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Study of Fluorocarbonyls for the Baylis−Hillman Reaction

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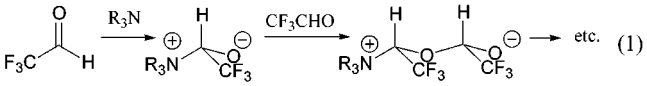
Abstract: A study of the effect of fluorine substitution in Baylis−Hillman reactions of various fluorocarbonyl partners with acrolein, methyl vinyl ketone, ethyl acrylate, and acrylonitrile has been made.

Fluorine substitution in organic molecules often influences the biological properties of medicinal compounds[1] and the physical properties of several optoelectronic devices.[2] Fluorinated allylic alcohols are important building blocks in synthetic fluoroorganic chemistry.[3] The possibility to synthesize novel functionalized fluorinated allylic alcohols in a single step led us to the investigation of the operationally simple, atom-economical, environmentally friendly Baylis−Hillman (BH) reaction[4] of fluorocarbonyls. Unfortunately, a literature search revealed that the simplest fluorocarbonyls, fluoral and 1,1,1-trifluoroacetone, polymerize instantaneously in the presence of amines (eqs 1 and 2).[5,6] Our desire to find



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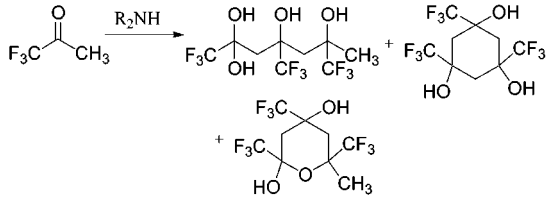
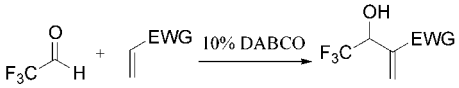


(2)

conditions to suppress the polymerization and obtain the products led to a systematic study achieving the reaction of both of these compounds with activated olefins under controlled conditions.[7]

We chose acrolein (**1a**), methyl vinyl ketone (**1b**), ethyl acrylate (**1c**), and acrylonitrile (**1d**) as the olefin partners in the reaction. Acrolein is also known to polymerize in the presence of amines, similar to the case of fluoral.[8] Michael-type dimerization of methyl vinyl ketone in the presence of DABCO has also been reported.[9] We were faced with the difficult task to find conditions to react these amine-sensitive olefins with fluorinated aldehydes and ketones. Optimum yields of the fluorinated allyl alcohol products are obtained by matching the reactivities of the olefin and carbonyl partners, whereas a mismatch results in the decomposition or side reaction of the faster reacting partner. The reactions are discussed below according to the class of fluorocarbonyl studied.

Fluoroaldehydes. The reactions of fluoral (**2**) with **1a**−**d** were examined first. As feared, mixing **2** with **1a** at room temperature (rt) under neat conditions resulted in the polymerization of both reactants. Addition of THF as a solvent for the reaction provided a very low yield of the expected product along with the polymers of the starting materials. With the hope of arresting the polymerization, we lowered the reaction temperature to −25 °C and obtained a 40% yield of the BH product, **3a** (eq 3). However, we could not suppress the polymerization



2

1a: EWG = CHO
1b: EWG = $COCH_3$
1c: EWG = CO_2Me
1d: EWG = CN

3a: EWG = CHO, 40% (-25 °C)
3b: EWG = $COCH_3$, 65% (-25 °C)
3c: EWG = CO_2Me, 20% (rt)
3d: EWG = CN, 0% (rt)

(3)

completely. Further lowering of the temperature to −78 °C had a deleterious effect on the BH reaction, since polymerization of both reactants was faster than the BH reaction at this temperature.

Reaction of **2** with **1b** provided the product **3b** in 35% yield under neat conditions, at rt, 1 h, and 65% yield in THF at −25 °C (eq 3). Reaction with **1c** provided a 20% yield of the product **3c** at rt under neat conditions (eq 3). However, decreasing the reaction temperature suppressed the BH reaction completely, and only polymeric fluoral was obtained. Olefin **1d** did not yield any BH product **3d** at rt or at lower temperature.

Reaction of 2,2,3,3,4,4,4-heptafluorobutanal (**4**) showed identical reaction patterns with slightly improved yields of the allylic alcohols. While acrolein and methyl vinyl ketone provided 50% and 70% yield, respectively, of products at −25 °C, ethyl acrylate provided only 18% yield of the product **5c** and acrylonitrile failed to provide any product at rt.

We then studied a perfluorinated aldehyde that does not undergo polymerization under the BH reaction condi-

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(2) For several recent reviews, see: *Asymmetric Fluoroorganic Chemistry;* Ramachandran, P. V., Ed.; ACS Symposium Series 746; American Chemical Society: Washington, DC, 1999.

(3) For a review on fluorinated allylic alcohols as building blocks, see: Allmendinger, T.; Angst, C.; Karfunkel, H. *J. Fluorine Chem.* **1995**, *72*, 247.

(4) For recent reviews, see: (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (b) This reaction is also known as the Morita−Baylis−Hillman reaction. Ciganek, E. In *Organic Reactions;* Paquette, L. A., Ed.; John Wiley: New York, 1997; Vol. 51, p 201.

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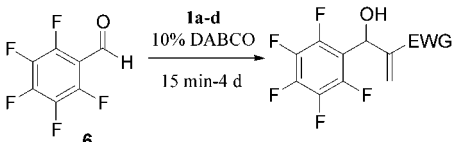
TABLE 1. Baylis−Hillman Reactions of Fluoroaldehydes

aldehyde, R_FCHO		$H_2C{=}CH{-}EWG$		reaction conditions			product	
no.	R_F	no.	EWG	solvent	temp, °C	time, h	no.	isol yld, %
2	CF_3	**1a**	CHO	THF	−25	1	**3a**	40
2	CF_3	**1b**	$COCH_3$	THF	−25	1	**3b**	65
2	CF_3	**1c**	CO_2Et	none	25	4	**3c**	20[a]
2	CF_3	**1d**	CN	none	25	4	**3d**	0
4	C_3F_7	**1a**	CHO	THF	−25	1	**5a**	50
4	C_3F_7	**1b**	$COCH_3$	THF	−25	1	**5b**	70
4	C_3F_7	**1c**	CO_2Et	none	25	4	**5c**	18[a]
4	C_3F_7	**1d**	CN	none	25	4	**5d**	0
6	C_6F_5	**1a**	CHO	THF	0	0.25	**7a**	95
6	C_6F_5	**1b**	$COCH_3$	none	25	48	**7b**	70
6	C_6F_5	**1c**	CO_2Et	none	25	96	**7c**	70[b]
6	C_6F_5	**1d**	CN	none	25	96	**7d**	75[b]

[a] Two minor products accounting for a total of ~20% mass balance were not characterized. [b] On the basis of the recovered aldehyde.

tions (in the presence of a tertiary -amine). Accordingly, we tested pentafluorobenzaldehyde (**6**) for BH reaction with **1a**−**d**. While the reactions of **1b**−**d** under neat



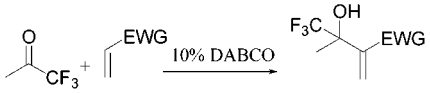
6

7a: EWG = CHO, 95% (0 °C)
7b: EWG = COMe, 70%
7c: EWG = CO_2Et, 70%
7d: EWG = CN, 75%

(4)

conditions at rt took 2−4 days to afford 70−75% of the products **7b**−**d**, **1a** polymerized under these conditions. However, it reacted in THF at 0 °C within 0.25 h to provide **7a** in near quantitative yield (eq 4). All of the Baylis−Hillman reactions of fluorinated aldehydes are summarized in Table 1.

Fluoroketones. Although 1,1,1-trifluoroacetone (**8**) is also known to trimerize in the presence of amines (eq 2),[6] our partial success with fluoral persuaded us to undertake the reaction at low temperatures. We obtained



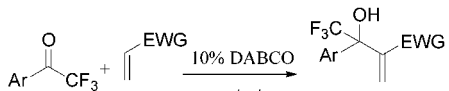
8 **1c-d**

9a: EWG = CHO, 12%
9d: EWG = CN, 10%

(5)

a 10−12% yield of the products **9a** with **1a** in THF at −25 °C and **9d** with **1d** at rt (eq 5). However, only a polymeric material was isolated during the reaction of olefins **1b** and **1c** with **8**.

To avoid the polymerization initiated by abstraction of the α-hydrogen atom, we focused our attention on aryl trifluoromethyl ketones. The treatment of 2,2,2-trifluoroacetophenone (**10**) with 2 equiv of **1a** in the presence of 10% DABCO, under neat conditions, at rt, did not provide any product. Decreasing the reaction temperature to −25 °C yielded 15% of acrolein dimer along with its polymer. Olefin **1b** also did not provide any of the expected BH product at rt, although we obtained a 30% yield of the dimer. Lowering the temperature resulted only in the suppression of the dimerization. In contrast, a slow reaction (7 days) between **10** and **1c** resulted in 71% yield of the expected allylic alcohol **11c**. The reaction with **1d** was faster, complete within 24 h, and provided 94% yield of the product **11d** (eq 6).



10: Ar = Ph
12: Ar = 2-Thioph

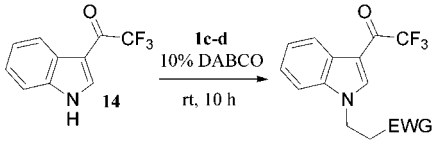
1c-d

11c: Ar = Ph; EWG = CO_2Et, 70%
11d: Ar = Ph; EWG = CN, 94%
13c: Ar = 2-Thioph; EWG = CO_2Et, 65%
13d: Ar = 2-Thioph; EWG = CN, 82%

(6)

2-Trifluoroacetylthiophene (**12**) underwent reaction with **1c** within 7 days, providing the product **13c** in 65% yield, and with **1d** within 24 h, providing the product allylic alcohol **13d** in 82% yield (eq 6). Again, **1a** and **1b** did not undergo BH reaction.

3-Trifluoroacetylindole (**14**) was included in the study to determine whether the Baylis−Hillman reaction competes with the possible Michael reaction under the conditions. We limited the olefins to **1c** and **1d**. As feared, the Michael addition was faster than the BH reaction with these olefins. We isolated 80% and 82% of the corresponding Michael addition products **15c** and **15d**, respectively (eq 7).

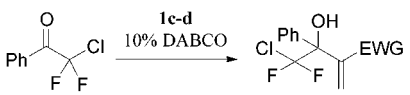


14

15c: EWG = CO_2Et, 80%
15d: EWG = CN, 82%

(7)

We then compared the reactivity of the chlorine analogue of **10**. 2,2,2-Trichloroacetophenone (**16**) failed to react with all of the above four olefins, **1a**−**d**. The reaction was too slow to be of any practical value, and the thin layer chromatogram of the reaction mixture revealed several minor products along with the starting material. However, 2-chloro-2,2-difluoroacetophenone (**17**) has a reactivity similar to that of the trifluoromethyl analogue. Ethyl acrylate reacted within 7 days, providing



17

18c: EWG = CO_2Et, 68%
18d: EWG = CN, 90%

(8)

TABLE 2. Baylis−Hillman Reactions of Fluoroalkyl Ketones

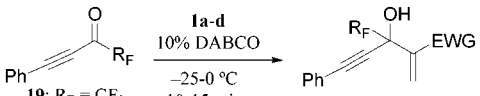
ketone, RCORF			H_2C=CH−EWG		reaction condition			product	
no.	R	R_F	no.	EWG	solvent	temp, °C	time	no.	yld, %
8	Me	CF_3	**1a**	CHO	THF	−25	1 h	**9a**	12
8	Me	CF_3	**1b**	COMe	none	−25	1 h	**9b**	0[a]
8	Me	CF_3	**1c**	CO_2Et	none	−25	1 h	**9c**	0
8	Me	CF_3	**1d**	CN	THF	rt	1 h	**9d**	10
10	Ph	CF_3	**1c**	CO_2Et	none	rt	7 d	**11c**	70
10	Ph	CF_3	**1d**	CN	none	rt	1 d	**11d**	94
12	2-thioph	CF_3	**1c**	CO_2Et	none	rt	7 d	**13c**	65
12	2-thioph	CF_3	**1d**	CN	none	rt	1 d	**13d**	82
14	3-indolyl	CF_3	**1c**	CO_2Et	THF	rt	10 h	**15c**	80[b]
14	3-indolyl	CF_3	**1d**	CN	THF	rt	10 h	**15d**	82[b]
17	Ph	CF_2Cl	**1c**	CO_2Et	none	rt	7 d	**18c**	68
17	Ph	CF_2Cl	**1d**	CN	none	rt	1 d	**18d**	90

[a] 30% of MVK dimer was formed at rt. [b] Only 1,4-addition took place.

the corresponding allylic alcohol **18c** in 68% yield, and acrylonitrile provided the product **18d** within 24 h, in 90% yield (eq 8).The reactions of fluoroalkyl ketones are summarized in Table 2.

α-Acetylenic α′-Trifluoroalkyl Ketones. We expected a fast Baylis−Hillman reaction of α-acetylenic α′-perfluoroalkyl ketones because of the increased electrophilic nature of the carbonyl carbon. However, the extreme amine sensitivity of these ketones was a concern. During our projects involving the asymmetric reduction of the above ketones, we observed that they decompose very rapidly in the presence of amines.[10] Indeed, the reactions of 1,1,1-trifluoro-4-phenyl-3-butyn-2-one (**19**) and 4,4,5,5,6,6,6-heptafluoro-1-phenyl-2-hexyn-3-one (**21**) with **1a**−**d** were found to be extremely sensitive to the reaction conditions. Every parameter, such as temperature, solvent concentration, amount of catalyst, and so forth influenced the reaction drastically. After repeated attempts, we arrived at the optimal conditions and achieved the fastest Baylis−Hillman reaction at very low temperatures.

The reaction of 1,1,1-trifluoro-4-phenyl-3-butyn-2-one (**19**) with **1c**, neat, was very vigorous at rt and was conducted at 0 °C, complete within 15 min providing a 75% isolated yield of the product **20c** (eq 9). Prolonged reaction times had a deleterious effect. We observed that **19** by itself decomposed in the presence of DABCO to provide a mixture of compounds.



20a: $R_F = CF_3$, EWG = CHO, 54%
20b: $R_F = CF_3$, EWG = COMe, 50%
20c: $R_F = CF_3$, EWG = CO_2Et, 75%
20d: $R_F = CF_3$, EWG = CN, 40%
22a: $R_F = n\text{-}C_3F_7$, EWG = CHO, 50%
22b: $R_F = n\text{-}C_3F_7$, EWG = COMe, 46%

(9)

The reaction of **19** with **1d** was even more vigorous at rt and at 0 °C. We conducted the reaction under controlled conditions, at −25 °C, and isolated a 40% yield of the product **20d** after 10 min. With the more reactive olefin partner **1a** or **1b**, we had to carry out the reaction in 2 M THF at −25 °C. A reaction at 0 °C or rt resulted in the decomposition of the ketone. Acrolein provided a 54% yield of the product within 10 min, and methyl vinyl ketone yielded 50% of product **20b**, along with 10% of the starting material, within the same time (eq 9). Again, prolonging the reaction had a destructive effect.

4,4,5,5,6,6,6-Heptafluoro-1-phenyl-1-hexyn-3-one (**21**) decomposed faster than **19** in the presence of DABCO. Yet, we obtained 50% and 46% of the products **22a** and **22b** with **1a** and **1b**, respectively, at −25 °C (eq 9). The reactions of α-acetylenic α′-perfluoroalkyl ketones are summarized in Table 3.

TABLE 3. Baylis−Hillman Reaction of α-Acetylenic α′-Perfluoroalkyl Ketones

Ph−C≡C−COR_F		H_2C=CH−EWG		product	
no.	R_F	no.	EWG	no.	yld, %
19	CF_3	**1a**	CHO	**20a**	54
19	CF_3	**1b**	$COCH_3$	**20b**	50[a]
19	CF_3	**1c**	CO_2Et	**20c**	75
19	CF_3	**1d**	CN	**20d**	40
21	C_3F_7	**1a**	CHO	**22a**	50[a]
21	C_3F_7	**1b**	$COCH_3$	**22b**	46[b]

[a] On the basis of the 10% of recovered ketone. [b] On the basis of the 40% of recovered ketone. Longer reaction times resulted in decomposition of **21**.

In conclusion, a study of the effect of fluorine substitution in the Baylis−Hillman reaction of various fluorocarbonyl partners with acrolein, methyl vinyl ketone, ethyl acrylate, and acrylonitrile has been made. We succeeded in preparing multifunctionalized fluorinated allyl alcohols with amine-sensitive aldehydes and olefins by balancing their reactivities.

The results suggest that when the olefin is capable of reacting with itself in the presence of an amine (e.g. acrolein), the electrophile has to be very reactive as well (e.g. fluoral) to obtain a modest to good yield of BH products. The reaction of a moderately reactive olefin (e.g. ethyl acrylate or acrylonitrile) and a very reactive electrophile (e.g. fluoral) results in self-reaction of the electrophile or very low yield of the allylic alcohol product. A moderately reactive electrophile (e.g. trifluoroacetophenone) provides a good yield of products with moderately reactive olefins (e.g. ethyl acrylate and acrylonitrile). Thus, a match between the reactivities of the olefin and carbonyl partners is essential for obtaining reasonable yields of the products.

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Experimental Section

Materials. Tetrahydrofuran was distilled from benzophenone ketyl prior to use. 2,2,2-Trifluoroacetaldehyde and 2,2,3,3,4,4,4-heptafluorobutyraldehyde hydrates were prepared from the corresponding carboxylic acids by reduction with 0.5 molar equiv of lithium aluminum hydride in ethyl ether at −10 °C for 4 h, followed by quenching with water and concd sulfuric acid.[11] The aldehydes were obtained by the dehydration of the corresponding hydrates using phosphorus pentoxide in concentrated sulfuric acid at 90 °C and were distilled twice at rt prior to use. α-Acetylenic α′-fluoroalkyl ketones were prepared according to a literature procedure.[12]

The reaction conditions varied depending on the alkene and fluorocarbonyl compound. General procedures for different classes of carbonyl compounds are described below. The reaction yields and physical data of individual reactions are provided in the Supporting Information.

General Procedure for Baylis−Hillman Reaction of Perfluoroalkyl Aldehydes. The reaction of a methyl vinyl ketone with fluoral is representative. To a stirred solution of methyl vinyl ketone (0.70 g, 10 mmol, 0.83 mL) in THF (5 mL) was added 2,2,2-trifluoroacetaldehyde (0.49 g, 5 mmol) at −25 °C. To this was added DABCO (0.056 g, 0.5 mmol) in 0.5 mL of THF. The reaction mixture was stirred at this temperature for an additional hour (in the case of ethyl acrylate, the reaction was carried out at rt, under neat conditions for 4 h). The solvent was evaporated under vacuum, and the crude reaction mixture was purified by silica gel chromatography (hexanes/ethyl acetate 9:1) to yield 0.55 g (65%) of the pure product.

General Procedure for Baylis−Hillman Reaction of Fluoroaryl Aldehydes. The reaction of 2′,3′,4′,5′,6′-pentafluorobenzaldehyde with methyl vinyl ketone is representative. To a stirred solution of methyl vinyl ketone (0.7 g, 10 mmol, 0.83 mL) and pentafluorobenzaldehyde (0.98 g, 5 mmol, 0.62 mL) was added DABCO (0.056 g, 0.5 mmol) at rt. The reaction was complete in 2 days. Following the evaporation of the volatiles, the crude reaction mixture was purified by silica gel chromatography (hexanes/ethyl acetate 9:1) to yield 0.93 g (70%) of the pure product.

General Procedure for Baylis−Hillman Reaction of Perfluoroalkyl- and -aryl Ketones. The reaction of 2,2,2-trifluoroacetophenone with acrylonitrile is representative. To a stirred solution of acrylonitrile (0.53 g, 10 mmol, 0.66 mL) and 2,2,2-trifluoroacetophenone (0.87 g, 5 mmol, 0.70 mL) was added DABCO (0.056 g, 0.5 mmol) at rt. The reaction was complete within 24 h. In the case of ethyl acrylate, the reaction was complete in 7 days. The volatiles were removed under vacuum, and the crude reaction mixture was purified by silica gel chromotography (hexanes/ethyl acetate 95:5) to obtain 1.07 g (94%) of the pure compound.

General Procedure for Baylis−Hillman Reaction of α-Acetylenic α′-Fluoroalkyl Ketones. The reaction of 4-phenyl-1,1,1-trifluoro-3-butyn-2-one with acrolein is representative. To a stirred solution of acrolein (0.56 g, 10 mmol, 0.67 mL) and THF (5 mL) at −25 °C was added 4-phenyl-1,1,1-trifluoro-3-butyn-2-one (0.99 g, 5 mmol). DABCO (0.056 g, 0.5 mmol) was then added, and the reaction was mixed for 10 min at this temperature. The crude reaction mixture was directly purified by silica gel chromotography (hexanes/ethyl acetate 9:1) to yield the pure product **20a** (0.70 g, 54%).

In the case of methyl vinyl ketone, 10-mmol-scale reactions were conducted in 2.5 mL of THF at −25 °C with 0.14 g (1.25 mmol) of DABCO.

In the case of ethyl acrylate, the reactants were mixed under neat conditions at 0 °C in the presence of 0.056 g (0.5 mmol) of DABCO and kept at rt for 15 min.

In the case of acrylonitrile, the reactants were mixed at −25 °C in the presence of 0.14 g (1.25 mmol) of DABCO, and the mixture was maintained for 10 min and filtered through a silica gel column (hexanes/ethyl acetate 9:1).

Acknowledgment. Financial assistance from Eastman Kodak Co. is gratefully acknowledged.

Supporting Information Available: The spectral data and other physical characteristics of all of the compounds described (5 pages). ^{1}H, ^{13}C, and ^{19}F NMR spectra of all compounds (74 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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