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Wittig *gem*-difluoroolefination of aldehydes with difluoromethyltriphenylphosphonium bromide

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ABSTRACT

Wittig reaction of aldehydes with difluoromethyltriphenylphosphonium bromide leading to *gem*-difluoroolefins in moderate yields is described. The reaction displays a good substrate scope including aryl, heteroaryl and α,β-unsaturated aldehydes. Difluoromethyltriphenylphosphonium bromide could be easily prepared and stored for a long time under air atmosphere. The salt exhibits high thermal stability demonstrated by thermogravimetric analysis. Its structure was confirmed by NMR spectroscopy and single crystal X-ray analysis.

1. Introduction

The introduction of fluorine or fluorine-containing functional groups usually furnishes the target molecules with unique physical, chemical and biological properties [1–4]. As an important class of fluorinated compounds, *gem*-difluoroolefins have been widely used in a variety of research areas, such as medical and agricultural chemistry and material sciences [5–10]. Due to their versatility, intense research efforts have been directed toward the exploration of applicable protocols for the construction of *gem*-difluorovinylidene moiety (CF_2=C) [11–22]. Previously, we have shown that decarboxylative Witting reaction and Julia–Kocienski reaction are quite efficient for the synthesis of *gem*-difluoroolefins under mild conditions [23,24]. In the study on the decarboxylative Wittig reaction, we found difluoromethylene phosphonium ylide could be generated *in situ* from the decarboxylation of difluoromethylene phosphobetaine without the presence of base [23]. We speculated that deprotonation of difluoromethyltriphenylphosphonium salt might also lead to the *in situ* formation of difluoromethylene phosphonium ylide, which could undergo Wittig reaction with carbonyl compounds. Even though the synthesis of difluoromethyltriphenylphosphonium salt has been reported [25–28], its reactivity has been largely unexplored. As part of our continuing research interest in ylide chemistry [23,24,29], we have now investigated the Wittig *gem*-difluoroolefination of aldehydes with difluoromethyltriphenylphosphonium bromide in the presence of base.

2. Results and discussion

Difluoromethyltriphenylphosphonium bromide was easily prepared *via* a quaternization reaction of triphenylphosphine with trimethylsilyl bromodifluoroacetate, which could be synthesized on a large scale from bromodifluoroacetate in a 2-step sequence, and the subsequent desilylation and decarboxylation in the presence of TBAF (tetra-*n*-butylammonium fluoride) (Scheme 1). The structure of the salt was confirmed by NMR spectroscopy and single crystal X-ray analysis [30]. Difluoromethyltriphenylphosphonium bromide is stable to air and water, and exhibits high thermal stability demonstrated by thermogravimetric analysis (T_d = 223 °C).

With the stable salt in hand, we then investigated its application as an ylide precursor in Wittig *gem*-difluoroolefination with 4-phenylbenzaldehyde. The desired reaction performed at rt in DMF by employing DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (2 equiv.) as the base was observed, even though the yield was quite low (entry 1, Table 1). Other bases including organic bases and inorganic bases were not effective for this reaction (entries 2–7). Elevating the reaction temperature to 50 °C

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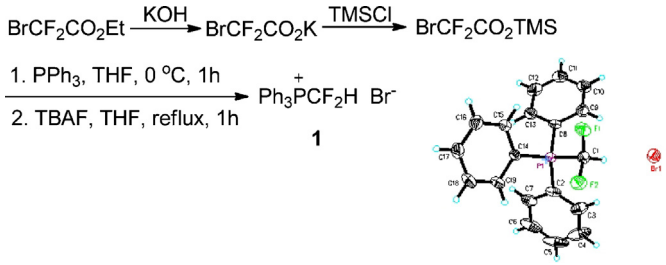


Scheme 1. The preparation of difluoromethyltriphenylphosphonium bromide.

improved the yield significantly (entry 8), but further elevation of temperature resulted in inferior results (entries 9 and 10). The examination of solvent effect revealed that solvent is quite important for the reaction (entries 11–16). The reactions in DMF and in DMSO gave the same result (entry 8 and 11). The yield was increased with the increasing of molar ratio of **1**:base:aldehyde to 3:3:1 (entry 17). Shortening the reaction time from 12 h to 4 h did not influence the yield (entry 18 *vs.* 17). The effect of molar ratio of **1**:base:aldehyde on the reaction proceeding for 4 h was further examined (entries 19–22). It was found that the ratio of 3:3:1 was quite efficient for the desired conversion (entry 18).

Then a variety of carbonyl compounds were tested for their suitability for use in this *gem*-difluoroolefination under the optimal reaction conditions (entry 18, Table 1). As shown in Scheme 2, the reaction displayed a good tolerance toward different electron-donating and -withdrawing groups on the aryl ring, giving the desired difluoroolefinated products in moderate yields (**2a**–**2h**). The reaction proceeded equally well for heteroaromatic substrates (**2i**–**2j**). In the case of α,β-unsaturated aldehyde, only low yield was obtained (**2k**). The reaction is not applicable for ketone.

3. Conclusion

In conclusion, we have described the Wittig *gem*-difluoroolefination of aldehydes with difluoromethyltriphenylphosphonium bromide in the presence of DBU, giving the corresponding products in moderate yields. Difluoromethyltriphenylphosphonium bromide could be easily prepared and exhibits high thermal stability. Further studies on the reactivity of difluoromethyltriphenylphosphonium bromide are currently underway.

4. Experimental

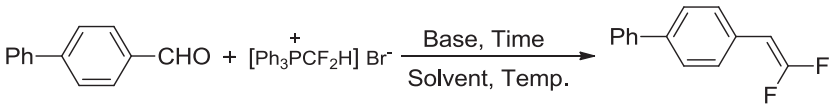
4.1. The procedure for the synthesis of difluoromethyltriphenylphosphonium bromide (*1*)

Into the solution of KOH (56 g, 1 mol) in methanol (500 mL) was slowly added $BrCF_2CO_2Et$ (203 g, 1 mol) at room temperature. The resulting mixture was stirred at the same temperature until $BrCF_2CO_2Et$ was completely consumed. The solvent was removed by concentration to give $BrCF_2CO_2K$ as a solid (202 g, 95%).

The mixture of $BrCF_2CO_2K$ (21.3 g, 100 mmol) and TMSCl (44 mL, 500 mmol) was refluxed until $BrCF_2CO_2K$ was completely consumed. Distillation gave $BrCF_2CO_2SiMe_3$ as a liquid (22.1 g, 90%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.40 (s, 9H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.36 (s, 2F).

Into the solution of PPh_3 (3.93 g, 15 mmol) in THF (30 mL) was added $BrCF_2CO_2SiMe_3$ (2.47 g, 10 mmol) in 1 h at 0 °C under N_2. The mixture was stirred for another 1 h. The solution of TBAF

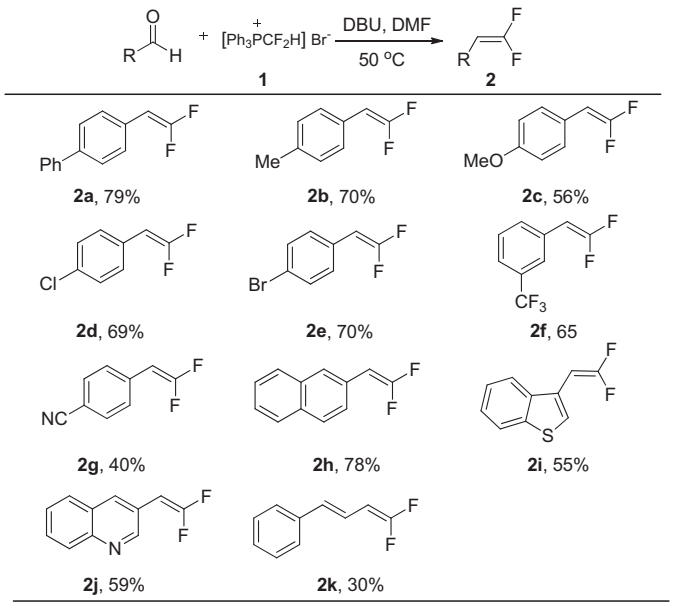
Table 1
Optimization of reaction conditions for *gem*-difluoroolefination.[a]



1 2a

Entry	Base	Solvent	Temp. (°C)	Time (h)	**2a** (%)[b]
1	DBU	DMF	r.t.	12	13
2	$^{i}Pr_2NH$	DMF	r.t.	12	ND
3	Et_3N	DMF	r.t.	12	ND
4	Et_2NH	DMF	r.t.	12	ND
5	t-BuOK	DMF	r.t.	12	8
6	KOH	DMF	r.t.	12	ND
7	K_2CO_3	DMF	r.t.	12	ND
8	DBU	DMF	50	12	60
9	DBU	DMF	80	12	50
10	DBU	DMF	100	12	46
11	DBU	DMSO	50	12	60
12	DBU	DMAc	50	12	N.R.
13	DBU	THF	50	12	11
14	DBU	DCE	50	12	20
15	DBU	Toluene	50	12	15
16	DBU	Xylene	50	12	20
17[c]	DBU	DMF	50	12	84
18[c]	DBU	DMF	50	4	84
19[d]	DBU	DMF	50	4	38
20[e]	DBU	DMF	50	4	68
21[f]	DBU	DMF	50	4	60
22[g]	DBU	DMF	50	4	ND

[a] Reaction conditions: 4-phenylbenzaldehyde (0.2 mmol), **1** (0.4 mmol) and base (0.4 mmol) in solvent (2 mL).
[b] Determined by ^{19}F NMR.
[c] 0.6 mmol of **1** and 0.6 mmol of base were used.
[d] 0.2 mmol of **1** and 0.2 mmol of base were used.
[e] 0.8 mmol of **1** and 0.8 mmol of base were used.
[f] 0.6 mmol of **1** and 0.3 mmol of base were used.
[g] 0.6 mmol of **1** and 1.2 mmol of base were used.



Scheme 2. *gem*-Difluoroolefination of aldehydes. Reaction conditions: aldehyde (0.2 mmol), salt **1** (0.6 mmol) and DBU (0.6 mmol) (molar ratio of aldehyde:**1**:DBU was 1:3:3) in DMF (2 mL) at 50 °C for 4 h. Isolated yields.

(tetra-*n*-butylammonium fluoride, 10 mL, 1 M) was added. The resulting mixture was refluxed for 1 h. The crude product precipitated as a solid. After filtration, the solid was washed with THF (40 mL) and Et_2O (40 mL) to give the pure product as a white solid (3.34 g, 85%). M.P. = 184 °C; T_d = 223 °C; ^{1}H NMR (400 MHz, DMF) δ 9.50 (td, J = 46.6, 29.6 Hz, 1H), 8.16–8.06 (m, 9H), 7.99–7.90 (m, 6H). ^{19}F NMR (376 MHz, DMF) δ −127.78 (dd, J = 77.9, 46.6 Hz, 2F). ^{31}P NMR (162 MHz, DMF) δ 19.29 (t, J = 77.9 Hz, 1P).

4.2. Typical procedure for gem-difluoroolefination

Into the mixture of difluoromethyltriphenylphosphonium bromide (236 mg, 0.6 mmol), aldehyde (0.2 mmol) and DBU (90 μL, 0.6 mmol) was added DMF (2 mL) under N_2. The resulting mixture was stirred at 50 °C for 4 h. After being cooled to room temperature, the solution was diluted with CH_2Cl_2 (10 mL) and washed with water (5 mL × 2). The organic phase was dried over sodium sulfate. The solvent was removed by concentration and the residue was subjected to column chromatography to give the pure product.

4-(2,2-Difluorovinyl)-1,1′-biphenyl (**2a**): 79% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.54 (m, 4H), 7.48–7.30 (m, 5H), 5.31 (dd, J = 26.3, 3.6 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.78 (dd, J = 30.4, 26.3 Hz, 1F), −83.72 (dd, J = 30.4, 3.6 Hz, 1F).

1-(2,2-Difluorovinyl)-4-methylbenzene (**2b**): 70% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 5.24 (dd, J = 26.4, 3.9 Hz, 1H), 2.34 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −83.06 (dd, J = 33.6, 26.4 Hz, 1F), −85.20 (dd, J = 33.6, 3.9 Hz, 1F).

1-(2,2-Difluorovinyl)-4-methoxybenzene (**2c**): 56% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.23 (dd, J = 26.4, 3.8 Hz, 1H), 3.82 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −84.56 (dd, J = 36.7, 26.4 Hz, 1F), −86.36 (dd, J = 36.7, 3.8 Hz, 1F).

1-Chloro-4-(2,2-difluorovinyl)benzene (**2d**): 69% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 5.24 (dd, J = 25.9, 3.7 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.54 (dd, J = 29.7, 25.9 Hz, 1F), −83.36 (dd, J = 29.7, 3.7 Hz, 1F).

1-Bromo-4-(2,2-difluorovinyl)benzene (**2e**): 70% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 5.23 (dd, J = 26.0, 3.4 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.20 (dd, J = 29.1, 26.0 Hz, 1F), −83.05 (dd, J = 29.1, 3.4 Hz, 1F).

1-(2,2-Difluorovinyl)-3-(trifluoromethyl)benzene (**2f**): 65% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.54–7.39 (m, 3H), 5.31 (dd, J = 25.6, 3.3 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.02 (s, 3F), −80.43 to −80.73 (m, 1F), −82.30 (dd, J = 27.2, 3.3 Hz, 1F).

4-(2,2-Difluorovinyl)benzonitrile (**2g**): 40% yield; 1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 5.33 (dd, J = 25.5, 3.3 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.89 (dd, J = 25.5, 20.6 Hz, 1F), −79.54 (dd, J = 20.6, 3.3 Hz, 1F).

2-(2,2-Difluorovinyl)naphthalene (**2h**); 78% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.70 (m, 4H), 7.54–7.40 (m, 3H), 5.42 (dd, J = 26.4, 3.6 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.86 (dd, J = 30.7, 26.4 Hz, 1F), −83.59 (dd, J = 30.7, 3.6 Hz, 1F).

3-(2,2-Difluorovinyl)benzo[b]thiophene (**2i**): 55% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.51–7.33 (m, 3H), 5.60 (dd, J = 25.8, 1.7 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.67 (t, J = 25.8 Hz, 1F), −84.51 (dd, J = 25.8, 1.7 Hz, 1F).

3-(2,2-Difluorovinyl)quinolone (**2j**): 59% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 2.0 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.69 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.57–7.52 (m, 1H), 5.45 (dd, J = 26.2, 3.0 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.60 (t, J = 25.8 Hz), −80.96 (dd, J = 25.3, 3.0 Hz).

(*E*)-(4,4-Difluorobuta-1,3-dien-1-yl)benzene (**2k**): 30% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5H), 6.66 (dd, J = 15.9, 10.8 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 5.14 (dd, J = 24.1, 10.8 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −85.13 to −85.37 (m, 1F), −86.97 (d, J = 26.4 Hz, 1F).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2014.04.011.

References

[1] P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, Wiley-VCH, Weinheim, Germany, 2004.
[2] A.M. Thayer, Chem. Eng. News 84 (2006) 15–24.
[3] S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320–330.
[4] X.-L. Qiu, X. Yue, F.-L. Qing, Fluorine-containing chiral drugs, in: G.-Q. Lin, Q.-D. You, J.-F. Cheng (Eds.), Chiral Drugs, John Wiley & Sons, Inc., Hoboken, NJ, 2011, pp. 195–252.
[5] I.A. McDonald, J.M. Lacoste, P. Bey, M.G. Palfreyman, M. Zreika, J. Med. Chem. 28 (1985) 186–193.
[6] T. Kato, S. Matsui, H. Takeuchi, Y. Kubo, E. Nakagawa, EP1170352A2, 2002.
[7] P.M. Weintraub, A.K. Holland, C.A. Gates, W.R. Moore, R.J. Resvick, P. Bey, N.P. Peet, Bioorg. Med. Chem. 11 (2003) 427–431.
[8] J.-M. Altenburger, G.Y. Lassalle, M. Matrougui, D. Galtier, J.-C. Jetha, Z. Bocskei, C.N. Berry, C. Lunven, J. Lorrain, J.-P. Herault, P. Schaeffer, S.E. O'Connor, J.-M. Herbert, Bioorg. Med. Chem. 12 (2004) 1713–1730.
[9] P. Maienfisch, R.G. Hall, Chimia 58 (2004) 93–99.
[10] T. Pitterna, M. Boeger, P. Maienfisch, Chimia 58 (2004) 108–116.
[11] M.J. Tozer, T.F. Herpinb, Tetrahedron 52 (1996) 8619–8683.
[12] D. Burton, Z.-Y. Yang, W. Qiu, Chem. Rev. 96 (1996) 1641–1716.
[13] J. Ichikawa, J. Fluorine Chem. 105 (2000) 257–263.
[14] G. Chelucci, Chem. Rev. 112 (2012) 1344–1462.
[15] G.K.S. Prakash, Y. Wang, J. Hu, G.A. Olah, J. Fluorine Chem. 126 (2005) 1361–1367.
[16] N. Ireneusz, J.R. Morris, Org. Lett. 7 (2005) 721–724.
[17] J. Ichikawa, R. Nadano, N. Ito, Chem. Commun. (2006) 4425–4427.

[18] L. Zhang, Y. Li, J. Hu, J. Fluorine Chem. 128 (2007) 755–761.
[19] T.M. Gøgsig, L.S. Søbjerg, A.T. Lindhardt, K.L. Jensen, T. Skrydstrup, J. Org. Chem. 73 (2008) 3404–3410.
[20] T. Miura, Y. Ito, M. Murakami, Chem. Lett. 37 (2008) 1006–1007.
[21] Y. Zhao, W. Huang, L. Zhu, J. Hu, Org. Lett. 12 (2010) 1444–1447.
[22] C.S. Thomoson, H. Martinez, W.R. Dolbier Jr., J. Fluorine Chem. 150 (2013) 53–59.
[23] J. Zheng, J. Cai, J.-H. Lin, Y. Guo, J.-C. Xiao, Chem. Commun. 49 (2013) 7513–7515.
[24] X.-P. Wang, J.-H. Lin, J.-C. Xiao, X. Zheng, Eur. J. Org. Chem. 2014 (2014) 928–932.
[25] D.J. Burton, D.G. Naae, R.M. Flynn, B.E. Smart, D.R. Brittelli, J. Org. Chem. 48 (1983) 3616–3618.
[26] S.-Z. Zhu, Q.-C. Huang, K. Wu, Inorg. Chem. 33 (1994) 4584–4585.
[27] G.K.S. Prakash, C. Weber, S. Chacko, G.A. Olah, Org. Lett. 9 (2007) 1863–1866.
[28] G.K.S. Prakash, Z. Zhang, F. Wang, C. Ni, G.A. Olah, J. Fluorine Chem. 132 (2011) 792–798.
[29] J. Zheng, J.-H. Lin, J. Cai, J.-C. Xiao, Chem. Eur. J. 19 (2013) 15261–15266.
[30] Summary of Data CCDC 973494.