

PAPER

View Article Online
View Journal | View IssueCite this: *RSC Adv.*, 2017, 7, 56034

Lithium triethylborohydride-promoted generation of α,α -difluoroenolates from 2-iodo-2,2-difluoroacetophenones: an unprecedented utilization of lithium triethylborohydride†

Peng Peng,^a Jing-jing Wu,^{ID} ^{ab} Jun-qing Liang,^a Tian-yu Zhang,^a Jin-wen Huang^{ab} and Fan-hong Wu^{*a}

Received 4th November 2017

Accepted 4th December 2017

DOI: 10.1039/c7ra12130j

rsc.li/rsc-advances

Lithium triethylborohydride was found to promote the generation of α,α -difluoroenolates from 2-iodo-2,2-difluoroacetophenones, and applied to the synthesis of polyfluorinated β -hydroxy ketones via self-condensation or aldol reaction. The reaction indicates an unprecedented utilization of lithium triethylborohydride and provides novel access to the generation of α,α -difluoroenolates.

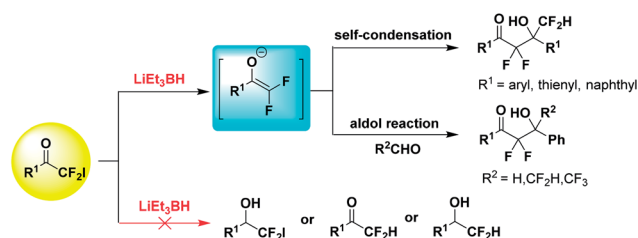
Difluoroenolates are useful fluorinated synthons for preparing difluoromethylene compounds,¹ with significant application in medicinal chemistry.² Accordingly, the protocols to generate difluoroenolates have attracted much attention. Colby firstly reported that compounds trifluoromethyl- α,α -difluoro- β -keto *gem*-diols could be used to give difluoroenolates by the release of trifluoroacetate.³ Additionally, more difluorinated compounds have been developed as valuable precursors of difluoroenolates, such as α,α -difluoroketones,⁴ α,α -difluoro- α -(trimethylsilylacet)amides,⁵ α,α -difluoro- β -ketoesters,⁶ α,α,α -trifluoroketones,⁷ and 2,2-difluoro-1,3-diketones.⁸ Furthermore, difluoroenoxyasilanes or difluoroenol *O*-Boc esters were often served as difluoroenolates in different difluoromethylation reactions,⁹ as well as transition-metal difluoroenolates.¹⁰

2-Iodo-2,2-difluoroacetophenones are one of the important building blocks to introduce α,α -difluoromethyl ketone fragment into molecules.¹¹ Our group has reported several reactions with 2-iodo-2,2-difluoroacetophenones to construct structurally diverse difluoromethylene compounds.^{11d-f} As part of our continued research, further structure modification of 2-iodo-2,2-difluoroacetophenones was investigated. Lithium triethylborohydride (LiEt_3BH , a superhydride, 1 M in THF) is a powerful reducing agent and can efficiently reduce a wide range of functional groups, especially halogen atoms.¹² However, the reaction with 2-iodo-2,2-difluoroacetophenones and LiEt_3BH result in the generation of difluoroenolates instead of reduction products. Herein, we disclosed the

LiEt_3BH -promoted *in situ* generation of difluoroenolates from 2-iodo-2,2-difluoroacetophenones and their application in aldol-type self-condensation and aldol reactions to give various α,α -difluoro- β -hydroxy ketones (Scheme 1).

Initially, we chose LiEt_3BH as one of the reducing agents to selectively reduce the carbonyl group or iodine atom of 2-iodo-2,2-difluoroacetophenones. Surprisingly, our initial attempt to perform the reaction between 2,2-difluoro-2-iodo-1-phenylethanone **1a** and LiEt_3BH at -78°C did not furnish any reduction product, instead leading to a self-adduct $\alpha,\alpha,\gamma,\gamma$ -tetrafluoro- β -hydroxy ketone **2a** with high yield (Table 1, entry 1). Raising the temperature of LiEt_3BH only led to a little increasing of the yield of reduction product **3a** and **4a** (entries 2 and 3). It was speculated that a difluoroenolate **5** was generated from 2,2-difluoro-2-iodo-1-phenylethanone with LiEt_3BH , then the difluoroenolate **5** went through protonation process to form α,α -difluoroacetophenone **6**. The aldol reaction between **5** and **6** gave the $\alpha,\alpha,\gamma,\gamma$ -tetrafluoro- β -hydroxy ketone **2a** (Scheme 2).

We wonder that whether the fluorine atom in 2-iodo-2,2-difluoroacetophenone play an important role in the fortuitous reaction. Therefore, the reaction of 2-halo-acetophenone or 2-chloro(bromo, fluoro)-2,2-difluoroacetophenone or 2,2-

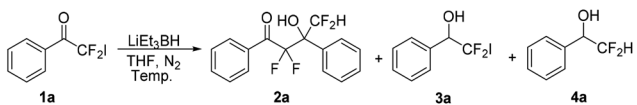


Scheme 1 The novel utilization of LiEt_3BH for the generation of α,α -difluoroenolates from 2-iodo-2,2-difluoroacetophenones.

^aSchool of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai 201418, China. E-mail: wfh@sit.edu.cn

^bKey Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra12130j

Table 1 The influence of temperature to reaction of 2,2-difluoro-2-iodo-1-phenylethanone with LiEt₃BH^a


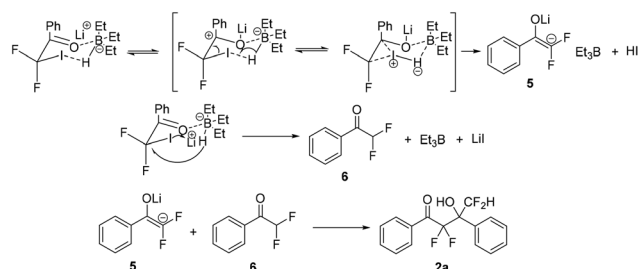
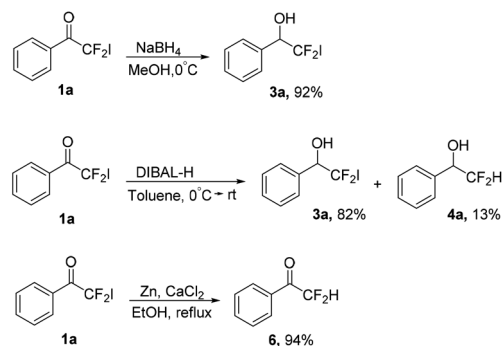
Entry	Temp.	Yield ^b (%)		
		2a	3a	4a
1	−78 °C	98.9	0.8	0.3
2	0 °C	43.9	6.9	49.2
3	rt	42.3	7.9	49.8

^a Reaction conditions: **1a** (1 mmol), LiEt₃BH (1.2 mmol, 1.2 equiv.), THF (dry), N₂, 4 h. ^b Yield based on GC.

difluoroacetophenone with LiEt₃BH were also performed in THF at −78 °C. The results showed that all these reduction reactions proceeded well leading to the formation of different reduction products (see Scheme 1 in ESI[†]), which demonstrates the specific characteristic of substrate 2-iodo-2,2-difluoroacetophenone owing to the adjacent fluorine atoms of carbonyl group.

Then, other reducing agents were also investigated using 2,2-difluoro-2-iodo-1-phenylethanone **1a** as substrate, only led to the formation of different reduction products (Scheme 3). It was noteworthy that the reducing agents sodium borohydride and Zn power show high selectivity, affording 2,2-difluoro-2-iodo-1-phenylethan-1-ol **3a** and 2,2-difluoro-1-phenylethanone **6** as major products separately.

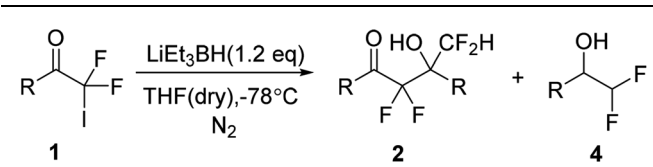
Next, the scope of 2,2-difluoro-2-iodo-1-phenylethanone **1** was explored through the LiEt₃BH promoted self-condensation (Table 2). The 2-iodo-2,2-difluoroacetophenones **1b–f** bearing electron-donating groups, electron-withdrawing group or halogen atoms, 2,2-difluoro-2-iodo-1-(thiophen-2-yl)ethanone **1g** and 2,2-difluoro-2-iodo-1-(naphthalen-2-yl)ethanone **1h** were subjected to the self-condensation reaction and all were found applicable to the reaction, giving the corresponding $\alpha,\alpha,\gamma,\gamma$ -tetrafluoro- β -hydroxy ketones **2a–h** in good yields. Few of the reduction products **4d**, **4f**, **4g** were still observed in low yields. The results indicated that 2-iodo-2,2-difluoroacetophenone derivatives bearing different aryl or heterocyclic ring could be served as difluoroenolates precursors

**Scheme 2** Proposed mechanism of LiEt₃BH-promoted aldol-type self-condensation.**Scheme 3** The reduction reactions of 2-iodo-2,2-difluoro-1-phenylethanone **1a**. ^aYield based on GC.

through the reaction with LiEt₃BH, which provided a novel and efficient access to difluoromethylation reactions.

α,α -Difluoro- β -hydroxy ketones are an important class of substructure in medicinal chemistry,¹³ which could be obtained *via* aldol reaction with difluoroenolates.¹⁴ Accordingly, to further demonstrate the utility of LiEt₃BH, aldol reaction of 2-iodo-2,2-difluoroacetophenones with aldehydes promoted by LiEt₃BH were conducted. 2-Iodo-2,2-difluoro-1-phenylethanone **1a** and benzaldehyde **7** was selected as model reaction substrates to optimize the reaction condition (Table 3). The corresponding aldol product **8** was produced in the presence of LiEt₃BH (1.2 equiv. to compound **1a**) at −78 °C in THF (entry 1). The results showed that raising the temperature led to an increased yield of reduction product **4a** (entries 2–4) and the conversion decreased with the decreasing of the amount of LiEt₃BH (entry 5).

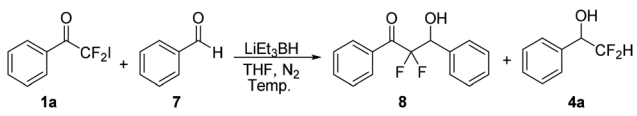
Hence, more aldol reactions were carried out under the optimized condition (Scheme 4). To our delight, the aldol products polyfluorinated β -hydroxy ketones were obtained in high yields by employing the fluorinated aldehydes such as 2,2-

Table 2 LiEt₃BH-promoted self-condensation of 2,2-difluoro-2-iodo-1-phenylethanones^a


Entry	R	Yield ^a (%)	
		2	4
1	Ph	2a , 86	4a , —
2	4-MeC ₆ H ₄	2b , 83	4b , —
3	4-BrC ₆ H ₄	2c , 85	4c , —
4	3-FC ₆ H ₄	2d , 72	4d , 20
5	4-ClC ₆ H ₄	2e , 87	4e , —
6	4-CF ₃ C ₆ H ₄	2f , 71	4f , 14
7	Thienyl	2g , 70	4g , 15
8	Naphthyl	2h , 84	4h , —

^a Isolated yields.



Table 3 The optimization of aldol reaction of 2-iodo-2,2-difluoroacetophenone **1a** and benzaldehyde **7**^a


Entry	LiEt ₃ BH (equiv.)	Temp.	Conv.(1a) ^b (%)	Yield ^b (%)	
				8	4a
1	1.2	−78 °C	100	95.2	4.8
2	1.2	−40 °C	100	85.2	14.8
3	1.2	0 °C	100	79.6	20.4
4	1.2	rt	100	74.7	25.3
5	1.0	−78 °C	91.6	90.1	9.9

^a Reaction conditions: **1a** (1.0 mmol), **7** (1.0 mmol), THF (dry), N₂, 4 h.^b Yield based on GC.

difluoro-1-phenylethanone or 2,2,2-trifluoro-1-phenylethanone (Scheme 4a and b). The substrate 1-(4-bromophenyl)-2,2-difluoro-2-iodoethan-1-one **1c** was also suitable for the aldol reaction (Scheme 4c). Furthermore, 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-phenylbutan-1-one **12** was also used to react with benzaldehyde in the present of LiEt₃BH. The reaction gave the aldol product 2,2-difluoro-3-hydroxy-1,3-diphenylpropan-1-one **8** and self-condensation product 2,2,4,4-tetrafluoro-3-hydroxy-1,3-diphenylbutan-1-one **2a** with 4 : 1 ratio (Scheme 4d), which indicated that difluoroenolate can be generated from 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-phenylbutan-1-one with LiEt₃BH either.

In summary, we have demonstrated an unprecedented utilization of LiEt₃BH for the generation of α,α-difluoroenolates from 2-iodo-2,2-difluoroacetophenones in THF. Applications of the protocol led to the synthesis of polyfluorinated β-hydroxy ketones *via* self-condensation reaction and aldol reaction. The effectiveness of LiEt₃BH was discussed by the variation of α-halogen acetophenones and reducing agents in the reduction reaction. It turned out that LiEt₃BH was served as a reducing agent with most α-halogen acetophenones, resulting in the formation of different reduction products. The result disclosed

the specific property of 2-iodo-2,2-difluoroacetophenones, which might due to that the fluorine atoms of 2-iodo-2,2-difluoroacetophenones have significant impact and change the property of the adjacent C–I bond. Further study to apply the protocol for the preparation of diverse difluoromethylene compounds are in progress in our laboratory.

Conflicts of interest

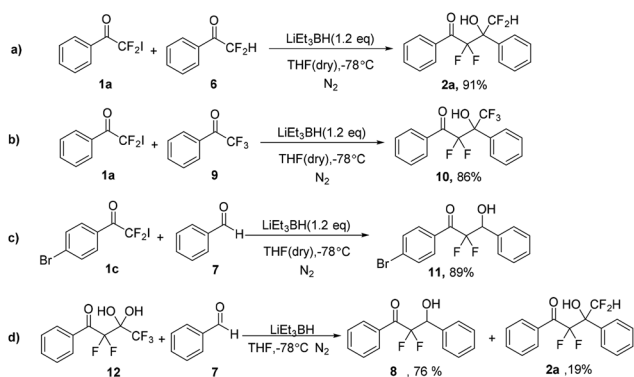
There are no conflicts to declare.

Acknowledgements

We are grateful for financial supports from the National Natural Science Foundation of China (No. 21472126, 21672151).

References

- (a) D. Stolz and U. Kazmaier, in *Chemistry of Metal Enolates*, ed. J. Zabicky, Wiley, London, 2009, p. 355; (b) B. M. Stoltz, N. B. Bennett, D. C. Duquette, A. F. G. Goldberg, Y. Liu, M. B. Loewinger and C. M. Reeve, in *Comprehensive Organic Synthesis II*, ed. P. Knochel and G. A. Molander, Elsevier, Oxford, 2014, vol. 3, p. 1.
- (a) J. Wang, M. Sánchezroselló, J. L. Aceña, P. C. Del, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (b) J. O. Link, J. G. Taylor, L. Xu, M. Mitchell, H. Guo, H. Liu, D. Kato, T. Kirschberg, J. Sun, N. Squires, J. Parrish, T. Keller, Z.-Y. Yang, C. Yang, M. Matles, Y. Wang, K. Wang, G. Cheng, Y. Tian, E. Mogalian, E. Mondou, M. Cornpropst, J. Perry and M. C. Desai, *J. Med. Chem.*, 2014, **57**, 2033; (c) F. Xue, H. Li, S. L. Delker, J. Fang, P. Martíásek, L. J. Roman, T. L. Poulos and R. B. Silverman, *J. Am. Chem. Soc.*, 2010, **132**, 14229; (d) M. O. Anderson, J. Zhang, Y. Liu, C. Yao, P.-W. Phuan and A. S. Verkman, *J. Med. Chem.*, 2012, **55**, 5942.
- (a) C.-H. Han, E. H. Kim and D. A. Colby, *J. Am. Chem. Soc.*, 2011, **133**, 5802; (b) C.-H. Han, A. E. Salyer, E. H. Kim, X.-Y. Jiang, R. E. Jarrard, M. S. Powers, A. M. Kirchhoff, T. K. Salvador, J. A. Chester, G. H. Hockerman and D. A. Colby, *J. Med. Chem.*, 2013, **56**, 2456; (c) R. A. Hazlitt, Q.-L. Tran, M. F. Sowaileh and D. A. Colby, *J. Org. Chem.*, 2017, **82**, 2231; (d) R. A. Hazlitt, J. P. John, Q.-L. Tran and D. A. Colby, *Tetrahedron Lett.*, 2016, **57**, 1906.
- S. Ge, W. Chaladaj and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 4149.
- Q. Chen, J. Zhou, Y. Wang, C. Wang, X. Liu, Z. Xu, L. Lin and R. Wang, *Org. Lett.*, 2015, **17**, 4212.
- M. Yang, D. L. Orsi and R. A. Altman, *Angew. Chem., Int. Ed.*, 2015, **54**, 2361.
- R. Doi, M. Ohashi and S. Ogoshi, *Angew. Chem., Int. Ed.*, 2016, **55**, 341.
- J.-L. Qian, W.-B. Yi, X. Huang, J. P. Jasinski and W. Zhang, *Adv. Synth. Catal.*, 2016, **358**, 2811.
- (a) Y.-L. Liu and J. Zhou, *Chem. Commun.*, 2012, **48**, 1919; (b) Y.-L. Liu, X.-P. Zeng and J. Zhou, *Chem.-Asian J.*, 2012, **7**, 1759; (c) J.-S. Yu, Y.-L. Liu, J. Tang, X. Wang and J. Zhou,

**Scheme 4** The aldol reactions promoted by LiEt₃BH.

- Angew. Chem., Int. Ed.*, 2014, **53**, 9512; (d) S. Sasaki, T. Suzuki, T. Uchiya, S. Toyota, A. Hirano, M. Tanemura, H. Teramoto, T. Yamauchi and K. Higashiyama, *J. Fluorine Chem.*, 2016, **192**, 78.
- 10 (a) R. Doi, M. Ohashi and S. Ogoshi, *Angew. Chem., Int. Ed.*, 2016, **55**, 341; (b) R. Doi, K. Kikushima, M. Ohashi and S. Ogoshi, *J. Am. Chem. Soc.*, 2015, **137**, 3276; (c) P. V. Ramachandran and A. Chatterjee, *Org. Lett.*, 2008, **10**, 1195.
- 11 (a) Z.-M. Qiu and D. J. Burton, *Tetrahedron Lett.*, 1993, **34**, 3239; (b) K. C. Kwak, H. Oh, Y. G. Yun, B. H. Kim, Y. H. Lee and K. Y. Chai, *Bull. Korean Chem. Soc.*, 2002, **23**, 157; (c) Z.-M. Qiu and D. J. Burton, *J. Org. Chem.*, 1995, **60**, 6798; (d) J.-X. Wang, J.-J. Wu, H. Chen, S.-W. Zhang and F.-H. Wu, *Chin. Chem. Lett.*, 2015, **26**, 1381; (e) D.-F. Wang, J.-J. Wu, J.-W. Huang, J.-Q. Liang, P. Peng, H. Chen and F.-H. Wu, *Tetrahedron*, 2017, **73**, 3478; (f) H. Chen, J.-X. Wang, J.-J. Wu, Y.-J. Kuang and F.-H. Wu, *J. Fluorine Chem.*, 2017, **200**, 41.
- 12 (a) S. Krishnamurthy, R. M. Schubert and H. C. Brown, *J. Am. Chem. Soc.*, 1973, **75**, 8486; (b) S. Krishnamurthy and H. C. Brown, *J. Am. Chem. Soc.*, 1973, **95**, 1669; (c) F.-P. Liang, H. W. Schmalle and H. Berke, *Eur. J. Inorg. Chem.*, 2006, 5081; (d) J.-J. Wu and S. Cao, *ChemCatChem*, 2011, **3**, 1582; (e) S. Chowdhury and R. F. Standaert, *J. Org. Chem.*, 2016, **81**, 9957; (f) L. Silva, R. F. Affeldt and D. S. Lüdtkke, *J. Org. Chem.*, 2016, **81**, 5464; (g) B. Denolf, E. Leemans and N. De Kimpe, *J. Org. Chem.*, 2007, **72**, 3211; (h) H. Tanaka and K. Ogasawara, *Tetrahedron Lett.*, 2002, **43**, 4417.
- 13 (a) C.-H. Han, A. E. Salyer, E. H. Kim, X.-Y. Jiang, R. E. Jarrard, M. S. Powers, A. M. Kirchhoff, T. K. Salvador, J. A. Chester, G. H. Hockerman and D. A. Colby, *J. Med. Chem.*, 2013, **56**, 2456; (b) M.-H. Yang, J. R. Hunt, N. Sharifi and R. A. Altman, *Angew. Chem., Int. Ed.*, 2016, **55**, 9080; (c) A. M. Doherty, I. Sircar, B. E. Kornberg, J. Quinlll, R. Thomas Winters, J. S. Kaltenbronn, M. D. Taylor, B. L. Batley and S. R. Rapundalo, *J. Med. Chem.*, 1992, **35**, 2.
- 14 (a) P. Zhang and C. Wolf, *J. Org. Chem.*, 2012, **77**, 8840; (b) P. Zhang and C. Wolf, *Angew. Chem., Int. Ed.*, 2013, **52**, 7869; (c) C. Xie, L.-M. Wu, H.-B. Mei, V. A. Soloshonok, J.-L. Han and Y. Pan, *Tetrahedron Lett.*, 2014, **55**, 5908; (d) H.-B. Mei, C. Xie, J. L. Aceña, V. A. Soloshonok, G.-L. Röschenthaler and J.-L. Han, *Eur. J. Org. Chem.*, 2015, 6401.

