ORGANIC LETTERS

2011
Vol. 13, No. 9
2392–2394

A Practical and Convenient Fluorination of 1,3-Dicarbonyl Compounds Using Aqueous HF in the Presence of Iodosylbenzene

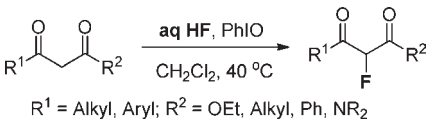
Tsugio Kitamura,* Satoshi Kuriki, Mohammad Hasan Morshed, and Yuji Hori

Department of Chemistry and Applied Chemistry, Graduate School of Science and Engineering, Saga University, Honjo-machi, Saga 840-8502, Japan

kitamura@cc.saga-u.ac.jp

Received March 10, 2011

ABSTRACT



A simple, practical, and convenient fluorination of 1,3-dicarbonyl compounds was achieved by direct use of aqueous hydrofluoric acid and iodosylbenzene (PhIO). The reaction of ethyl benzoylacetate with the reagent system of aqueous HF and PhIO in CH_2Cl_2 gave ethyl 2-fluoro-2-benzolyacetate in 98% yield. Other 1,3-dicarbonyl compounds including β-keto esters and 1,3-diketones underwent the fluorination reaction to give the corresponding fluorinated products in good yields.

Introduction of fluoride atom(s) into a molecule brings about valuable properties, which are applicable to pharmaceuticals, agrochemicals, and materials bearing an outstanding property. The synthetic method for organofluorine compounds includes direct fluorination replacing an atom or group by a fluorine atom and an indirect procedure using a fluorinated component as a building block.[1] Although direct fluorination reactions have been conducted by using a molecular fluorine or other electrophilic fluorinating reagents, there still remain many drawbacks such as the possibility of explosion due to instability, difficulty of handling, and the requirement of specific apparatus. Recently, the chemistry of hypervalent iodine compounds has accomplished remarkable progress, and it has been proven that hypervalent iodine compounds are useful to organic synthesis.[2] Among them, difluoroiodoarenes ($ArIF_2$) attract much attention as a stable fluorination reagent.[3] Various difluoroiodoarenes are prepared by fluorination of iodoarenes with powerful fluorinating reagents such as F_2[4] and XeF_2,[5] conveniently by direct replacement of dichloroiodoarenes with HF in the presence of HgO,[6] and more simply by reaction of iodosylarenes with HF.[7] For a fluorination reaction, however, difluoroiodoarenes must be activated by a HF reagent such as HF-amine complexes.[3,8] Accordingly, HF is essential both for the preparation of $ArIF_2$ and for the fluorination reaction.

To develop a convenient fluorination reaction, it is better to conduct both the preparation of $ArIF_2$ and their activation for a fluorination reaction in one pot. Thus, we used an easily available aqueous hydrofluoric acid for this purpose. The aqueous HF was considered to play the following important roles in the fluorination reaction: (1) as the reagent for the synthesis of $ArIF_2$ and (2) as the

(1) (a) Olah, G. A.; Chambers, R. D.; Prakash, G. K. S. *Synthetic Fluorine Chemistry*; John Wiley: New York, 1992. (b) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II*; American Chemical Society: Washington, DC, 1995. (c) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell Publishing: Oxford, 2004.

(2) For recent reviews on hypervalent iodine compounds, see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358. (b) Zhdankin, V. V. *ARKIVOC* **2009**, No. i, 1–62.

(3) Yoneda, N. *J. Fluorine Chem.* **2004**, *125*, 7–17.

(4) Neumann, D.; Ruther, G. *J. Fluorine Chem.* **1980**, *15*, 213–222.

(5) Zupan, M.; Pollak, A. *Chem. Commun.* **1975**, 715–716.

(6) Carpenter, W. *J. Org. Chem.* **1966**, *31*, 2688–2689.

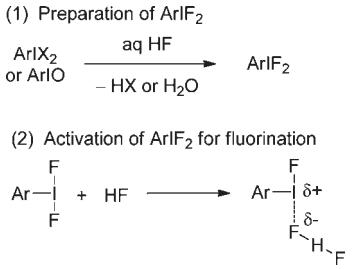
(7) (a) Sawaguchi, M.; Ayuba, S.; Hara, S. *Synthesis* **2002**, 1802–1803. (b) Arrica, M. A.; Wirth, T. *Eur. J. Org. Chem.* **2005**, 395–403.

(8) Sawaguchi, M.; Hara, S.; Yoneda, N. *J. Fluorine Chem.* **2000**, *105*, 313–317.

10.1021/ol200632d
Published on Web 04/07/2011

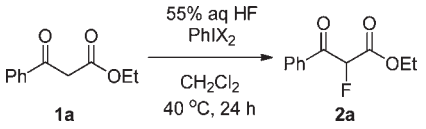
activating agent for the fluorination reaction, as shown in Scheme 1.

Scheme 1. Role of HF



In order to prove the above-mentioned hypothesis, we planned the fluorination reaction of 1,3-dicarbonyl compounds. Synthesis of 2-fluoro-1,3-dicarbonyl compounds has so far been performed by the fluorination reaction of 1,3-dicarbonyl compounds with F_2[9] and various fluorinating agents such as XeF_2,[10] fluoroxy compounds,[11] and fluoronitrogen compounds.[12] However, those many are dangerous or expensive. The fluorination reaction of 1, 3-dicarbonyl compounds was recently reported by Hara and Yoneda.[13] They indicated that difluoroiodotoluene was a useful fluorinating reagent. However, the difluoroiodotoluene was prepared by the reaction of iodosyltoluene with aqueous HF.[7] According to the above hypothesis, we examined the direct fluorination of 1,3-dicarbonyl compounds using a commercially available aqueous hydrofluoric acid and a hypervalent iodine compound, to develop a convenient fluorination reaction. Here we want to report for the first time a practical, direct fluorination of

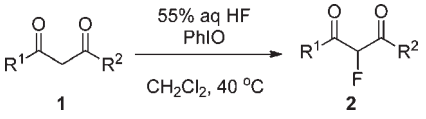
Table 1. Optimization of the Fluorination Reaction of **1a**[a]

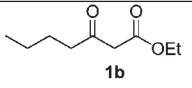
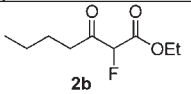
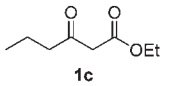
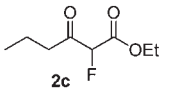
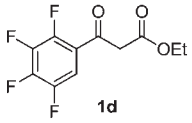
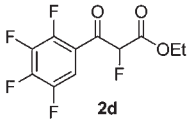
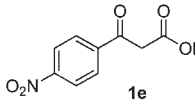
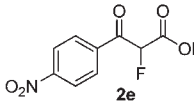
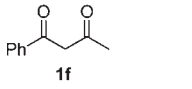
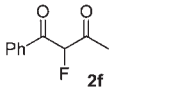
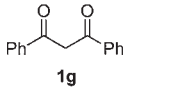
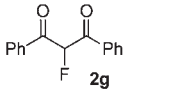
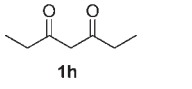
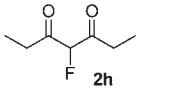
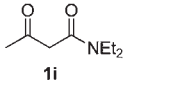
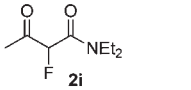
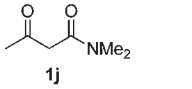
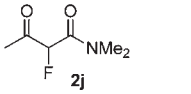


entry	iodine reagent	time (h)	yield (%)[b]
1	$PhI(OAc)_2$	24	39
2	$PhI(OAc)_2$	12	43
3	$PhI(OCOCF_3)_2$	24	0
4	PhIO	24	98

[a] The reaction was conducted at 40 °C by using 55% aqueous HF (10 mmol HF), a hypervalent iodine reagent (1.2 mmol), and **1a** (1 mmol) in CH_2Cl_2 (2 mL). [b] Isolated yield.

Table 2. Direct Fluorination of 1,3-Dicarbonyl Compounds with PhIO/aq. HF Reagent System[a]



entry	substrate	time (h)	product	yield (%)
1	 1b	1	 2b	73
2	 1c	1	 2c	93
3	 1d	24	 2d	70
4	 1e	24	 2e	58
5	 1f	24	 2f	47
6	 1g	36	 2g	90
7[b]	 1h	2	 2h	34
8	 1i	2	 2i	52
9	 1j	2	 2j	25

[a] Reaction conditions: substrate (1 mmol), PhIO (1.2 mmol), 55% aqueous HF (10 mmol HF), and CH_2Cl_2 (2 mL) at 40 °C. [b] At room temperature.

(9) Chambers, R. D.; Greenhall, M. P.; Hutchinson, J. *Tetrahedron* **1996**, *52*, 1–8.

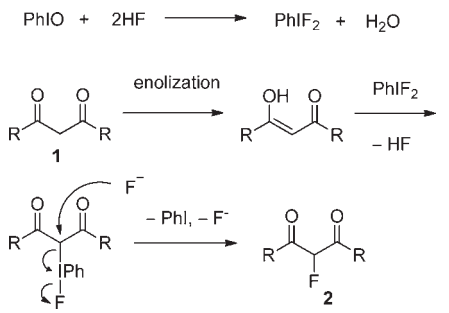
(10) (a) Zajc, B.; Zupan, M. *J. Chem. Soc., Chem. Commun.* **1980**, 759–760. (b) Yemul, S. S.; Kagan, H. B.; Setton, R. *Tetrahedron Lett.* **1980**, *21*, 277–280. (c) Zajc, B.; Zupan, M. *J. Org. Chem.* **1982**, *47*, 573–575.

(11) (a) Inman, C. E.; Oesterling, R. E.; Tyczkowski, E. A. *J. Am. Chem. Soc.* **1958**, *80*, 6533–6535. (b) Machleidt, H.; Hartmann, V. *Liebigs Ann. Chem.* **1964**, *679*, 9–19. (c) Lerman, O.; Rozen, S. *J. Org. Chem.* **1983**, *48*, 724–727. (d) Rozen, S.; Brand, M. *Synthesis* **1985**, 665–667. (d) Rozen, S.; Hebel, D. *J. Org. Chem.* **1990**, *55*, 2621–2623. (e) Rozen, S.; Menahem, Y. *Tetrahedron Lett.* **1979**, *20*, 725–728. (f) Stavber, S.; Zupan, M. *J. Chem. Soc., Chem. Commun.* **1981**, 795–796.

(12) (a) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563–8575. (b) Resnati, G.; DesMarteau, D. D. *J. Org. Chem.* **1991**, *56*, 4925–4929. (c) Banks, R. E.; Murtagh, V.; Tsiliopoulos, E. *J. Fluorine Chem.* **1991**, *52*, 389–401. (d) Xu, Z.-Q.; DesMarteau, D. D.; Gotoh, Y. *J. Fluorine Chem.* **1992**, *58*, 71–79. (e) Resnati, G.; DesMarteau, D. D. *J. Org. Chem.* **1992**, *57*, 4281–4284. (f) Banks, R. E.; Lawrence, N. J.; Popplewell, A. L. *J. Chem. Soc., Chem. Commun.* **1994**, 343–344. (g) Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60*, 4730–4737. (h) Cabrera, I.; Appel, W. K. *Tetrahedron* **1995**, *51*, 10205–10208. (i) Umemoto, T.; Nagayoshi, M.; Adachi, K.; Tomizawa, G. *J. Org. Chem.* **1998**, *63*, 3379–3385. (j) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709–1712. (k) Gupta, O. D.; Shreeve, J. M. *Tetrahedron Lett.* **2003**, *44*, 2799–2801. (l) Stavber, G.; Zupan, M.; Stavber, S. *Tetrahedron Lett.* **2007**, *48*, 2671–2673.

(13) (a) Hara, S.; Sekiguchi, M.; Ohmori, A.; Fukuhara, T.; Yoneda, N. *Chem. Commun.* **1996**, 1899–1900. (b) Yoshida, M.; Fujikawa, K.; Sato, S.; Hara, S. *ARKIVOC* **2003**, No. vi, 36–42.

Scheme 2. Possible Mechanism



1,3-dicarbonyl compounds using aqueous hydrofluoric acid in the presence of a hypervalent iodine compound.

The fluorination reaction was conducted by treating a mixture of a hypervalent iodine compound and aqueous HF with a 1,3-dicarbonyl compound in CH_2Cl_2.

To optimize the reaction conditions, three easily available hypervalent iodine compounds [$PhI(OAc)_2$, $PhI(OCOCF_3)_2$, and PhIO] were examined by using ethyl 3-oxo-3-phenylpropionate (**1a**) as the substrate in the fluorination reaction (Table 1). First, $PhI(OAc)_2$ was employed because it was the most stable hypervalent iodine reagent among them. After mixing $PhI(OAc)_2$ (1.2 mmol) with aqueous HF (55%, 10 mmol HF) in CH_2Cl_2 (2 mL), **1a** (1 mmol) was added and then the mixture was stirred at 40 °C for 24 h. After separation by column chromatography, 2-fluoro-3-oxo-3-phenylpropionate (**2a**) was obtained in 39% yield. The yield was slightly increased to 43% when the reaction was carried out for 12 h. Next, the fluorination reaction with $PhI(OCOCF_3)_2$ was conducted but **2a** was not obtained. Finally, it was found that PhIO was the best reagent. Under the same conditions the reaction with PhIO gave **2a** in 98% yield.

(14) According to the literature,[2b] it is good to use it without isolation.

To find the scope of the fluorination reaction, several 1,3-dicarbonyl compounds were examined. The results are given in Table 2. Similarly, 3-ketoesters including aliphatic and aromatic 3-ketoesters **1b**−**1e** gave good to high yields of 2-fluorinated 3-ketoesters **2b**−**2e**. Among them, aliphatic 3-ketoesters showed higher reactivity than aromatic ones. In addition to 3-ketoesters, 1,3-diketones **1f**−**1h** and 3-ketoamides **1i** and **1j** also underwent fluorination to give the corresponding 2-fluorinated products **2f**−**2j**.

A possible mechanism for a fluorination reaction of 1,3-dicarbonyl compounds is shown in Scheme 2. First, $PhIF_2$ should be formed in situ by reaction of PhIO with HF.[7] This reaction took place, and $PhIF_2$ was isolated in the reaction without the substrate **1**.[14] The reaction of $PhIF_2$ with **1** is considered to proceed effectively after enolization of **1** because it has been reported that the enol form of **1** reacts with hypervalent iodine compounds.[3] The resulting 2-iodanyl-1,3-dicarbonyl compound readily undergoes displacement by a fluoride ion due to the high leaving ability of the phenyliodonio group,[15] to give the fluorine-containing product **2**.

In summary, we have developed a practical and convenient fluorination reaction of a 1,3-dicarbonyl compound just by mixing with aqueous HF and PhIO. This simple and easy procedure is applicable to a wide variety of fluorination reactions. The scope of this fluorination will be reported in the near future.

Supporting Information Available. Experimental procedures, spectral data, and ^1H and ^{13}C NMR spectra of for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Although the mechanism via the intermediate of an enolate structure has been proposed in the literature,[3] it is reasonable to consider the mechanism through an iodanyl ketone intermediate judging from the α-tosyloxylation of ketones and 1,3-dicarbonyl compounds.[16]

(16) (a) Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487–2489. (b) Moriarty, R. M.; Koser, G. F. *Synthesis* **1990**, 431–447.