮表现出一定的亲核能力.



1960年, Vasil'eva等人^[24-27]用悉尼酮与 α,β -不饱和和羧酸酯或腈反应, 分别得到二氢吡唑9和吡唑10(图3). 然而他们未能对这些反应的反应机理做出详细的解释.

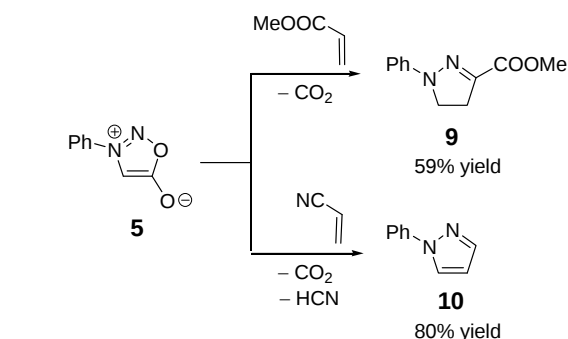


图3 悉尼酮与丙烯酸甲酯和丙烯腈的环加成反应

Figure 3 The cycloaddition reaction of sydnone with methyl acrylate and acrylonitrile

事实上, 除了上述内盐式结构以外, 没有办法用一个中性的共价结构来描述该五元杂环化合物. 这也是Earl和Mackney最初试图将其描述成稠环结构的原因. 另一方面, 尽管可以写成内盐式结构, 但其共振杂化的结果, 使得电荷在环上处于一种离域状态, 而不是集中在个别原子之上. 为了准确表达悉尼酮上述结构特点, Baker和Ollis^[4]引入了介离子化合物的概念, 用来表示悉尼酮以及其他类似化合物与一般内盐或两性离子化合物的区别^[13-17].

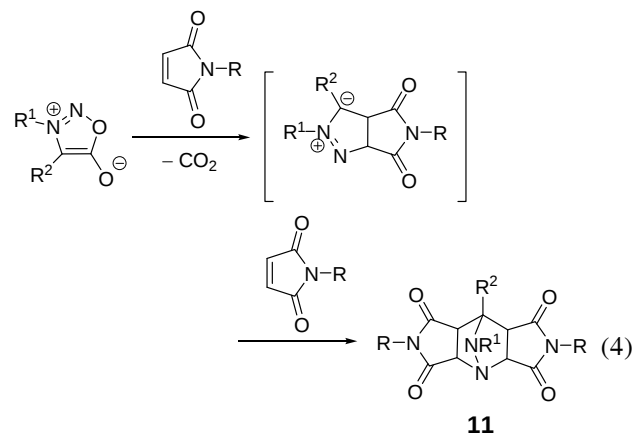
随后对悉尼酮结构的深入研究^[18-20], 证实了Baker和Ollis的观点. 这些研究极大地推动了悉尼酮的合成和性质的探索. 基于N-亚硝基氨基酸脱水制备悉尼酮的方法, 所用的脱水剂从乙酸酐扩展到三氟乙酸酐(TFAA)和二氯亚砷等; 原料N-亚硝基氨基酸也可以通过氨基酸与亚硝酸以外的其他硝化试剂反应来制备^[21].

正如悉尼酮的一些共振式满足6电子芳香性环状结构的要求, 悉尼酮的确具有一定的芳香性. 这种芳香性不仅表现在它所具有的稳定性的, 还表现在其环上可以发生各种亲电取代反应. 例如, 悉尼酮5可发生4-位氯代^[20]、溴代^[18]、硝化^[18]以及酰基化^[22]等一系列亲电取代反应(图2).

最为重要的是, 研究发现悉尼酮可以作为1,3-偶极体与不饱和键发生[3+2]环加成反应. 1956年,

直到1962年, Huisgen^[28,29]在研究偶极环加成反应过程中, 对悉尼酮与炔类^[30,31]和烯类^[32,33]的反应进行了深入研究. 他们认为, 反应过程实际上包含悉尼酮与不饱和碳碳键发生1,3-偶极环加成, 所得中间产物再失去1分子二氧化碳, 最终得到吡唑类衍生物(图4). 这是首次认识到悉尼酮可作为环状1,3-偶极体发生环加成反应. 该反应体现了结构6对悉尼酮共振杂化体的贡献.

此后, 悉尼酮的偶极环加成反应得到了广泛的研究和应用. 例如, Sun^[34]研究了悉尼酮与马来酰亚胺的反应. 类似于Huisgen等人^[32,33]发现的悉尼酮与茚烯的反应, 他发现其加成产物可以与第2个马来酰亚胺发生加成, 得到稠环化合物11(式(4)). 利用这个反应, Sun^[35]还巧妙设计并合成了聚合物12(式(5)).



81%–99% yield

R = H, Me, Ph, *p*-Tol; R¹ = Ph, *n*-Pr; R² = H, Ph, Et

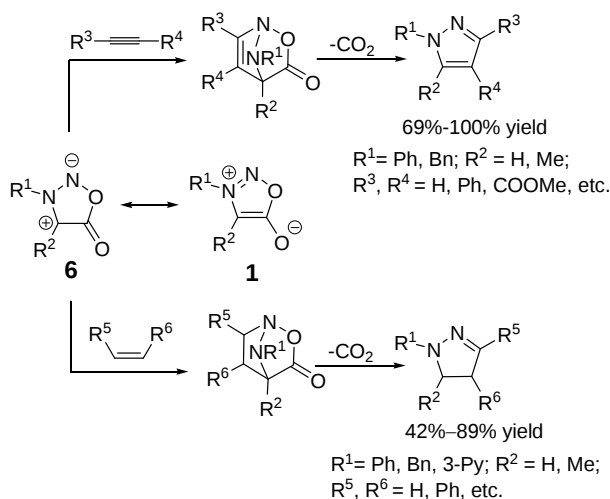
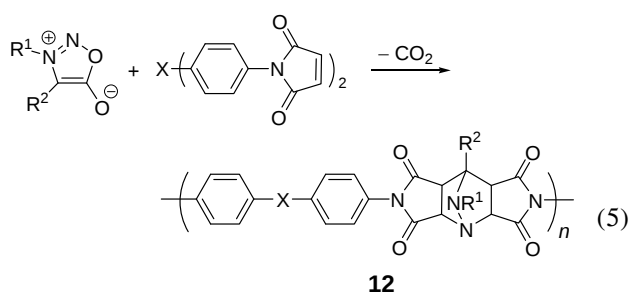


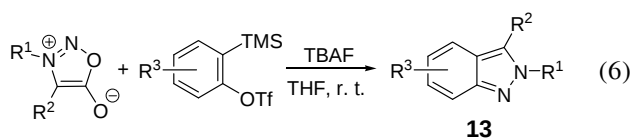
图4 悉尼酮对炔和烯的1,3-偶极环加成反应

Figure 4 The 1,3-cycloaddition reaction of sydnone with alkynes and alkenes



R¹ = Ph, *n*-Pr; R² = H, Ph, Et; X = O, CH₂

Larock课题组^[36,37]详细研究了悉尼酮与苯炔的环加成反应, 反应在温和的条件下得到2*H*-吡唑衍生物13(式(6)).

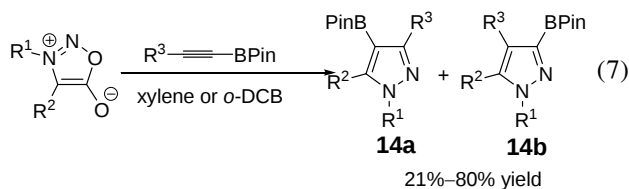


63%–95% yield

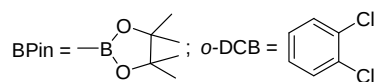
TBAF = *n*-Bu₄NF

R¹ = Aryl; R² = Alkyl, Aryl, Heterocycles, -(CH₂)₃-, I; R³ = OMe, Me

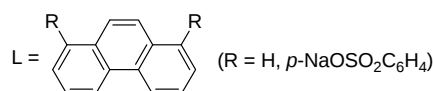
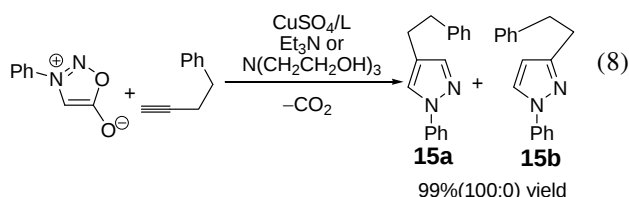
Harrity课题组^[38–40]研究了悉尼酮与炔基硼酸酯的反应, 反应所生成的带有硼酸酯基的吡咯14(式(7)), 可以用作Suzuki反应的原料.



R¹ = Alkyl, Aryl; R² = Alkyl, Aryl, H; R³ = Alkyl, Aryl, H, SiMe₃



2013年, Taran课题组^[41]通过高通量筛选的方法, 发现能够高效催化悉尼酮与炔烃环加成反应的铜催化剂(式(8)), 使该反应成为一种新的可选择的点击反应类型(click reactions)^[42].

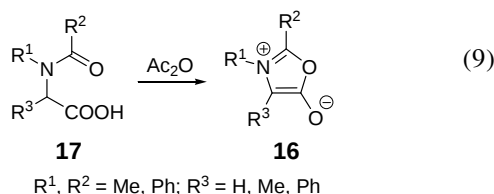


这一发现引起了人们对铜催化的这类反应的浓厚兴趣. 这方面研究至今方兴未艾^[43–45].

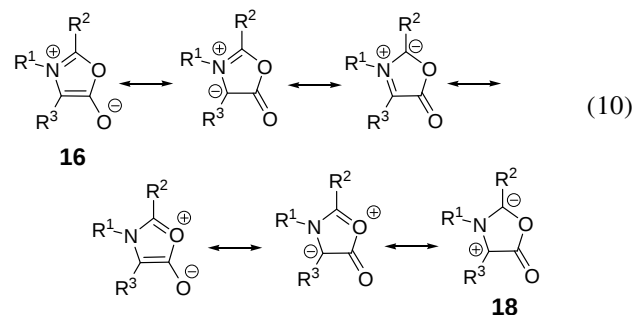
2 慕尼黑酮

慕尼黑酮(münchnones), 全名为1,3-噁唑-5-氧化物(1,3-oxadiazolium-5-olate), 结构式如图5所示. 和悉尼酮一样, 慕尼黑酮也是一种介离子化合物^[46~48].

1964年, Huisgen等人^[49]在发现了悉尼酮作为第1个环状偶极体的基础上, 试图寻找新的环状偶极体产物. 他们通过用乙酸酐处理*N*-酰基氨基酸**17**得到一种亮黄色晶体, 并发现后者是一种新的介离子化合物**16**(式(9)).



与悉尼酮类似, 该介离子化合物**16**也是一系列内盐式结构式的共振杂化体, 且其环状结构同样满足6电子的芳香性要求(式(10)).



有趣的是, 该化合物也可作为环状偶极体, 与炔烃^[49,50]和烯烃^[51,52]发生1,3-偶极环加成反应, 其机理与悉尼酮类似, 都是先与不饱和键发生1,3-偶极环加成反应, 中间体再通过逆环加成放出1分子CO₂, 所得到的产物分别是吡咯和二氢吡咯类化合物(图6).

仿照悉尼酮的例子, 他们用所在的慕尼黑大学(University of München)坐落的慕尼黑市(München)的名字, 将这类化合物命名为慕尼黑酮(münchnones)^[53].

与悉尼酮不同, 慕尼黑酮极易发生水解生成*N*-

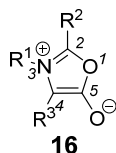


图5 慕尼黑酮的结构

Figure 5 The structure of münchnones

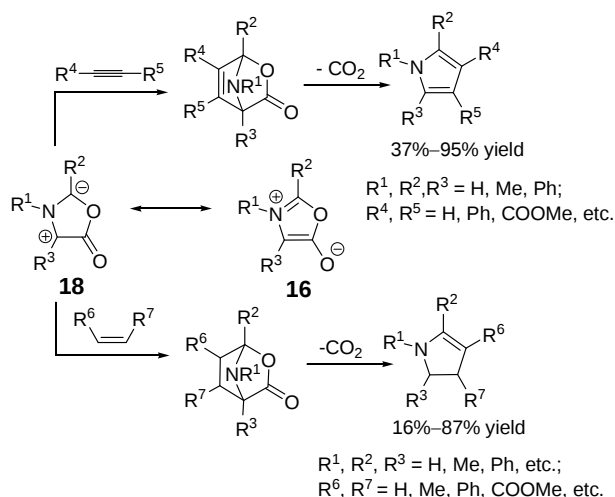
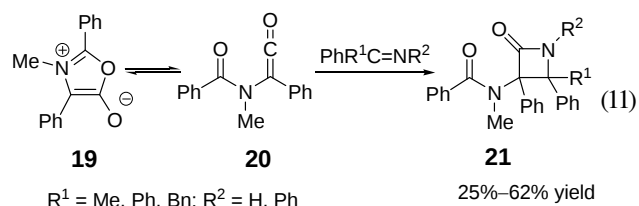


图6 慕尼黑酮与炔和烯的1,3-偶极环加成反应

Figure 6 The 1,3-cycloaddition reaction of münchnones with alkynes and alkenes

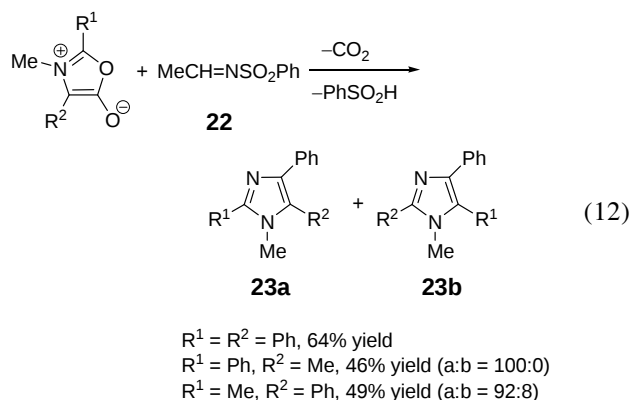
酰基氨基酸, 这也是慕尼黑酮在很长时间内没有被分离到的原因之一. 醇、胺等亲核试剂也可以使慕尼黑酮开环, 得到相应的*N*-酰基氨基酸酯和酰胺类衍生物^[53]. 此外, 慕尼黑酮也能和氧气发生反应^[54,55], 因此涉及到慕尼黑酮的实验需要在无水无氧的条件下进行.

Huisgen等人^[56,57]还发现, 慕尼黑酮并非完全以五元环介离子结构存在, 它可与烯酮**20**以互变异构体形式共存, 在其红外光谱上可观察到烯酮的存在; 也可通过其与亚胺反应生成β-内酰胺**21**来证明这一点(式(11)).

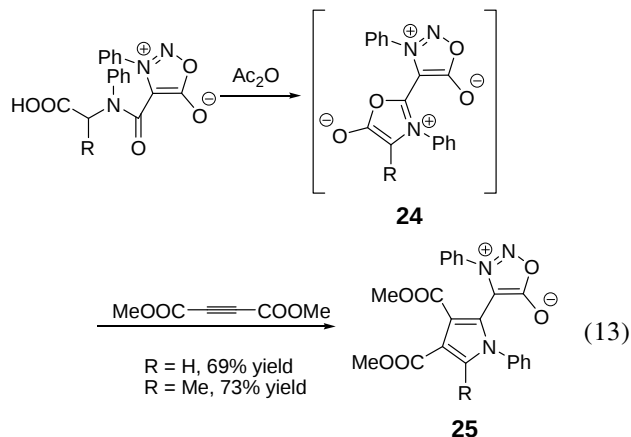


以*N*-酰基氨基酸为底物合成慕尼黑酮, 除了可利用酸酐(最常用的是乙酸酐)作为脱水剂之外, 还可以用碳*N,N'*-二环己基碳二亚胺(DCC)^[58]或1-(3-二甲胺基丙基)-3-乙基碳二亚胺(EDC)^[59]等作脱水剂. 后者可降低反应温度和减少副反应的发生. 需要进行下一步反应时, 慕尼黑酮可以不必分离出来.

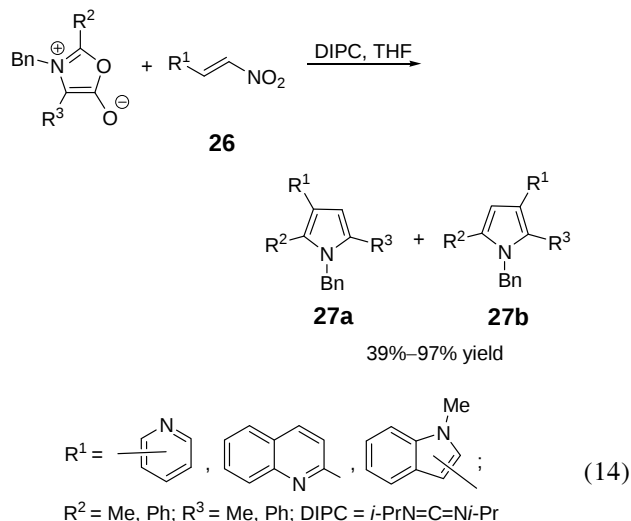
慕尼黑酮还可以和含有其他元素的多重键发生环加成反应. 例如Ferracioli课题组^[60,61]用慕尼黑酮与*N*-苯磺酰基亚胺**22**反应得到了咪唑衍生物**23**(式(12)). 这也是咪唑杂环的合成方法之一.



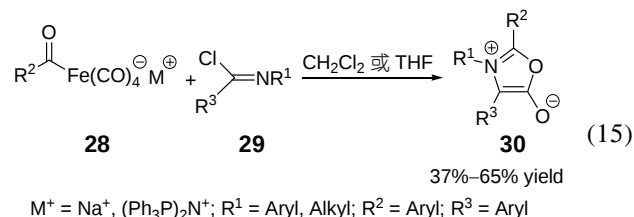
1999年, Chan课题组^[62]制备了同时含有悉尼酮环和慕尼黑酮环的化合物**24**, 原位与丁炔二酸二甲酯(DMAD)反应, 结果得到连有悉尼酮环的吡咯衍生物**25**, 从这一点可以说明慕尼黑酮比悉尼酮更活泼(式(13)).



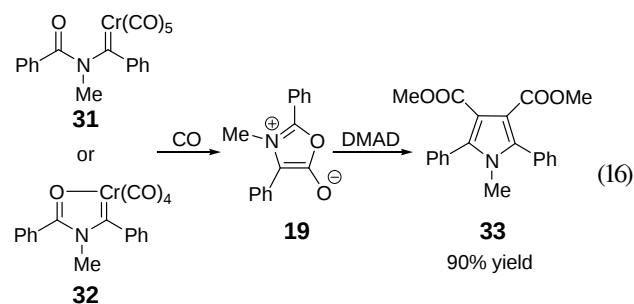
Lopchuk和Gribble^[63,64]使用连有硝基乙烯基化合物**26**与慕尼黑酮进行环加成反应, 生成了吡咯类化合物**27**, 反应过程中脱掉了硝基(式(14)).



最近的研究发现, 合成慕尼黑酮还可以使用金属有机的方法. Alper和Tanaka^[65]用酰基四羰基铁**28**与亚胺基氯**29**在室温下反应, 分离出慕尼黑酮**30**(式(15)), 尽管这个反应产率不高, 但是这也提供了一个不以N-酰基氨基酸为原料制备慕尼黑酮的新方法.



Merlic等人^[66]发现酰胺基铬卡宾配合物**31**以及**32**在一定压力CO下可以生成慕尼黑酮**19**, 之后它再与炔反应获得吡咯**33**(式(16)). 反应同样也不需要以N-酰基氨基酸为原料.



2001年, Arndtsen课题组^[67,68]于CO气氛下, 以酰氯**34**和亚胺**35**为原料, 在催化剂 $\text{Pd}_2(\text{dba})_3$ 作用下得到了咪唑啉类产物**36**. 他们认为反应过程中生成了慕尼黑酮**37**^[69]. 此后, Arndtsen课题组^[70]利用这种方法合成并分离出了慕尼黑酮**37**, 并通过醇解得到酰基氨基酸酯**38**. 接着, 他们^[71–73]在后续的研究工作中, 合成了一系列慕尼黑酮环加成反应衍生物, 包括吡咯**39**、 β -内酰胺**40**和吡唑**41**(图7), 这个方法也是最近广受关注的多组分反应(multicomponent reaction, MCR)之一.

由于慕尼黑酮的原料为N-酰基化氨基酸, 后者是多肽中常见的结构单元, 因此在多肽合成研究中会经常涉及生成慕尼黑酮的反应发生. 例如, 本课题组^[74]最近在利用金属钴催化亚胺和一氧化碳交替共聚反应合成多肽的研究中发现, 慕尼黑酮**42**及其环加成产物的生成是造成聚合反应链终止的重要原因. 在所得到的多肽类聚合物**43**中, 常带有此类结构的端基(式(17)).

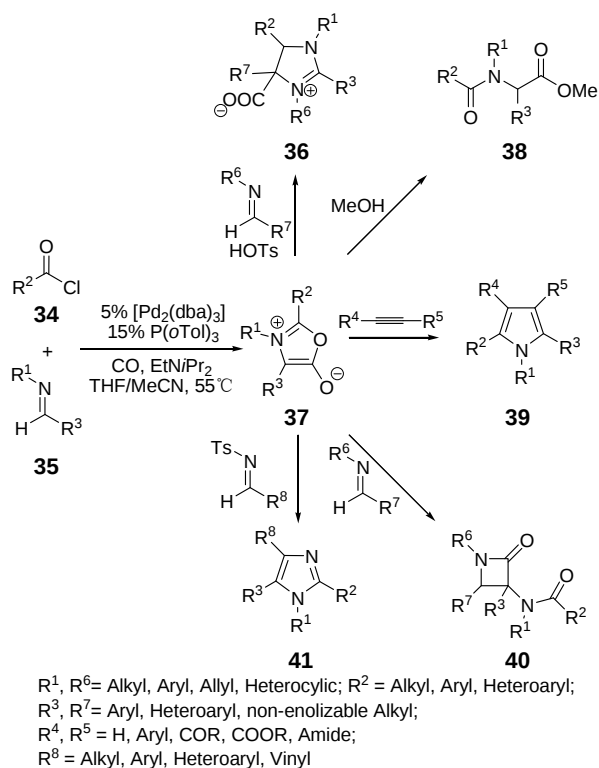
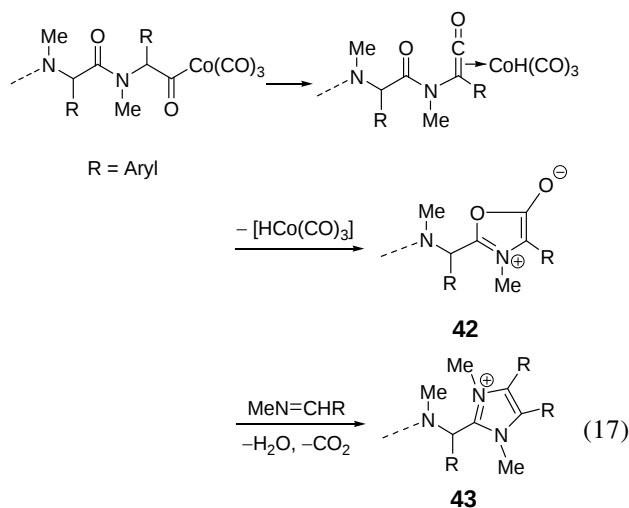
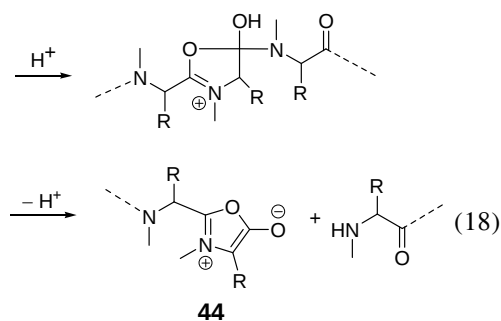
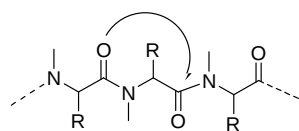


图7 多组分反应法合成的慕尼黑酮及其应用

Figure 7 The multicomponent reaction of the synthesis of münchnones and its application

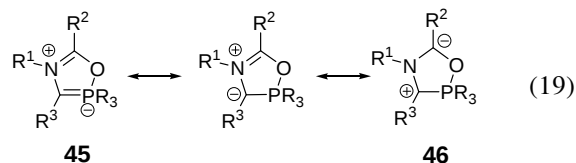


此外, 在多肽类聚合物降解的过程中, 慕尼黑酮也可作为重要的中间体 44 存在(式(18))^[74].

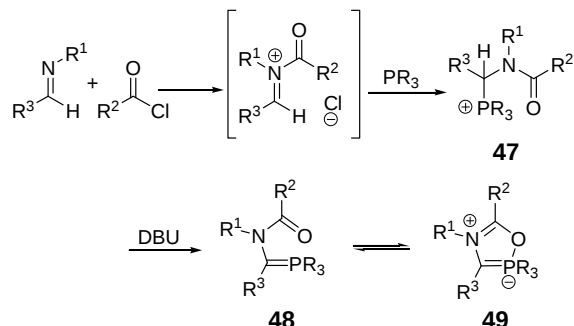


3 蒙特利尔酮

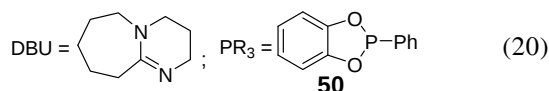
蒙特利尔酮(montréalones)是最近发现的另一类新的含磷环状1,3-偶极体, 或简称为磷杂慕尼黑酮(phospha-münchnones), 其结构如图8所示. 它也是一种介离子化合物, 同样也可用一系列共振结构来描述, 并且这些共振结构也都满足6个 π 电子的芳香性要求(式(19)).



这一化合物是Arndtsen小组^[75]发现的. 2007年, 他们在利用钯催化方法合成慕尼黑酮的过程中, 设计并制备出这种新的含磷环状化合物. 即先用酰氯、亚胺和三价磷化合物反应得到磷盐 47 , 后者在碱的作用下生成蒙特利尔酮 49 . 从结构上看, 它相当于以一个三取代磷基团 PR_3 代替了慕尼黑酮中原有的羰基(式(20)).



$R^1 = \text{Alkyl, Aryl, Allyl, Heterocyclic};$
 $R^2 = \text{Aryl, Heterocyclic, } i\text{-Pr, } t\text{-Bu};$
 $R^3 = \text{H, Aryl, Heteroaryl, } i\text{-Pr};$



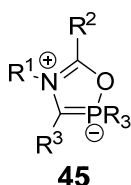


图8 蒙特利尔酮的结构

Figure 8 The structure of montréalones

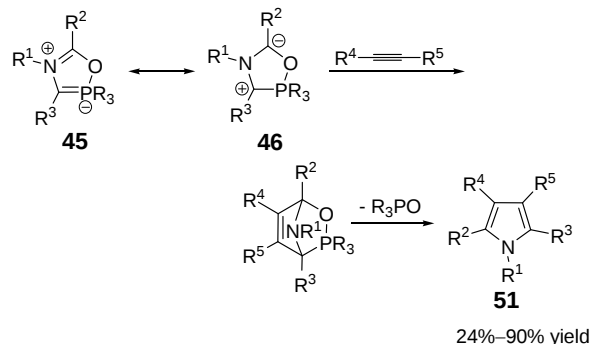
后来, 该化合物被以Arndtsen小组所在的麦吉尔大学(McGill University)坐落的蒙特利尔市(Montréal)命名为蒙特利尔酮(montréalones)^[76].

蒙特利尔酮不仅可以以成环的介离子结构**49**存在, 而且也可以以开环异构体Wittig试剂**48**的结构存在. R为贫电子基时, 介离子结构**49**占优势; R为富电子基时, Wittig结构**48**占优势. 此外R的空间效应也会影响该平衡. 采用儿茶酚基苯基膦PPh(catechyl)**50**时具有比较好的效果(式(20))^[75,77].

蒙特利尔酮与多重键1,3-偶极环加成反应的机理与慕尼黑酮相似, 不同之处在于蒙特利尔酮最终失去的是1分子氧磷; 二者与炔烃的反应都生成吡咯**51**(图9)^[75,77].

Couture等人^[78]用酰氯、亚胺以及三价磷化合物**52**制得酰胺基取代的Horner-Wadsworth-Emmons试剂**53**. Arndtsen课题组^[79]对化合物**52**做了进一步研究, 他们用Lewis酸处理**52**, 结果得到了蒙特利尔酮**54**, 其进而可与炔烃发生环加成生成吡咯**55**(图10).

Arndtsen课题组^[80]使用连有碳碳双键的亚胺**56**制备蒙特利尔酮**57**, 利用其与分子内烯烃的1,3-偶极环加成合成了一系列多环2-吡咯啉化合物**58**(式(21)).



PR₃ = PhP(catechyl); R¹, R², R³ = Alkyl, Aryl, etc.; R⁴, R⁵ = H, Aryl, etc.

图9 蒙特利尔酮与炔类的1,3-偶极环加成反应

Figure 9 The 1,3-cycloaddition reaction of montréalones with alkynes

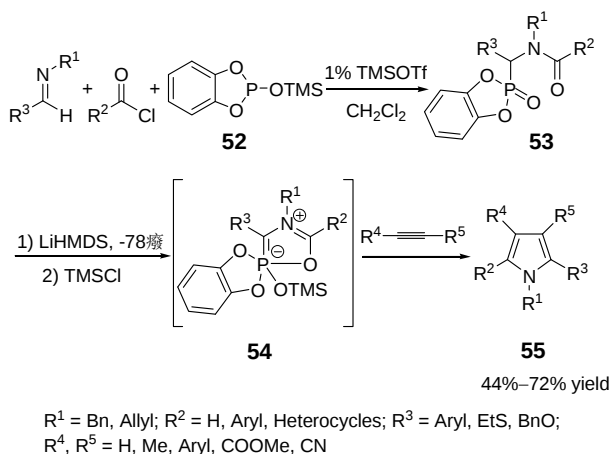
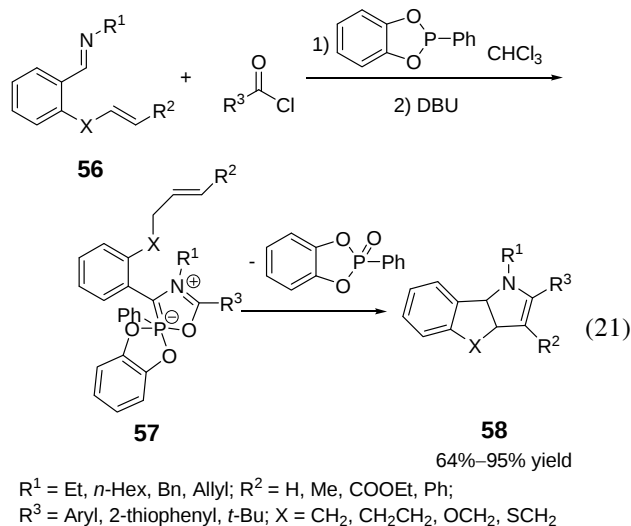
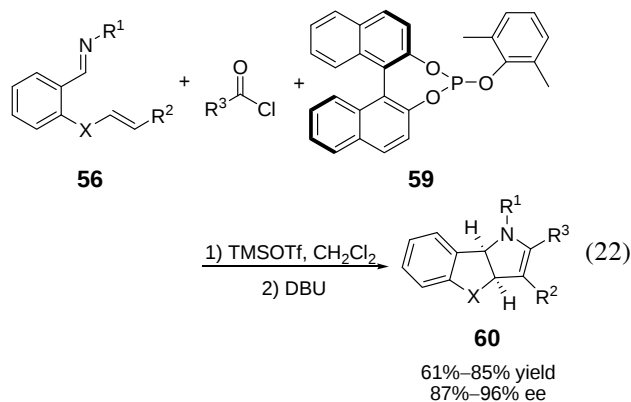


图10 蒙特利尔酮的新合成方法

Figure 10 The new method of montréalones synthesis



此后, Arndtsen课题组^[81]使用带有手性基团的膦化合物**59**来进行同样的反应, 获得了高立体选择性的多环2-吡咯啉化合物**60**(式(22)).



R¹ = Et, *n*-Hex, Bn; R² = H, Me, COOEt;
R³ = Aryl, Heterocycles, *i*-Pr, cyclo-Hex; X = CH₂, OCH₂, SCH₂

总之,从悉尼酮到慕尼黑酮再到蒙特利尔酮的发现,这80年来经久不衰的研究历史,充分揭示了这类介离子环状偶极体的丰富的结构和反应特性.尤其是最近蒙特利尔酮的发现,激起了人们对这类

化合物及其偶极环加成反应更浓厚的兴趣.新的这类化合物的继续发现,将让更多城市的名字进入这一行列,构成有机化学之中一道亮丽的独特风景.

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Sydnones, münchnones and montréalones: Organic compounds named after cities

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Compounds named after cities are rarely seen in organic chemistry. Sydnones, münchnones and montréalones are three such interesting examples. These compounds, which were discovered by scientists at University of Sydney in 1935, at University of München in 1964 and at McGill University in Montréal in 2007, respectively, are all mesoionic five-membered heterocycles. None of them are simple ketones actually, although the suffix “-ones” has been used in their names. For example, the systematic nomenclature of sydnones is 1,2,3-oxadiazolium-5-olate, while münchnones are 1,3-oxadiazolium-5-olate, and montréalones are actually 5-phosphamünchnones. All of these cyclic structures have aromatic characters. The most important common features are, however, that they can all act as 1,3-dipoles to undergo [3+2] cycloaddition to unsaturated bonds, such as alkenes and alkynes. In recent years, there is a growing interest in such compounds, due partly to the new finding of montréalones. In this review, the history for finding of these important compounds and their structural and chemical properties, especially the application in dipolar cycloaddition reactions, will be briefly discussed.

sydnones, münchnones, montréalones, mesoionic compounds, dipolar cycloaddition, heterocycles

doi: 10.1360/N972015-00209