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Radical Hydro-Ethoxycarbonyldifluoromethylation of Alkenes with $BrCF_2CO_2Et$

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The difluoromethylene (CF_2) group, valued for its unique electronic and steric properties, plays a critical role in pharmaceutical and agrochemical design, as exemplified by drugs like lubiprostone, which requires ethyl 2,2-difluorohexanoate as a key intermediate for its synthesis. Consequently, developing efficient methods to incorporate the ethoxycarbonyldifluoromethyl group into alkanes is highly desirable. Herein, we describe a mild, versatile, and efficient radical hydro-ethoxycarbonyldifluoromethylation of alkenes with $BrCF_2CO_2Et$. This process is applicable to both unactivated alkyl alkenes and active aryl alkenes. The protocol is characterized by mild reaction conditions, the absence of expensive reagents, and the elimination of transition metals.

1. Introduction

The difluoromethylene (CF_2) group, owing to its distinctive electronic and steric properties, can serve as a bioisostere for oxygen atoms or carbonyl groups, holding significant application value in the molecular design of pharmaceuticals and agrochemicals.[1–4] The CF_2 group, as a key functionality, has been pivotal in the development of several clinically important drugs, such as Voxilaprevir,[5] Lvosidenib,[6,7] Maraviroc,[8] and Lubiprostone.[9] Specifically, lubiprostone, used for treating chronic idiopathic constipation, exemplifies this utility. Its synthesis necessitates the production of ethyl 2,2-difluorohexanoate as a crucial intermediate, an alkane containing an ethoxycarbonyldifluoromethyl group (Scheme 1A). Given the unique attributes of the CF_2 moiety[10–16] and the requirement of ethyl 2,2-difluorohexanoate for the synthesis of lubiprostone, considerable attention has been directed toward efficiently incorporating an ethoxycarbonyldifluoromethyl group into alkanes.

Currently, two distinct methods have been developed: difluorination of active substrates (Scheme 1B) and hydro-ethoxycarbonyldifluoromethylation of alkenes (Scheme 1C). Difluorination methods include the deoxydifluorination of carbonyls using DAST, which proceeds smoothly,[17] and the conversion of ethyl 2-bromohexanoate into the corresponding arylthioether followed by desulfurative difluorination using dibromohydantoin (DBH) and Olah's reagent (Py·9HF), yielding the desired product (Scheme 1B).[18] In comparison, direct hydro-ethoxycarbonyldifluoromethylation of alkenes is more straightforward and attractive. Commonly used reagents for this process include $BrCF_2CO_2Et$, ICF_2CO_2Et, and $TMSCF_2CO_2Et$ (Scheme 1C). Notable approaches include Bruno et al.'s method using AIBN as an initiator for the reaction of alkenes with ICF_2CO_2Et, followed by reductive deiodination with a $Zn/NiCl_2$ system. This constitutes a two-step process.[19] Burton et al. reported a nickel(II) chloride hexahydrate-catalyzed radical hydro-ethoxycarbonyldifluoromethylation using $ICF_2CF_2CO_2Et$.[20] Cho and Itoh's team developed a photocatalytic radical pathway to achieve addition reactions of alkenes with $BrCF_2CO_2Et$ under LED irradiation.[21,22] Niu et al. established a nickel-catalyzed system utilizing $PhSiH_3$ as the hydride source for unactivated alkenes.[23] Hao's group reported a silver- or hypervalent iodine-mediated oxidative system to construct C-CF_2CO_2Et bonds via $TMSCF_2CO_2Et$.[24] Despite their effectiveness, these methods face limitations. These include the use of hazardous reagents like explosive DAST, reliance on transition metals, the need for costly reagents, or requirements for two-step processes. As a result, the development of novel

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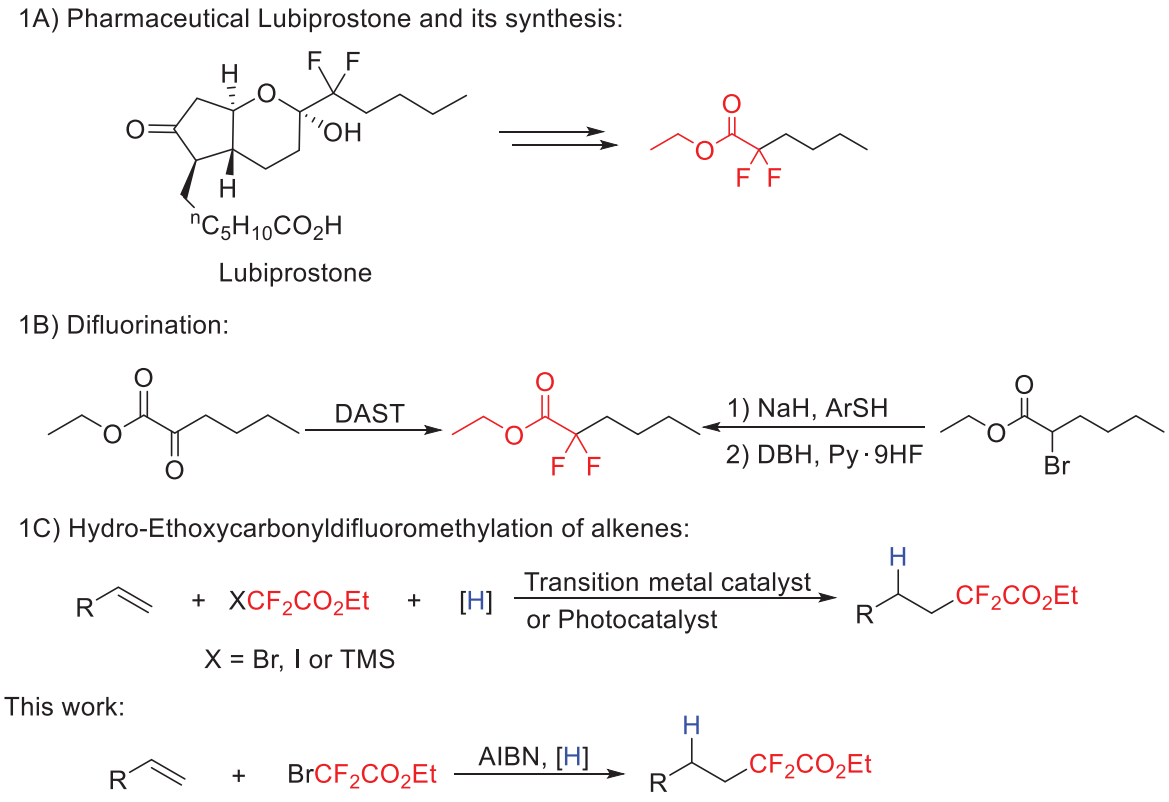


Scheme 1. The pharmaceutical lubiprostone and the incorporation of CF_2CO_2Et into alkanes.

methods for hydro-ethoxycarbonyldifluoromethylation remains a significant focus in synthetic chemistry.

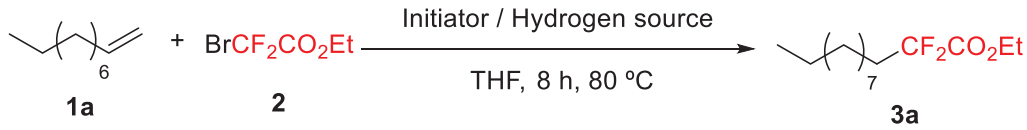
We have been actively exploring the chemistry of fluorinated group incorporation and have developed a novel strategy for constructing ethoxycarbonyldifluoromethyl alkanes via AIBN-catalyzed reactions of unactivated alkenes with $BrCF_2CO_2Et$. This study introduces a convenient reaction system that utilizes diphenylsilane (Ph_2SiH_2) as the hydrogen source to achieve radical-mediated hydro-ethoxycarbonyldifluoromethylation. Notably, this approach offers several key advantages: it eliminates the need for pre-functionalization, operates under mild conditions, and does not require the use of transition metal catalysts or expensive reagents.

2. Results and Discussion

We employed compound **1a** as a model substrate and $BrCF_2CO_2Et$ as the reagent, systematically screening various radical initiators and hydrogen sources to optimize the reaction conditions (Table 1). During the optimization of reaction conditions, we initially screened various radical initiators. The results indicated that when AIBN (entry 1) was used as the initiator, the yield of product **3a** reached 87%, outperforming BPO and DTBP (entries 2 and 3). Subsequently, we evaluated the solvent system and found that THF not only provided the highest reaction yield but also effectively dissolved AIBN. In contrast, AIBN exhibited poor solubility in other solvents, leading to the formation of white solid precipitates post-reaction, which was likely the primary reason for the reduced yields (see Supporting Information). After identifying the optimal solvent, we systematically screened various hydrogen sources and discovered that Ph_2SiH_2 significantly enhanced the yield of **3a** (entry 1 vs entries 4 to 10). Further investigation into the equivalents of AIBN revealed a clear dependency on radical initiation (entries 1 and 11 to 13): the reaction did not proceed in the absence of AIBN; when the AIBN equivalent was 0.4, the yield of **3a** reached its maximum (entry 1); however, increasing the AIBN equivalent further (to 1.0 equivalent) resulted in a decrease in yield (entry 13). Optimization experiments on the amount of hydrogen source demonstrated that 1.5 equivalents of Ph_2SiH_2 offered the best cost-performance ratio (entry 15). Screening experiments on reaction temperature (entries 16 to 18) revealed that 100 °C is the optimal initiation temperature (entry 18), with GC-MS analysis confirming complete conversion of the substrate alkene at this temperature, whereas trace amounts remained at 80 °C. Finally, the reaction time screening results (entries 19 and 20) indicated that the starting material was completely consumed (below the GC-MS detection limit) after 6 hours, at which point the reaction reached completion with maximum product yield (entry 20). We also conducted the reaction under atmospheric pressure at THF reflux temperature, obtaining the product in 62% yield (entry 21).

With the optimal reaction conditions in hand (Table 1, entry 23), the substrate scope of the radical hydro-ethoxycarbonyldifluoromethylation process was subsequently investigated. The research results indicate that the transformation exhibits excellent substrate applicability and functional

Table 1. The optimization of the reaction conditions.



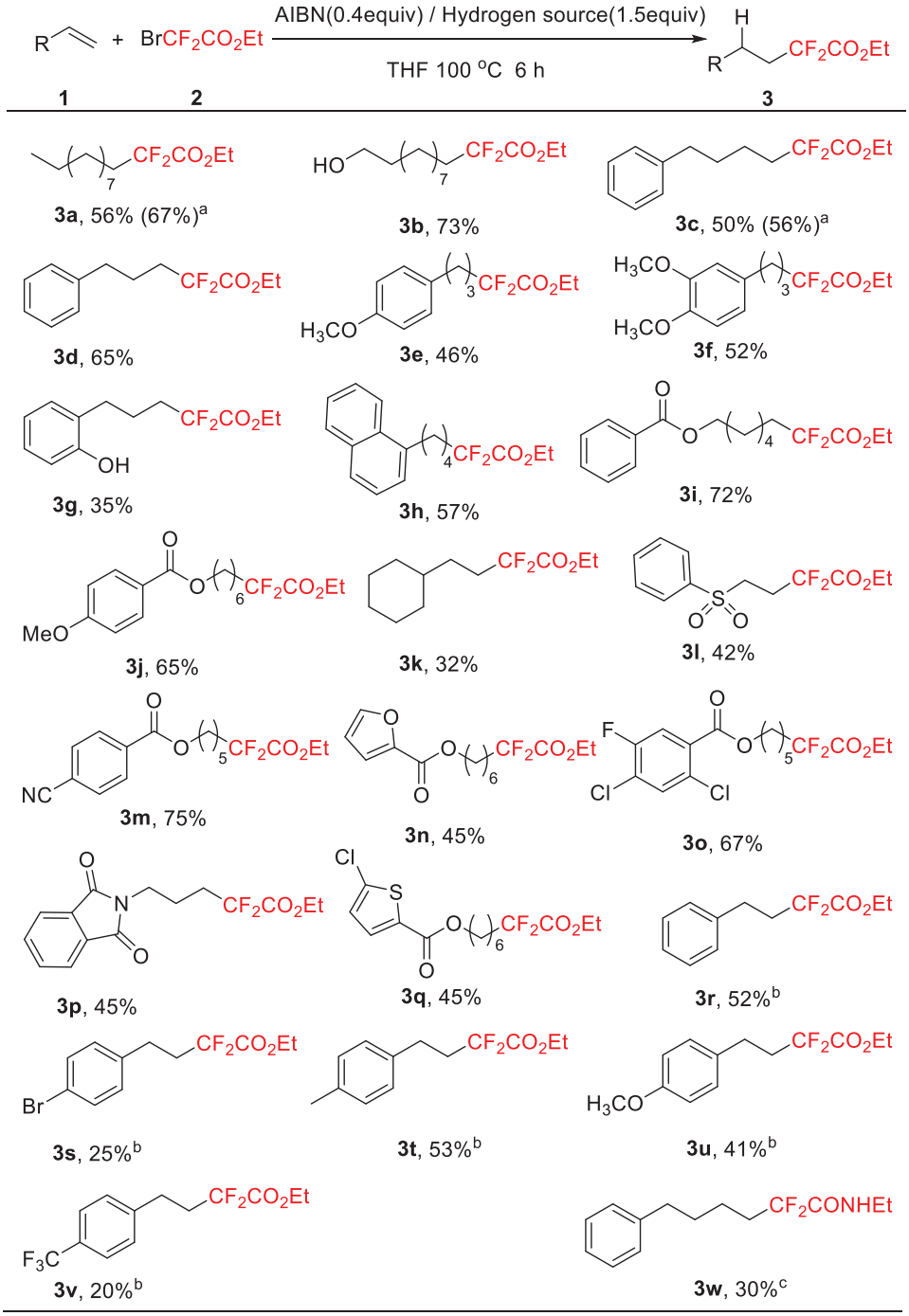
1a **2** **3a**

Entry	Initiator	Hydrogen source	Ratio[a]	Yield[%][b]
1	AIBN	Ph_2SiH_2	1: 1.5: 0.4: 1	87
2	BPO	Ph_2SiH_2	1: 1.5: 0.4: 1	24
3	DTBP	Ph_2SiH_2	1: 1.5: 0.4: 1	Trace
4	AIBN	$PhSiH_3$	1: 1.5: 0.4: 1	61
5	AIBN	TMS_3SiH	1: 1.5: 0.4: 1	66
6	AIBN	$(C_2H_5O)_3SiH$	1: 1.5: 0.4: 1	42
7	AIBN	Ph_2MeSiH	1: 1.5: 0.4: 1	43
8	AIBN	$PhCH_2SH$	1: 1.5: 0.4: 1	23
9	AIBN	Ph_3CSH	1: 1.5: 0.4: 1	Trace
10	AIBN	$(i\text{-}Pr)_3SiSH$	1: 1.5: 0.4: 1	43
11	AIBN	Ph_2SiH_2	1: 1.5: 0: 1	N.D.
12	AIBN	Ph_2SiH_2	1: 1.5: 0.2:1	86
13	AIBN	Ph_2SiH_2	1: 1.5: 1.0: 1	31
14	AIBN	Ph_2SiH_2	1: 1.5: 0.4: 0	15
15	AIBN	Ph_2SiH_2	1: 1.5: 0.4: 1.5	86
16[c]	AIBN	Ph_2SiH_2	1: 1.5: 0.4: 1.5	N.D.
17[d]	AIBN	Ph_2SiH_2	1: 1.5: 0.4: 1.5	42
18[e]	AIBN	Ph_2SiH_2	1: 1.5: 0.4: 1.5	92
19[f]	AIBN	Ph_2SiH_2	1: 1.5: 0.4: 1.5	72
20[g]	AIBN	Ph_2SiH_2	1: 1.5: 0.4: 1.5	93
21[h]	AIBN	Ph_2SiH_2	1: 1.5: 0.4: 1.5	62

Reaction conditions: In a sealed tube, **1a** (0.2 mmol), **2** ($BrCF_2CO_2Et$), initiator, a hydrogen source, and THF (1 mL) were added, and the reaction was stirred at 80 °C for 8 hours.
[a] Molar ratio of **1a**: **2**: initiator: Hydrogen source;
[b] The yield was determined by ^{19}FNMR using PhF as an internal standard;
[c] The reaction temperature was 40 °C;
[d] The reaction temperature was 60 °C;
[e] The reaction temperature was 100 °C;
[f] The reaction temperature was 100 °C and the reaction time was 4 hours;
[g] The reaction temperature was 100 °C and the reaction time was 6 hours.
[h] The reaction was carried out at reflux temperature for 6 hours.

group tolerance under mild conditions (Scheme 2), accommodating a variety of functional groups such as esters (**3i, 3j**), sulfones (**3l**), and aryl halides (**3o, 3s**). When 2-allylphenol (**3g**) is used as the substrate, the yield decreases compared to allylbenzene (**3d**). In addition to alkyl alkenes containing benzene ring frameworks, structurally diverse heterocyclic analogs (e.g., furan (**3n**), thiophene (**3q**)) were also investigated, although they exhibited lower yields compared to their benzene-ring counterparts (**3i**, **3j**). Notably, when Ph_2SiH_2 was used as the hydrogen source, styrene substrates did not react; however, upon replacing the hydrogen source with TMS_3SiH, styrene substrates successfully participated in the reaction (**3r** to **3v**). When styrene is employed as the substrate, the presence of electron-withdrawing effects adversely affects the reaction activity, leading to reduced efficiency (**3s**, **3v**). To enhance the practicality of our reaction, we attempted a gram-scale synthesis under atmospheric pressure, which proceeded smoothly with a yield of 67% (**3a**) and 56% (**3c**). We also evaluated analogous difluorination reagents (e.g., $BrCF_2CONHEt$) under identical conditions (**3w**). Although the reaction successfully afforded the desired product, the yield was significantly diminished, and it is hard to isolate the pure product.

To investigate the reaction mechanism, we conducted mechanistic studies by adding 1 equivalent of TEMPO to the system. ^{19}F NMR analysis revealed complete suppression of product formation, suggesting that a radical mechanism is operative (Scheme 3, eq 1). Based on the above results, we propose the reaction mechanism shown as follows (Scheme 3, eq 2). Under heating conditions, AIBN undergoes homolytic

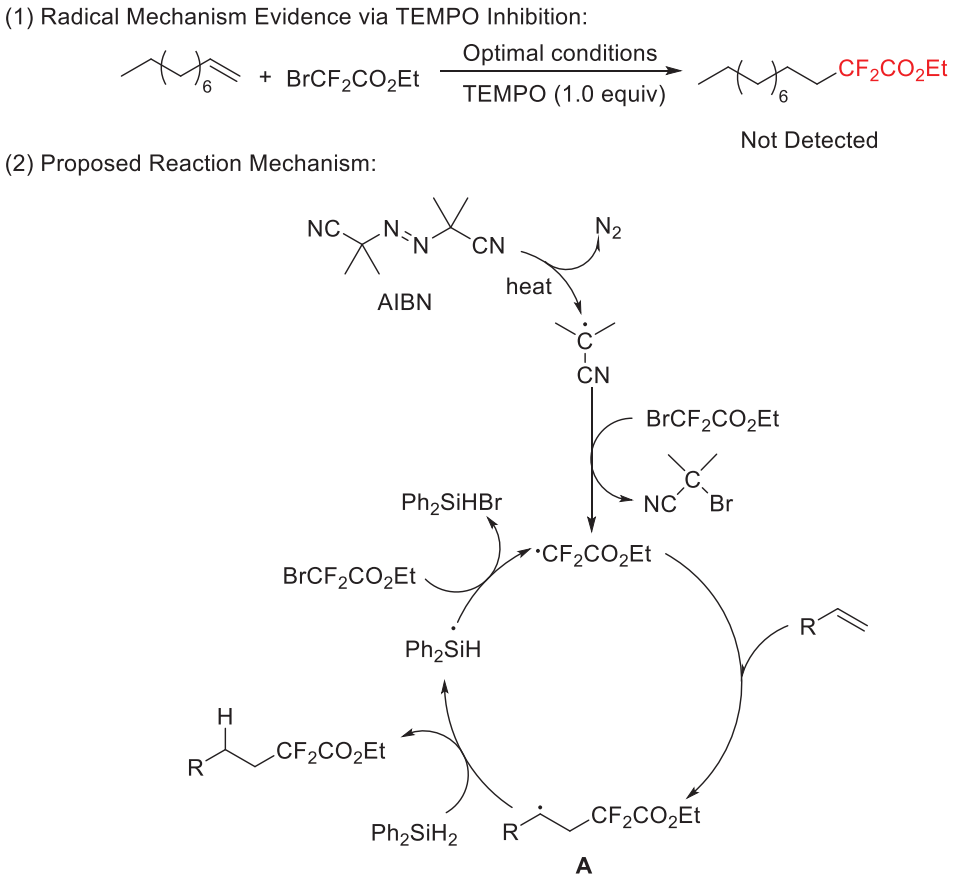


Scheme 2. The substrate scope of the radical hydro-ethoxycarbonyldifluoromethylation process. Isolated yields are shown. Reaction conditions: substrate **1** (0.5 mmol), $BrCF_2CO_2Et$ (0.75 mmol), AIBN (0.2 mmol), and Ph_2SiH_2 (0.75 mmol) in THF (2.5 mL) at 100 °C for 6 hours. [a]Yield of gram-scale reaction [b]TMS_3SiH (0.75mmol) was used as the hydrogen source, and the reaction temperature was 8 hours. [c]$BrCF_2CONHEt$ (0.75 mmol) was used instead of $BrCF_2CO_2Et$.

cleavage to generate radical initiators, which subsequently abstract a Br atom from $BrCF_2CO_2Et$ to form the key $\cdot CF_2CO_2Et$ radical intermediate. This electrophilic radical then undergoes addition to the alkene, yielding intermediate **A**. Subsequently, Ph_2SiH_2 mediates hydrogen atom transfer to convert intermediate **A** into the target product while generating a silyl radical. This silyl radical can further participate in atom transfer with $BrCF_2CO_2Et$, thereby generating the key $\cdot CF_2CO_2Et$ radical.

3. Conclusion

In summary, we have outlined a radical hydro-ethoxycarbonyldifluoromethylation process for alkenes with $BrCF_2CO_2Et$, triggered by AIBN. This methodology is applicable to both unactivated alkyl alkenes and active aryl alkenes. Our research highlights that the selection of the hydrogen source critically influences the reaction with double bonds; specifically, Ph_2SiH_2 is effective for alkyl alkenes, while TMS_3SiH is preferred



Scheme 3. The evidence for radical mechanism and the plausible reaction mechanism.

for aryl alkenes. Characterized by its operational simplicity and eco-friendliness, this approach offers an efficient pathway for introducing CF_2CO_2Et groups into alkanes, highlighting promising applications in the synthesis of CF_2-containing compounds. The presence of the CO_2Et moiety enhances versatility, providing a convenient handle for subsequent transformations to achieve diverse CF_2-containing compounds, thus showcasing promising applications in their synthesis.

Supporting Information

Additional references cited within the Supporting Information.[25–35]

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Conflict of Interest

There are no conflicts to declare.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: alkenes · ethoxycarbonyldifluoromethylation · fluorine · radical

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