ORGANIC LETTERS

2002
Vol. 4, No. 22
3871−3873

Synthesis of 1,3-Difluoroaromatics in One Pot by Addition of Difluorocarbene from Sodium Chlorodifluoroacetate to 1,2-Substituted Cyclobutenes

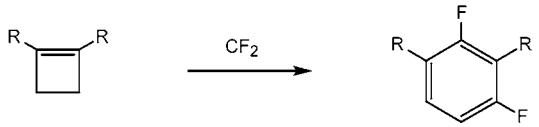
Heather M. Morrison, James E. Rainbolt, and Scott B. Lewis*

Department of Chemistry, James Madison University, MSC 7701, Harrisonburg, Virginia 22807

lewissb@jmu.edu

Received August 8, 2002

ABSTRACT



R= phenyl or *n*-propyl

The synthesis of 1,3-difluoro-2,4-diphenylbenzene has been accomplished in one step from 1,2-diphenylcyclobutene using the environmentally benign difluorocarbene precursor sodium chlorodifluoroacetate. In addition, the preparation of the previously unknown compound 1,3-difluoro-2,4-di-*n*-propylbenzene has been accomplished in one step from 1,2-di-*n*-propylcyclobutene using Seyferth's reagent (Ph–Hg–CF_3) and sodium chlorodifluoroacetate.

Fluorinated organic compounds are a fascinating class of compounds that continue to grow in importance in society. They tend to possess markedly different physical, chemical and electronic properties from those exhibited by compounds that have no fluorine atoms present.[1] In nature, fluorine is not widely distributed among organic compounds, with only thirteen fluorine containing natural products having been isolated and characterized.[2] Despite their scarcity in nature, synthetically prepared organofluorine compounds have found a wide variety of uses. Fluorinated aromatics, in particular, have found uses in areas such as antibacterials,[3] antiinflammatory agents,[4] anticonvulsants,[5] pesticides[6] and liquid crystals.[7]

Due to the electronegativity of the fluorine atom and its directing influence during electrophilic substitution reactions, it is difficult to obtain a 1,3-difluoroaromatic compound when starting from benzene. Some years ago, we reported a one-pot preparation of 1,3-difluoro-2,4-diphenylbenzene (**1**) in 77% yield from the difluorocarbene addition to 1,2-diphenylcyclobutene.[8] Recently, only the second paper known to describe dihalocarbene additions to 1,2-disubstituted cyclobutenes showed that both dichloro- and dibromocarbene (each generated by three sources) do in fact add to 1,2-diphenylcyclobutene to produce 1,3-dihalo-2,4-diphenylbenzenes.[9]

To date, work involving dihalocarbene additions to cyclobutenes has used 1,2-diphenylcyclobutene, while the difluorocarbene previously used had only been generated by Seyferth's method using Ph−Hg−CF_3.[8,9] Herein, we wish to report the use of difluorocarbene generated from sodium chlorodifluoroacetate for the preparation of **1** and difluorocarbene generated from two sources (Ph−Hg−CF_3 and

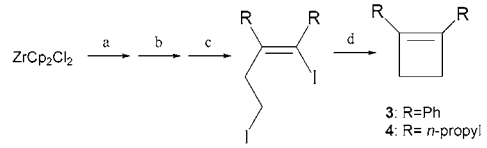
(1) Hudlicky, M.; Pavlath, A. E., Eds. *Chemistry of Organic Fluorine Compounds II. A Critical Review*. ACS Monograph 187; American Chemical Society: Washington, DC, 1995.
(2) O'Hagen, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, *100*, 127.
(3) Ziegler, C. B., Jr.; Kuck, N. A.; Strohmeyer, T. W.; Lin, Y. *J. Heterocycl. Chem*. **1990**, *27*, 2077.
(4) Hewitt, C. D.; Silvester, M. J. *Aldrichimica Acta* **1988**, *21*, 3.
(5) Bergman, K. J. *Clin. Neuropharmacol.* **1985**, *7*, 105.
(6) Szczepanik, M. *Prog. Plant Prot.* **1998**, *28*, 385.
(7) Kirsch, P.; Huber, F.; Lenges, M.; Taugerbeck, A. *J. Fluorine Chem.* **2001**, *112*, 69.
(8) Lewis, S. B.; Borden, W. T. *Tetrahedron Lett.* **1994**, *35*, 1357.
(9) Wagner, R. A.; Weber, J.; Brinker, U. H. *Chem. Lett.* **2000**, 246.

10.1021/ol020158j CCC: $22.00
Published on Web 10/08/2002

sodium chlorodifluoroacetate) for the preparation of the previously unknown compound 1,3-difluoro-2,4-di-*n*-propylbenzene (**2**) from the appropriate 1,2-disubstituted cyclobutenes.

Preparation of 1,2-diphenylcyclobutene (**3**) was accomplished in four steps (39% overall yield) from diphenylacetylene adapting the method of Negishi for preparing cyclobutenes. The synthesis of 1,2-di-*n*-propylcyclobutene (**4**) was also accomplished in four steps from 4-octyne following exactly the procedure of Negishi (Scheme 1).[10]

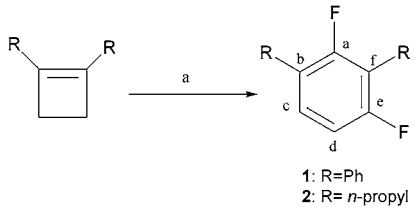
Scheme 1[a]



[a] Reaction conditions: (a) 2EtMgBr/THF/−78 °C; (b) diphenylacetylene or 4-octyne/THF/0 °C; (c) I_2/THF/−78 °C. (d) BuLi/THF/−78 °C.

Compound **4** was then reacted with Ph−Hg−CF_3 in refluxing benzene[11] to produce the new compound **2** in 60% yield. Following this, compounds **3** and **4** were individually subjected to sodium chlorodifluoroacetate in refluxing diglyme (Scheme 2).[12] This resulted in the formation of **1** and **2** in 53 and 41% yields, respectively (Table 1).

Scheme 2[a]



[a] Reaction conditions: (a) Ph−Hg−CF_3 or $NaCClF_2CO_2$.

The molecular formula of **2** (produced from Ph−Hg−CF_3) was established by high-resolution mass spectrometry (calcd for $C_{12}H_{16}F_2$, 198.1220; found, 198.1225). The ^{1}H NMR spectrum indicated the presence of two inequivalent propyl groups, showing that **2** has no symmetry. This was most easily detected by the signals for the two benzyl methylenes [δ 2.65 (t, J = 7.95 Hz, 2H) and δ 2.58 (t, J = 7.65 Hz, 2H)]. The other notable feature of the proton spectrum involved the two aromatic resonances. These appeared as a quartet-like multiplet centered at δ 6.94 and a triplet-like multiplet at δ 6.74. A ^{19}F-decoupled ^{1}H spectrum simplified these two proton signals to a set of doublets (J = 8.4 Hz),

Table 1. Yields of 1,3-Difluoroaromatics

		yield	
entry	source of carbene	**1**	**2**
1	Ph−Hg−CF_3/NaI/benzene reflux/48 h	77[a]	60
2	$NaCClF_2CO_2$/diglyme reflux/60 min	53	41

[a] Reference 8.

with no significant changes observed in upfield signals. The ^{19}F NMR spectrum has features similar to the proton spectrum: a quartet-like multiplet centered at δ −120.35 and a triplet-like multiplet at δ −121.43 (relative to $CFCl_3$ at δ 0.00).

The most compelling evidence for the structure of **2** comes from the proton-decoupled ^{13}C NMR spectrum in conjunction with a DEPT 135 experiment. The two aromatic carbons with protons attached (δ 127.5 and 110.1), as shown by the DEPT experiment, are both split into doublets of doublets. The resonance at δ 127.5 (C_c) shows nearly equal coupling (J_{CF} = 9.71 and 7.07 Hz) to the two fluorines, indicating it is meta to both fluorines. The other protonated aromatic carbon (C_d) has coupling constants to the two fluorines of J_{CF} = 22.43 Hz and J_{CF} = 3.71 Hz. The magnitude of these coupling constants indicates that this carbon is ortho to one fluorine and para to the other.[13]

Similar C−F coupling constant arguments can be made for the doublets of doublets at δ 124.7 (C_b) and 117.4 (C_f), which are the carbons holding the propyl groups. The carbon atoms bonded to the fluorines appear as doublets of doublets centered at δ 159.8 (J_{CF} = 243.17 Hz, J_{CF} = 8.83 Hz) and δ 159.5 (J_{CF} = 244.94 Hz, J_{CF} = 8.83 Hz). The magnitude of the smaller C−F coupling constant in these carbon resonances clearly indicates that the two fluorine atoms are meta to one another.[13] Taken together, these data firmly establish the structure of the previously unknown compound **2**.

Spectral data collected (^{1}H, ^{13}C, and ^{19}F NMR and GCMS) of compounds **1** and **2** made from the acetate salt match those of the compounds made with Ph−Hg−CF_3. Attempts to find an effective but lower boiling solvent for the reaction with the acetate salt included 1,4-dioxane (bp = 102 °C), ethylene glycol diethyl ether (bp = 121 °C), and dibutyl ether (bp = 142 °C). All of these solvents were regrettably unsuccessful at initiating the reaction that produces 1,3-difluoroaromatics.

The mechanism originally proposed for this reaction involved cationic intermediates that did not require any assistance from the mercury atom of Ph−Hg−CF_3.[8] The use of sodium chlorodifluoroacetate to produce 1,3-difluoroaromatics clearly indicates that mercury is not involved in the mechanism that produces these compounds (Figure 1).

While the organomercury compound (Ph−Hg−CF_3) was the first reagent used to produce 1,3-difluoroaromatics in one step from cyclobutenes, its use has significant drawbacks

(10) Negishi, E.; Liu, F.; Choueiry, D.; Mohamud, M. M.; Silveria, A.; Reeves, M. *J. Org. Chem.* **1996**, *61*, 8325.
(11) Seyferth, D.; Hopper, S. P. *J. Org. Chem.* **1972**, *37*, 4070.
(12) Csuk, R.; Eversmann, L. *Tetrahedron* **1998**, *54*, 6445.
(13) Kalinowski, H.-O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; Wiley and Sons: Chichester, UK, 1984; pp 581−585.

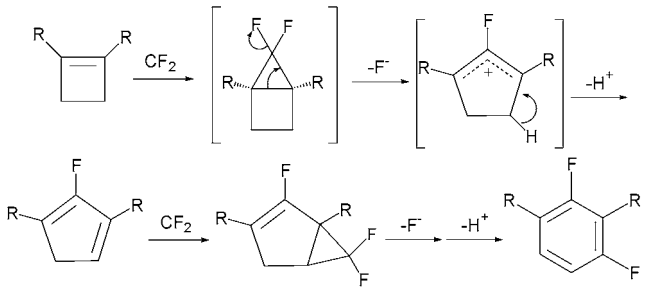


Figure 1. Proposed mechanism for the formation of 1,3-difluoroaromatics from the difluorocarbene addition to substituted cyclobutenes.

not shared by the acetate salt. First, the salt is commercially available, or easily prepared in one step from the acid.[12] Reaction times are reduced to 60 min with the salt compared with 24−48 h when using Ph−Hg−CF_3. The number of fluorines lost is reduced to one when using the acetate salt from five when using Ph−Hg−CF_3 as the difluorocarbene precursor.[14] Most important of all, no toxic metals are present with the salt and the only byproducts of the reaction are NaCl and CO_2.

The preparation of 1,3-difluoroaromatics in one step by the ring expansion of a cyclobutene represents a unique way to make this class of compounds that are very difficult to obtain starting from benzene. The ability to prepare these difluoroaromatics with predictable regiochemistry from a convenient source that does not require the presence of a toxic heavy metal organometallic makes this reaction a powerful tool for synthetic chemists.

Acknowledgment. We thank the Virginia Academy of Science (Thomas F. and Kate Miller Jeffress Memorial Trust Fund, J-645), The NSF-REU (CHE-0097448), and The Department of Chemistry at James Madison University for financial support, Thomas N. Gallaher for technical help with NMR experiments, and the Center for Mass Spectrometry at The University of Nebraska−Lincoln for HRMS.

Supporting Information Available: Experimental procedure for use of the acetate salt and all spectra for compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL020158J

(14) Five fluorine atoms in total are lost when using Ph−Hg−CF_3 as the difluorocarbene source. This is figured on the basis of starting from CF_3CO_2H and HgO to initially make $(CF_3CO_2)_2Hg$. Three fluorines are lost when the Ph−Hg−CF_3 is made, and two more are lost from each molecule of Ph−Hg−CF_3 during the production of the 1,3-difluoroaromatic.