Regioselective Synthesis of Rare 3-Halomethylphenols Based on Formal [3+3] Cyclizations of 1,3-Bis(trimethylsilyloxy)-1,3-butadienes

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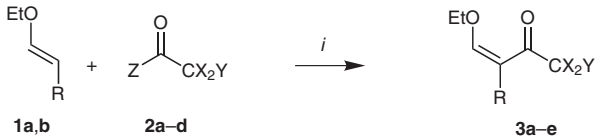
Abstract: The cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with halo-substituted enones afforded 3-difluorochloromethyl-, 3-difluorobromomethyl-, 3-dichloromethyl-, and 3-trichloromethylphenols with very good regioselectivity. The hydrolysis of the dichloromethyl group gave functionalized 3-formylphenols, which are not readily available by other methods.

Key words: arenes, cyclization, regioselectivity, silyl enol ethers

Mixed trihalomethylarenes constitute a small, but important group of fluorinated and chlorinated arenes which are of considerable relevance in medicinal chemistry.[1] For example, chlorodifluoromethylarenes have been shown to act as tyrosine kinase inhibitors.[2] Chlorodifluoromethyl-substituted benzene derivatives have been prepared by reaction of arenes with bis(chlorodifluoroacetyl)peroxide.[3] In addition, the UV-mediated reaction of difluoromethylarenes with chlorine has been reported.[4] Chlorodifluoromethylarenes are also available by reaction of (ethylthio)difluoromethylarenes with BrF_3[5] and by fluorination of trichloromethylarenes (using Olah's reagent or KF in ionic liquids).[6] Bromodifluoromethylarenes have only scarcely been reported in the literature to date. They have been prepared by reaction of tribromomethylarenes with SbF_3,[7] and by UV-mediated bromination of difluoromethylarenes (using bromine[8] or NBS[9]). Dichloromethyl-substituted arenes have been reported to show antiasthmatic activity,[10] irreversible inhibition of yeast α-glucosidase,[11] and antibiotic activity.[12] Most syntheses of dichloromethylarenes rely on the chlorination of an aldehyde group using chlorine/triphenyl phosphite,[13] PCl_5,[14] $SOCl_2$,[15] or Ni/Cu/CCl_4.[16] In addition, the reaction of arenes with dichlorocarbene has been reported.[17] Known methods for the synthesis of di- or trihalomethylarenes are limited, despite their utility, by several drawbacks such as harsh reaction conditions, extremely long reaction times (up to 42 d),[8] and low chemo-[14,15] or regioselectivity.[3,17]

Some years ago, Chan and coworkers developed[18] an elegant approach to salicylates based on formal [3+3] cyclizations[19] of 1,3-bis(trimethylsilyloxy)-1,3-butadienes.[20] Recently, we reported the application of this method to the synthesis of trifluoromethyl-substituted arenes.[21] Herein, we report, for the first time, the synthesis of difluorochloromethyl-, difluorobromomethyl-, dichloromethyl-, and trichloromethyl-substituted phenols. The 3-dichlorophenols were transformed into preparatively functionalized 3-formylphenols which are not readily available by other methods. In contrast to the halogenation reactions outlined above, our approach to 3-halomethylphenols relies on a building block strategy. Noteworthy, the starting materials, 3-(halomethyl)prop-2-en-1-ones, are readily available by condensation of enol ethers with halomethylacetic acid derivatives.

The reaction of difluorochloroacetic anhydride (**2a**) with ethylvinyl ether (**1a**) afforded the known[22] enone **3a** (Scheme 1, Table 1). The reaction of acid chlorides **2b–d** with enol ethers **1a**,**b** gave the difluorobromomethyl-, dichloromethyl-, and trichloromethyl-substituted enones **3b–e**. The synthesis of **3d** has been previously reported.[23]



1a,**b** **2a–d** **3a–e**

Scheme 1 Synthesis of **3a–e**. *Reagents and conditions*: (*i*) $TiCl_4$, CH_2Cl_2, –78 to 20 °C.

The $TiCl_4$-mediated reaction of **3a** with 1,3-bis(silyloxy)-1,3-butadiene **4a**, readily available from acetylacetone,[18,24] afforded 2-acetyl-3-(chlorodifluoromethyl)phenol **5a** (Scheme 2).[25] During the optimization of this reaction, it proved to be important that the reaction is carried out in a (highly) concentrated solution. The regioselective formation of **5a** can be explained by conjugate

Table 1 Synthesis of **3a–e**

1	2	3	Z	R	X	Y	Yield of **3** (%)[a]
a	**a**	**a**	ClF_2CCO_2	H	F	Cl	91
b	**b**	**b**	Cl	H	F	Br	71
a	**b**	**c**	Cl	Et	F	Br	21
a	**c**	**d**	Cl	H	Cl	H	67
a	**d**	**e**	Cl	H	Cl	Cl	54

[a] Yields of isolated products.

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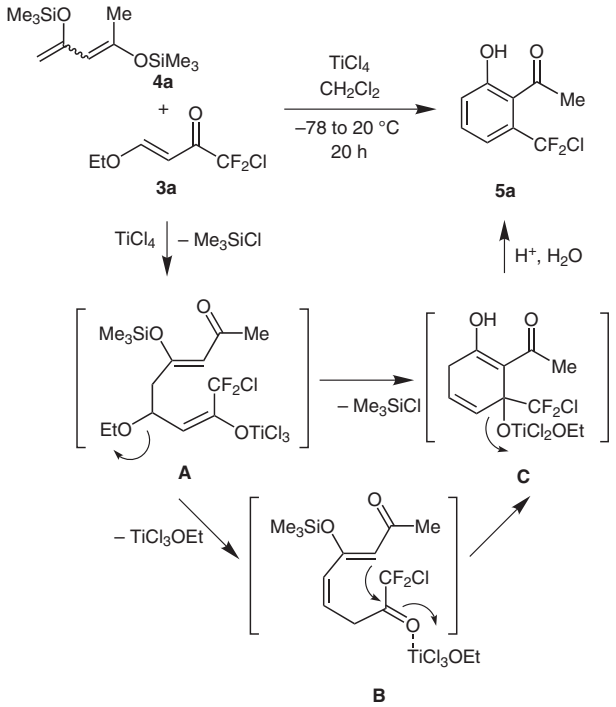
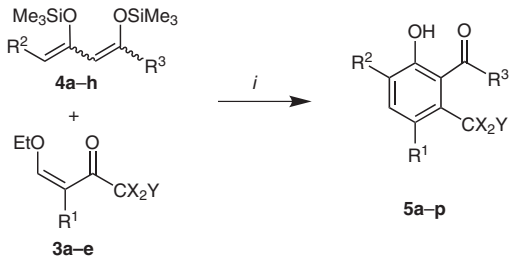


Scheme 2 Possible mechanism of the formation of **5a**



Scheme 3 Synthesis of **5a**–**p**. *Reagents and conditions*: (*i*) $TiCl_4$, CH_2Cl_2, –78 to 20 °C.

addition of the terminal carbon atom of the 1,3-bis(silyl enol ether) to the enone, cyclization by attack of the central carbon atom onto the carbonyl group, and subsequent aromatization.

The $TiCl_4$-mediated reaction of **3a**–**e** with 1,3-bis(silyloxy)-1,3-butadienes **4a**–**h**, readily available from the corresponding 1,3-dicarbonyl compounds,[18,24] gave the 3-difluorochloromethyl-, 3-difluorobromomethyl-, 3-dichloromethyl-, and 3-trichloromethyl-phenols **5a**–**p** (Scheme 3, Table 2). The structures of all products were established by spectroscopic methods.

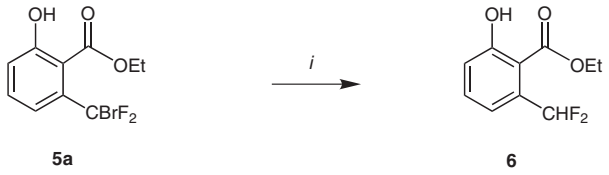
The reduction of 3-(bromodifluoromethyl)phenol **5a**, following a procedure reported by Dolbier and co-workers,[26] afforded the 3-(difluoromethyl)phenol **6** (Scheme 4). Noteworthy, the direct synthesis of **6** from **4a** and the corresponding enone failed.

The 3-dichloromethylphenols **5k**–**p** also represent useful synthetic building blocks. For example, the 6-formyl-2-hydroxybenzoate **6** was prepared in good yield by reaction of **5l** with NaOMe and MeOH and subsequent addition of hydrochloric acid (Scheme 5). Related transformations of

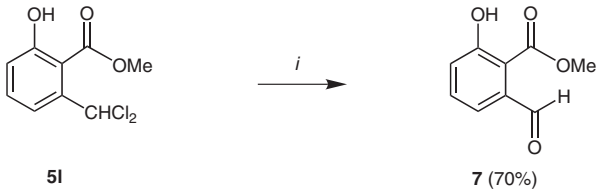
Table 2 Synthesis of **5a**–**p**

3	4	5	X	Y	R^1	R^2	R^3	Yield of **5** (%)[a]
a	**a**	**a**	F	Cl	H	H	Me	43
a	**b**	**b**	F	Cl	H	OMe	OMe	50
a	**c**	**c**	F	Cl	H	Et	OMe	40
b	**d**	**d**	F	Br	H	H	OEt	55
b	**e**	**e**	F	Br	H	*n*Pr	OMe	53
b	**a**	**f**	F	Br	H	H	Me	33
b	**b**	**g**	F	Br	H	OMe	OMe	67
b	**f**	**h**	F	Br	H	Et	OEt	47
b	**g**	**i**	F	Br	H	H	OMe	57
c	**f**	**j**	F	Br	Et	Et	OEt	48
d	**a**	**k**	Cl	H	H	H	Me	34
d	**g**	**l**	Cl	H	H	H	OMe	46
d	**h**	**m**	Cl	H	H	H	Ph	37
d	**c**	**n**	Cl	H	H	Et	OMe	50
d	**b**	**o**	Cl	H	H	OMe	OMe	36[b]
e	**d**	**p**	Cl	Cl	H	H	OEt	34

[a] Yields of isolated products.
[b] Hydrolysis of the $CHCl_2$ group into CHO.



Scheme 4 Synthesis of **6**. *Reagents and conditions*: (*i*) $Na_2S_2O_4$, $NaHCO_3$, DMF–H_2O (4:1), 65 °C, 4 h.



Scheme 5 Synthesis of **7**. *Reagents and conditions*: (*i*) 1) NaOMe (3.0 equiv), MeOH, 48 h, 20 °C; 2) HCl (10%).

other derivatives also proved to be successful. This transformation is of preparative utility, since functionalized 3-formyl-phenols are not readily available by other methods.

In conclusion, we reported a convenient and regioselective synthesis of 3-difluorochloromethyl-, 3-difluorobromomethyl-, 3-dichloromethyl-, and 3-trichloromethylphenols. The hydrolysis of the dichloromethyl group allows for a convenient and regioselective synthesis

of functionalized 3-formylphenols. The scope of this method and applications are currently being studied.

Acknowledgment

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(25) **General Procedure for the Synthesis of 5a–p**
To CH_2Cl_2 solution (4 mL) of **3a–e** (2.0 mmol) and of **4a–i** (2.0 mmol) was added $TiCl_4$ (2.0 mmol) at –78 °C under argon atmosphere. The temperature of the solution was allowed to rise to 20 °C during 20 h. The solution was poured into an aq solution of HCl (10%). The organic and the aqueous layer were separated and the latter was extracted (3×) with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, heptane–EtOAc = 10:1).
Methyl 6-(Dichlorofluoromethyl)-2-hydroxy-3-methoxybenzoate (5b)
Starting with **3a** (370 mg, 2.0 mmol), **4b** (581 mg, 2.0 mmol), and $TiCl_4$ (380 mg, 2.0 mmol), **5b** was isolated as a colorless oil (261 mg, 50%); mp 50–51 °C; R_f = 0.78 (*n*-heptane–EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (s, 1 H, OH), 7.23 (d, ^3J = 8.8 Hz, 1 H, CH), 6.94 (d, ^3J = 8.8 Hz, 1 H, CH), 3.97, 3.96 (s, 3 H, OMe). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.4 (O–C=O), 149.7, 146.6 (C–O), 126.5 (t, $J_{C,F}$ = 27.0 Hz, C-6), 125.3 (t, $J_{C,F}$ = 289.8 Hz, CF_2Cl), 117.9 (t, $J_{C,F}$ = 7.8 Hz, C-5), 115.2 (t, $J_{C,F}$ = 2.8 Hz, C-1), 111.5 (C-4), 56.3, 52.7 (OMe). ^{19}F NMR (235 MHz, $CDCl_3$): δ = –45.0 (CF_2Cl). IR (KBr): ν = 3466 (br, m), 2969 (w), 2843 (w), 1735 (s), 1616 (m), 1590 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 268 (21) [M$^+$, ^{37}Cl], 266 (62) [M$^+$, ^{35}Cl], 236 (37), 234 (100), 211 (64), 198 (90). HRMS (EI, 70 eV): *m/z* calcd for $C_{10}H_9F_2ClO_4$ [M$^+$, ^{35}Cl]: 266.01519; found: 266.015398.

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