Pergamon

Tetrahedron Letters 39 (1998) 8791–8794

TETRAHEDRON LETTERS

Vinylalumination of Fluoro-carbonyl Compounds[1†]

P. Veeraraghavan Ramachandran*, M. Venkat Ram Reddy[2a], Michael T. Rudd[2b], and Javier Read de Alaniz[2c]

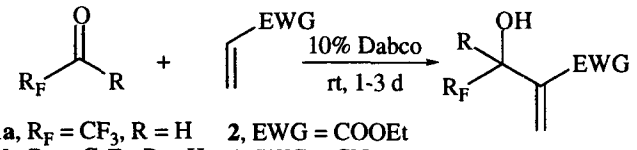
H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907-1393

Received 10 July 1998; accepted 15 September 1998

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. © 1998 Elsevier Science Ltd. All rights reserved.

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.

0040-4039/98/$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)01974-1

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.

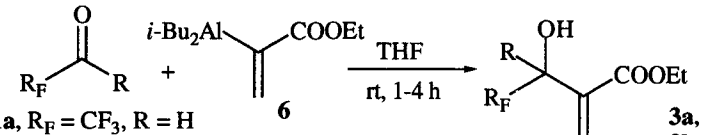
Table 1. Baylis-Hillman Reaction of Fluorinated Aldehydes

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]



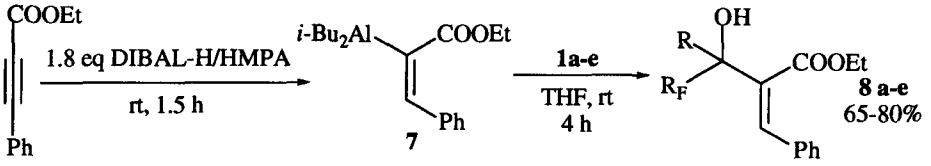
(2)

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]]aluminum 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).

Acknowledgments. The financial assistance from the Purdue Borane Research Fund is gratefully acknowledged. We are thankful to Professor Herbert C. Brown for helpful discussions and encouragement.

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.
2. (a) Post-doctoral research associate on a grant from the Purdue Borane Research Fund. (b) Pfizer Summer Undergraduate Research Fellow (c) Purdue University Summer Undergraduate Research Fellow from Fort Lewis College, Fort Lewis, CO.
3. For several recent reviews see: *Biomedical Frontiers of Fluorine Chemistry*, Ojima, I.; McCarthy, J. R.; Welch, J. T. Eds. ACS Symposium Series 639, American Chemical Society, Washington DC, **1996**.
4. Ramachandran, P. V.; Brown, H. C. in *EPC-Synthesis of Fluoro-Organic Compounds*, Soloshonok, V. A. Ed. Wiley: Chichester, U. K. , **1998**, in press.
5. For the most recent review on Baylis-Hillman reaction, see: Ciganek, E. in *Organic Reactions* **1997**, *51*, 201. Paquette, L. A. ed. John Wiley, New York, NY.
6. Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 1037.
7. Golubev, A. S.; Galakhov, M. V.; Kolomiets, A. F.; Fokin, A. V. *Izv. Akad. Nauk Ser. Khim.* **1992**, 2763.
8. Fluoral polymerizes instantaneously in the presence of a trialkylamine. Busfield, W. K.; Whalley, E. *Polymer* **1966**, *7*, 541.
9. CF_3COMe is known to polymerize in the presence of *secondary* amines. Dhingra, M. M.; Tatta, K. R. *Org. Mag. Res.* **1977**, *9*, 23.
10. Zu, L. H.; Kundig, E. P. *Helv. Chim. Acta* **1994**, *77*, 1480.
11. Génisson, Y.; Massardier, C.; Gautier-Luneau, I.; Greene, A. E. *J. Chem. Soc. Perkin Trans. I* **1996**, 2869.
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.