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UV Initiated Addition of Iododifluoromethyl Ketones to Electron-Deficient Olefins

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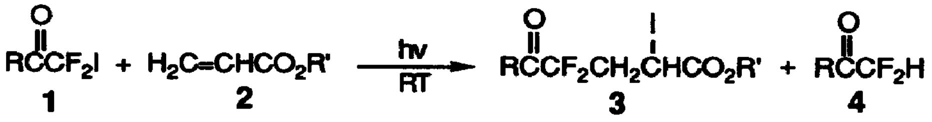
Abstract: *Under UV irradiation, iododifluoromethyl ketones reacted with electron-deficient olefins in the absence of solvent to give high yields of the 1:1 adducts, providing a useful method for the synthesis of α,α-difluoro-γ-iodo-γ-(electron-withdrawing-group) substituted ketones.*

The addition of perfluoroalkyl iodides to olefins is one of the most important methods for the introduction of perfluoroalkyl groups into organic molecules.[1] However, since the perfluoroalkyl radical is electrophilic, this reaction is mainly limited in application to electron-rich olefins.[2] Although efforts have been made to extend this useful reaction to electron-deficient olefins,[3] usually the results were unsatisfactory with low conversion, low selectivity, and undesired coupling or telomeric products were observed. More recently, improved results were reported for the reactions of perfluoroalkyl iodides[4], difluorodibromomethane[5] and diethyl bromodifluoromethylphosphonate[6] with electron-deficient olefins with a bimetallic redox system.

On the other hand, it is well known that selectively fluorinated analogues of biochemically important compounds demonstrate dramatic changes and distinctive modifications in their biological activities.[7] Therefore, efficient methods for the synthesis of selectively fluorinated compounds are increasingly required. Considering the excellent biological activity of fluoroketones as inhibitors of hydrolytic enzymes,[8] we recently developed a new general route for the synthesis of α,α-difluoroketones *via* reaction of iododifluoromethyl ketones with electron-rich olefins[9]. Herein, we report the UV initiated reaction of iododifluoromethyl ketones with electron-deficient olefins.

Although Pd(0) is a highly efficient initiator for the reaction of perfluoroalkyl iodides[10] and iododifluoromethyl ketones[9] with normal alkenes, we found that it does not satisfactorily initiate the reaction of iododifluoromethyl phenyl ketone (**1a**) with ethyl acrylate. Only ~15% conversion of **1a** was observed in the attempted addition of **1a** to ethyl acrylate *via* Pd(0) (5-10 mol%), and the predominant reaction was the polymerization of the acrylate. However, a high yield of the 1:1 addition product, **3a**, was produced when the reaction mixture was initiated with UV light at ambient temperature in the absence of solvent. Also, satisfactory results were obtained when alkyl (**1b**, **1c**) and chlorodifluoromethyl (**1d**) iododifluoromethyl ketones were utilized in the reaction. Small amounts of difluoromethyl ketones (4) and 1:2 adducts, $RCOCF_2CH_2CH(CO_2Et)CH_2CHICO_2Et$, were formed as by-products, possibly involving hydrogen abstraction by $RCOCF_2^{\bullet}$ and further reaction of $RCOCF_2CH_2\dot{C}HCO_2R'$ with a second molecule of **2**, respectively. The results are summarized in **Table** I.



$$\underset{\mathbf{1}}{RC(=O)CF_2I} + \underset{\mathbf{2}}{H_2C{=}CHCO_2R'} \xrightarrow[RT]{h\nu} \underset{\mathbf{3}}{RC(=O)CF_2CH_2CH(I)CO_2R'} + \underset{\mathbf{4}}{RC(=O)CF_2H}$$

R: Ph (**a**), n-C_4H_9 (**b**), n-C_6H_{13} (**c**), $ClCF_2$ (**d**)

R': Et, n-C_4H_9, t-C_4H_9

Table I: The Reaction of Iododifluoromethyl Ketones with Acrylate under UV Irradiation

Entry	1	2 (R')	1:2	T(h)	Conversion of 1 (%)[a]	Yield (%) 3[a,b]
1	1a	Et	1:3.4	4.5	88	84
2	1a	Et	1:3.4	9	92	83(62)
3	1a	Et	1:3.4	24	94	93(79)
4	1a	Et	1:2	18	82	94
5	1b	Et	1:3	3.5	17	89
6	1b	Et	1:3	10	58	86
7	1b	Et	1:3	20	81	89(58)
8	1c	Et	1:3	24	62	82(50)
9	1c	Et	1:2	48	50	85
10	1d	Et	1:3	6	100	100(78)
11	1a	n-Bu	1:3.4	24	59	97
12	1a	n-Bu	1:3	72	77	86(60)
13	1a	t-Bu	1:3	72	65	90(54)[c]

[a]: Determined by ^{19}F NMR analysis; small amount of **4** (<10%) and 1:2 adducts (3-10%) were observed in ^{19}F NMR and GC-MS spectra.

[b]: NMR yield based on consumed **1**; isolated yield in parentheses based on **1**.

[c]: The isolated product, $PhCOCF_2CH_2CH_2CO_2H$.

The reactivity of iododifluoromethylketones with ethyl acrylate exhibited the following order : **1d** > **1a** > **1b**~**1c**. The reactions of **1a** with *n*-butyl and *t*-butyl acrylate also gave high yield of 1:1 addition products (Entry 11-13)[11].

Similarly, the reaction of iododifluoromethyl ketones with N,N-dimethyl acrylamide (**5**) gave high yields of the 1:1 adducts under similar conditions.[12] These results are illustrated in **Table II**.

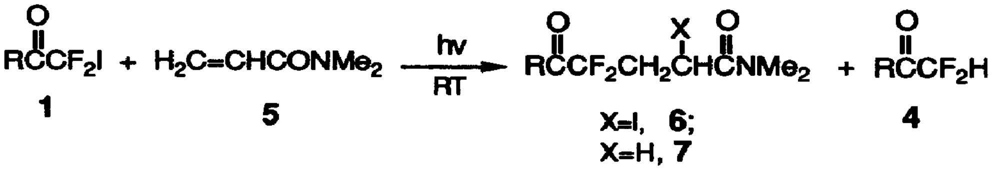


Table II: The Reaction of Iododifluoromethyl Ketones with N,N-Dimethyl Acrylamide (5) under UV Irradiation

Entry	**1** (R)	1:5	T(h)	Conversion[a] (%)	Yield (%)[a,b] **6**	**7**
14	Ph	1:4	4.5	88	95	–
15	Ph	1:4	15	94	95(81)	–
16	Ph	1:3	24	93	93	–
17	n-C_4H_9	1:2	66	85	59	31[c]
18	n-C_6H_{13}	1:3	36	86	76(60)	19

[a]: Determined by ^{19}F NMR analysis; small amount of **4** was observed in ^{19}F NMR spectrum.

[b]: NMR yield based on consumed **1**; isolated yield in parentheses based on **1**.

[c]: 56% of **7** was isolated by distillation because of the partial decomposition of **6** at high temperature.

A typical reaction procedure is as follows. Into a 50 mL quartz tube, 3.7 g (36 mmol) ethyl acrylate and 3.0 g (10.6 mmol) iododifluoromethyl phenyl ketone (**1a**) were charged. The mixture was irradiated with 254 nm UV light at ambient temperature (~35°C) in a Rayonet photochemical reactor for 24 hours. ^{19}F NMR analysis of the reaction mixture indicated a 94 % conversion of **1a**, and the formation of 93% of the 1:1 adduct and 6% of **4a**. Distillation gave 3.2 g of ethyl 2-iodo-4,4-difluoro-4-benzoyl butyrate (**3a**, isolated yield: 78.5%).[13] All new products were characterized by ^{19}F, ^{1}H, and ^{13}C NMR, GC-MS and FTIR spectra.

In conclusion, the UV initiated reaction of iododifluoromethyl ketones with electron-deficient olefins provides a novel general route for the synthesis of α,α-difluoro-γ-(electron-withdrawing-group) substituted ketones. Further study of the reaction and the application of these ketones in the synthesis of selectively fluorinated compounds continues.

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11. The reaction of **1a** with methyl acrylate gave 53 % of 1:1 adduct and 40 % of 1:2 adduct, in which the ester groups showed great effect on the reaction.
12. **7** might be formed by the hydrogen abstraction involving the radical intermediate, $RCOCF_2CH_2\dot{C}HCONMe_2$.
13. **3a**: bp: 158-160 °C / 4 mmHg; ^{19}F NMR ($CDCl_3$, $CFCl_3$): -100.75 (t, J = 17.09 Hz) ppm; ^1H NMR ($CDCl_3$, TMS): 8.03 (d, J = 7.42 Hz, 2H), 7.63 (dt, J = 7.4 Hz, 1H), 7.48 (t, J = 7.74 Hz, 2H), 4.67 (dd, J = 10.64, 3.47 Hz, 1H), 4.22 (q, J = 7.12 Hz, 2H), 3.34 (ddt, J = 10.65, 15.64, 16.86 Hz, 1H), 2.88(ddt, J=3.48, 15.23, 17.55 Hz, 1H), 1.26(t, J=7.12 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, TMS): 187.79 (t, J = 30.49 Hz), 170.74 (s), 134.66 (s), 131.29 (s), 130.22 (s), 128.79 (s), 118.32 (t, J = 256.19), 62.14 (s), 41.4 (t, J = 22.64 Hz), 13.63 (s), 7.97 (s) ppm; GC-MS (m / e, relative intensity): 382 (M^+, 0.12), 336 (M^+-EtOH, 3.19), 309 (M^+-CO_2Et, 2.52), 255 (M^+-I, 36.08), 182 (3.90), 127 (I^+, 2.67), 105 ($PhCO^+$, 100), 77 (Ph^+, 84.31), 51 (31.76); HR-MS: Obs: 382.9967, $C_{13}H_{14}O_3F_2I$, Cal: 382.9956; FTIR (CCl_4): 2984, 2939, 1741, 1704, 1599, 1450, 1325, 1282, 1254, 1196, 1188, 802 cm^{-1}.

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