JOC Notes

New Stereoselective Preparation of (*Z*)-3-Perfluoroalkyl-3-magnesiated Enoates by an Iodine−Magnesium Exchange Reaction

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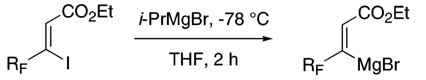
Abstract: (*Z*)-Ethyl-3-perfluoroalkyl-3-magnesiated crotonates were prepared from (*Z*)-ethyl-3-perfluoroalkyl-3-iodo enoates by iodine−magnesium exchange reaction with isopropylmagnesium bromide in THF at −78 °C. These new reagents reacted with a range of electrophiles, leading to polyfunctional products bearing a perfluoroalkyl group.

Generation and nucleophilic reactions of α-perfluoroalkyl carbanion would provide a promising entry to the synthesis of perfluoroalkylated compounds, the unique properties of which play an important role in medicinal and agricultural chemistry and material sciences.[1] The introduction of a fluorine or perfluoroalkyl group into organic compounds often dramatically changes their structure, stability, reactivity, and biological activity.[2] Perfluoroalkylated vinylmetals have been demonstrated in which lithium,[3] magnesium,[4] zinc,[5] silver,[6] and palladium[7] species were prepared and alkylated with electrophiles specific to carbon attached to the metal. However, no report of the chemistry of the perfluoroalkylated-enoate carbanion has been published to date.

SCHEME 1



1a: $R_F = CF_3$
1b: $R_F = CF_3\text{-}CF_2$

2a: $R_F = CF_3$
2b: $R_F = CF_3\text{-}CF_2$

The development of a simple method to obtain perfluoroalkylated building blocks and for their further utilization in the synthesis of R_F-containing compounds is therefore essential to organofluorine chemistry. Iodine−magnesium exchange also opens the way for the preparation of stereochemically pure *E*- or *Z*-alkenylmagnesium derivatives.[8,9] We report here the application of this exchange reaction to the preparation of a new magnesium reagent type **2**, using the available (*Z*)-ethyl-3-perfluoroalkyl-3-iodocrotonates[10] **1** and isopropylmagnesium bromide. Treatment of iodide **1a** or **1b** with *i*-PrMgBr (1.2 equiv) in THF at −78 °C cleanly generated stable magnesium species **2** bearing a perfluoroalkyl group within 2 h, as indicated by GC analysis of hydrolyzed reaction aliquots, without defluorination of α-CF_3 or C_2F_5-attached carbanions (Scheme 1).[3a,11]

These reagents are known to be thermally unstable due to their tendancy for β-elimination,[12] in which difluoroallene is formed via defluorination of α-(trifluoromethyl)-vinylmetal. Nucleophilic reactions of magnesium species **2a**,**b** with various electrophiles were examined to determine the scope and limitations of the reaction. After quenching with electrophiles, good yields of fluoro acrylates **3**−**12** were obtained with complete retention of the

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(1) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320. (b) *Fluorine-Containing Molecules*; Liebman, J. F., Greenberg, A., Dolbier, W. R., Jr., Eds.; VCH: New York, 1988. (c) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991. (d) *Chemistry of Organic Fluorine Compounds II*; Hudlicky, M., Pavlath, A. E., Eds.; American Chemical Society: Washington, DC, 1995. (e) Filler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Kodansha: Tokyo, Japan, 1982. (f) Hudlicky, M. *Chemistry of Organo Fluorine Compounds*; Ellis Horwood: New York, 1976.

(2) (a) Smart, B. E. *Chem. Rev.* **1996**, *96*, 1555. (b) Resnatic, G.; Solshnok, V. A. *Tetrahedron*, **1996**, *52*, 1. (c) *Organofluorine Chemistry: Principle and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994.

(3) (a) Drakesmith, F. G.; Stewart, O. J.; Tarrant, P. *J. Org. Chem.* **1967**, *33*, 280. (b) Morken, P. A.; Lu, H.; Nakamura, A.; Burton, D. J. *Tetrahedron Lett.* **1991**, *32*, 4271. (c) Watanabe, H.; Yamashita, F.; Uneyama, K. *Tetrahedron Lett.* **1993**, *34*, 1941. (d) Watanabe, H.; Yan, F.; Sakai, T.; Uneyma, K. *J. Org. Chem.* **1994**, *59*, 758. (e) Uneyama, K.; Noritake, C.; Sadamune, K. *J. Org. Chem.* **1996**, *61*, 6055.

(4) Kobayashi, T.; Nakagawa, T.; Amii, H.; Uneyama, K. *Org. Lett.* **2003**, *5*, 4297.

(5) (a) Hansen, S. W.; Spawn, T. D.; Burton, D. J. *J. Fluorine Chem.* **1987**, *35*, 415. (b) Heinze, P. L.; Burton, D. J. *J. Org. Chem.* **1988**, *53*, 2714. (c) Jiang, B.; Xu, Y. *J. Org. Chem.* **1991**, *56*, 7336. (d) Morken, P. A.; Lu, H.; Nakamura, A.; Burton, D. J. *Tetrahedron Lett.* **1991**, *32*, 4271. (e) Jiang, B.; Xu, Y. *Tetrahedron Lett.* **1992**, *33*, 511. (f) Morken, P. A.; Burton, D. J. *J. Org. Chem.* **1993**, *58*, 1167. (g) Shi, G.-Q.; Huang, X.-H.; Hong, F. *J. Org. Chem.* **1996**, *61*, 3200. (h) Davis, C. R.; Burton, D. J. *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford University Press: New York, 1999; pp 57−76.

(6) (a) Miller, W.; Snider, R. H.; Hummel, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 6532. (b) Banks, R. E.; Haszeldine, R. N.; Taylor, D. R.; Webb, G. *Tetrahedron Lett.* **1970**, 5215.

(7) (a) Fuchikami, T.; Ojima, I. *Tetrahedron Lett.* **1982**, *23*, 4099. (b) Fuchikami, T.; Yamanouchi, A.; Ojima, I. *Synthesis* **1984**, 766. (c) Fuchikami, T.; Yamanouchi, A. *Chem. Lett.* **1984**, 1595.

(8) (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701. (b) Abarbri, M.; Knochel, P. *Synlett* **1999**, 1577. (c) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottlander, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618.

(9) (a) Rottländer, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080. (b) Sapountzis, I.; Dohle, W.; Knochel, P. *Chem. Commun.* **2001**, 2068.

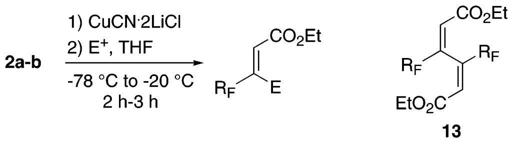
(10) (a) Prié, G.; Thibonnet, J.; Abarbri, M.; Duchêne, A.; Parrain, J.-L. *Synlett* **1998**, 839. (b) Qing, F. L.; Zhang, Y. *Tetrahedron Lett.* **1997**, *38*, 6729.

(11) (a) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds: Chemistry and Applications*; Springer-Verlag: Berlin, Germany, 2000. (b) Kitazume, T.; Yamazaki, T. *Experimental Methods in Organic Fluorine Chemistry*; Kodansha and Gordon and Breach Science: Tokyo, Japan, 1998.

(12) (a) Nemoto, H.; Satoh, A.; Fukumoto, K. *Synlett* **1995**, 199. (b) Yamazaki, T.; Hiraoka, S.; Kitazame, T. *J. Org. Chem.* **1994**, *59*, 5100. (c) Watanabe, H.; Yan, F.; Sakai, T.; Uneyama, K. *J. Org. Chem.* **1994**, *59*, 758.

10.1021/jo049960k CCC: $27.50

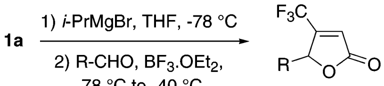
SCHEME 2



13

13a: $R_F = CF_3$
13b: $R_F = CF_3\text{-}CF_2$

SCHEME 3



14a-c

14a: R = *n*-Hex (75%); **14b**: R = *n*-Bu (73%); **14c**: R = Ph (82%)

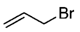
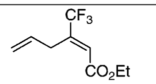
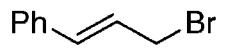
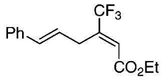
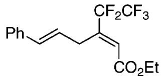
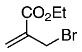
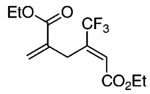
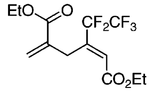
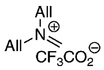
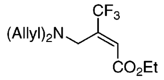
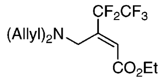
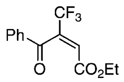
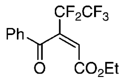
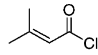
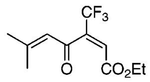
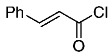
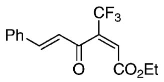
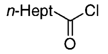
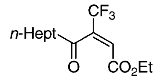
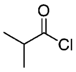
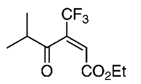
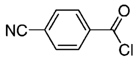
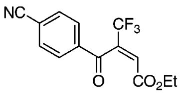
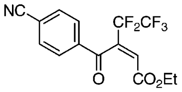
double bond configuration (Scheme 2). The results obtained by the reaction of **2a**,**b** with various electrophiles are summarized in Table 1.

Transmetalation of **2a** or **2b** with the THF-soluble copper salt CuCN·2LiCl[13] provided a functionalized copper reagent bearing a perfluoroalkyl group. When the intermediate organocopper was trapped with both aromatic and aliphatic acid chlorides at −78 °C, a mixture of the desired products **7**−**12** and the homocoupling product type **13** (minor product, <15%) was obtained. The formation of the homocoupling reaction product could be explained by a competitive reductive elimination step of the divinylcuprate formed after transmetalation. Reasonable yields of 1,4-ketoesters **7**−**12** were isolated (63−88%, entries 8−15). The choice of reaction temperature was quite important in obtaining a single isomer (−78 °C; >99% *Z*), and we noted that a significant amount of *E*-isomer was formed ($Z/E = 70/30$) when the temperature of the exchange reaction was around −30 °C. The magnesium species deriving from iodides **1a** and **1b** were stable in our experimental conditions and no isomerization occurred in the temperature range −78 to −60 °C. Allylation with allyl or 3-phenylallyl bromide in the presence of a catalytic amount of CuCN (10%) yielded 95%, 63%, and 52% of allylated products **3** and **4a**,**b**, respectively (entries 1−3; >99% *E*). Similarly, the reaction of the cuprate derived from **2** with ethyl (2-bromoethyl)acrylate[14] provided 85% and 70% yields of (*E*)-unsaturated diester **5a** and **5b** (entries 4−5; >99% *E*). The reaction of magnesium species **2** with immonium trifluoroacetate[15] proceeded efficiently, leading to 90% and 76% yields of 3-aminomethylcrotonates **6a** and **6b**, respectively, bearing a perfluoroalkyl group (entries 6 and 7). It should be noted that the immonium reacted efficiently both with copper salt or with Lewis acid without activation.

Aldehydes such as benzaldehyde or aliphatic aldehydes such as heptanal were found to react slowly, providing very poor yields (<15%) of the corresponding unsaturated lactones **14**. To increase the reactivity of the aldehydes, we investigated the use of Lewis acid as activator. Yields of butenolides **14a**−**c** obtained were increased to 82% by adding 1.2 equiv of Lewis acid ($BF_3{\cdot}OEt_2$) at −78 °C (Scheme 3). The intermediate allylic alcohols were not detected in these cases.

As shown in Table 1, better yields were obtained when the perfluoroalkyl group of starting material was CF_3 (compound type **a**) than $CF_3{-}CF_2$ (compound type **b**).

TABLE 1. Stereoselective Preparation of 3-Perfluoroalkyl-3-substituted Acrylates 3−12

Entry	Grignard reagent	Electrophile	Product		Yield (%)[a]
1[b]	**2a**			**3**	95
2[b]	**2a**			**4a**	63
3[b]	**2b**	“		**4b**	52
4[c]	**2a**			**5a**	85
5[c]	**2b**	“		**5b**	70
6	**2a**			**6a**	90
7	**2b**	“		**6b**	76
8[c]	**2a**	PhCOCl		**7a**	71
9[c]	**2b**	“		**7b**	64
10[c]	**2a**			**8**	72
11[c]	**2a**			**9**	88
12[c]	**2a**			**10**	86
13[c]	**2a**			**11**	69
14[c]	**2a**			**12a**	72
15[c]	**2b**	“		**12b**	63

[a] Isolated yield of analytically pure products. [b] 10 mol % of CuCN was added after addition of allyl bromide derivative. [c] Transmetalation to a copper reagent with CuCN·2LiCl was performed prior to the addition of the electrophile.

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(13) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(14) Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924.

(15) Millot, N.; Piazza, C.; Avolio, S.; Knochel, P. *Synthesis* **2000**, 941.

Extension of this exchange to other classes of functionalized α-perfluoroalkyl vinylmetal compounds is currently being studied in our laboratory.

In summary, we have developed a convenient preparation method for a new type **2** α-perfluoroalkyl carbanion reagent via iodine−magnesium exchange without the occurrence of defluorination, starting from isomerically pure (*Z*)-3-iodo-3-perfluoroalkylpropenoate. Species **2** magnesium was trapped with a range of electrophiles either directly or after transmetalation to the corresponding alkenylcopper to give excellent yields of a variety of polyfunctional compounds bearing a perfluoroalkyl group.

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Supporting Information Available: Experimental procedure, characterization data for **3**−**14**, and lists of the ^{1}H and/or ^{13}C chemical shifts of compounds **3**, **4a**, **6b**, **12a**, and **14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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