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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 9279–9281

Base-catalyzed cyclization of monofluorodienynes: a new route to substituted fluorobenzene derivatives

Yi Wang and Donald J. Burton*

Department of Chemistry, University of Iowa, Iowa City, IA 52242, USA

Received 18 October 2006; accepted 20 October 2006

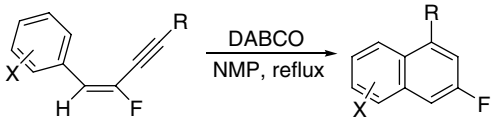
Abstract—The Sonogashira reaction of 1-bromo-1-fluoro-4-phenyl-1,3-butadienes and terminal alkynes, followed by cyclization in the presence of DABCO in refluxing NMP affords fluorinated benzene derivatives site-specifically in good yields.

Due to the unique properties of fluorine, organofluorine compounds have attracted increasing interest in the areas of polymer chemistry, pharmaceutical chemistry, and agricultural chemistry.[1,2] Fluorinated aromatic compounds have been of interest to us because of the growing demand of these compounds as pharmaceutical and agricultural agents and the lack of efficient synthetic methodologies.[3–5]

There are limited methodologies for the preparation of mono-fluorinated aromatic compounds. The Balz–Schiemann reaction[6,7] suffers from hazardous starting diazonium salts, intolerance of certain functional groups and tarry byproducts. Other methods utilizing electrophilic fluorination of aromatic compounds often give regioisomeric mixtures.[8–12] Sanford and co-workers recently reported a palladium-catalyzed fluorination of C–H bonds under microwave irradiation.[13] However, the presence of a pyridine or quinoline group as the directing group was required in the substrate.

Recently, we reported a site-specific preparation of fluorinated naphthalene and phenanthrene derivatives via a novel base-catalyzed cyclization of (*E*)-monofluoroenynes[14,15] (Scheme 1).

In this work, we demonstrated that 1-aryl-2-fluoroenynes afforded the cyclized products via attack on the π system of the substituted aryl ring. If cyclization could occur on a simple olefinic π system of dienynes, a new methodology for the preparation of fluorobenzene derivatives could be achieved. The only cyclizations of dienynes were reported by Hopf[16] and Zimmermann.[17,18] Hopf and Musso obtained ~50% of benzene via flow pyrolysis of *cis*-1,3-hexadien-5-yne at 274 °C. In addition to benzene, ca. 20% of a high-boiling mixture containing at least 15 components was isolated.[16] Zimmermann reported a similar work with various 1,3-hexadien-5-ynes under different thermal conditions.[18] His results indicated that three types of radical mechanisms can account for the complex reaction behavior (depending on distinct temperature ranges). Thus, although Hopf and Zimmermann documented the first reports of cyclization of dienynes to form aromatic hydrocarbons, the methodology was not selective for any one aromatic derivative, achieved only under high temperature conditions, and not an overall useful preparative procedure. Since our base-catalyzed cyclization process is mechanistically different than the previous reported radical cyclization work,[18] we were thus encouraged to attempt our base-catalyzed cyclization with a simple olefinic π system as the terminus for cyclization. We chose 1-phenyl-1,3-dien-5-ynes as the model system to demonstrate the utility of the base-catalyzed route to fluorobenzene derivatives.



Scheme 1. Cyclization of 1-aryl-2-fluoroenynes.

Keywords: Cyclization; Biphenyls; Dienynes; Fluorinated benzene derivatives.
* Corresponding author. Tel.: +1 319 335 1363; fax: +1 319 335 1270; e-mail: donald-burton@uiowa.edu

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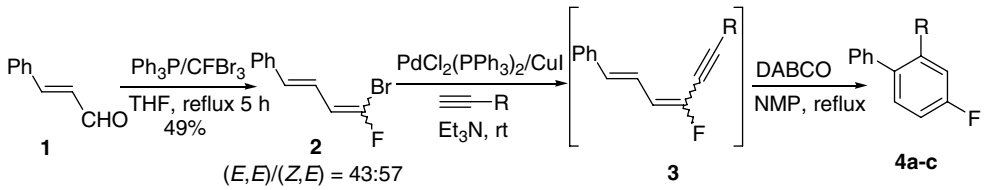
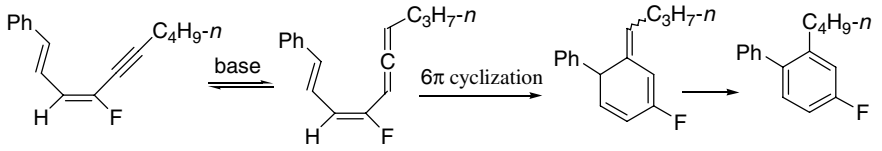
doi:10.1016/j.tetlet.2006.10.100

Table 1. Cyclization of fluorinated dienynes



Entry	R	Time (h)	Product	Isolated yield [a,b] (%) (two steps)
1	*n*-C_4H_9	6.5	**4a**	72
2	*n*-C_5H_{11}	5.5	**4b**	71
3	$PhCH_2CH_2$	5.5	**4c**	85

[a] Based on the (*Z*,*E*)-1-bromo-1-fluoro-4-phenyl-1,3-butadiene **2**.
[b] All of the products gave satisfactory ^1H, ^{19}F, ^{13}C NMR, and HRMS data.



Scheme 2. Proposed mechanism for the formation of **4a**.

trans-Cinnamaldehyde **1** was employed as the starting material, which reacted with $CFBr_3$ and 2 equiv Ph_3P in THF[19] to afford a mixture of (*E*,*E*)- and (*Z*,*E*)-1-bromo-1-fluoro-4-phenyl-1,3-butadienes **2** in a 49% yield ((*E*,*E*)/(*Z*,*E*) = 43:57).[20] The ratio of the two isomers was determined by integrations of the vinyl fluorine in the ^{19}F NMR spectrum of **2**. The Sonogashira reaction[21] of the mixture of **2** with terminal alkynes in Et_3N gave the corresponding dienynes **3**, which were utilized directly in the next step.

The reaction of **3** and 6 equiv of DABCO in refluxing NMP yielded 2-substituted-4-fluorobiphenyls **4a**–**c** in good yields.[22] Note that the yields were calculated from two steps and were based on the (*Z*,*E*)-1-bromo-1-fluoro-1,3-butadiene in the mixture **2**. These results are summarized in Table 1.

Similar to the mechanism proposed in our previous report,[14] the reaction pathway is illustrated in Scheme 2. First, the base catalyzes the isomerization of the dienyne to the allene, which undergoes a 6π cycloaddition to form a cyclized intermediate. The final product could be formed consequently due to the favorable formation of the aromatic ring.

In conclusion, we have demonstrated that a simple olefinic π system can serve as the terminus of attack in the cyclization of 1-subsituted-1,3-dien-5-ynes and can provide a new synthetic entry to substituted fluorinated benzene derivatives. This site-specific cyclization gives only the aryl derivatives in good yields and it can be achieved under relatively mild reaction conditions. Our work continues to explore the overall scope of this novel base-catalyzed cyclization process.

Acknowledgment

The authors thank the National Science Foundation for financial support.

Supplementary data

Supplementary data contains copies of ^1H, ^{19}F and ^{13}C NMR spectra of compounds **2** and **4a**–**c**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.100.

References and notes

1. *Organofluorine Chemistry: Principle and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994.
2. *Organofluorine Chemicals and Their Industrial Applications*; Banks, R. E., Ed.; Ellis Horwood Ltd.: Chichester, 1979.
3. Meio, G. D.; Morgan, J.; Pinhey, J. T. *Tetrahedron* **1993**, *49*, 8129–8138.
4. Diorazio, L. J.; Widdowson, D. A.; Clough, J. M. *Tetrahedron* **1992**, *48*, 8073–8088.
5. Tagat, J. R.; McCombie, S. W.; Nazareno, D.; Boyle, C. D.; Kozlowski, J. A.; Chackalamannil, S.; Josien, H.; Wang, Y.; Zhou, G. *J. Org. Chem.* **2002**, *67*, 1171–1177.
6. Balz, G.; Schiemann, G. *Chem. Ber.* **1927**, *60*, 1186–1190.
7. Roe, A. *Org. React.* **1949**, *5*, 193–228.
8. Poss, A. J.; Shia, G. A. *Tetrahedron Lett.* **1999**, *40*, 2673–2676.
9. Lerman, O.; Tor, Y.; Rozen, S. *J. Org. Chem.* **1981**, *46*, 4629–4631.
10. Stavber, S.; Zupan, M. *J. Chem. Soc., Chem. Commun.* **1981**, 148.

11. Shamma, T.; Buchholz, H.; Prakash, G. K. S.; Olah, G. A. *Isr. J. Chem.* **1999**, *39*, 207–210.
12. Chambers, R. D.; Holling, D.; Sandford, G.; Batsanov, A. S.; Howard, J. A. K. *J. Fluorine Chem.* **2004**, *125*, 661–671.
13. Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134–7135.
14. Xu, J.; Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 2555–2558.
15. Wang, Y.; Xu, J.; Burton, D. J. *J. Org. Chem.* **2006**, *71*, 7780–7784.
16. Hopf, H.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 680.
17. Schulz, K.; Hofmann, J.; Findeisen, M.; Zimmermann, G. *Eur. J. Org. Chem.* **1998**, 2135–2142.
18. Zimmermann, G. *Eur. J. Org. Chem.* **2001**, 457–471.
19. Vanderhaar, R. W.; Burton, D. J.; Naae, D. G. *J. Fluorine Chem.* **1971/72**, *1*, 381–383.
20. *Preparation of* (*E*,*E*)- *and* (*Z*,*E*)-*1-bromo-1-fluoro-4-phenyl-1,3-butadienes* **2**: A three necked flask (50 mL) equipped with a stirring bar, a cold water condenser and N_2 tee was charged with *trans*-cinnamaldehyde (0.60 mL, 4.76 mmol), $CFBr_3$ (0.70 mL, 7.14 mmol), PPh_3 (2.62 g, 10 mmol) and 10 mL of THF. The mixture was refluxed for 6 h, then cooled to room temperature, poured into 100 mL of hexane and filtered. After the solvent of the filtrate was removed by rotary evaporation, the residue was subjected to column chromatography (100% hexanes as the eluent) and 0.53 g of a colorless oil was obtained (49% yield), (*E*,*E*)/(*Z*,*E*) = 43:57. ^{19}F NMR ($CDCl_3$) δ −71.3 (d, J = 12.9 Hz, F in major product), −72.5 (d, J = 30.3 Hz, F in minor product) ppm; ^{1}H NMR ($CDCl_3$) δ 7.43–7.22 (m, ArH), 6.86 (ddd, J = 15.9, 11.0, 1.2 Hz, 3-H in minor product), 6.67–6.55 (m, 3-H and 4-H in major product), 6.49 (d, J = 15.8 Hz, 4-H in minor product), 6.33 (ddd, J = 12.9, 11.7, 2.9 Hz, 2-H in major product), 5.85 (ddd, J = 29.4, 11.0, 0.6 Hz, 2-H in minor product) ppm; HRMS Calcd 227.9773 for $C_{10}H_8{}^{81}BrF$. Found 227.9773.
21. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
22. *Typical procedure for the preparation of* **4a**–**c**: A 10 mL round bottom flask equipped with stirring bar was charged with $PdCl_2$ $(PPh_3)_2$ (40 mg, 0.057 mmol) and 3 mL of Et_3N. A mixture of (*E*,*E*)- and (*Z*,*E*)-1-bromo-1-fluoro-4-phenyl-1,3-butadienes **2** (400 mg, containing 1.0 mmol of the (*Z*,*E*) isomer) was added. The mixture was stirred for 10 min and the terminal alkyne (1.2 mmol) was added. Then CuI (10 mg, 0.050 mmol) was added and the reaction mixture was stirred at room temperature for 48 h. After the reaction was completed (the progress of the reaction was monitored by ^{19}F NMR), the mixture was directly poured onto a silica gel column (100% hexanes as the eluent) and the monofluorodienyne was obtained. The dienyne was used directly in the next step. An oven dried 10 mL round-bottom flask equipped with a stirring bar and a cold water condenser was charged with DABCO (0.67 g, 6 mmol) and NMP (4 mL) and monofluorodienyne (1 mmol). Then the mixture was refluxed for about 5.5–6.5 h. When the reaction was completed, the mixture was cooled to room temperature and poured onto a silica gel column (100% hexanes as the eluent) and the pure product was obtained. 2-Butyl-4-fluorobiphenyl (**4a**): ^{19}F NMR ($CDCl_3$) δ −116.4 (m) ppm; ^{1}H NMR ($CDCl_3$) δ 7.42–7.24 (m, 5H), 7.14 (dd, J = 8.4, 6.0 Hz, 1H), 6.98 (dd, J = 10.2, 2.7 Hz, 1H), 6.90 (td, J = 8.4, 2.7 Hz, 1H), 2.54 (t, J = 8.0 Hz, 2H), 1.47–1.42 (m, 2H), 1.24–1.17 (m, 2H), 0.78 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 162.2 (d, J = 243.7 Hz), 142.7 (d, J = 7.2 Hz), 141.1, 137.8 (d, J = 3.0 Hz), 131.4 (d, J = 8.0 Hz), 129.4, 128.1, 126.9, 115.5 (d, J = 20.7 Hz), 112.3 (d, J = 20.8 Hz), 33.2, 32.8 (d, J = 1.3 Hz), 22.4, 13.8 ppm; HRMS Calcd 228.1314 for $C_{16}H_{17}F$. Found 228.1315. 2-Pentyl-4-fluorobiphenyl (**4b**): ^{19}F NMR ($CDCl_3$) δ −116.4 (m) ppm; ^{1}H NMR ($CDCl_3$) δ 7.50–7.31 (m, 5H), 7.22 (dd, J = 8.4, 6.1 Hz, 1H), 7.06 (dd, J = 10.1, 2.6 Hz, 1H), 6.98 (td, J = 8.5, 2.8 Hz, 1H), 2.61 (t, J = 7.9 Hz, 2H), 1.56–1.51 (m, 2H), 1.29–1.24 (m, 4H), 0.88 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 162.1 (d, J = 243.6 Hz), 142.8 (d, J = 7.2 Hz), 141.1, 137.8 (d, J = 3.0 Hz), 131.4 (d, J = 8.1 Hz),129.4, 128.1, 126.9, 115.5 (d, J = 20.7 Hz), 112.3 (d, J = 20.8 Hz), 33.0 (d, J = 1.3 Hz), 31.5, 30.7, 22.3, 13.9 ppm; HRMS Calcd 242.1471 for $C_{17}H_{19}F$. Found 242.1468. 2-(2-Phenylethyl)-4-fluorobiphenyl (**4c**): ^{19}F NMR ($CDCl_3$) δ −116.1 (m) ppm; ^{1}H NMR ($CDCl_3$) δ 7.32–6.84 (m, 13H), 2.80–2.72 (m, 2H), 2.68–2.60 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 162.1 (d, J = 244.0 Hz), 141.5 (d, J = 7.2 Hz), 141.3, 140.8, 138.0 (d, J = 3.1 Hz), 131.5 (d, J = 8.0 Hz), 129.3, 128.29, 128.28, 128.15, 127.0, 125.9, 115.7 (d, J = 20.8 Hz), 112.7 (d, J = 20.8 Hz), 37.3, 35.4 (d, J = 1.3 Hz) ppm; GC–MS m/z (relative intensity): 65 (13), 159 (20), 165 (47), 183 (50), 185 (100), 276 (M^+, 39); HRMS Calcd 276.1314 for $C_{20}H_{17}F$. Found: 276.1317.