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Synthesis of 2-Fluoro-3-phenylthio-1,3-butadiene and 2-Trifluoromethyl-3-phenylthio-1,3-butadiene and Their Reactivities toward Various Dienophiles

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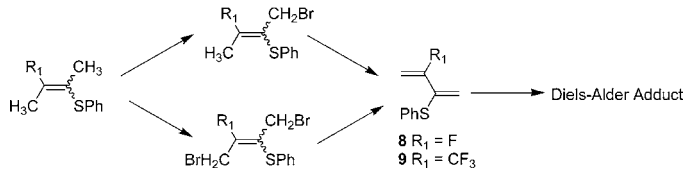
ABSTRACT



A general approach for the synthesis of novel 2-fluoro-3-phenylthio-1,3-butadiene (8) and 2-trifluoromethyl-3-phenylthio-1,3-butadiene (9) from monobromoalkene and dibromoalkenes has been developed. Subsequent Diels−Alder reactions of these dienes with symmetrical and unsymmetrical dienophiles in the presence of Lewis acids gave a variety of fluorinated six-membered carbocycles in moderate to high yields.

The Diels−Alder reaction has proven to be an exceptionally powerful method for carbon−carbon bond formation in organic synthesis.[1] Modification of diene and dienophile components led to a significant extension of synthetic utility of the Diels−Alder reaction. The introduction of heterosubstituents has a significant influence on the reactivity, regioselectivity, and stereochemistry of the diene and also adds versatility in further reactions of the cycloadducts.[2] Consequently, these dienes are becoming well established as useful intermediates in organic synthesis. The comprehensive review by Boger and Weinreb elaborates the various examples of [4+2]-cycloadditions with heteroatom containing dienes and dienophiles.[3] In the past several decades, much effort has been devoted to introduce the fluorine or trifluoromethyl functionality into organic molecules because of the dramatic effects of functionality on their structure stability, reactivity, and biological activity of the resulting compounds.[4] Fluorine-containing molecules have many applications in various fields such as pharmaceutical, agricultural chemistry, and material science.[5] Consequently, a wide variety of methods have hitherto been developed for the preparation of these fluorine-incorporated compounds,[6] but only scarce examples are known for fluorinated dienes.[7] Especially, there

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

(2) (a) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753. (b) Bridges, A. J.; Fischer, J. W. *Tetrahedron Lett.* **1983**, *24*, 447. (c) Bridges, A. J.; Fischer, J. W. *J. Chem. Soc., Chem. Commun.* **1982**, 665. (d) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3548. (e) McDonald, E.; Suksamrarn, A.; Wylie, R. D. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1893. (f) Clennan, E. L.; Nagraba, K. *J. Org. Chem.* **1987**, *52*, 294. (g) Jeganathan, S.; Okamura, W. H. *Tetrahedron Lett.* **1982**, *23*, 4763. (h) Garratt, P. J.; Tsotinis, A. *Tetrahedron Lett.* **1986**, *27*, 2761. (i) Pollok, T.; Schmidbaur, H. *Tetrahedron Lett.* **1987**, *28*, 1085.

(3) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987.

(4) (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (b) Welch, J. T.; Eswarakrishnam, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (c) Resnati, G. *Tetrahedron* **1993**, *49*, 9385. (d) *Organofluorine Componds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolski, L. M., Eds.; Elsevier Science Publishers B.V.: Amsterdam, The Netherlands, 1993. (e) *Organofluorine Chemistry, Principles and Chemical Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994. (f) *Inventory of Industrial Fluorobiochemicals*; Becker, A., Ed.; Eyrolles: Pairs, France, 1996. (g) Smart, B. E. *Chem. Rev.* **1996**, *96*, 1555. (h) Resnatic, G.; Soloshnok, V. A. *Tetrahedron* **1996**, *52*, 1. (i) Hudlicky, M.; Pavlath, A. E., Eds. *Chemistry of Organic Fluorine Compounds*; American Chemical Society: Washington, DC, 1996; p 187.

(5) (a) *Selective Fluorination in Organic and Bioorganic Chemistry*; ACS Symp. Ser. No. 456; Welch, J. T., Ed.; American Chemical Society: Washington, DC, 1991. (b) *Biomedical Frontiers of Fluorine Chemistry*; ACS Symp. Ser. No. 639; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996.

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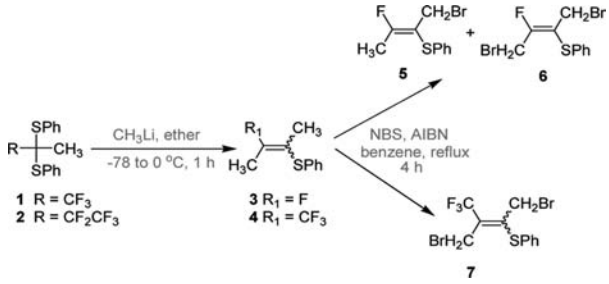
has been only one report on the preparation of phenylthio-substituted 1,1-difluoro-1,3-butadienes.[8] Herein, we report a new methodology and useful synthetic applications of monofluoro butadiene and trifluoromethyl butadiene toward dienophiles. Despite their synthetic potential, there have been no reports for the preparation of 2,3-substituted 1,3-butadienes **8** and **9**.

Different strategies have been used for the synthesis of 2,3-substituted-1,3-butadiene, from but-2-yn-1,4-diol, 1,4-dichloro-but-2-yne,[9] and 3-chloro-4-(phenylthio)-3-sulfolene.[10] These methods have some limitations of attaining poor yields due to lower reactivity of triple bonds toward electrophiles and nonavailability of starting materials.

To obtain butadienes **8** and **9**, we have used easily available starting material 1,1,1-trifluoro-2,2-bis(phenylthio)-propane **1**. Stirring **1**[11] with methyllithium in ether at −78 to 0 °C for 1 h gave an *E* and *Z* isomeric mixture (70:30) of 2-fluoro-3-phenylthio-2-butene **3** in 78% yield (Scheme 1).[12]

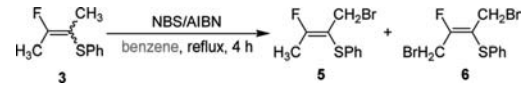
Scheme 1. Synthetic Approach for the Construction of Monobromoalkene and Dibromoalkene



The ^{19}F NMR spectrum shows the multiplet at δ −83.56 ppm in *Z* form and the quartet at δ −83.54 ppm in *E* form. Similarly, a reaction of 3,3-bis(phenylthio)-1,1,1,2,2-pentafluorobutane (**2**) with CH_3Li in ether at −78 to 0 °C gave an *E* and *Z* isomeric mixture (68:32) of 2-trifluoromethyl-3-phenylthio-2-butene (**4**) in 79% yield.

To achieve substituted-1,3-butadiene, we have tried the reaction of **3** and **4** with various oxidizing agents like DDQ, CrO_3, $KMnO_4$, and MnO_2 under a wide range of reaction conditions but in every case, only starting material was recovered. Thus, we have approached another route for the synthesis of diene by the reaction of an *E* and *Z* isomeric mixture of **3** with NBS in the presence of a catalytical amount of AIBN on refluxing benzene for 4 h, in which *E* and *Z* isomeric mixtures of 1-bromo-3-fluoro-2-phenylthio-2-butene (**5**) and 1,4-dibromo-2-fluoro-3-phenylthio-2-butene (**6**) were obtained (Scheme 1). With an increase in equivalents of NBS, there is an increase of dibromoalkene **6**. Thus, 1.5 equiv of NBS gave **5** as the major product with 60% yield and only 20% of **6** was formed, but with 3.0 equiv of NBS only **6** was obtained with 72% yield as shown in Table 1.

Table 1. Reactions of Alkene **3** at Various Equivalents of NBS



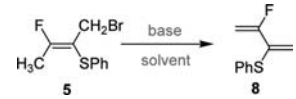
		yield (%)[a]	
entry	NBS (equiv)	**5**	**6**
1	0.5	35	0
2	1.0	40	10
3	1.5	60	20
4	2.0	45	31
5	3.0	0	72

[a] Isolated yields.

Similarly, the reaction of an *E* and *Z* isomeric mixture of **4** with 3.0 equiv of NBS in the presence of a catalytic amount of AIBN at the same reaction conditions gave dibromoalkene **7** in 76% yield (Scheme 1).

With both the precursors in hand, we have used monobromoalkene **5** and dibromoalkene **6** for the synthesis of 2-fluoro-3-phenylthio-1,3-butadiene (**8**) by using a different synthetic methodology. Reaction of **5** with potassium carbonate in acetonitrile at refluxing temperature for 3 days gave **8** in 30% yield, but potassium-*tert*-butoxide in THF at room temperature for 1 h gave **8** in 77% yield (Table 2); ^{19}F NMR analysis of

Table 2. Reactions of **5** at Various Conditions



entry	base	solvent	*t* (°C)	time	yield (%)[a]
1	K_2CO_3	CH_3CN	80	3 d	30
2	NaH	THF	25	3.5 h	71
3	Et_3N	DCM	50	15 h	69
4	Cs_2CO_3	THF	80	15 h	43
5	*t*-BuO$^-$K$^+$	THF	25	1 h	77
6	LDA	THF	−78	10 min	40
7	*n*-BuLi	THF	−78	10 min	42

[a] Isolated yield.

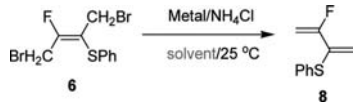
the reaction mixture shows the disappearance of signal at δ −75.60 ppm and the appearance of a doublet signal at δ −106.98 ppm to which we assigned the structure of substituted 1,3-butadiene **8**. The ^{1}H NMR spectrum consists of one proton doublet of triplet, doublet of doublet, triplet, and singlet at δ 4.81, 4.99, 5.54 and 6.02 ppm, respectively, and a multiplet of five protons at δ 7.37 ppm. Other weak bases such as Cs_2CO_3

(6) (a) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A., Ed.; Wiley: Chichester, UK, 1999. (b) *Experimental Methods in Organic Fluorine Chemistry*; Kitazume, T., Yamazaki, T., Eds.; Kodansha: Tokyo, Japan, 1998. (c) Qiu, X.; Meng, W.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711. (d) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1. (e) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, 1917. (f) Prakesch, M.; Gre'e, D.; Chandrasekhar, S.; Gre'e, R. *Eur. J. Org. Chem.* **2005**, 1211. (g) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613. (h) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (i) Steenis, J. H.; Gen, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2117. (j) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555. (k) Ojima, I. *Chem. Rev.* **1988**, *88*, 1011.

and Et_3N and strong bases such as LDA, NaH, and BuLi have also been used as shown in Table 2.

These dienes have very limited thermal stability but they could be stored in ether or hexane at low temperature in their pure state. It has been known that 2-halo-3-phenythio-1,3-butadiene polymerized readily when neat.[13] In the case of dibromoalkene **6**, refluxing of **6** with Zn dust in THF or MC resulted in polymerized products due to thermal instability, and also after workup and column chromatography, residual $ZnBr_2$ was not removed completely. This problem could be overcome by the use of an $NH_4Cl-MeOH$ solvent system.[14] The reaction of **6** with Zn dust in the presence of $NH_4Cl-MeOH$ for 1 h at room temperature gave 91% yield of **8** (entry 1, Table 3). Other metals such as Zn(Cu), Mg, and In have also been used but in all cases, less yield was obtained. When **6** was treated with Zn dust and NH_4Cl in nonpolar or less polar solvents such as THF and CH_3CN, either no product was formed or less yield was detected after prolonged stirring of the reaction mixture. Other solvents such as dimethoxyethane and diglyme have also been used but the yield was again low in both cases. $NH_4Cl-MeOH$ is a very important factor for the reaction of dibromoalkene. In the absence of NH_4Cl, only 35% product was formed (entry 5, Table 3). Similarly, the reaction of 1,4-dibromo-2-trifluoromethyl-3-phenylthio-2-butene (**7**) with Zn dust and NH_4Cl-CH_3OH at room temperature for 1 h gave 2-trifluoromethyl-3-phenylthio-1,3-butadiene (**9**) in 90% yield (Scheme 2).

Table 3. Reactions of **6** with Various Metals and Solvents

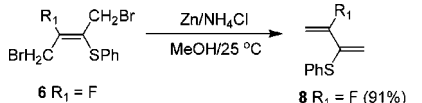


6 **8**

entry	metal	solvent	time (h)	yield (%)[a]
1	Zn	MeOH	1	91
2	Zn(Cu)	MeOH	1	64
3	Mg	MeOH	2	81
4	In	MeOH	6	37
5	Zn	MeOH	10	35[b]
6	Zn	THF	10	0
7	Zn	CH_3CN	10	45
8	Zn	DGE	1	85
9	Zn	DME	2	72

[a] Isolated yields. [b] Absence of NH_4Cl.

Scheme 2. Synthesis of Substituted 1,3-Butadiene from Dibromoalkene



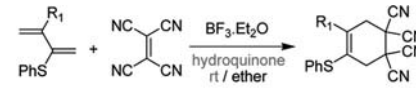
6 R_1 = F
7 R_1 = CF_3

8 R_1 = F (91%)
9 R_1 = CF_3 (90%)

The remarkable efficiency of the NH_4Cl-CH_3OH system can be explained by a better solubility of NH_4Cl in CH_3OH to give ionic NH_4^+ from which the Zn metal could be activated to promote the insertion reaction of the C−Br bond. Although the NH_4Cl-CH_3OH system has been reported as catalyst for the synthesis of various organic compounds, the use of the NH_4Cl-CH_3OH system was not applied to the dehalogenation reaction.

In this paper we wish to report that the dienes **8** and **9** are all reactive in Diels−Alder cycloadditions, and that, despite the instability of these dienes, moderate to excellent yields of cycloadducts can be obtained with Lewis acid catalysis. A variety of conditions for the Diels−Alder reaction of **8** and **9** with symmetrical and unsymmetrical dienophiles were explored. The reaction of a molar solution of **8** with symmetrical diene tetracyanoethylene and a catalytic amount of hydroquinone, which acts as stabilizer in refluxing dichloromethane, for 8 h gave only 32% yield of cycloaddition product **10**; this is due to the polymerization of diene with heating. Therefore, when diene was added as a solution in ether to 1.2 equiv of tetracyanoethylene containing hydroquinone and traces of $BF_3{\cdot}Et_2O$ catalyst, a Diels−Alder reaction occurred. After 30 h of the reaction, workup and column chromatography gave 71% yield of cycloaddition product **10** (Scheme 3). ^{19}F NMR shows the disappearance of signal at δ −106.98 ppm and appearance of the new signal at δ −93.27 ppm of Diels−Alder product.

Scheme 3. Diels−Alder Reactions of Dienes with Dienophiles

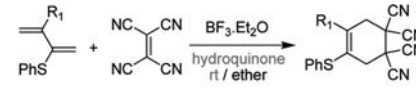


8 R_1 = F
9 R_1 = CF_3

10 R_1 = F
11 R_1 = CF_3

Other reactive Lewis acids such as $ZnCl_2$, $MgBr_2$, $AlCl_3$, $TiCl_4$, and $SnCl_4$ in both ether and methylene chloride established that the best results were obtained with $BF_3{\cdot}Et_2O$ in ether (Table 4).

Table 4. Diels−Alder Reactions of Dienes **8** with Dienophile, Using Different Lewis Acids



8 R_1 = F
9 R_1 = CF_3

10 R_1 = F
11 R_1 = CF_3

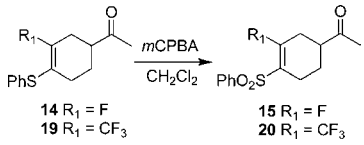
entry	catalyst	time (h)	yield (%)[a]
1	$BF_3{\cdot}Et_2O$	30	71
2	$ZnCl_2$	30	62
3	$SnCl_4$	30	58
4	$AlCl_3$	30	traces
5	$TiCl_4$	30	traces
6	$MgBr_2$	30	43
7	—[b]	8	32

[a] Isolated yields. [b] Absence of catalyst.

Similarly, the reaction of **8** with 1.2 equiv of symmetrical dienophiles such as benzoquinone and *N*-phenylmaleimide

at the same reaction conditions gave the Diels−Alder products **12** and **13** with 65% and 77% yields, respectively. The Diels−Alder reaction with an excess of unsymmetrical dienophile, methyl vinyl ketone, in the presence of Lewis acids (BF_3·Et_2O) at room temperature for 3 days gave **14** in 70% yield. Of great interest is the regioselectivity of this process, which was proven by sequential oxidation to the corresponding sulfone by stirring of **14** with *m*CPBA in dichloromethane at rt for 2 h to provide **15** in 96% chromatographed yield (Scheme 4). GCMS and HPLC show

Scheme 4. Oxidation of **14** and **19** with mCPBA



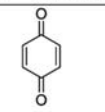
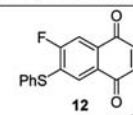
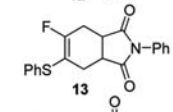
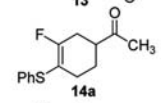
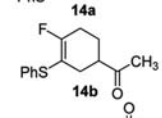
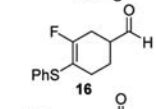
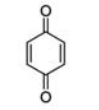
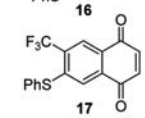
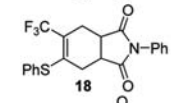
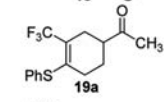
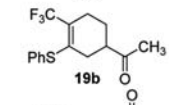
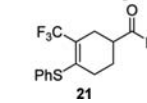
a 10:1 regioisomer ratio of **15**. Similarly in a BF_3·Et_2O-catalyzed reaction with excess acrolein, diene gave a single product **16** in 51% yields. It has been well known that sulfur is a more polarizing substituent for the diene than fluorine, so when the two are in direct competition sulfur should dominate the para regiochemistry. The orbital HOMO coefficients for 2-fluorobutadiene show a difference of 0.065 whereas those for 2-(phenylthio) butadiene show a much larger difference of 0.149.[15]

The reactions of **9** with tetracyanoethylene in the presence of BF_3·Et_2O for 48 h gave **11** in 65% yield. The reactions of **9** with symmetrical dienophiles like benzoquinone and *N*-phenylmaleimide under similar reaction conditions gave Diels−Alder adducts **17** and **18** in 60% and 70% yields, respectively. Similarly, the reaction of **9** with excess methyl vinyl ketone gave **19** with 62% yield. Oxidation of **19** with *m*CPBA gave compound **20** with an 8.5:1.5 regioisomer ratio in GCMS and HPLC. A BF_3·Et_2O-catalyzed reaction of diene **9** with excess acrolein gave a single product **21** in 40% yield (Table 5). More reaction time is required in the Diels−Alder reaction of trifluoromethyl butadiene because it is less reactive than the monofluoro-substituted diene due to the electron-withdrawing nature of trifluoromethyl group.

The other dienophiles such as methyl acrylate, chloroacrylonitrile, DDQ, maleic anhydride, and acrylonitrile did not react with these dienes in all conditions. We have also tried the reaction of dienes **8** and **9** and dimethyl acetylenedicarboxylate but the starting material was recovered.

In conclusion, the readily available starting materials and high efficiency of these methodologies should find utility in organic synthesis. It is noted that the diene is formed by the condition of a BF_3·Et_2O catalyst and that thermal ratios would be considerably lower. The monofluoro-substituted diene is more reactive than the trifluoromethyl-substituted diene toward the reaction with symmetrical and unsymmetrical dienophiles due to the electron-withdrawing nature of fluorine and decreases the electron density of the diene.

Table 5. BF_3.Et_2O Catalyzed Diels−Alder Reaction of **8** and **9**

entry	diene	dienophile	diels-alder Product[a]	yield (%)[b]
1	8		 **12**	65
2	8		 **13**	77
3	8		 **14a** +  **14b**	70
4	8		 **16**	51
5	9		 **17**	60
6	9		 **18**	70
7	9		 **19a**  **19b**	62
8	9		 **21**	40

[a] BF_3·Et_2O, hydroquinone, ether, 25 °C, 24−72 h. [b] Isolated yield.

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Supporting Information Available: The preparation and characterization of compounds **3**−**21** and ^{1}H, ^{13}C, and ^{19}F spectra of **3**−**10** and **12**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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