铜催化苯甲酰亚胺高烯丙酯的分子内胺化全氟烷基化反应

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摘要 报道了铜催化苯甲酰亚胺高烯丙酯底物的分子内胺化全氟烷基化反应。该反应以全氟碘代烷为全氟烷基化试剂, 醋酸铜为催化剂, 邻菲罗啉为配体, 在醋酸银存在下以中等的收率实现苯甲酰亚胺高烯丙酯底物末端双键的胺化全氟烷基化, 最终生成 1,3-噁嗪类分子。多种官能团取代的苯甲酰亚胺高烯丙酯和具有不同碳链长度的全氟碘代烷烃都能适用于该反应, 为多氟烷基取代的 1,3-噁嗪类化合物的合成提供了一种简洁的方法。多氟烷基取代的 1,3-噁嗪类化合物还可在温和条件下高效转化为 γ 氨基醇衍生物。初步的机理研究证明该反应经历了全氟烷基自由基对碳碳双键的亲电加成, 之后苯甲酰亚胺基团作为分子内亲核性胺源经历分子内亲核取代途径生成 1,3-噁嗪骨架。

关键词 苯甲酰亚胺高烯丙酯; 全氟碘代烷烃; 胺化全氟烷基化反应; 1,3-噁嗪; 铜催化

Copper-catalyzed Intramolecular Aminoperfluoroalkylation Reaction of *O*-Homoallyl Benzimidates

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Abstract Azaheterocycles have been broadly applied in the development of therapeutic agents, agrochemicals and functional material molecules. Azaheterocycles equipped with perfluoroalkyl group usually manifest superior physical and biological properties than their parent molecules, such as showing improved metabolic stability and high lipophilicity. The synthesis of perfluoroalkyl modified azaheterocycles has attracted considerable research interest in recent years. The strategy of intramolecular aminoperfluoroalkylation of alkenes, which functionalize C=C bond with an external perfluoroalkyl group and an internal amine nucleophile in one pot, provides a streamlined synthesis of perfluoroalkyl substituted azaheterocycles. This strategy has been applied by Liu, Sodeoka and other research groups in the synthesis of perfluoroalkyl substituted aziridines, pyrrolidines, lactams and pyrazolines featuring the use of pendent amine, amide, hydrazone or urea group as internal amine source. We have previously developed a copper(I)-catalyzed intramolecular aminotrifluoromethylation reaction of *O*-homoallyl benzimidates with Togni reagent I for the synthesis of trifluoromethyl containing chiral 1,3-oxazines using a chiral BOX ligand. However, this method is limited to aminotrifluoromethylation reaction as other perfluoroalkyl substituted hypervalent iodine reagents are not easily accessible. Herein, we report our recent research results on the synthesis of perfluoroalkyl substituted 1,3-oxazines using commercial available perfluoroalkyl iodides as perfluoroalkyl source. This intramolecular aminoperfluoroalkylation reaction proceeds selectively in the presence of Cu(OAc)₂ catalyst, 1,10-phenanthroline ligand and AgOAc additive. A broad range of *O*-homoallyl benzimidates and perfluoroalkyl iodides are compatible with the reaction conditions, affording perfluoroalkyl substituted 1,3-oxazines in moderate to good yields. The 1,3-oxazine product can be prepared in gram scale and readily hydrolyzed under mild conditions to give perfluoroalkyl substituted 1,3-amino alcohols. Preliminary mechanism studies revealed that this intramolecular aminoperfluoroalkylation reaction initiated with the addition of a perfluoroalkyl radical to the terminal alkene, and the subsequent functionalization with the benzimidate motif via intramolecular substitution generated 1,3-oxazine products.

Keywords *O*-homoallyl benzimidates; aminoperfluoroalkylation; perfluoroalkyl iodides; 1,3-oxazines; copper catalysis

1 引言

氟原子具有较小的原子半径和较大的电负性, 其与

碳原子形成的碳氟键具有较强的键能和化学稳定性^[1]。这些特殊的理化性质使得含氟化合物在材料和医药开发领域得到了广泛的应用。例如, 引入氟原子或多氟烷

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基能改变母体化合物的偶极矩、亲脂性和化学稳定性等理化性质,是改善母体化合物生物活性的重要策略^[2].氮杂环骨架是众多医药分子的核心结构,因此多氟烷基取代的氮杂环骨架的合成近年来受到了广泛的关注^[3].通过碳碳双键的分子内胺化多氟烷基化反应能在引入多氟烷基官能团的同时构筑氮杂环骨架,是制备多氟烷基取代氮杂环化合物的高效策略之一^[4,5]. Sodeoka^[6a-6c]和刘心元^[6d-6f,7]等课题组在这一领域做出了开创性的工作,通过在烯炔类分子中预先引入氨基、脲等含氮亲核片段,发展了铜催化的分子内胺化多氟烷基化反应,实现了多种全氟烷基取代的氮杂环化合物的合成(图 1A).我们课题组在之前工作中发现酰亚胺酯片段可以作为分子内亲核性胺源^[8],发展了脂肪醇骨架的分子内碳氢键氨基化反应^[9,10].受此启发,我们采用 Togni 试剂作为三氟甲基源,在铜催化剂和手性双齿噁唑啉配体调控下,实现了酰亚胺高烯丙酯的对映选择性分子内胺化三氟甲基化反应,合成了三氟甲基取代的 1,3-噁唑类化合物(图 1B)^[11]. Togni 试剂的制备繁琐,且局限于三氟甲基化转化^[12].因此,发展更廉价易得、种类丰富的氟烷基化试剂参与的胺化全氟烷基化反应仍然值得进一步探索.全氟碘代烷烃是一类在化工领域广泛使用的大宗化

学品,品种多样且商业可得^[13].陈庆云等^[14]课题组系统研究了全氟碘代烷烃在过渡金属催化或者光照等条件下产生全氟烷基自由基的历程,并与烯烃、富电子芳环等亲电物种发生加成反应实现了全氟烷基的引入^[15-17].在此基础上,我们发展了全氟碘代烷参与的苯甲酰亚胺高烯丙酯衍生物的分子内胺化全氟烷基化反应,为全氟烷基取代的 1,3-噁唑类化合物的制备提供了新的方法(图 1C)^[18].

2 结果与讨论

2.1 反应条件优化

首先采用苯甲酰亚胺高烯丙酯 **1** 为模板底物,全氟碘代丁烷为氟烷基化试剂对反应条件进行了考察(表 1).在之前的三氟甲基化条件下(Entry 1)预期反应不能发生,大部分原料剩余.经过一系列的尝试,发现加入 2

表 1 反应条件优化

Table 1 Reaction condition optimization

Entry	Catalyst	Additive	Solvent	Yield ^d / % of 2
1 ^b	Cu(CH ₃ CN) ₄ PF ₆	BOX ligand	DCE	NR
2	Cu(CH ₃ CN) ₄ PF ₆	AgOAc	DCE	44
3	CuCl	AgOAc	DCE	54
4	CuBr	AgOAc	DCE	62
5	CuI	AgOAc	DCE	60
6	Cu(acac) ₂	AgOAc	DCE	54
7	Cu(OTf) ₂	AgOAc	DCE	45
8	Cu(OAc) ₂	AgOAc	DCE	72 (64) ^c
9	Cu(OAc) ₂	AgOTFA	DCE	19
10	Cu(OAc) ₂	AgOTf	DCE	47
11	Cu(OAc) ₂	Ag ₂ CO ₃	DCE	53
12	Cu(OAc) ₂	Cs ₂ CO ₃	DCE	20
13	Cu(OAc) ₂	AgOAc	CH ₃ CN	67
14	Cu(OAc) ₂	AgOAc	THF	52
15	Cu(OAc) ₂	AgOAc	EtOAc	63
16	Cu(OAc) ₂	—	DCE	NR
17	—	AgOAc	DCE	<5
18 ^d	Cu(OAc) ₂	AgOAc	DCE	<5
19 ^e	Cu(OAc) ₂	AgOAc	DCE	53

^a Yields are based on ¹H NMR analysis of reaction mixture with 1,1,2,2-tetrachloroethane as internal standard on a 0.2 mmol scale. ^b See Supporting Information for detailed results. ^c Isolated yield on a 0.2 mmol scale. ^d The reaction was conducted in air. ^e Without 1,10-phenanthroline. NR: no reaction, and most of **1** was recovered.

(A) Copper catalyzed intramolecular aminoperfluoroalkylation of unactivated alkene

(B) Aminotrifluoromethylation of O-homoallyl benzimidates with Togni reagent I

(C) Aminoperfluoroalkylation of O-homoallyl benzimidates with perfluoroalkyl iodides

图 1 分子内胺化多氟烷基化反应制备多氟烷基取代的氮杂环骨架

Figure 1 Perfluoroalkylative intramolecular difunctionalization of unactivated alkene

equiv.的 AgOAc 能有效地促进反应的进行,以中等的收率得到产物 **2** (Entry 2). 之后通过对反应的其他因素进行考察,我们发现: (1)一价铜和二价铜试剂都能催化反应的进行,其中 $\text{Cu}(\text{OAc})_2$ 给出最优的转化率,能以 72% 的核磁收率和 64% 的分离收率得到目标产物 **2** (Entries 2~8). (2) AgOAc 是最优的添加剂,采用其他银盐或者碳酸铯时,反应收率大幅下降(Entries 9~12). (3)反应在乙腈、四氢呋喃等其他溶剂中给出稍低的收率(Entries 13~15). (4)反应在空气气氛下只能产生少量产物,大部分原料未能转化(Entry 18).

2.2 底物拓展

在得到最优的反应条件后(Table 1, Entry 8),使用全氟碘代丁烷为氟烷基化试剂对苯甲酰亚胺高烯丙酯类底物的适用范围进行了考察(图 2). 苯环上带有给电子取代基(如甲基、甲氧基, **3~6**)和缺电子取代基(如硝基, **10**)的底物都适用于该反应,能以中等的收率得到相应的 1,3-噁嗪类化合物. 反应收率不高的原因主要是因为部分原料剩余以及少量原料发生水解反应. 苯环上带有卤素(氯、溴、碘, **7~9**)的底物在标准条件下也能以

图 2 苯甲酰亚胺高烯丙酯类底物的适用范围

Figure 2 Scope of *O*-homoallyl benzimidate substrates
All yields are based on isolated product on a 0.2 mmol scale

中等偏上的收率给出相应产物,为分子结构的进一步修饰和转化提供了便利. 萘环(**11**)或者呋喃(**12**)、噻吩(**13**)等杂芳环取代的底物也适用于该反应,能以中等的收率得到相应的产物. 然而,带有多取代双键的苯甲酰亚胺高烯丙酯类底物和三氯乙酰亚胺高烯丙酯(**14**)底物,在最优反应条件下未能得到相应成环产物^[19]. 如图 3 所示,具有不同碳链长度的全氟碘代烷烃如 $\text{C}_3\text{F}_7\text{I}$, $\text{C}_5\text{F}_{11}\text{I}$, $\text{C}_6\text{F}_{13}\text{I}$ 和 $\text{C}_8\text{F}_{17}\text{I}$ 都适用于该铜催化的分子内氨化全氟烷基化反应,以中等收率得到全氟烷基取代的 1,3-噁嗪类化合物.

图 3 全氟碘代烷烃的适用范围

Figure 3 Scope of perfluoroalkyl iodides
All yields are based on isolated product on a 0.2 mmol scale

2.3 反应实用性考察

为了考察该铜催化分子内氨化全氟烷基化反应的实用性,首先尝试了反应产物的克级制备(图 4). 当用 0.8 g 原料 **23** 反应时,以 64% 的收率得到多氟烷基取代的 1,3-噁嗪产物 **4** (1.1 g). 1,3-噁嗪产物在温和条件下可以发生开环反应,生成在有机合成中应用广泛的 γ -氨基醇衍生物.

2.4 反应机理研究

2.4.1 反应机理假设

根据已有文献和观察到的具体实验现象^[6],提出了

图4 克级反应和产物的进一步转化

Figure 4 Gram scale reaction and transformation of 1,3-oxazine

如图 5A 所示的反应机理. 二价铜首先发生歧化反应生成少量一价铜和三价铜. 全氟碘代烷与一价铜发生单电子转移反应, 之后碳碘键均裂产生全氟烷基自由基中间体 $R_f\cdot$. 该自由基中间体与底物 **1** 中的末端双键发生区域选择性的自由基加成反应, 生成碳自由基中间体 **I**. 该中间体可能经过下面三种途径最终生成目标产物: (a) 碳自由基中间体 **I** 与全氟碘代烷反应, 生成碘代中间体 **II** 和全氟烷基自由基, 碘代中间体 **II** 经过分子内亲核取代反应得到成环产物; (b) 碳自由基中间体 **I** 可被二价铜氧化生成碳正离子中间体 **III**, 经过后续分子内成环反应得到产物; (c) 中间体 **I** 还可以被反应体系中的二价铜捕获, 形成三价铜中间体 **IV**, 最后经过还原消除反应得到产物.

2.4.2 机理实验

为了验证反应的历程, 进行了初步的机理验证试验 (图 5B). 在标准反应条件下向反应体系中加入自由基抑制剂四甲基哌啶氮氧化物 (TEMPO) 和 2,6-二叔丁基-4-甲基苯酚 (BHT) 时, 反应被严重抑制, 只能得到微量的产物. 通过氟谱分析观测到了九氟丁基自由基被 TEMPO 捕获的产物 **25**, 从而证实了该反应的启动经历自由基反应历程. 当采用烯丙基苯 **26** 作反应物时, 以中等收率得到了双键碘代全氟烷基化的产物 **27**. 通过其他途径制备了碘代中间体 **28**, 化合物 **28** 在标准反应条件下可顺利发生分子内亲核取代反应得到成环产物 **2**. 这一结果表明铜催化苯甲酰亚胺高烯丙酯的氟化全氟烷基化反应很可能经历了反应路径 a, 首先生成中间体 **II**, 之后在银盐的作用下发生分子内关环反应得到目标产物.

3 结论

使用廉价易得的全氟碘代烷烃为全氟烷基化试剂, 发展了铜催化的苯甲酰亚胺高烯丙酯的分子内胺化全氟烷基化反应. 该反应有较好的底物适用范围和官能团兼容性, 克服了之前使用 Togni 试剂难以多样化的缺陷,

图5 反应可能机理

Figure 5 Proposed mechanism

^a Yields are based on ¹H NMR analysis of reaction mixture with 1,1,2,2-tetrachloroethane as internal standard on a 0.2 mmol scale

为合成多氟烷基取代的 1,3-噁嗪类化合物提供了实用的新方法.

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Unreactive substrates:

(Cheng, F.)