ORGANIC
LETTERS

2001
Vol. 3, No. 20
3103−3105

Difluorinated Danishefsky's Diene: A Versatile C_4 Building Block for the Fluorinated Six-Membered Rings

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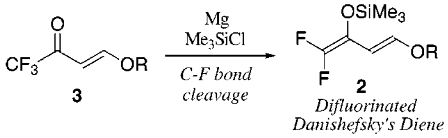
Received June 28, 2001

ABSTRACT



A Mg(0)/Me_3SiCl system was found to be effective for the preparation of difluoro Danishefsky's dienes 2, which involves selective C–F bond cleavage of trifluoromethyl ketones 3. Subsequent hetero Diels–Alder reactions of 2 with aldehydes and imines gave a variety of fluorinated six-membered heterocycles.

The Diels−Alder reaction has proven to be an exceptionally powerful method for carbon−carbon bond formation in organic synthesis.[1] Its widespread application arises from the versatility and predictability of the stereochemical and regiochemical outcome of the reaction based on well-defined rules. Modification of the diene and dienophile components led to significant extension of synthetic utility of the Diels−Alder reaction. The conspicuous success encountered by dienes bearing lone pair electron-containing heteroatom substituents is certainly worth emphasizing.[2] For instance, oxygenated 1,3-dienes have found many applications as a result of their high reactivity to dienophiles with improved regioselectivity in the cycloaddition. The most widely used compound of this class, 1-methoxy-3-(trimethylsiloxy)-butadiene (Danishefsky's diene, **1**)[3] provides elegant access to several important natural products.

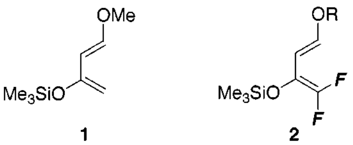


Figure 1. Difluorinated Danishefsky's Dienes (**2**).

Because of the unique chemical, physical, and in some cases biological characteristics of difluoromethylene compounds, 1-alkoxy-4,4-difluoro-3-(trimethylsiloxy)-1,3-butadienes **2**, fluorinated analogues of Danishefsky's diene, are one of the most fascinating C_4 building blocks. However, despite their synthetic potential, to our knowledge there has been no report of the preparation of **2** and very little is known about fluorinated 1,3-dienes.[4,5] Herein, we report the first preparation and useful synthetic applications of difluoro Danishefsky's dienes **2**, which involve Mg(0)-promoted selective C−F bond cleavage of trifluoromethyl ketones **3** as a key step.

The process shown in Scheme 1 provides access to difluoro Danishefsky's dienes **2** in a simple and efficient

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(1) Oppolzer, W. Intermolecular Diels−Alder Reactions. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Vol. 5, pp 315−400.

(2) (a) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753. (b) Fringuelli, F.; Taticchi, A. *Dienes in the Diels−Alder Reaction*; Wiley: New York, 1990.

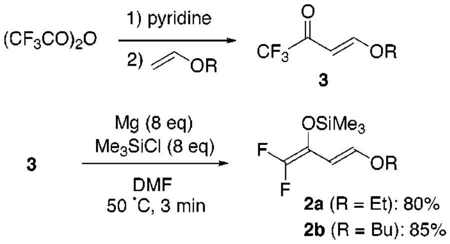
(3) Reviews: (a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. (b) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. (c) Danishefsky, S. *Chemtracts-Org. Chem.* **1989**, *2*, 273.

(4) Synthesis and application of difluorinated 1,3-dienes: (a) Shi, G. Q.; Schlosser, M. *Tetrahedron* **1993**, *49*, 1445. (b) Jin, F.; Xu, Y.; Huang, W. *J. Chem. Soc., Chem. Commun.* **1993**, 814. (c) Jin, F.; Xu, Y.; Huang, W. *J. Fluorine Chem.* **1995**, *71*, 1. (d) Shen. Q.; Hammond, G. B. *Org. Lett.* **2001**, *3*, 2213

(5) Taguchi, T.; Kodama, Y.; Kanazawa, M. *Carbohydr. Res.* **1993**, *249*, 243.

10.1021/ol0163631 CCC: $20.00

Scheme 1. Preparation of Difluorinated Danishefsky's Dienes



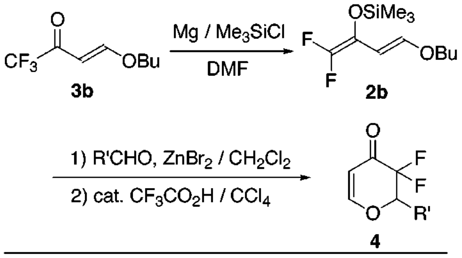
fashion. The starting ketones **3** were easily prepared from the reaction of trifluoroacetic anhydride (TFAA) with vinyl ethers in 80−90% yields.[6,7] Upon treatment with 8 equiv of Mg and Me_3SiCl in DMF, defluorinative silylation of trifluoromethyl ketones **3** proceeded to afford difluorobutadienes **2** in 80−85% yield (^{19}F NMR).[8] The reactions were completed within 3 min at 50 °C. Compounds **2** are thermally unstable, moisture-sensitive, and less reactive than nonfluorinated Danishefsky's diene, so **2** was used for next step without further purification.

In general, the cleavage of a C−F bond is not easy because of the large bond energy (ca. 552 kJ mol^{-1}). However, the bond breaking does rather easily occur when a CF_3 group is attached to the π-electron system, because electron acceptance into the π-system and subsequent extrusion of a fluoride ion may make large contributions to the driving force of the reaction.[9] Electrochemical methods have hitherto been developed for reductive defluorination of a trifluoromethyl group, and they can be successfully applied to the preparation of difluoromethylene building blocks.[10] Very recently, we have found that Mg(0) metal proves useful for the C−F bond-breaking process of trifluoromethyl ketones to provide a highly efficient access to silyl difluoroenol ethers.[11]

The defluorinative silylation route for the preparation of difluoro Danishefsky's dienes **2** has several advantages: (i) the starting materials **3** are readily available directly from TFAA; (ii) Mg as a reducing agent is inexpensive and easy to handle; and (iii) formation of 2,2-difluoroenol silyl ethers is highly selective (further reduction of the C−C double bonds of **2** did not occur). Additional features of interest in this route are the short reaction time and the easy workup procedure, which are important for the preparation of the labile products **2** to avoid decomposition. After decantation to remove the excess metal and extraction with hexane, the crude products **2** were of sufficient purity (>90%) to be used directly in the next reaction without further purification.

In particular, the synthetically useful application of difluoro Danishefsky's dienes **2** has been made for the hetero Diels−Alder reaction.[12] As shown in Table 1, the reaction of **2b** with benzaldehyde in the presence of $ZnBr_2$, followed by treatment with catalytic trifluoroacetic acid gave the fluorinated dihydropyrone **4a** in total yield of 64% from **3b** (entry 1). This procedure worked well for both aromatic (entries 1−3) and aliphatic (entry 4) aldehydes to afford the corresponding dihydropyrones **4** in moderate yields (from trifluoromethyl ketone **3b**).

Table 1. Lewis Acid Catalyzed Hetero Diels−Alder Reactions of **2b** with Aldehydes



entry	R'	product **4**	yield (%)[a]
1	Ph	**4a**	64
2	4-$MeOC_6H_4$	**4b**	53
3	4-ClC_6H_4	**4c**	50
4	Et	**4d**	50

[a] Isolated yields from α,β-unsaturated ketone **3b**.

Instead of aldehydes, aldimines were used as a dienophile in this reaction providing the nitrogen-containing adducts. ZnI_2-promoted hetero Diels−Alder reaction of **2b** worked well with various *N*-aryl- and *N*-alkyl-substituted imines **5** to give the corresponding difluoro dihydropyridones **6** (Table 2). Interestingly, the reaction of *N*-*p*-methoxyphenyl imine of ethyl glyoxylate **5d**[13] gave, upon aqueous acidic hydrolysis of the intermediate cycloadduct, difluorinated cyclic amino acid precursor **6d** in 54% yield (entry 4). The reaction of cyclic imine **5e** afforded the mono-fluorinated cycloadduct **6e** in 52% yield by a sequence of the cycloaddition followed by dehydrofluorination of the corresponding difluorinated cycloadduct (entry 5). The arylquinolizine ring system is common in many naturally occurring alkaloids.[14,15] The interesting biological activities of many of these compounds

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(6) Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, 499.

(7) Colla, A.; Martins, M. A. P.; Clar, G.; Krimmer, S.; Fischer, P. *Synthesis* **1991**, 483.

(8) Compounds **2** decompose at room temperature for several hours. Because of the instability of **2**, the yields were estimated by ^{19}F NMR using 4, 4′-difluoro diphenylmethane as an internal standard.

(9) (a) Chaussard, J.; Folest, J.-C.; Nedelec, J.-Y.; Périchon, J.; Sibille, S.; Troupel, M. *Synthesis* **1990**, 369. (b) Saboureau, C.; Troupel, M.; Sibille, S.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1989**, 1138. (c) Cavel, P.; Legar-lambert, M. P.; Biran, C.; Serein-Spirau, F.; Bordeau, M.; Roques, N.; Marzouk, H. *Synthesis* **1999**, 829. (d) Andrieux, C. P.; Combellas, C.; Kanoufi, F.; Savéant, J.-M.; Thiébault, A. *J. Am. Chem. Soc.* **1997**, *119*, 9527.

(10) Electrochemical preparation of difluoromethyl compounds: (a) Uneyama, K.; Maeda, K.; Kato, T.; Katagiri, T. *Tetrahedron Lett.* **1998**, *39*, 3741. (b) Uneyama, K.; Kato, T. *Tetrahedron Lett.* **1998**, *39*, 587. (c) Uneyama, K.; Mizutani, G. *Chem. Commun.* **1999**, 613. (d) Uneyama, K.; Mizutani G.; Maeda, K.; Kato, T. *J. Org. Chem.* **1999**, *64*, 6717.

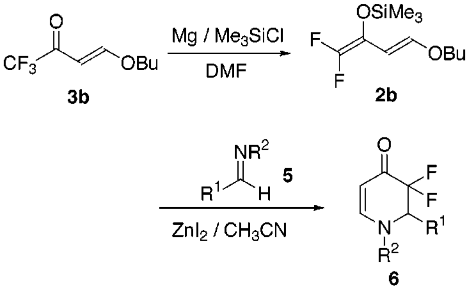
(11) Mg(0)-promoted preparation of difluoro silyl enol ethers: (a) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun.* **1999**, 1323. (b) Amii, H.; Kobayashi, T.; Uneyama, K. *Synthesis* **2000**, 2001. (c) Mae, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett.* **2000**, *41*, 7893.

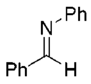
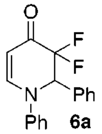
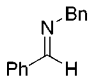
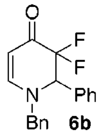
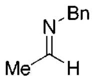
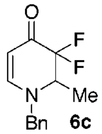
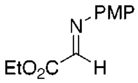
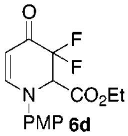
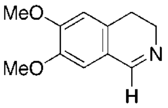
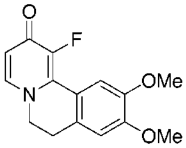
(12) Hetero Diels−Alder reaction of fluorinated aldimines: Crousse, B.; Begue, J.-P.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 5009.

(13) Preparation of iminoester **5d**: Tietze, L. F.; Bratz, M. *Synthesis* **1989**, 439.

(14) Monteiro, H. J. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1968; Vol. XI, p 145.

Table 2. Lewis Acid Catalyzed Hetero Diels−Alder Reactions of **2b** with Imines



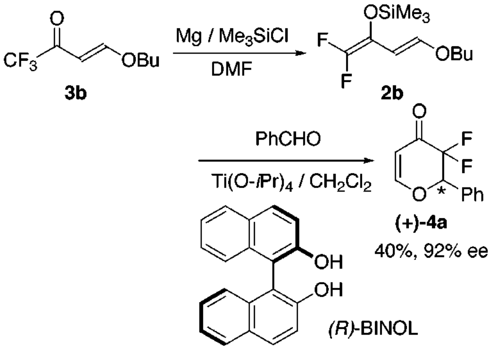
entry	imine **5**	product **6**	yield (%)[a]
1	 **5a**	 **6a**	60
2	 **5b**	 **6b**	56
3	 **5c**	 **6c**	53
4	 **5d**	 **6d**	54
5	 **5e**	 **6e**	52

[a] Isolated yields from α,*β*-unsaturated ketone **3b**.

and their derivatives have promoted considerable effort directed toward the construction of this system.[16]

Thus, Lewis acid catalyzed hetero Diels−Alder cycloaddition reactions of **2** represent a versatile synthetic methodology for the construction of a variety of fluorinated heterocyclic compounds. Moreover, enantioselective hetero Diels−Alder reaction of **2** is worth investigating since a new stereogenic carbon center next to the difluoromethylene group is generated in the product. Though an equimolar amount of chiral Lewis acid catalyst was needed because of the lower reactivity of the fluorodiene **2** compared to that of (nonfluorinated) Danishefsky's diene **1**,[17] the reaction of **2b** with benzaldehyde afforded corresponding dihydropyrone (+)-**4a** in 92% ee in the presence of equimolar of chiral titanium(IV)-BINOL system (Scheme 2).[18,19]

Scheme 2



In conclusion, a Mg(0)-promoted C−F bond cleavage route for the preparation of difluoro Danishefsky's diene was developed, and this novel C_4 building block will be widely employed in organic synthesis for fluorinated compounds.

Acknowledgment. This work has been supported by Ministry of Education, Science, Sports and Culture of Japan (124501356, 13555254). We also thank the SC-NMR laboratory of Okayama University for ^{19}F NMR analysis.

Supporting Information Available: Experimental procedures and details of compound characterization for **2**, **4**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Hava, M., The Pharmacology of Vinca Species and their Alkaloids. *The Vinca Alkaloids*; Taylor, W. I., Farnsworth, N. R., Eds.; Marcel Dekker: New York, 1973; Chapter 6, p 305.

[16] Archibald, J. L.; Beardsley, D. R.; Ward, T. J.; Waterfall, J. F.; White, J. F. *J. Med. Chem.* **1983**, *26*, 416. (b) Klioze, S. S.; Ehrgott, F. J., Jr. *J. Med. Chem.* **1979**, *22*, 1497.

[17] Competitive reaction of **1** and **2b** with benzaldehyde in $CDCl_3$ revealed that **1** reacts much faster than **2b**. (Compound **1** disappeared almost within 5 min, whereas a large amount of **2b** remained unreacted.)

[18] For chiral titanium(IV)−BINOL catalyzed enantioselective hetero Diels−Alder reaction, see also: (a) Mikami K.; Shimizu M. *Chem. Rev.* **1992**, *92*, 1021. (b) Keck G. E.; Li X.-Y.; Krishnamurthy D. *J. Org. Chem.* **1995**, *60*, 5998.

[19] The absolute configurations of the primary adduct and the final product (+)-**4a** have not been determined yet. Precise mechanistic studies on hetero Diels−Alder reactions of **2** including stereochemical information are in progress. In this communication, we have disclosed the first practical preparation of **2** and its hetero Diels−Alder reactions as an example of useful synthetic applications. Further applications of **2** for [4 + 2]-cycloaddition with alkenes and reaction mechanisms will be described in a future full paper.