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叔丁醇钠促进酮的选择性二氟甲基化反应

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摘要 有机氟化合物广泛应用于医药、农药、新型功能材料、生命科学等领域. 由于其独特的化学、物理和生物性能, 近年来, 发展与之相关的高效引氟方法和手段, 受到了合成化学家的高度关注. 相对来说, 三氟甲基化反应研究较多, 二氟甲基化反应发展滞后. 二氟甲基作为醇羟基和硫羟基的生物电子等排体, 可提高生物活性分子代谢稳定性和生物利用度, 发展经济高效的选择性二氟甲基化方法对相关含氟药物的合成具有重要的意义. 本研究以廉价的二氟溴乙酸乙酯为二氟卡宾来源, 采用叔丁醇钠促进, 在温和简单的反应条件下, 实现了芳基酮的选择性二氟甲基化, 表现出较高的选择性和良好的底物适用性. 在该反应中, 叔丁醇钠作为碱发挥了双重促进作用, 在促使酮向烯醇式转变的同时, 还促进二氟溴乙酸乙酯产生二氟卡宾, 烯醇式中间体捕获二氟卡宾从而实现了芳基酮α位的选择性二氟甲基化. 该反应底物适用性广, 且方法绿色经济.

关键词 叔丁醇钠, 芳基酮, 二氟卡宾, 二氟甲基化, 合成

二氟甲基作为一种重要的含氟改性基团广泛存在于诸多含氟药物当中[1,2], 相关的研究也一直备受关注, 因此, 在有机物中选择性地引入二氟甲基成为广大化学科研工作者, 尤其是氟化学家热切关注的课题[3~5]. 二氟卡宾作为一种活性中间体, 本质上是一种亲电试剂, 易与亲核试剂发生反应, 因而通过二氟烷基试剂产生二氟卡宾、亲核试剂捕获二氟卡宾是实现有机物二氟甲基化的一种有效策略.

近年来, 采用醇[6~12]、硫酚[13~18]、胺[19~24]、膦[25]、肟[26]等杂原子亲核试剂捕获二氟卡宾的二氟甲基化方法被相继报道. 同时, 炔烃[27~29]和烯烃[30]作为碳亲核试剂捕获二氟卡宾的反应也有较多报道, 但通过捕获二氟卡宾实现C(sp^3)的选择性二氟甲基化反应的报道相对较少. 2018年, Hibata课题组[31]以常用的二氟甲基化试剂二氟溴甲基三甲基硅烷($TMSCF_2Br$)在碱的条件下产生二氟卡宾, 实现了β-酮酸酯类底物的二氟甲基化, 反应表现出较好的活性和较高的选择性, 但反应底物类型局限于β-酮酸酯类化合物, 从而应用性受到较大限制(图1(a)). 同年, 刘国凯课题组[32]和沈其龙课题组[33]分别用硫鎓盐和硫叶立德为亲电二氟甲基化试剂, 实现了对β-酮酸酯类化合物的二氟甲基化. 2019年, 胡金波课题组[3]同样采用碱促进$TMSCF_2Br$产生二氟卡宾的策略, 实现了酯类底物、酰胺类底物, 乃至芴类底物的二氟甲基化, 全面深入地研究了$TMSCF_2Br$/Base反应体系, 拓展了该反应体系的底物适用范围. 尽管$TMSCF_2Br$已经比较廉价, 但对于医药化工而言, 发展更为经济高效的二氟甲基化试剂依然具有不言而喻的重要意义. 二氟溴乙酸乙酯作为一种更经济的二氟

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烷基化试剂，在一定条件下既能形成二氟乙酸乙酯自由基[34]，又能产生二氟卡宾[19,35]，前者自由基的产生往往需要使用过渡金属或光敏剂，尤其是昂贵的铱光敏剂的使用带来了较高的经济成本，且反应得到的是含酯的二氟烷基(-CF_2COOEt)，需要进一步脱酯才能得到二氟甲基. 而后者则直接实现二氟甲基化，免去了脱酯化过程，反应条件往往较前者更为简单. 因此，发展以二氟溴乙酸乙酯产生二氟卡宾进而直接实现二氟甲基化的方法具有很好的应用前景.

最近，本课题组[36,37]对光催化的二氟烷基化反应取得较好的研究进展. 我们发现在蓝光催化下，无需氧化剂，能够实现炔烃、烯烃分别与二氟碘乙酸乙酯的二氟烷基化反应[36]；进一步研究实现了光催化芳基酮的二氟烷基化反应(图1(b))[37]. 二氟烷基化的最终目的往往是二氟甲基化，而这需要进一步的脱酯化. 在前期的研究工作中发现[37]，底物芳基酮**1a**(2-苯基-四氢萘酮)与二氟溴乙酸乙酯在叔丁醇钾的条件下，无需光催化条件，以29%的收率得到了二氟甲基化产物**2a**. 初步分析是叔丁醇钾作为碱起到了烯醇式互变和促进产生二氟卡宾的双重作用. 因此，我们拟在此基础上对反应条件进行深入细致的探索，从而发现和建立芳基酮类化合物与二氟溴乙酸乙酯发生二氟甲基化反应的新型、高效反应体系. 经过系统研究，发现仅使用叔丁醇钠促进，在温和简单的反应条件下，实现了芳基酮的选择性二氟甲基化，以高达96%的收率得到相应的二氟甲基化产物(图1(c)).

1 实验

(ⅰ) 试剂与仪器. 核磁共振氢谱、碳谱和氟谱采用Bruker超导傅里叶数字化核磁共振仪(400 MHz，德国)于室温下测定，以四甲基硅烷作内标. 高分辨质谱采用Bruker CompassMaxis高分辨率质谱仪(德国)测定. 实验所用溶剂均经活化的分子筛干燥后使用，实验所用其他试剂均为分析纯，没有经过其他处理. 反应后处理均采用分析纯溶剂.

(ⅱ) 芳基酮二氟甲基化的一般方法. 在手套箱中将^{t}BuONa(0.6 mmol)、**1a**(0.2 mmol)依次称量并装入有搅拌子的史奈克管中，加入溶剂二氯甲烷(DCM, 2 mL). 取出手套箱后加入$BrCF_2COOEt$(0.4 mmol)，置于低温反应器中于0°C反应5 h，反应期间，用尖头微量进样器取样并TLC(薄层色谱)检测反应进行情况，当反应完全时停止低温反应釜，并放置至室温，将反应液旋蒸只留极少溶剂后用硅胶柱纯化(具体详见补充材料).

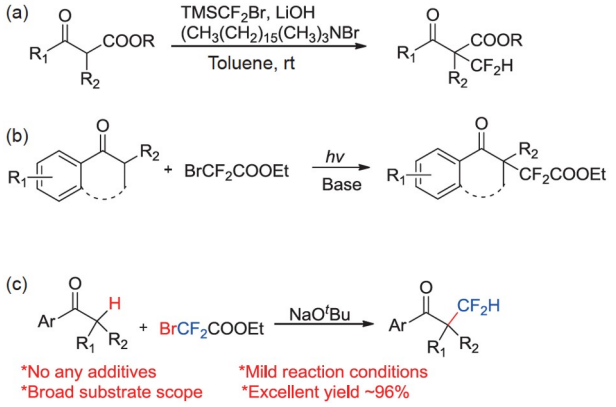

图 1 酮的二氟烷基化反应. (a) Hibata课题组前期工作; (b) 本课题组前期工作; (c) 本工作

Figure 1 Difluoroalkylation of ketones. (a) Previous work of Hibata research group; (b) previous work of our research group; (c) this work

(ⅲ) 芳基酮二氟甲基化的控制实验. 在手套箱中将^{t}BuONa(0.6 mmol)、化合物**3**(0.2 mmol)依次称量并装入有搅拌子的史奈克管中，加入溶剂DCM(2 mL). 取出手套箱后置于低温反应器中于0°C反应5 h，反应期间，用尖头微量进样器取样并TLC(薄层色谱)检测反应进行情况，当反应完全时停止低温反应釜，并放置至室温，将反应液旋蒸只留极少溶剂后用硅胶柱纯化.

2 结果与讨论

2.1 反应条件的筛选及优化

以**1a**作为标准底物，采用二氟溴乙酸乙酯作为二氟甲基试剂，我们尝试采用各类强碱促进二氟溴乙酸乙酯产生二氟卡宾，同时促进**1a**烯醇式互变，进而实现二氟甲基化反应. 首先，在−20°C的低温条件下，以四氢呋喃作为溶剂，添加1.6 eq.的叔丁醇钾，5 h以29%的收率得到了二氟甲基化目标产物**2a**(表1，序号1). 将碱换成双三甲基硅基氨基锂(LiHMDS)，仅有10%的收率(表1，序号2)，而其他与之类似的二异丙基氨基锂、双三甲基硅基氨基钠、双三甲基硅基氨基钾均没有促进效果或仅有痕量的产物(表1，序号3~5). 与叔丁醇钾类似的强碱都有着不同程度的促进效果，叔丁醇钠和甲醇钠的促进效果略有提升，收率分别为43%和37%(表1，序号6，8)，叔丁醇锂的促进效果则更差，仅有17%的收率(表1，序号7).

为了进一步提高产物收率，将叔丁醇钠的用量增加至3 eq.，收率有明显提升，达60%(序号9)，但继续增

表 1 反应条件优化[a)]

Table 1 Reaction conditions optimization

序号	碱(eq.)	溶剂	温度(°C)	收率(%)[b)]
1	^{t}BuOK(1.6)	THF	–20	29
2	LiHMDS (1.6)	THF	–20	10
3	LDA(1.6)	THF	–20	未测到
4	NaHMDS (1.6)	THF	–20	痕量
5	KHMDS (1.6)	THF	–20	痕量
6	^{t}BuONa(1.6)	THF	–20	43
7	^{t}BuOLi(1.6)	THF	–20	17
8	MeONa(1.6)	THF	–20	37
9	^{t}BuONa(3.0)	THF	–20	60
10	^{t}BuONa(4.0)	THF	–20	59
11	^{t}BuONa(3.0)	THF	0	62
12	^{t}BuONa(3.0)	THF	室温	54
13	^{t}BuONa(3.0)	甲苯	0	痕量
14	^{t}BuONa(3.0)	CH_3CN	0	72
15	^{t}BuONa(3.0)	DMF	0	32
16	^{t}BuONa(3.0)	DCM	0	88
17	^{t}BuONa(3.0)	DCE	0	86

a) 反应条件: **1a**(0.2 mmol), $BrCF_2COOEt$(0.4 mmol), 碱(0.32 mmol), 溶剂(2 mL), 5 h; b) 分离收率

加至4 eq.时, 收率几乎没有变化(表1, 序号10), 因此3 eq.被认为是碱的最佳用量. 接着对反应温度进行了考察, 当温度升高至0°C时, 得到62%的收率(表1, 序号11), 但升至室温, 收率下降到54%(表1, 序号12), 因此反应的最佳温度为0°C. 最后, 对反应溶剂进行了考察, 甲苯仅得到痕量的产物(表1, 序号13), 乙腈的收率提高至72%(表1, 序号14), *N*,*N*-二甲基甲酰胺则使收率降低至32%(表1, 序号15). 令人可喜的是, 二氯甲烷和二氯乙烷分别得到了88%和86%的较高收率.

2.2 底物适用性研究

在最佳的反应条件下, 我们对该二氟甲基化反应体系进行了底物适用性考察研究(图2). 首先, 对底物的空间位阻效应进行考察, 分别采用2号位苯环的对位、间位、邻位甲基取代的底物进行实验, 结果表明对位和间位的取代都具有76%和89%的较好收率(**2b**, **2c**), 但位阻效应大的邻位取代底物的反应收率有53% (**2d**), 可见空间位阻效应对反应结果都没有明显的影响.

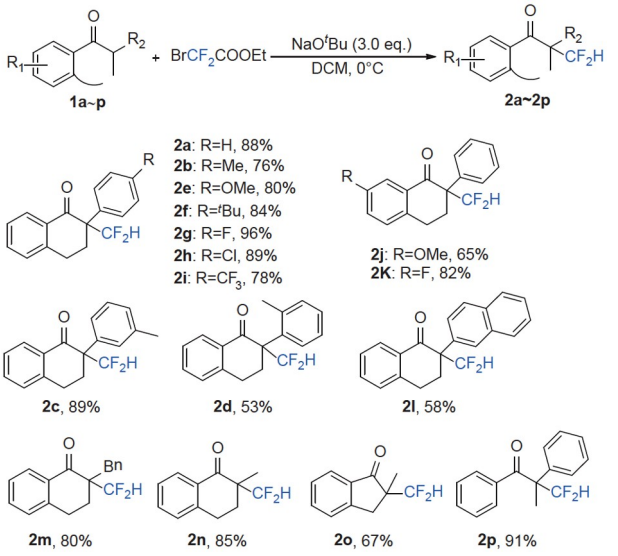

图 2 二氟甲基化反应底物适用性研究

Figure 2 Substrate scope for difluoromethylation of aryl ketones with ethyl difluorobromoacetate

随后, 考察了取代基的电性、类型对反应结果的影响. 实验结果表明, 供电子基团都能到较好的反应结果(**2e**, **2f**, **2j**). 在吸电子基团取代的底物考察实验中, 氟原子取代的底物分别得到96%和82%的较高收率(**2g**, **2k**). 氯原子和三氟甲基取代的底物也分别具有89%和78%的较好收率, 可见, 具有吸电子基团的底物表现出更好的适用性.

此外, 对其他类型的底物也进行了适用性考察, 结果表明, 萘环取代的底物也能适用于该条件, 但收率只有58%(**2l**). 2-位苄基取代和甲基取代的底物分别得到了80%和85%的较好收率(**1m**, **1n**). 五元环底物2-甲基茚酮得到了67%的中等收率(**2o**). 直链芳基酮底物也具有较好的适用性, 二苯丁酮得到了91%的较高收率(**2p**). 上述这些结果表明该催化体系具有较好的底物适用性.

2.3 反应机理探究

将化合物**3**加入至标准反应条件, 但没有得到二氟甲基化产物**2a**(图3), 说明在该二氟甲基化体系中反应历程没有经过中间体**3**发生脱酯化的过程, 很可能存在同时发生脱溴与脱酯的过程.

同样，在标准的反应条件下，以$TMSCF_2Br$为二氟卡宾的供体试剂，反应不完全，只能以46%的收率得到二氟甲基化产物**2a**．说明该反应体系促进了二氟溴乙酸乙酯产生二氟卡宾.

根据所有的实验结果，参考相关二氟甲基化反应的文献[19,23,37]报道，提出了以下可能的反应机理(图4)．首先，二氟溴乙酸乙酯在叔丁醇钠的条件下同时脱溴和脱酯得到二氟卡宾，其中-COOEt脱去与-O^{t}Bu形成相应的原酸酯**B**(通过气质联用仪检测)．与此同时，叔丁醇钠促使底物**1a**向烯醇式转变，烯醇式中间体**A**与二氟卡宾反应得到碳负离子中间体**C**，中间体**C**攫取烯醇式转变过程中产生的叔丁醇的氢得到二氟甲基化目标产物**2a**.

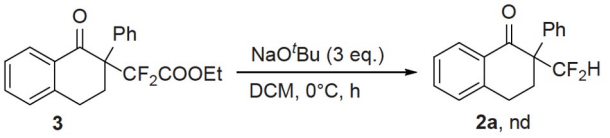

图 3 控制实验
Figure 3 Control experiments

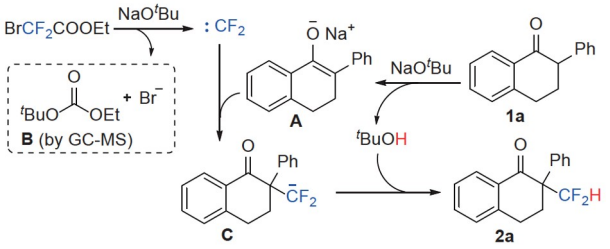

图 4 推测的反应机理
Figure 4 Proposed reaction mechanism

3 结论

采用廉价的二氟烷基试剂$BrCF_2COOEt$在仅添加叔丁醇钠的简单条件下，以叔丁醇钠同时促使产生二氟卡宾与烯醇式中间体的双重催化策略，实现了芳基酮的高效二氟甲基化，以较好的收率、较高的选择性得到了二氟甲基芳基酮类化合物，比以往报道的二氟甲基化方法更为绿色经济.

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补充材料

附录 实验操作步骤、产物表征数据及核磁共振谱图

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Summary for “叔丁醇钠促进酮的选择性二氟甲基化反应”

Selective difluoromethylation of ketones promoted by sodium tert-butoxide

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The incorporation of fluorine atoms into organic compound may lead to changes in the properties such as lipophilicity, metabolic stability, and bioavailability. Therefore, the fluorine-containing compounds are privileged molecules in the research and development of new medicines. From the synthetic perspective, the selective introduction of fluorine into the drug candidates represents a most straightforward and powerful strategy in drug design and screening. Therefore, the selective difluoromethylation has stood out as an effective tool for the access of fluorine-containing compounds. One of the strategies is using difluorocarbons as an active reaction intermediate for the incorporation of difluoromethyl group and has attracted considerable attention from the organic synthetic community. Recently the reaction of difluorocarbons with hetero-atoms such as alcohols, thiophenols, amines, and phosphine were studied, and provided the difluoromethyl products. However, the reaction of difluorocarbons with C(sp^3)−H bond is relatively less developed. To solve this problem, ethyl 2-bromo-2,2-difluoroacetate has come into our sight, as it can generate the ethyl 2,2-difluoroacetate free radical and difluorocarbons. And the difluorocarbons can lead to the direct difluoromethylation reaction without the decarbonylation process, thus has offered a convenient preparation method for the fluorine-containing compounds. On the basis of our recent research in the photocatalyzed reactions and oxidant free difluoroalkylation reactions of alkynes, alkenes and aryl ketones with ethyl difluoroiodoacetate, the selective difluoromethylation of aryl ketones was studied and reported herein. In order to develop an effective direct difluoromethylation reaction with simple reaction conditions, some bases were screened as catalyst. The inorganic bases such as sodium tert-butoxide, lithium tert-butoxide, and potassium tert-butoxide were able to promote the reaction. When the relation was performed in dichloromethane (DCM) under 0°C with three equivalent of sodium tert-butoxide as additive, the desired difluoromethylation product was obtained in 88% yield. Subsequently, the substrate scope of current transformation was studied. It was proved the reaction yields were affected by the steric demanding groups in the *ortho*-positions of the phenyl rings of the 2-phenyl-3,4-dihydronaphthalen-1(2*H*)-one. The reaction yields were not sensitive with electron withdraw and electron donating groups. Substrates with naphthyl and cyclohexyl moieties were also well tolerated to give the difluoromethylation products. The reaction was achieved under mild and simple reaction conditions, using cheap ethyl difluorobromoacetate as the source of difluorocarbene, promoted by sodium tert-butanol, showing high selectivity and good substrate applicability. To gain some insights in the reaction mechanism, some control experiments were conducted. The reaction of ethyl 2,2-difluoro-2-(1-oxo-2-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)acetate under current reaction system failed to give any desired product, which has ruled out the possibility with it as decarbonylation intermediate. And only 46% yield was given by using (bro-modifluoromethyl) trimethylsilane instead of ethyl 2-bromo-2,2-difluoroacetate. According to the control experiment, we believe the present difluoromethylation reaction may initiate with the difluorocarbon, which generates from the $BrCF_2CO_2Et$ by the debromination and decarbonylation process. And the tert-butyl ethyl carbonate was observed by GC-MS analysis as side-product. Meanwhile, the enol intermediate captures difluorocarbon to realize the selective difluoromethylation of aryl ketone saturated carbon. In this reaction, sodium tert-butanol, as a base, plays a dual catalytic role. In addition to promoting the conversion of ketone to enol, ethyl difluorobromoacetate is also applied to produce difluorocarbons. According to the results of control experiments and related references, sodium tert-butanol was proposed as an effective reagent for the generation of difluorocarbon from ethyl difluorobromoacetate. Therefore, the present study has provided an easy-handling and cost-effective method for the preparation of the valuable difluoromethyl compounds under mild reaction conditions with good functional group tolerance.

sodium tert-butoxide, aryl ketones, difluorocarbene, difluoromethylation, synthesis

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