Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 62 (2006) 11760–11765
Tetrahedron

Transition metal-catalyzed formation of CF_3-substituted α,β-unsaturated alkene and the synthesis of α-trifluoromethyl substituted β-amino ester

Wan Pang,[a,b] Shifa Zhu,[b] Huanfeng jiang[a,*] and Shizheng Zhu[b,*]

[a] *College of Chemistry, South China University of Technology, Guangzhou 510640, China*
[b] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*

Received 12 July 2006; revised 11 September 2006; accepted 12 September 2006

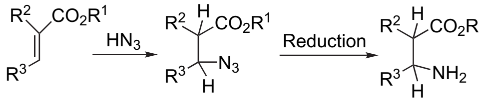
Abstract—A new transition metal-catalyzed formation of CF_3-substituted α,β-unsaturated alkenes through the ylide intermediate from the reaction between methyl 3,3,3-trifluoro-2-diazopropionate **1** and aryl aldehydes has been developed. Further transformation of the alkene affords the α-trifluoromethyl substituted β-amino ester, a valuable intermediate in the synthesis of fluorine-containing amino acids with potential biological application.

1. Introduction

It is well documented that the replacement of hydrogen with fluorine in organic molecules can make a profound and unexpected influence on the physical and biological properties of organic compounds.[1] Much attention has been directed toward the fluoro substitution during the last decade.[2] What is more, due to the unique physical and biological properties impacted by the CF_3 group, trifluoromethylation is an ongoing area of research. Thus, the preparation of trifluoromethyl containing molecules has been of great interest not only to biochemists and medicinal chemists, but also to the synthetic organic fluorine chemists.[3]

Amino acids are the basic units of proteins. More than 200 different amino acids are found in living organisms.[4] Hence, synthesis of novel amino acids has always been one of the research focuses of organic chemists. Among them, fluorine-containing amino acids have attracted considerable attention and enjoyed widespread bioorganic applications.[5] The strong carbon–fluorine bond is particularly resistant to metabolic transformations, and the electronegativity of fluorine can have a significant effect on the basicity or acidity of neighboring groups and on the electron distribution, and can change the overall reactivity and stability of the molecules.[6] Fluorinated amino acids also play an important role in the field of biological tracers, mechanistic probes, enzyme inhibitors, and medical applications including control of blood pressure, treatment of allergies, and inhibition of tumor growth.[7] Additionally, fluorinated β-amino acids are now recognized as potentially exciting building blocks for the synthesis of β-peptides, antibiotics, and enzyme inhibitors.[8]

Usually, β-amino acid can be synthesized from the α,β-unsaturated carboxylic ester. Michael addition of hydrazoic acid (HN_3) produces the azide compound, which can be easily converted to the corresponding β-amino ester using well established chemistry (Scheme 1).[9] In this paper, in order to avoid the explosive hydrazoic acid, we chose the readily available and relatively stable sodium azide as the direct azide source. Advantages of the protocol include high-yielding reaction and mild reaction condition.



Scheme 1.

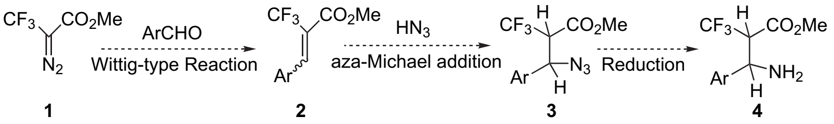
In our previous work, we have developed several methods to synthesize fluorinated alkene from fluorinated diazo compounds and aldehydes through the ylide intermediate.[10a] Therefore, we wondered whether methyl 3,3,3-trifluoro-2-diazopropionate **1** could react with aldehydes to give the

---

Keywords: Catalysis; CF_3-substituted; Ylide; α,β-Unsaturated alkenes; β-Amino ester.

[*] Corresponding authors. Tel.: +86 21 54925184; fax: +86 21 64166128; e-mail: zhusz@mail.sioc.ac.cn

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.09.041



Scheme 2.

corresponding CF_3-containing α,β-unsaturated alkenes **2** through the ylide intermediate, which could be easily transformed into the corresponding trifluoromethyl containing β-amino esters (Scheme 2).

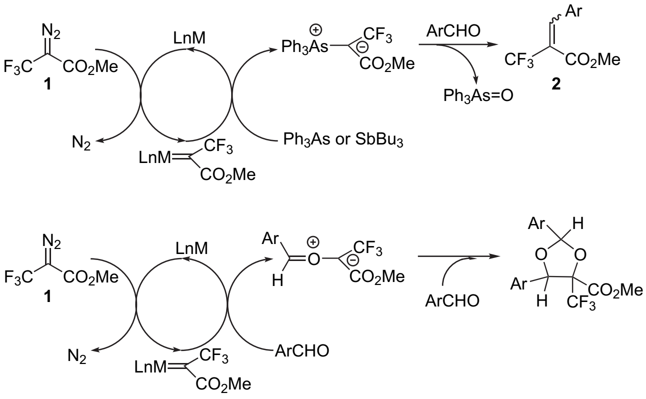
Herein, we wish to report a successful synthesis of trifluoromethylated β-amino esters from diazo compound **1**.

2. Results and discussion

Initially, arsonium ylide intermediate was used to prepare alkene **2**. 4-Nitrobenzaldehyde was used as the substrate, 1 mol % $Rh_2(OAc)_4$ was used as the catalyst, and refluxing THF as the solvent. The expected alkene **2b** was isolated in only 9% yield. In the meantime, trace amount of 1,3-dioxolane **5** (3%) was isolated (Table 1, entry1). It should come from the 1,3-dipolar addition of the carbonyl ylide intermediate and the aldehyde (Scheme 3).[3a]

The proposed reaction mechanism is depicted in Scheme 4. Due to the electron-withdrawing properties of the flanking trifluoromethyl and methoxyl carbonyl groups, the ylide intermediate could be too stable to react with the aldehyde to give alkene **2**. To improve the yield, more severe reaction conditions were employed. Increasing the reaction temperature to 80 °C (refluxing in benzene), improved the yields of alkene **2b** and 1,3-dioxolane **5** to 19 and 14%, respectively (Table 1, entry 2). Further increasing the reaction temperature to 110 °C (refluxing in toluene), improved the yield of **2b** to 36%. But the yield of **5** fell to 7% (Table 1, entry 3).

As indicated in Table 1, the reaction yields, through arsonium ylide intermediate, are unsatisfied even using refluxing toluene. It is known that antimony ylide is more reactive than the arsonium ylide. We envisioned that antimony ylide could give better reaction results. When $SbBu_3$ was used instead of Ph_3As, under the same reaction conditions, however, no alkene product was detected (Table 1, entries 4 and 5). It may be explained that the rhodium catalyst was poisoned by the strong reductive $SbBu_3$. When cuprous bromide (CuBr) was used as the catalyst, alkene **2c** was isolated in moderate yield in refluxing benzene (Table 1, entry 6). The yield of product **2c** was not improved at higher temperature (refluxing in toluene) (Table 1, entry 7). Inorganic or organic copper catalyst such as CuBr, $Cu(acac)_2$, and $Cu(hfacac)_2$

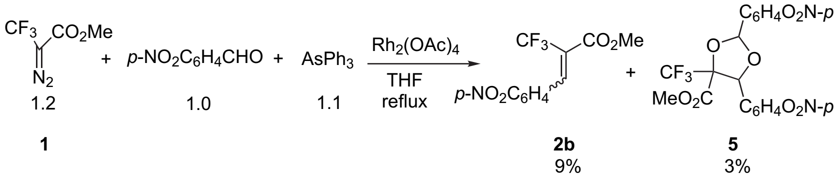


Scheme 4.

Table 1. The optimization of reaction condition

Entry	ArCHO (Ar=)	Lewis base	Catalyst	Solvent	Product yield (%)[a]	
					2	**5**
1	p-$NO_2C_6H_4$-	Ph_3As	$Rh_2(OAc)_4$	THF	9 (**2b**)	3
2	p-$NO_2C_6H_4$-	Ph_3As	$Rh_2(OAc)_4$	Benzene	19 (**2b**)	14
3	p-$NO_2C_6H_4$-	Ph_3As	$Rh_2(OAc)_4$	Toluene	36 (**2b**)	7
4	p-BrC_6H_4-	$SbBu_3$	$Rh_2(OAc)_4$	Benzene	—	—
5	p-BrC_6H_4-	$SbBu_3$	$Rh_2(OAc)_4$	Toluene	—	—
6	p-BrC_6H_4-	$SbBu_3$	CuBr	Benzene	55 (**2c**)	—
7	p-BrC_6H_4-	$SbBu_3$	CuBr	Toluene	59 (**2c**)	—
8	p-BrC_6H_4-	$SbBu_3$	$Cu(acac)_2$	Benzene	57 (**2c**)	—
9	p-BrC_6H_4-	$SbBu_3$	$Cu(hfacac)_2$	Toluene	54 (**2c**)	—

[a] Isolated yields based on aldehyde.



Scheme 3.