ORGANIC LETTERS

2004
Vol. 6, No. 23
4359−4361

Rhodium-Catalyzed Novel Trifluoromethylation at the α-Position of α,*β*-Unsaturated Ketones

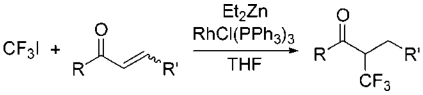
Kazuyuki Sato, Masaaki Omote, Akira Ando,* and Itsumaro Kumadaki*

Faculty of Pharmaceutical Sciences, Setsunan University,
45-1, Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan

aando@pharm.setsunan.ac.jp; kumadaki@pharm.setsunan.ac.jp

Received September 15, 2004

ABSTRACT



Treatment of α,*β*-unsaturated ketones with CF_3I in the presence of Et_2Zn and $RhCl(PPh_3)_3$ gave novel α-trifluoromethylation products in good yields. Hydrogen transfer from the ethyl group on the rhodium complex to the *β*-position of the enone seems to play an important role in this reaction.

Highly functionalized molecules containing fluorine atoms have significantly interesting features, and these are attracting much attention in the field of medicine, agricultural chemicals, and functional materials.[1] Therefore, the methods for introducing a fluorine functional group into an organic compound have been investigated extensively.[2] Trifluoromethylation is one of the most fascinating reactions among them, and many methodologies have been reported. For example, Kobayashi−Kumadaki's trifluoromethylation[3] using CF_3Cu derived from CF_3X and Burton−Wiemers' trifluoromethylation[4] using CF_2X_2/Zn or Cd gave coupling products by reacting with various halides. When treated with a fluoride ion, CF_3-TMS reacted with carbonyl compounds to afford the corresponding trifluoromethyl carbinols.[5] Furthermore, a CF_3 radical derived from CF_3I with $Na_2S_2O_4$,[6] SmI_2,[7] or Et_3B[8] added to olefins.

On the other hand, transition-metal-catalyzed C−C bond formations are playing important roles in organic synthesis. Among them are a lot of reactions using a rhodium catalyst, including catalytic hydrogenation, carbonylation, and metathesis.[9] Furthermore, 1,4-addition reaction of organoboronic acids, organostannanes, or organosilanes to α,*β*-unsaturated carbonyl compounds has been reported.[10]

Recently, we reported that ethyl bromodifluoroacetate (**1**) and α,*β*-unsaturated ketones (**2**) reacted with Et_2Zn in the presence of rhodium catalyst to give an unexpected product (**3**), in which the CF_2COOEt group was introduced to the α-carbon of α,*β*-unsaturated ketones, and a 1,2-addition product (**4**) in good yields depending on the solvents (Scheme 1).[11]

---

[1] (a) Smart, B. E. *Chem. Rev.* **1996**, *96*, 1555−1823. (b) Resnati, G.; Soloshonok, V. A. *Tetrahedron* **1996**, *52*, 1−330. (c) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993. (d) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123−3197.

[2] Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619−8683.

[3] (a) Koyama, M.; Takagi, T.; Ando, A.; Kumadaki, I. *Chem. Pharm. Bull.* **1995**, *43*, 1466−1474. (b) Kobayashi, Y.; Yamamoto, K.; Kumadaki, I. *Tetrahedron Lett.* **1979**, *20*, 4071−4072. (c) Kobayashi, Y.; Kumadaki, I. *Tetrahedron Lett.* **1969**, 4095−4096.

[4] Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014−5015.

[5] Prakash, G. S. K.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393−395.

[6] (a) Wang, Z.; Lu, X. *Tetrahedron* **1995**, *51*, 2639−2658. (b) Lu, Z.; Wang, Z.; Ji, J. *Tetrahedron Lett.* **1994**, *35*, 613−616.

[7] Lu, X.; Ma, S.; Zhu, J. *Tetrahedron Lett.* **1988**, *29*, 5129−5130.

[8] (a) Yajima, T.; Nagano, H.; Saito, C. *Tetrahedron Lett.* **2003**, *44*, 7027−7029. (b) Takeyama, Y.; Ichinose, Y.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 3159−3162.

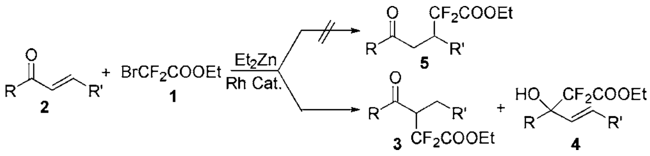
[9] (a) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons Inc.: Chichester, 2002. (b) *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C. Eds.; VCM: Weinheim, 1998.

[10] (a) Hayashi, T. *Bull. Chem. Soc. Jpn*. **2004**, *77*, 13-21. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196. (c) Hayashi, T. *Synlett* **2001**, 879−887.

[11] Sato, K.; Tarui, A.; Kita, T.; Ishida, Y.; Tamura, H.; Omote, M.; Ando, A.; Kumadaki, I. *Tetrahedron Lett.* **2004**, *45*, 5735−5737.

10.1021/ol048134v CCC: $27.50

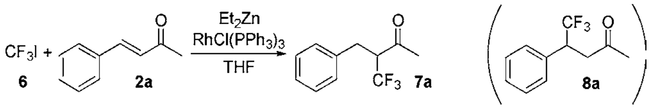
Scheme 1. Reaction of Ethyl Bromodifluoroacetate with α,β-Unsaturated Ketones



On the basis of the previous result, we expected that treatment of α,β-unsaturated ketones (**2**) with CF_3I (**6**) in the presence of Et_2Zn and $RhCl(PPh_3)_3$ would give a novel α-trifluoromethylation product (**7**). To our knowledge, the reactions for introducing a CF_3 group at the α-position of ketones are limited only to electrophilic trifluoromethylation using calcogenium reagents[12] and photochemical reaction of enamine with CF_3I.[13] However, these reactions have some problems: electrophilic trifluoromethylcalcogenim salts are hardly soluble in organic solvents and are expensive, enamins are not so stable, and photochemical reaction are troublesome to do. Recently, Rozen et al. reported trifluoromethylation of carboxylic esters at the α-position.[14] The reaction also needs to use highly reactive BrF_3.

Herein, we would like to report a simple and novel synthesis of α-trifluoromethylated ketones from α,β-unsaturated ketones (**2**) and CF_3I (**6**).

Scheme 2. Reaction of 4-Phenyl-3-buten-2-one with CF_3I



First, we chose 4-phenyl-3-buten-2-one as a substrate and examined various reaction conditions (Scheme 2). The product **7a** was not obtained at all in the absence of Rh catalyst, although **2a** was consumed during the reaction (entry 1). We found that $RhCl(PPh_3)_3$ allowed the reaction to proceed effectively and that THF was the best solvent to obtain **7a** (Table 1).

Table 1. Examination of Reaction Conditions

entry	catalyst (mol %)	Et_2Zn (equiv)	temp (°C)	time (h)	solvent	yield of **7a** (%)
1	none	1.5	0	24	THF	0
2	$RhCl(PPh_3)_3$ (1)	1.5	0	2	THF	69
3	$RhCl(PPh_3)_3$ (1)	2.5	0	0.5	THF	61
4	$RhCl(PPh_3)_3$ (2)	1.5	0	0.5	THF	69
5	$RhCl(PPh_3)_3$ (2)	1.5	−30	25	THF	nr[a]
6	$RhCl(PPh_3)_3$ (2)	1.5	0 to rt	0.5	THF	77
7	$RhCl(PPh_3)_3$ (2)	1.5	0 to rt	24	toluene	0
8	$RhCl(PPh_3)_3$ (2)	1.5	0 to rt	24	Et_2O	nr
9	$RhCl(PPh_3)_3$ (2)	1.5	0 to rt	1	DME	51
10	$RhCl(PPh_3)_3$ (2)	1.5	0 to rt	24	CH_3CN	nr

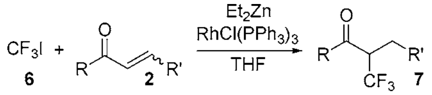
[a] No reaction.

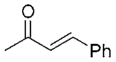
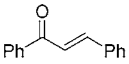
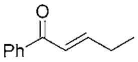
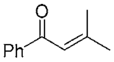
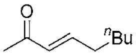
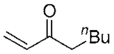
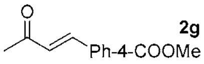
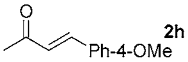
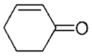
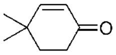
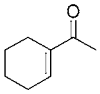
Next, we examined several substrates to clarify the scope and limitation of this reaction (Table 2). As shown in entries 1−3, β-monosubstituted enones gave the corresponding CF_3 compounds (**7a**−**c**), but as shown in entry 4, β,β-dimethyl enone did not give the expected product **7d**. Thus, two substituents on the β-position seem to inhibit the reaction.

On the other hand, as shown in entries 2 and 3, the yields of **7** were not good compared with that of entry 1. The phenyl group next to the ketone appeared to decrease the yields, probably because the electron on the carbonyl group might be dispersed. The substrates without a phenyl group bound to the carbonyl group gave **7** in good yields as expected (entries 5−8).

The reaction similarly proceeded with cyclic ketones in moderate to good yields, as shown in entries 9 and 10. However, an enone that had the substituent on the α-position did not give the corresponding product (**7k**), and the product (**8k**) with a CF_3 group on β-position was obtained in

Table 2. Reaction of Various α,β-Unsaturated Ketones with CF_3I



entry	2	time (h)	yield of **7** (%)[a]
1	 **2a**	0.5	77
2	 **2b**	1	31
3	 **2c**	1	35
4	 **2d**	3	0
5	 **2e**	1	67
6	 **2f**	1	59
7	 **2g**	1	65
8	 **2h**	1	65
9	 **2i**	0.5	55
10	 **2j**	1	53
11	 **2k**	0.5	0[b]

[a] Isolated Yield. [b] 1,4-Adduct (**8k**) was obtained in 54%.

---

[12] (a) Ma, J.-A.; Cahard, D. *J. Org. Chem.* **2003**, *68*, 8726−8729. (b) Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692−5699.

[13] (a) Crusiani, G.; Margaretha, P. *J. Fluorine Chem.* **1987**, *37*, 95−101. (b) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186−5191.

[14] Hagooly, A.; Rozen, S. *Chem. Commun.* **2004**, 594−595.

moderate yield (entry 11). Namely, the 1,4-addition reaction proceeded in this case.

When we examined this reaction using Et_2Zn in the presence of 1 mol % $RhCl(PPh_3)_3$, formation of the corresponding saturated ketone from the α,β-unsaturated ketone (**2**) was confirmed during the reaction. On the basis of the above results, we propose the reaction mechanism tentatively as shown in Figure 1.

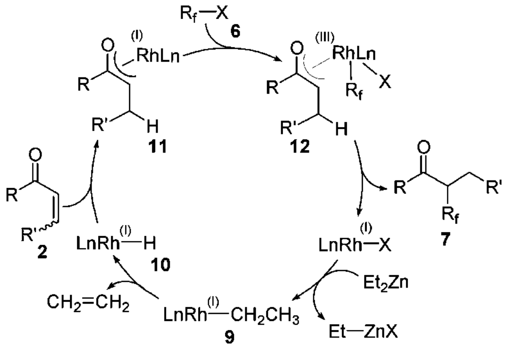


Figure 1. Tentative reaction mechanisim.

First, $RhCl(PPh_3)_3$ reacted with Et_2Zn to give the rhodium hydride complex (**10**) through an ethyl rhodium complex (**9**) along with the elimination of ethylene. The 1,4-reduction of enone by **10** to form rhodium enolate (**11**) is followed by oxidative addition of CF_3I to give another rhodium complex (**12**). The reductive elimination generated the novel α-trifluoromethylation product (**7**) and regenerated a rhodium catalyst.

Recently, Krische and co-workers reported that α,β-unsaturated carbonyl compounds formed a rhodium enolate derived from a rhodium catalyst under a H_2 atmosphere.[15] When their methodology was applied for our trifluoromethylation under a H_2 atmosphere without Et_2Zn, 7 was not obtained. However, when 4-phenyl-3-buten-2-one (**2a**) was treated with Et_2Zn and $RhCl(PPh_3)_3$ in the absence of CF_3I under an Ar atmosphere, the saturated ketone, 4-phenyl-2-butanone, was obtained. Furthermore, use of Me_2Zn or Ph_2Zn instead of Et_2Zn did not give the objective product (**7**) in both cases. These results would support that the mechanism is as shown in Figure 1 and the ethyl group of Et_2Zn must play an important role. Tandem acylation of similar rhodium enolates was reported by Krische and co-workers.[16]

In conclusion, we established a new trifluoromethylation reaction at the α-position of α,β-unsaturated ketones. The mechanism is not fully clarified, but rhodium hydride derived from Et_2Zn and $RhCl(PPh_3)_3$ seems to play an important role. We believe that this reaction could be widely used in organofluorine chemistry as a novel trifluoromethylation reaction.

Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048134V

---

[15] (a) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653−661. (b) Huddleston, R. R.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1143−1146. (c) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 15156−15157.

[16] Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5421−5424.