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Diels–Alder Reactions of Hexafluoro-2-butyne with 2-Heterosubstituted Furans: A Facile and General Synthesis of 1,4-Disubstituted 2,3-Di(trifluoromethyl)benzenes

Gui-Dong Zhu,* Michael A. Staeger, and Steven A. Boyd

Abbott Laboratories, Pharmaceutical Products Division, Metabolic Diseases Research, D4MJ, AP10, 100 Abbott Park Road, Abbott Park, Illinois 60064-6101

gui-dong.zhu@abbott.com

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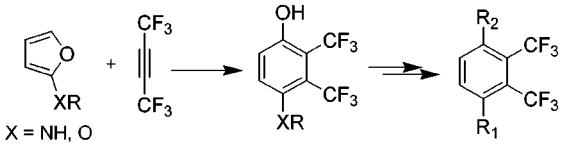
ABSTRACT



An electron-donating heteroatom substituent at position-2 of a furan promotes regiospecific opening of the 7-oxa bridge of the Diels–Alder cycloadduct with hexafluoro-2-butyne, producing a 4-heterosubstituted 2,3-di(trifluoromethyl)phenol building block in a single step. The phenol and heteroatom substituent are easily transformed to the corresponding iodide or triflate that readily undergoes Heck, Suzuki, and Stille reactions to install a variety of substituents in high yields. This methodology provides a facile and general synthesis of 1,4-disubsituted 2,3-di(trifluoromethyl)benzenes.

Fluorine-containing organic molecules have been of great interest to organic and medicinal chemists due to the unique physical and biological properties imparted by fluorine. Introduction of one or more fluorine atom(s) to a given biologically active compound often significantly improves its biological activities and/or physical properties.[1] In our search for anti-inflammatory agents, incorporation of trifluoromethyl groups into the core of our lead molecule provided significant biological improvement. Synthesis of the required 1,4-disubstituted-2,3-di(trifluoromethyl)benzene core structure on large scale, however, was challenging.[2−4]

Hexafluoro-2-butyne **2** is an established synthon for introducing two trifluoromethyl groups into furan[2−8] or benzenoid[2−4] systems. The initial cycloaddition reactions of furans **1** with **2** led to 7-oxabicyclo[2.2.1]hepta-2,5-dienes **3** which were then converted to 2,3-di(trifluoromethyl)phenols by various ring-opening procedures, including Lewis acid mediated reactions.[2,3] The major drawbacks of these protocols include lower regiochemical predictability and the intolerance of many functional groups in the ring-opening process. To our best knowledge, the reported syntheses thus far only involved acid-stable functional groups (i.e., H, CH_3, OH) which are difficult to functionalize further.[2−4,9,10] Herein we report an efficient means to promote a regiospecific rearrangement of the Diels−Alder cycloadduct **3**, derived from **1** and **2**, to form 1,4-difunctionalized 2,3-di(trifluoromethyl)-

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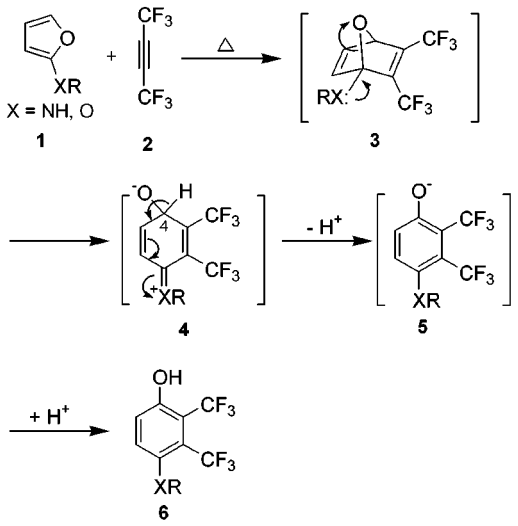
benzene systems in one chemical operation. These compounds can be easily transformed to many other 1,4-disubstituted-2,3-di(trifluoromethyl)benzenes, thus providing a general synthesis of this class of biologically attractive compounds.

As illustrated in Scheme 1, the 2-heteroatom-substituted furan would undergo a Diels−Alder reaction with **2** to give cycloadduct **3**. We envisioned that the 2-hetero substituent would donate electrons along the X−C−O bonds in cycloadduct **3** and promote the opening of the 7-oxa bridge to form unstable intermediate **4**. A self-assisted deprotonation of the H_4 would lead to an aromatization to form phenoxide **5**, which after protonation would give 4-functionalized 2,3-di(trifluoromethyl)phenol **6**.[11−16]

Scheme 1



In an initial experiment, when hexafluoro-2-butyne **2** was heated with readily available furan **1a** (XR = NHBOC)[16] in THF at 120 °C for 18 h, neither desired phenol **6a** nor cycloadduct **3a** was observed. A careful chromatography of the crude reaction mixture furnished 6% of 4-amino-2,3-di-(trifluoromethyl)phenol (**6**, XR = NH_2) along with other unidentified side products. Obviously, cleavage of the BOC protecting group occurred under these conditions. Examination of the reaction at a series of temperatures (60, 82, and 100 °C) revealed that BOC deprotection occurred at 120 °C but did not occur at 82 °C. The cycloaddition reaction was incomplete when run at 60 °C (for 15 h). No solvent effect was observed among THF, acetonitrile, and benzene. Thus, when **1a** was heated with **2** in a pressure tube in benzene at 82 °C for 5 h, evaporation of the solvent gave essentially pure desired carbamate **6a** (Table 1/entry1). Further purification by recrystallization followed by flash chromatography of the mother liquor afforded a 92% yield of analytically pure sample. As shown in Table 1/entry 2, the Diels−Alder reaction of 2-methoxyfuran **1b** with **2** furnished either **3b** or **6b** depending on the isolation method. After heating **1b** with **2** in benzene or THF at 82 °C for 6 h, removal of the solvent afforded pure **3b**. **3b** is stable for storage at −30 °C for at least 1 month and slowly rearranged to phenol **6b** with a half-life of about 2 days at 25 °C. To remove trace amounts of solvent present in the volatile product, **3b** was distilled under vacuum (0.4 mmHg) at 25 °C. Surprisingly, complete conversion to compound **6b** was observed within 10 min. Perhaps self-solvation stabilizes **3b** as a bicyclic molecule, whereas such self-stabilization is lost in the gas state. The cycloaddition of 2-trimethylsilyloxyfuran **1c** with **2** in benzene or THF initially gave a 93% yield of pure bicyclic compound **3c**. **3c** was more stable than **3b** and could be distilled without aromatization at 35 °C. Complete conversion of **3c** to **6c** took 2 months at room temperature as the neat material. However, this rearrangement is accelerated on silica gel, giving exclusively **6c** during flash chromatography. Less electron-donating substituents such as methyl carbonate (entry 4) and pivaloyloxy groups (entry 5) failed to promote the rearrangement of **3d** or **3e** at room temperature, even with assistance of 1% HCl in aqueous THF. Only bicyclic products **3d** and **3e** were isolated in 100 and 98% yields, respectively. To introduce a tributylstannyl functionality at position-4 of **6** for Stille-type coupling reactions, tributylstannylfuran **1f** was subjected to the Diels−Alder reaction. 7-Oxabicyclic tin derivative **3f** was isolated in quantitative yield as a stable compound (entry 6). An attempt to convert **3f** into the corresponding phenol, using $BF_3{\cdot}OEt_2$ as a catalyst, provided a mixture of materials. Clearly, the ease of rearrangement of **3** to **6** is on the order of NHBOC >

Table 1. Diels-Alder Reactions of Hexafluoro-2-butyne with 2-Heterosubstituted Furans

entry[a]	**1**, XR	product	yield[b]
1	**1a**, NHBOC	**6a**	92%
2	**1b**, OCH_3	**3b**/**6b**	87%
3	**1c**, OTMS	**3c**/**6c**	93%
4	**1d**, OCO_2CH_3	**3d**[c]	100%
5	**1e**, $O_2CC(CH_3)_3$	**3e**[c]	98%
6	**1f**, $Sn(Bu^n)_3$	**3f**[c]	100%

[a] All reactions were performed in benzene at 82 °C (entries 1−5) or at 110 °C (entry 6) for 5−15 h. [b] Isolated yields based on furans used. [c] No rearrangement to **6** was detected by ^1H NMR over 2 months at 25 °C.

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(14) Balthazor, T.; Williams, E. *Synth. Commun.* **1992**, *22*, 1023.
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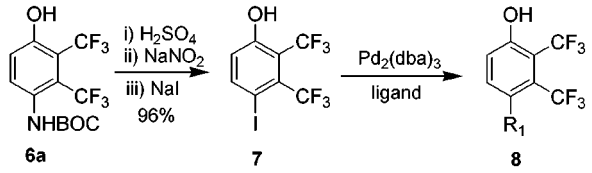
OCH_3 > $OSi(CH_3)_3$ > OCO_2CH_3 ~ $O_2CC(CH_3)_3$ ≫ $Sn(CH_3)_3$.

Phenols **6a**−**c** were convenient building blocks for more elaborate 1,4-disubstituted compounds. Carbamate **6a** was converted to iodophenol **7** in one pot, as shown in Scheme 2. When **6a** was heated in a mixture of 30% H_2SO_4 and

Scheme 2



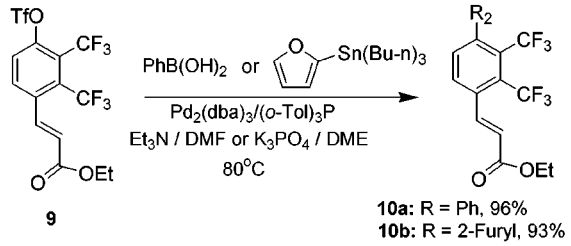
DMSO at 50 °C, complete BOC-deprotection was detected by HPLC within 2 h. The resulting aniline was then treated with $NaNO_2$ at 0 °C. Clean conversion to the corresponding diazonium salt was accomplished in 1 h as monitored by HPLC. After treating the diazonium salt with NaI, 2,3-di(trifluoromethyl)-4-iodophenol **7** was isolated in 96% yield. Because of the low aqueous solubility of both intermediates (the aniline and diazonium salt) in this sequence, a cosolvent (i.e., DMSO) was critical to the high-yielding three-step reaction. Iodophenol **7** served as a versatile building block for introducing substitutions ortho to both trifluoromethyl groups. This type of 1,2,3,4-subsitution pattern in general is not readily accessible by traditional electrophilic modifications.

As illustrated in Scheme 2 and Table 2, the 4-iodo functional group in **7** readily participates in Heck, Stille, and Suzuki reactions. Optimal conditions for the Heck reaction of **7** with ethyl acrylate employed $Pd_2(dba)_3$ as the palladium source and tri-*o*-tolylphosphine as ligand at 70 °C for 15 h, which gave cinnamate **8a** in excellent yield (Table 2/entry 1). Lower yields were obtained at higher temperatures. Tetrakis(triphenylphosphine)palladium(0) worked equally well for this transformation.

When iodophenol **7** was heated with tributylstannylfuran in DMF in the presence of $Pd_2(dba)_3$/(*o*-tol)$_3$P (entry 2), furyl phenol **8b** was obtained in 96% yield. An attempted Suzuki reaction of **7** with phenylboronic acid in the presence of tri-*o*-tolylphosphine led to a low yield of biphenyl **8c** (entry 3). The Buchwald ligand Cy-MAP (2-dicyclohexylphosphanyl-2′-dimethylaminobiphenyl)[17,18] was found to be superior for this coupling reaction (entry 4, 61% vs 42% for (*o*-tol)$_3$P as ligand). The Suzuki coupling of **7** and 5-acetylthiophene-2-boronic acid with Cy-MAP as ligand afforded a 94% yield of the corresponding thiophene derivative **8d**.

The hydroxy functionality of the iodophenol **7** provided a handle to introduce other functional groups. Representative examples for these transformations are shown in Scheme 3.

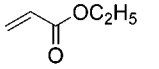
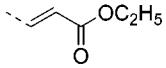
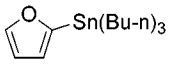
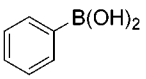
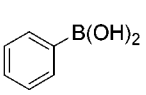
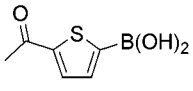
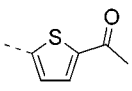
Scheme 3



Triflate **9**, which was prepared using standard conditions (Tf_2O/pyridine), was reacted with phenylboronic acid and $Pd_2(dba)_3$/(*o*-tol)$_3$P to afford phenyl analogue **10a** in nearly quantitative yield. Under a commonly employed Stille protocol for aryl triflate coupling ($Pd_2(dba)_3$/(*o*-tol)$_3$P/LiCl), conversion of **9** to its furan derivative stopped halfway through (52% conversion by HPLC at 80 °C for 2 h), even with extended reaction times (53% conversion at 80° for 24 h). No hydrolysis of the triflate group was detected. When LiCl was replaced with triethylamine, the same reaction with tributylstannylfuran completed within 2 h, affording 93% of furan derivative **10b**.

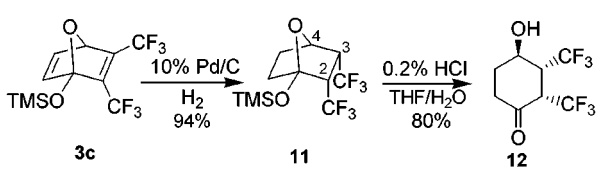
Depicted in Scheme 4 is a representative example of the conversion of **3c** to 2,3-di(trifluoromethyl)cyclohexanone

Table 2. Reactions of 4-Iodo-2,3-di(trifluoromethyl)phenol **7**

entry[a]	reagent	product (**8**, R_1 =)		yield[b]
1			**8a**	91%
2			**8b**	96%
3			**8c**	42%
4			**8c**	61%
5			**8d**	94%

[a] All of these reactions were performed in DME with (*o*-tol)$_3$P (entries 1−3) or Cy-MAP: 2-dicyclohexylphosphanyl-2′-dimethylaminobiphenyl (entries 4−5) as ligand and with Et_3N (entries 1−2) or K_3PO_4 (entries 3−5) as base at 70−80 °C for 3−15 h. [b] Isolated yields based on iodides used.

Scheme 4



derivative **12**, thus opening an entry to a regio- and stereospecific synthesis of ditrifluoromethylated cyclohexanone. Hydrogenation of **3c** with 10% palladium on carbon in ethyl acetate afforded only the endo isomer **11** in 94% yield. The exo hydrogen at C-3 was assigned by comparing its coupling constant to the bridge proton H_4 ($J_{3,4} = 5.2$ Hz) with the structually related literature precedent (~5 Hz for an exo hydrogen versus ~0 Hz for an endo hydrogen).[19−23] Treatment of **11** with 0.2% HCl in aqueous THF afforded cyclohexanone **12** in 80% yield. No epimerization was detected by ^{1}H NMR during the hydrolysis. Compound **12** could serve as a versatile building block for introduction of trifluoromethyl groups into more complex natural product-like compounds.

In summary, the 4-iodo-2,3-di(trifluoromethyl)phenol **7**, prepared in three steps from commercially available material, is a very convenient building block for installing a variety of substitutions at the 1- and 4-positions through Heck, Stille, and Suzuki reactions of the iodide or derived triflate.[24] All of these reactions proceeded in high yields and were amenable to large scale, thus constituting a facile and general synthesis of 1,4-disubsituted-2,3-di(trifluoromethyl)benzenes. Applications of this methodology for the synthesis of pharmaceutically interesting compounds are in progress and will be published in due course.

Supporting Information Available: Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Characterization of **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 9H), 1.69 (tdd, J = 12.8, 5.1, 1.8 Hz, 1H), 2.04 (m, 1H), 2.16 (m, 1H), 2.33 (ddd, J = 12.9, 8.8, 4.4 Hz, 1H), 2.79 (dqd, J = 12.5, 10.6, 2.3 Hz, 1H), 3.22 (dqdd, J = 12.5, 10.6, 5.1, 1.7 Hz, 1H), 4.53 (t, J = 5.2 Hz, 1H); MS (APCI) *m*/*e* 312 (90%), 342 (100%); IR (neat) 2964 (w), 1379 (m), 1150 (s) cm^{-1}. Anal. Calcd for $C_{11}H_{16}F_6O_2Si$: C, 40.99; H, 5.36. Found: C, 41.15; H, 5.42.

(24) **Procedure for preparation of 4-iodo-2,3-di(trifluoromethyl)-phenol 7:** Hexafluoro-2-butyne **2** (1.7 g, 10.5 mmol) was condensed to a 60 mL pressure tube by a dry ice/acetone cooling bath. A solution of furan-2-ylcarbamic acid *tert*-butyl ester **1** (XR = NHBOC, 1.60 g, 8.7 mmol)[16] in dry benzene (15 mL) was slowly added through a septum. The pressure tube was then capped and heated in a 82 °C oil bath for 5 h. After being cooled to rt, the reaction mixture was concentrated, and the residue was crystallized from a mixture of CH_2Cl_2 and hexane. The white crystalline material was collected by filtration, washed with CH_2Cl_2/hexane, and dried (1.83 g). The mother liquor was concentrated and purified by flash chromatography (30% EtOAc in hexane) to give a second batch of **6a** (0.93 g). Total yield: 92%. A solution of **6a** (3.32 g, 9.6 mmol) in a mixture of DMSO (50 mL) and 30% H_2SO_4 (50 mL) was heated at 50 °C for 2 h. The resulting clear solution was cooled to 0 °C, and a solution of $NaNO_2$ (994 mg, 14.4 mmol) in H_2O (5 mL) was added. The reaction mixture was stirred at 0 °C for 1 h, after which a solution NaI (4.3 g, 28.8 mmol) in H_2O (5 mL) was added. After 1 h of stirring at room temperature, another batch of NaI (4.3 g) in H_2O (5 mL) was then added. The reaction mixture was stirred for another hour. EtOAc was added, and the mixture was washed sequentially with brine, 10% $NaHSO_3$, and water. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (20% EtOAc in hexane) to give **7** as white solid (3.29 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.9 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.20 (q, J = 6.5 Hz, 1H); MS (APCI) *m*/*e* 355(M − H)$^-$; IR (KBr) 3356 (m), 1584 (w), 1148 (s) cm^{-1}. Anal. Calcd for $C_8H_3F_6IO$: C, 26.99; H, 0.85. Found: C, 26.87; H, 0.88.