Preparation of 4-trifluoroethylidene-1,3-dioxolane derivatives via new stable (trifluoromethyl)ethynylation reagent

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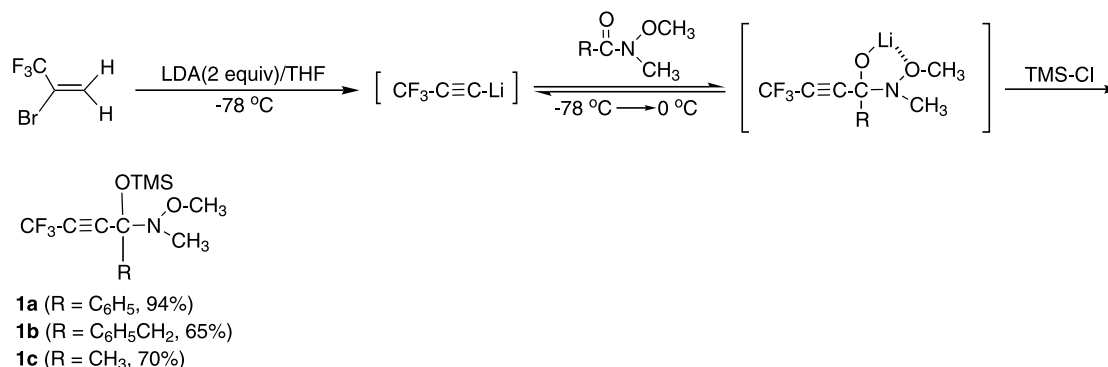[a]*Department of Chemistry, Yonsei University, Wonju, South Korea*
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Abstract—Perfluoroalkylated 4-trifluoroethylidene-1,3-dioxolane derivatives **2a**–**q** were prepared in excellent yields from the reaction of new stable (trifluoromethyl)ethynylation reagent **1a** with 1.3 equiv. of TBAF at –15°C for 10 min, followed by treatment with 2 equiv. of phenyl perfluoroalkylated ketone derivatives at room temperature. The reaction of **1a** with 1.3 equiv. of TBAF, followed by treatment with 1 equiv. of aldehyde or ketone at –15°C for 10 min and then with trifluoroacetophenone (1 equiv.) at room temperature afforded perfluoroalkylated 4-trifluoroethylidene-1,3-dioxolane derivatives **2t**–**u** in moderate yields. © 2003 Elsevier Ltd. All rights reserved.

In recent years, considerable effort has been paid to the synthesis of fluorinated 1,3-dioxolane compounds because of their application to material science. For example, 4-trifluoroethylidene-1,3-dioxolane derivatives exhibited nonlinear optical properties[1] and 2,2-bis(trifluoromethyl)-4,5-dichloro-4,5-difluoro-1,3-dioxolane is a precursor to 2,2-bis(trifluoromethyl)-4,5-difluoro-1,3-dioxole[2] which is a monomer for a new Teflon-AF fluorocopolymer showing outstanding thermal and chemical stability. Fluorinated dioxolane exocyclic olefins are also a quite useful intermediate to give corresponding epoxides which are useful as lubricants, curing materials, adhesives and coatings.[3] In spite of

their importance in material science, methodology for the preparation of fluorinated dioxolane derivatives has been quite limited. Generally, 4- or 5-fluorinated 1,3-dioxolanes were prepared from the fluorination of 4- or 5-chlorinated 1,3-dioxolane which can be prepared via chlorination of 1,3-dioxolane.[4] Radical addition reaction of 1,3-dioxolane with perfluoro-1-alkenes in the presence of BPO also afforded 4-fluoroalkylated 1,3-dioxolane in excellent yields.[5] 2,2-Bis(trifluoromethyl)-4-methylidene as an exocyclic olefin was synthesized via dehydrobromination of 2,2-bis(trifluoromethyl)-4-bromomethyl-1,3-dioxolane prepared from the reaction of epibromohydrin with hexafluoroacetone.[3] Ishihara

1a (R = C₆H₅, 94%)
1b (R = C₆H₅CH₂, 65%)
**1c** (R = CH₃, 70%)

Scheme 1.

reported that 2,5-disubstituted 4-trifluoroethylidene-1,3-dioxolanes as trifluoromethylated exocyclic olefin can be prepared from the reaction of trifluoropropyne with enol silyl ether generated from aldehyde in the presence of tetrabutylammoniun fluoride.[6] Similarly, the reaction of 2-bromotrifluoropropene with ketones having α-hydrogen from carbonyl group in the presence of sodium methoxide also afforded 2,2,5,5-tetra-substituted 4-trifluoroethylidene-1,3-dioxolanes in high yields.[1] Although the reaction mechanisms of these two reactions are not clear, it seems likely that generation of enolate as an intermediate is a key step to proceed those reactions. Therefore, aldehydes or ketones having α-hydrogen from carbonyl group must be used to give 4-trifluoroethylidene-1,3-dioxolanes in these reactions. To overcome this limitation and introduce perfluoro-alkyl group on the ring, we wish to describe a novel and efficient method for the synthesis of 4-trifluoroethyli-dene-1,3-dioxolane derivatives via new stable (trifl-uoromethyl)ethynylation reagent.[7,8]

New stable (trifluoromethyl)ethynylation reagents **1a–c** were easily prepared in 70–94% yields from the reaction of Weinreb amides with trifluoropropynyl lithium gen-erated from the reaction of 2-bromotrifluoropropene with LDA at −78°C,[9] followed by quenching with trimethylsilyl chloride (Scheme 1). The use of trifluoro-propynyl lithium generated from the reaction of trifl-uoropropyne with *n*-BuLi provided (trifluoromethyl)-ethynylation reagent **1a** in only 80% yield.[10] This result is different from Tipping's work in which treatment of an ethereal solution of the Weinreb amide with an ethereal solution of trifluoropropynyl lithium resulted in tar formation.[11]

We examined the potential of **1a–c** as (trifl-uoromethyl)ethynylation reagent via the reaction of **1a–c** with tetrabutylammonium fluoride (TBAF), fol-lowed by reaction with 2,2,2-trifluoroacetophenone at several reaction temperature to give 4-trifluoroethyli-dene-1,3-dioxolane derivative **2a**. It was found that the reaction of **1a** (1.3 equiv.) with TBAF (1.3 equiv.) in ether at −15°C for 10 min, followed by reaction with 2,2,2-trifluoroacetophenone (2 equiv.) at room tempera-ture for 1 h, afforded **2a** (1:1 diasteromer ratio) in 99% yield, while **1b** and **1c** provided **2a** under the same reaction conditions in 90% and 85% yields, respectively. When the reaction of **1a** with TBAF was performed at −35°C for 10 min, followed by reaction with 2,2,2-trifl-uoroacetophenone at room temperature for 1 h, **2a** was obtained in lower yield (80%). As was mentioned in previous paper,[10] intermediate A (Scheme 2) generated from the reaction of **1a** with TBAF was suggested to have an equilibrium with *N*-methoxy-*N*-methylbenza-mide and tetrabutylammonium trifluoropropynyl anion which acts as a (trifluoromethyl)ethynylation reagent to react with 2,2,2-trifluoroacetophenone. *N*-Methoxy-*N*-methylbenzamide which is a key reagent to synthesize **1** and relatively expensive was always recovered in quan-titative yield at the end of reaction. We also carried out the direct reaction of 2,2,2-trifluoroacetophenone (2 equiv.) with trifluoropropynyl lithium generated from the reaction of 2-bromotrifluoropropene with LDA at −78°C or from the reaction of trifluoropropyne with *n*-BuLi at −78°C, but desired product **2a** was obtained in only 35% yield. Tetrabutylammonium, the counter cation of trifluoropropynyl anion, plays an important role to afford **2a**.

The reactions of **1a** with 2,2,2-trifluoroacetophenone or pentafluoroethyl phenyl ketone derivatives having pro-ton, chloro, fluoro, methoxy, trifluoromethyl, vinyl and phenoxy group on the benzene rings afforded **2a–o** in 97–99% yields. However, the longer reaction time was required in reaction of **1a** with ketone derivatives hav-ing chloro, fluoro, 2-methoxy and trifluoromethyl on the benzene ring. Trifluoromethylated ketones having heterocyclic moieties such as a thiophene and a furan also reacted with tetrabutylammonium trifluoropropy-nyl anion to give the corresponding dioxolanes **2p** and **2q** in 98–99% yields. When **1a** was reacted with TBAF, followed by reaction with 1,1,1-trifluoroacetone under the same reaction condition, however, several products which could not be identified were obtained. The treat-ment of tetrabutylammonium trifluoropropynyl anion with 2 equiv. aldehyde such as butanal or cyclohexan-carbaldehyde resulted in the formation of the corre-sponding 4-trifluoroethylidene-1,3-dioxolane derivatives **2r** and **2s** in 72–74% yields, while the reaction with 2
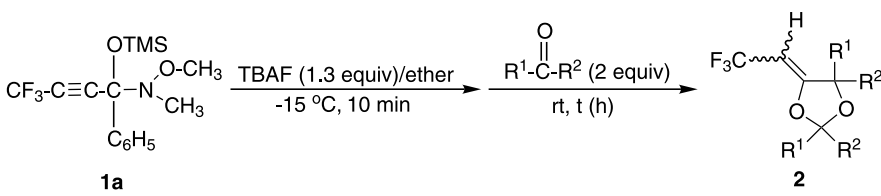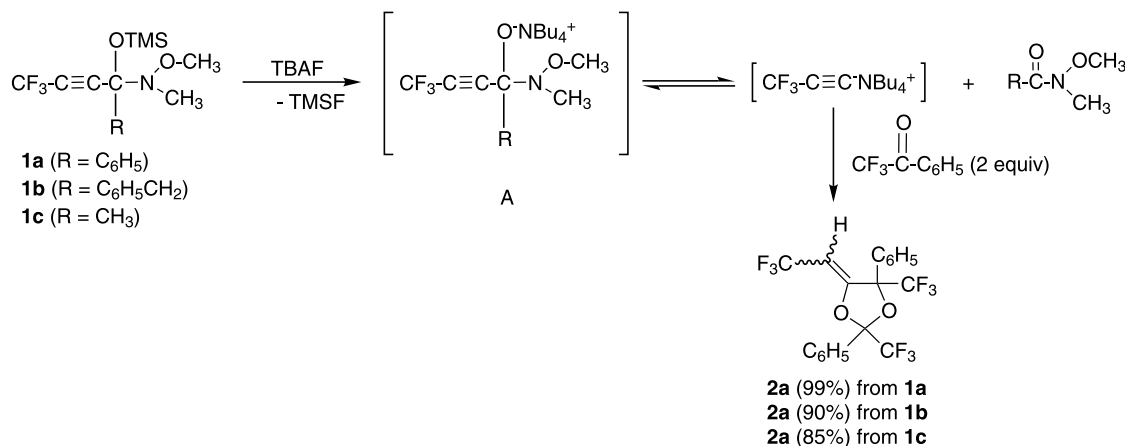

Scheme 2.

equiv. of ketones did not provide any desired products. The experimental results of these reactions are summarized in Table 1. When tetrabutylammonium trifluoropropynyl anion was treated with 1 equiv. of aldehyde or ketone, followed by treatment with 1 equiv. of trifluoroacetophenone, the corresponding 4-trifluoroethylidene-1,3-dioxolane derivatives **2t** and **2u** were obtained in 72% and 82% yields, respectively (Scheme 3).

A typical reaction procedure for the preparation of **2a** is as follows. A 25 mL two-neck round bottom flask equipped with a magnetic stirrer bar, a septum and reflux condenser connected to an argon source was charged with **1a** (0.430 g, 1.3 mmol) and ether (5 mL) and then cooled to −15°C. Tetrabutylammonium fluoride (1.3 mmol, 1.0 M solution in THF) was slowly added into flask and then the mixture was stirred for 10 min. After the reaction mixture was warmed to room temperature, trifluoroacetophenone (0.212 g, 2.0 mmol)

was added and then allowed to stir for another 1 h. The reaction mixture was extracted with ether twice. The ether solution was dried over anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (9:1) provided 0.219 g of **2a** ($E:Z=1:1$) in 99% yield. **2a** (one isomer): mp 64–65°C: ^{1}H NMR (CDCl$_3$) δ 7.70–7.66 (m, 4H), 7.52–7.48 (m, 6H), 5.40 (q, $J=7.1$ Hz, 1H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −58.64 (d, $J=7.1$ Hz, 3F), −77.17 (s, 3F), −82.51 (s, 3F); MS, m/z (relative intensity) 442 (M$^+$, 1), 373 (32), 199 (13), 171 (10), 151 (29), 105 (100), 77 (12); IR (KBr) 3136, 3078, 2937, 1709, 1500, 1454, 1279, 1207, 1132, 1063, 731, 698 cm^{-1}. Anal. calcd for $C_{19}H_{11}F_9O_2$: C, 51.60; H, 2.51. Found: C, 51.44; H, 2.47%. **2a** (other isomer): oil: ^{1}H NMR (CDCl$_3$) δ 7.52–7.17 (m, 10H), 5.43 (q, $J=7.1$ Hz, 1H); ^{19}F NMR (CDCl$_3$, internal standard CFCl$_3$) δ −58.53 (d, $J=7.1$ Hz, 3F), −76.84 (s, 3F), −83.18 (s, 3F); MS, m/z (relative intensity) 442 (M$^+$, 8), 373 (44),

Table 1. Preparation of 4-trifluoroethylidene-1,3-dioxolane derivatives **2**

Compound **2**	R^1	R^2	t (h)	Yield (%)^{a,b}
2a	CF$_3$	C$_6$H$_5$	1	99
2b	CF$_3$	4-F-C$_6$H$_4$	2	98
2c	CF$_3$	4-Cl-C$_6$H$_4$	2	97
2d	CF$_3$	4-CH$_3$O-C$_6$H$_4$	1	99
2e	CF$_3$	2-CH$_3$O-C$_6$H$_4$	3	99
2f	CF$_3$	4-CF$_3$-C$_6$H$_4$	5	98
2g	CF$_3$	3-CF$_3$-C$_6$H$_4$	5	98
2h	CF$_3$	4-CH$_2$=CH-C$_6$H$_4$	1	97
2i	CF$_3$	4-C$_6$H$_5$O-C$_6$H$_4$	1	99
2j	C$_2$F$_5$	C$_6$H$_5$	1	99
2k	C$_2$F$_5$	4-CH$_3$O-C$_6$H$_4$	1	99
2l	C$_2$F$_5$	4-CF$_3$-C$_6$H$_4$	12	97
2m	C$_2$F$_5$	4-Cl-C$_6$H$_4$	2	98
2n	C$_2$F$_5$	4-CH$_2$=CH-C$_6$H$_4$	1	97
2o	C$_2$F$_5$	4-C$_6$H$_5$O-C$_6$H$_4$	1	98
2p	CF$_3$	2-Thienyl	1	98
2q	CF$_3$	2-Furyl	1	99
2r	C$_3$H$_7$	H	1	72
2s	Cy	H	2	74

^{a} Isolated yield.
^{b} All products were obtained as a 1:1 diastereomer mixture.

2t (R^1 = C$_3$H$_7$, R^2 = H)

2u (R$_1$ = R$_2$ = -(CH$_2$)$_5$-)
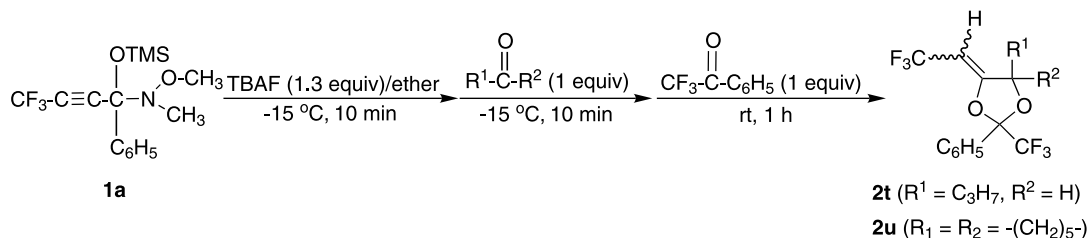
Scheme 3.

199 (93), 171 (70), 151 (100), 105 (20), 77 (66); IR (KBr) 3136, 3078, 2937, 1709, 1500, 1454, 1279, 1207, 1132, 1063, 731, 698 cm^{-1}. Anal. calcd for $C_{19}H_{11}F_9O_2$: C, 51.60; H, 2.51. Found: C, 51.48; H, 2.49%.

Acknowledgements

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