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Vinylalumination of Fluoro-carbonyl Compounds[1†]

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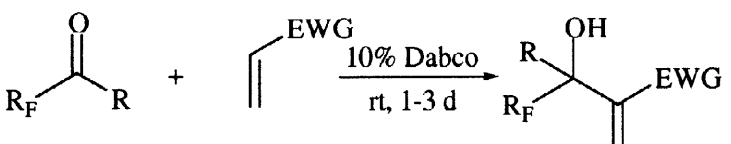
Abstract: Ethyl acrylate and acrylonitrile fail to undergo efficient Baylis-Hillman reaction with fluoral, but provide good yields of products with pentafluorobenzaldehyde. Alternately, unsubstituted and β-substituted [α-(ethoxycarbonyl)vinyl]aluminum react with perfluoroalkyl and -aryl aldehydes and ketones to provide the α-hydroxyalkenylated fluoro-organic compounds in good to excellent yields.

Achiral and chiral fluoro-organic compounds are commonly used in analytical, biological, materials, medicinal, organic, and polymer chemistry.[3] As part of our ongoing program to develop synthetic methodologies for fluoro-organics,[4] we examined the Baylis-Hillman reaction of fluorinated aldehydes and ketones.[5] The drawbacks of this reaction include long reaction times and inconsistent yields.[5] We envisaged that perfluoro-aldehydes might undergo fast reaction to provide fluoro-organics with multifunctional moieties and carried out the reactions of ethyl acrylate and acrylonitrile with perfluorinated aliphatic aldehydes and α,α,α-trifluoroacetone. However, success eluded us. Nonetheless, as described below, we achieved the synthesis of fluorinated Baylis-Hillman products *via* [α-(ethoxycarbonyl)vinyl]aluminum intermediates.[6]

The reaction of fluoral (**1a**) with two equiv of ethyl acrylate (**2**) was carried out in the presence of 10% 1,4-diazabicyclo[2.2.2]octane (Dabco) in a sealed tube, under neat condition, at 0 °C. On the basis of the reported reaction time (3 h) for hexafluoroacetone,[7] we quenched the above reaction after one hour and obtained a dismal 10% yield of the expected product **3a** along with 45% of fluoral hydrate. Extending the reaction time to 24 h at 0 °C or at room temperature (rt) did not improve the yield of **3a**. The reaction with 10 equiv of **1a** resulted in the polymerization of the aldehyde.[8] Using a tenfold equiv of **2** also did not improve the result. The outcome was similar for a reaction of **2** with heptafluorobutyraldehyde (**1b**) also. Nevertheless, an aromatic perfluorinated aldehyde, pentafluorobenzaldehyde (**1c**), reacted with **2** affording 71% of the expected product **3c** (eq 1).



1a, $R_F = CF_3$, R = H
1b, $R_F = C_3F_7$, R = H
1c, $R_F = C_6F_5$, R = H
1d, $R_F = CF_3$, R = Me

2, EWG = COOEt
4, EWG = CN

10-74%

3a, $R_F = CF_3$, R = H, EWG = COOEt
3b, $R_F = C_3F_7$, R = H, EWG = COOEt
3c, $R_F = C_6F_5$, R = H, EWG = COOEt
3d, $R_F = CF_3$, R = Me, EWG = COOEt
5a, $R_F = CF_3$, R = H, EWG = CN
5c, $R_F = C_6F_5$, R = H, EWG = CN

(1)

†Dedicated to Professor Dieter Seebach on the occasion of his sixtieth birthday.

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When the reaction of **1a** and **1b** was carried out with acrylonitrile (**4**), none of the expected products were realized. However, a 74% yield of the hydroxyalkenyl nitrile product **5c** was achieved with **1c**.

Attempts to condense a perfluoroalkyl alkyl ketone, α,α,α-trifluoroacetone (**1d**), also resulted in the polymerization of the ketone.[9] The results are summarized in Table 1.

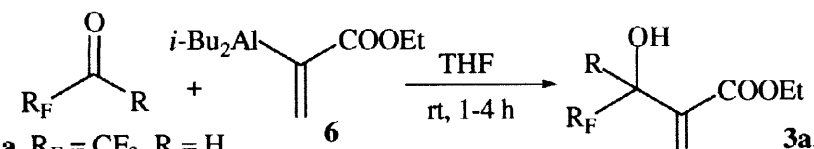
Table 1. Baylis-Hillman Reaction of Fluorinated Aldehydes

R_FCOR	R_F	R	olefin	Reaction conditions			product	isol. yield
				1: 2 or 4	temp., °C	time, h		
1a	CF_3	H	**2**	2	0	1	**3a**	10[a]
1a	CF_3	H	**2**	2	0	24	**3a**	14[a]
1a	CF_3	H	**2**	2	25	24	**3a**	19[a]
1a	CF_3	H	**2**	0.1	25	instant.	**3a**	0[b]
1a	CF_3	H	**2**	10	25	24	**3a**	20[a]
1b	C_3F_7	H	**2**	10	25	24	**3b**	16[a]
1c	C_6F_5	H	**2**	2	25	96	**3c**	71
1d	CF_3	CH_3	**2**	2	25	1	**3d**	0[b]
1a	CF_3	H	**4**	10	25	24	**5a**	0[c]
1b	C_3F_7	H	**4**	10	25	24	**5b**	0[c]
1c	C_6F_5	H	**4**	2	25	96	**5c**	74

[a]40-55% of the aldehyde hydrate was also isolated. [b]polymerization occurred.[8,9] [c]80-85% of the aldehyde hydrate was isolated.

On the basis of a 1988 report by Tsuda and co-workers,[6] Kundig[10] and Greene[11] had reported the preparation of Baylis-Hillman adducts via the reaction of aldehydes and imines with [α-(alkoxycarbonyl)vinyl]aluminum. We considered this procedure for the synthesis of fluorinated α-hydroxyalkenyl compounds.

The reaction of ethylpropiolate in THF with 1.5 equiv DIBAL-H-HMPA in hexane at 0 °C provided the [α-(ethoxycarbonyl)vinyl]aluminum reagent (**6**).[6] Fluoral (**1a**) was added to this reagent at –78 °C and was warmed to rt. The reaction, followed by quenching aliquots at periodic intervals and analyzing by gas chromatography (GC), was complete within 1 h. To ensure the completion of the reaction, the mixture was allowed to stand for 4 h in all of the cases studied. The generality of the reaction was examined by condensing a series of aliphatic and aromatic perfluoro-carbonyl compounds with **6**. In all of the cases, high yields of the product alkenols were obtained (eq 2, Table 2). It is noteworthy that, unlike in the case of the hydrocarbon analogs, the fluoro-ketones underwent reaction without any Lewis acid activation.[6]



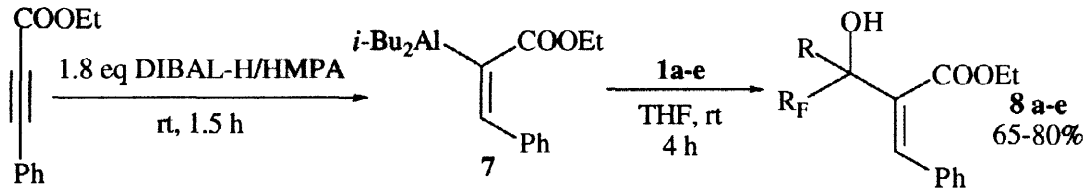
(2)

1a, $R_F = CF_3$, R = H
1b, $R_F = C_3F_7$, R = H
1c, $R_F = C_6F_5$, R = H
1d, $R_F = CF_3$, R = Me
1e, $R_F = CF_3$, R = Ph
1f, $R_F = CF_3$, R = 2-Thioph
1g, $R_F = CCl_3$, R = H

3a, $R_F = CF_3$, R = H
3b, $R_F = C_3F_7$, R = H
3c, $R_F = C_6F_5$, R = H
3d, $R_F = CF_3$, R = Me
3e, $R_F = CF_3$, R = Ph
3f, $R_F = CF_3$, R = 2-Thioph
3g, $R_F = CCl_3$, R = H

The reaction was then extended to β-substituted alkenylaluminums. It is known that the Baylis-Hillman reaction is limited to only unsubstituted acrylic acid derivatives.[5] We assumed that the [α-(ethoxycarbonyl)-β-

phenylvinyl]laluminum reagent **7** was formed under the same conditions optimized for the preparation of **6** (1h at 0 °C) and carried out the subsequent reaction of pentafluorobenzaldehyde (**1c**) at rt for 4 h. However, only a very poor yield of the expected product **8c** was achieved. To ensure that **7** was formed, the reaction was quenched prior to the addition of the aldehyde when it was noticed that only 28% hydroalumination had taken place.[12] We then established that a 1:1.8 ratio of ethyl phenylpropiolate to DIBAL-H-HMPA at rt for 1.5 h is the ideal condition for the hydroalumination.[12] The reaction of **1c** with **7** was complete within 4 h and 82% of the isomerically pure *Z*-product **8c** was realized (eq 3). The generality of the reaction was established with **1a-1e** and **1g**. In all of the cases studied, the *Z*-isomer was the only product obtained.[13] The results are summarized in Table 2. It is remarkable that no Lewis acid was necessary to activate any of the substrates.[14]



(3)

Table 2. Reaction of Fluoro-carbonyls with [α-(Ethoxycarbonyl)-vinyl]aluminum Reagents[a]

R_FCOR	R_F	R	Reagent	product	isol. yield
1a	CF_3	H	**6**	**3a**	72
1b	C_3F_7	H	**6**	**3b**	75
1c	C_6F_5	H	**6**	**3c**	82
1d	CF_3	CH_3	**6**	**3d**	68
1e	CF_3	Ph	**6**	**3e**	70
1f	CF_3	2-Thioph	**6**	**3f**	70
1g	CCl_3	H	**6**	**3g**	74
1a	CF_3	H	**7**	**8a**	73
1b	C_3F_7	H	**7**	**8b**	76
1c	C_6F_5	H	**7**	**8c**	80
1d	CF_3	CH_3	**7**	**8d**	50[b]
1e	CF_3	Ph	**7**	**8e**	68
1g	CCl_3	H	**7**	**8g**	71

[a]The reaction was performed in THF at rt for 4h. [b]15% of ethyl cinnamate was isolated.[13]

In conclusion, a study of the Baylis-Hillman reaction of fluorinated aldehydes was undertaken. The reaction provided mixed results. However, the synthesis of fluorinated Baylis-Hillman products in high yields was achieved *via* the [α-(ethoxycarbonyl)vinyl]aluminum intermediates. During this study, we standardized the conditions for the preparation of [(α-ethoxycarbonyl)-β-phenylvinyl]aluminum reagent **7**. This procedure is a substitute for the hitherto resistant Baylis-Hillman reaction of β-substituted acrylic acid derivatives.[14]

A typical experimental procedure is as follows. To a stirred solution of HMPA (3.88 g, 20 mmol) in anhydrous THF (55 mL), 15 mL of 1*M* DIBAL-H (15 mmol) in hexanes was added at 0 °C and stirred for 0.5 h. Ethyl propiolate (0.98 g, 1.01 mL, 10 mmol) was added and the mixture was stirred at 0 °C for 1 h, followed by the addition of **1e** (3.48 g, 2.8 mL, 20 mmol). The mixture was warmed to rt and stirred for 4 h, quenched with 50 mL of 0.5 *M* HCl at 0 °C, and extracted with ethyl ether (3x50 mL). The combined ether layers were washed with $NaHCO_3$ and dried over $MgSO_4$. Removal of the solvents and purification by column chromatography over silica gel (hexane:ethyl acetate :: 95:5) provided 1.9 g (7.0 mmol, 70%) of **3e** as a thick

liquid. ^{1}H NMR (300 MHz) δ ($CDCl_3$) (ppm): 1.23 (t, J = 7.14 Hz, 3H, CH_3), 4.17 (m, 2H, CH_2CH_3), 5.74 (s, 1H, exchangeable with D_2O, OH), 6.14 (s, 1H, =CH_2), 6.65 (s, 1H, =CH_2), 7.39 (m, 3H, Ph), 7.61 (m, 2H, Ph). ^{13}C NMR δ ($CDCl_3$) (ppm): 13.79, 61.99, 79.19 (q, J = 28.8 Hz, C-CF_3), 124.29 (q, J = 283.57 Hz, CF_3), 126.95, 128.33, 128.73, 128.98, 136.43 (C=C), 137.24 (C=C), 167.07 (C=O). ^{19}F NMR δ ($CDCl_3$) (ppm): -76.70 (s).

The procedure is similar for the preparation and reaction of **7** except that 18 mL of DIBAL-H was used and the mixture was stirred at rt for 1.5 h prior to the addition of **1e**. Workup as above provided 2.36 g (68%) of **8e** as a thick liquid. ^{1}H NMR (300 MHz) δ ($CDCl_3$) (ppm): 0.93 (t, J = 7.14 Hz, 3H, CH_3), 4.03 (q, J = 7.14 Hz, 2H, CH_2CH_3), 5.34 (s, 1H, exchangeable with D_2O, OH), 7.06 (s, 1H, =CH), 7.36 (m, 8H, Ph), 7.77 (m, 2H, Ph). ^{13}C NMR δ ($CDCl_3$) (ppm): 13.26, 61.91, 79.67 (q, J = 29 Hz, C-CF_3), 124.76 (q, J = 285 Hz, CF_3), 127.59, 128.24, 128.37, 128.93, 129.13, 129.40, 131.20, 134.94, 136.02 (C=C), 137.81 (C=C), 169.6 (C=O). ^{19}F NMR δ ($CDCl_3$) (ppm): -75.57 (s).

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REFERENCES AND NOTES

1. Preliminary results were presented at the 31st Great Lakes Regional Meeting (Paper # 233) of the American Chemical Society, Milwaukee, WI, June 2, 1998.
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12. The reaction was followed by quenching an aliquot and comparing with ethyl cinnamate using a GC. Allowing the reaction to warm to rt for 1 h achieved 80% hydroalumination, with no further improvement with time. Increasing the ratio of the DIBAL-H to propiolate to 1.8 improved the yield of the cinnamate to 90% after 1 h at rt, which was essentially complete in 1.5 h.
13. Upon quenching **7** with dil. HCl a 4:1 mixture of *Z*- and *E*-ethyl cinnamate (^{1}H NMR) was produced. The *Z*:*E* ratio of the recovered cinnamate is also 4:1. Yet, we obtained only the *Z*-isomer of **8** as confirmed by their NOESY ^{1}H NMR spectra. We believe that the reaction proceeds via an allenoate intermediate as described by Marino. Marino, J. P.; Linderman, R. J.; *J. Org. Chem.* **1983**, *48*, 4621.
14. While preparing this manuscript,[1] we noticed a report where the reagent **7** was utilized for similar reactions, *albeit* in moderate yields, with non-fluorinated substrates in presence of a Lewis acid. Li, G.; Wei, H. X.; Willis, S. *Tetrahedron Lett.* **1998**, *39*, 4607.