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A novel and facile synthesis of 2,3-dihydrofuran derivatives containing trifluoromethyl group

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Abstract

A series of CF_3-containing 2,3-dihydrofuran derivatives were prepared *via* the reaction of arsonium bromides **1** with β,β-di(trifluoroacetyl)ethylene derivatives **2** in the presence of K_2CO_3, usually in a stereoselective manner with moderate yields. The structures of these compounds were confirmed by ^1H NMR, ^{13}C NMR, IR, MS and HRMS as well.

Keywords: Arsenic ylides; 2,3-Dihydrofurans; Trifluoromethyl; Stereochemistry

1. Introduction

The synthesis of regio- and stereoselective poly- or perfluoroalkylated molecules has become important in the field of pharmaceutical research, owing to their unique physiological and biological properties imparted by a fluoroalkyl group [1]. The importance of dihydrofuran derivatives is apparent as they are present in a wide range of biologically active synthetic and natural products [2]. Moreover, some dihydrofurans are also potentially useful synthetic intermediates [3]. For example, they are precursors of furans by oxidation [4]. Therefore, efficient and general synthetic routes to these heterocycles are of strong interest.

The paper covers the reaction of arsenic ylides with β,β-di(trifluoroacetyl)ethylene derivatives to afford trifluoromethyl containing 2,3-dihydrofuran derivatives *via* Micheal addition in moderate yields with high stereoselectivity.

2. Results and discussion

The reaction of excess arsonium bromides **1a–c** [5] with β,β-di(trifluoroacetyl)ethylene derivatives **2a–c** proceeded rapidly in the presence of K_2CO_3, in anhydrous THF at room temperature to give trifluoromethyl containing 2,3-dihydrofuran derivatives **3** in moderate yields (Scheme 1 and Table 1).

The structure of product **3** was confirmed by means of IR, ^1H and ^{13}C NMR, MS and HRMS, and the configuration **3ab** was assigned *via* its 2D Proton NOESY spectrum. And **3ca** was assigned *via* its ^1H-^1H COSY and 2D Proton NOESY spectrum. According to the spectral analyses, it is believed that the tetrasubstituted dihydrofuran ring bears trifluoromethyl. It is noteworthy that in this reaction no similarly normal Wittig reaction products were detected. It is significant that when R is $–CO_2CH_3$ or –CN, the reaction gave 2,3-dihydrofuran **3** with high stereoselectivity and only one stereoisomer was isolated. In product **3ab**, two protons with chemical shifts δ 4.54 and δ 5.13 ppm attached to the two neighbouring carbon atoms in the ring, respectively showed strong NOE effect. Accordingly, on the basis of this evidence together with the coupling constants, it may be concluded that the dihydrofuran is in *cis* configuration. However, the ^1H-^1H COSY and 2D NOESY of **3ca** is different from those of **3ab**, showing two groups of

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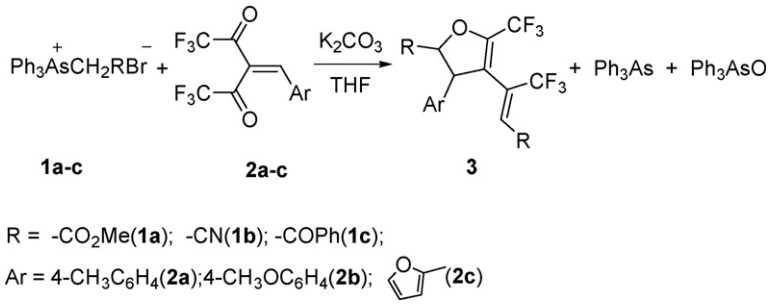


Scheme 1.

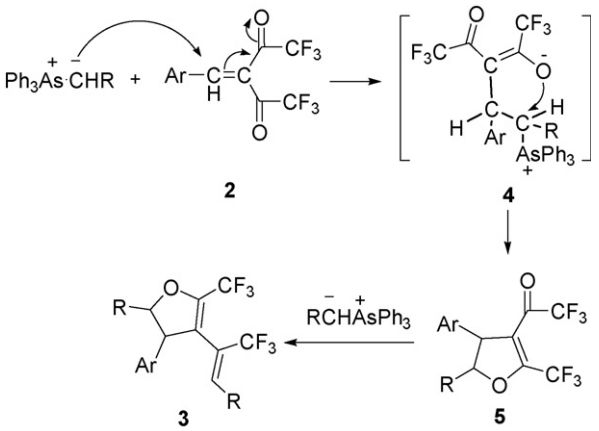
peaks, which indicated a mixture of *cis* and *trans* isomers. And we also proved the product **3c** is a *cis* and *trans* mixture by ^{13}C-^{1}H COSY technique. For example, in product **3cb**, the chemical shifts of C-2 and C-3 of the *cis* and *trans* isomers appear as a pair of peaks, respectively, and the aryl-C of the *cis* and *trans* isomers are no difference in ^{13}C NMR, which indicates the existence of a mixture of *cis* and *trans* isomers.

When one molar arsonium bromides **1** was used, the reaction products were the mixture of 2,3-dihydrofuran **3** and **5**. It is hard to separate. Whereas an excess of arsonium bromides **1** was used in the reaction, **3** was the sole product, as Wittig reaction occurred between arsenic ylide and **5** to form **3** (Scheme 2).

The reaction mechanism shown in Scheme 2 would account for the high stereoselectivity. The arsenic ylide attacked nucleophilically the carbon carbon double bond, by way of a Michael addition, forming intermediate **4**, which could exist in two conformations, **A** and **B** (Scheme 3). It was expected that conformation **B** would be destabilized as the result of the steric interaction of aryl and triphenylarsenylidene groups, and the preferred conformation **A** then underwent *anti*-attacking cyclization to form **5**. A further question concerns the stereoselectivity of **3c**, the *trans*-isomer was also obtained although the *cis*-isomer was the major product due to the competing reaction pathway involving conformation **B**. At the same time, we calculated the energy of conformation **A** and **B** by the computer software. When R was $-CO_2CH_3$ in arsonium bromides **1**, the difference of the energy of conformation **A** and **B** is 9.50×10^3 kcal/mol, so *cis*-isomer was prepared. However, when R was –COPh in arsonium bromides **1**, the difference of the energy of conformation **A** and **B** is 7.75×10^2 kcal/mol, then both the *cis* and *trans* isomers were formed.

Table 1
Preparation of compound **3**

Substrate **1**	Substrate **2**	Product **3**	State	Yield (%)	Ratio of isomers of **3** *cis*:*trans*
a	**b**	**ab**	Yellow oil	63	100:0
a	**c**	**ac**	Yellow oil	70	100:0
b	**b**	**bb**	Yellow oil	50	100:0
b	**c**	**bc**	Yellow oil	48	100:0
c	**b**	**cb**	Yellow oil	56	64:36
c	**c**	**cc**	Yellow oil	54	77:23
c	**a**	**ca**	Yellow oil	61	67:33



Scheme 2.

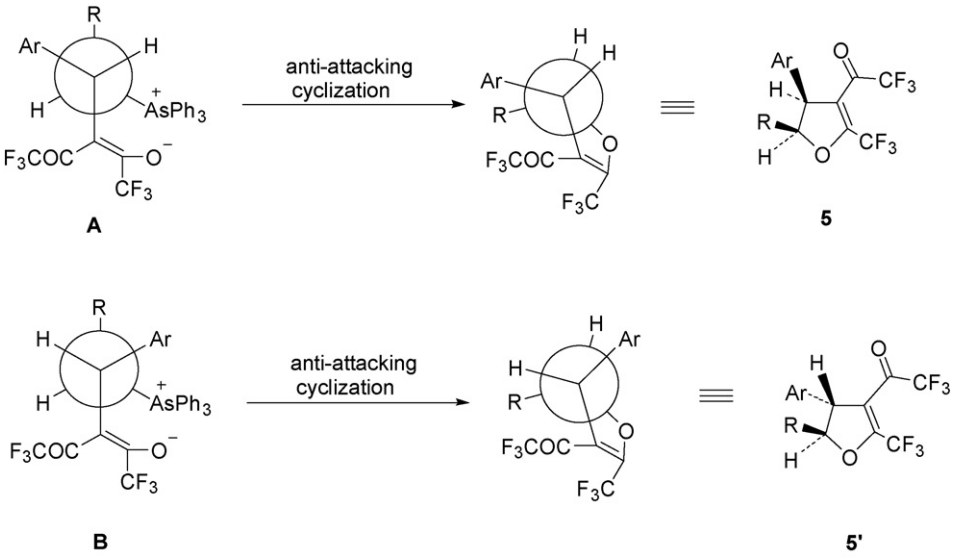
In short, the facile and highly stereoselective synthesis of trifluoromethyl-containing 2,3-dihydrofuran derivatives has been developed *via* the reaction of arsenic ylide with α,β-unsaturated ketones. The easy availability of the starting materials, the reproducibility of triphenylarsine, the simplicity of the procedure, the moderate yield and the high stereoselectivity of the products should offer a great promise for the synthesis of physiological active dihydrofuranoid drugs. Further studies are in progress.

3. Experimental

Melting points were uncorrected. IR spectra were recorded on an AVATAR370 FT spectrophotometer. NMR spectra were determined with DRX 500 MHz spectrometer, using solutions in deuterated chloroform with tetramethylsilane as the internal standard for ^{1}H and ^{13}C nuclei, respectively. ^{19}F NMR spectra were recorded on DRX 500 MHz spectrometer with C_6F_6. *J* values are given in Hz. LRMS spectra were run on a HP 5989A spectrometer. HRMS spectra were run on Waters Micromass GCT. The energy of conformation was calculated by HyPer Chem 7.

3.1. General procedure for the preparation of 2 [6]

A mixture of 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (10 mmol, 2.08 g), 4-methoxy-benzaldehyde (10 mmol, 1.36 g) and acetic anhydride (10 ml) in a 25 flask, equipped



Scheme 3.

with a reflux condenser, drying tube and magnetic stirring bar, was heated at 80 °C for 8 h. Ac_2O and AcOH were removed by distillation, the residue being distilled under vacuum to give **2b** (85%).

3.2. Typical procedure for the preparation of *3*

A mixture of **1** (2.5 mmol), **2b** (1 mmol) and anhydrous THF (3 ml) was added K_2CO_3 (4 mmol, 0.552 g) in a 10 ml flask, the mixture was stirred at room temperature (monitored by TLC). The solvent was removed by evaporation under the reduced pressure and the residue was separated on a silica gel column chromatography (GF_{254}) with petroleum ether–ethyl acetate mixture (v:v = 8:1) as eluent to give product **3**.

3.2.1. 4-(2-Methoxycarbonyl-1-trifluoromethyl-vinyl)-3-(4-methoxy-phenyl)-5-trifluoromethyl-2,3-dihydrofuran-2-carboxylic acid methyl ester (*3ab*)

Yellow oil; IR (film): ν 3390, 2925, 1744, 1515, 1177, 801 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{16}F_6O_4$ (M^+) *m/z* 454.0739, found 454.0743. MS *m/z* 477.1 (M + Na). ^{1}H NMR ($CDCl_3$): 3.69 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.54 (d, J = 7, 1H, furan-H), 5.13 (d, J = 7, 1H, furan-H), 6.42 (s, 1H, CH), 6.83–7.20 (4H, ArH) ppm. ^{19}F NMR ($CDCl_3$): −68.6 (s, CF_3), −66.3 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$): 169.4, 163.3, 159.5, 142.0 (q, 1C, $^2J_{C\text{-}F}$ = 37), 134.8 (q, 1C, $^2J_{C\text{-}F}$ = 37), 130.2, 129.2, 127.7, 125.2, 120.1 (q, 1C, $^1J_{C\text{-}F}$ = 240), 118.5 (q, 1C, $^1J_{C\text{-}F}$ = 237), 114.2, 86.1, 56.3, 55.2, 52.9, 52.1.

3.2.2. 4′-(2-Methoxycarbonyl-1-trifluoromethyl-vinyl)-5′-trifluoromethyl-2′,3′-dihydro-[2,3′]bifuranyl-2′-carboxylic acid methyl ester (*3ac*)

Yellow oil; IR (film): ν 3442, 2960, 1737, 1641, 1188 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{12}F_6O_6$ (M^+) *m/z* 414.0538, found 414.0538. MS *m/z* 436.9 (M + Na). ^{1}H NMR ($CDCl_3$): 3.73 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.80 (d, J = 7.5, 1H, furan-H), 5.34 (d, J = 7.5, 1H, furan-H), 6.23 (d, J = 3.5, 1H, furan-H), 6.31 (m, 1H, furan-H), 6.49 (s, 1H, CH), 7.73 (d, J = 1, 1H, furan-H) ppm. ^{19}F NMR ($CDCl_3$): −68.5 (s, CF_3), −67.0 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$): 169.3, 163.3, 149.3, 143.3 (q, 1C, $^2J_{C\text{-}F}$ = 37.5), 142.5 (q, 1C, $^2J_{C\text{-}F}$ = 37.5), 128.5, 126.7, 122.8, 119.3 (q, 1C, $^1J_{C\text{-}F}$ = 240), 110.9 (q, 1C, $^1J_{C\text{-}F}$ = 240), 110.6, 108.8, 82.7, 53.3, 52.5, 50.3.

3.2.3. 3-[5-Benzoyl-4-(4-methoxy-phenyl)-2-trifluoromethyl-4,5-dihydrofuran-3-yl]-4,4,4-trifluoro-1-phenyl-but-2-en-1-one (*3cb*)

Yellow oil; IR (film): ν 2923, 1693, 1514, 1178, 833, 763, 690 cm^{-1}. HRMS (EI) calcd for $C_{29}H_{20}F_6O_4$ (M^+) *m/z* 546.1266, found 546.1271. MS *m/z* 569.0 (M + Na). ^{1}H NMR ($CDCl_3$): *cis* 3.81 (s, 3H, OCH_3), 5.26 (d, J = 4.5, 1H, furan-H), 5.62 (d, J = 4.5, 1H, furan-H), 6.16 (s, 1H, CH), 7.37–7.80 (m, 14H, ArH) ppm. *Trans* 3.78 (s, 3H, OCH_3), 5.10 (d, J = 8, 1H, furan-H), 5.49 (d, J = 8, 1H, furan-H), 6.12 (s, 1H, CH), 7.30–7.78 (m, 14H, ArH) ppm. ^{19}F NMR ($CDCl_3$): *cis* −81.9 (s, CF_3), −63.9 (s, CF_3) ppm. *Trans* −84.6 (s, CF_3), −61.9 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$): 193.7, 192.6, 154.7, 154.2, 138.4 (q, 1C, $^2J_{C\text{-}F}$ = 37), 134.6, 134.1 (q, 1C, $^2J_{C\text{-}F}$ = 36), 131.3, 130.9, 130.0, 129.8, 129.7, 128.9, 128.8, 128.6, 126.3, 124.4 (q, 1C, $^1J_{C\text{-}F}$ = 245), 122.2 (q, 1C, $^1J_{C\text{-}F}$ = 237), 114.3, 95.3 (*trans*, CH=), 94.4 (*cis*, CH=), 89.6 (*trans*, furan-C), 88.7 (*cis*, furan-C), 55.4, 48.2 (*trans*, furan-C), 46.2 (*cis*, furan-C).

3.2.4. 3-(2′-Benzoyl-5′-trifluoromethyl-2′,3′-dihydro-[2,3′]bifuranyl-4′-yl)-4,4,4-trifluoro-1-phenyl-but-2-en-1-one (*3cc*)

Yellow oil; IR (film): ν 1684, 1592, 1175, 797, 766, 687 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{16}F_6O_4$ (M^+) *m/z* 506.0953, found 506.0953. MS *m/z* 507.0 (M^+ + 1). ^{1}H NMR ($CDCl_3$): *cis* 5.13 (d, J = 3, 1H, furan-H), 6.09 (d, J = 3, 1H, furan-H), 6.15 (s, 1H, CH), 6.27 (d, J = 3, 1H, furan-H), 6.39 (m, 1H, furan-H), 7.44 (d, J = 1, 1H, furan-H), 7.45–

7.77 (m, 10H, ArH) ppm. *Trans* 5.22 (d, $J = 7$, 1H, furan-H), 5.67 (d, $J = 7$, 1H, furan-H), 6.17 (s, 1H, CH), 6.29 (m, 1H, furan-H), 6.33 (m, $J = 3$, 1H, furan-H), 7.36 (d, $J = 1$, 1H, furan-H), 7.40–7.70 (m, 10H, ArH) ppm. ^{19}F NMR ($CDCl_3$): *cis* −82.9 (s, CF_3), −64.2 (s, CF_3) ppm. *Trans* −84.9 (s, CF_3), −63.4 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$): 193.1, 192.0, 155.2, 154.4, 147.2 (q, 1C, $^2J_{C\text{-}F} = 38$), 142.6 (q, 1C, $^2J_{C\text{-}F} = 37$), 134.7, 134.3, 134.0, 129.7, 129.5, 129.0, 128.9, 128.8, 128.4, 126.5 (q, 1C, $^1J_{C\text{-}F} = 235$), 126.3 (q, 1C, $^1J_{C\text{-}F} = 240$), 110.9, 106.0, 95.0 (*trans*, CH=), 93.9 (*cis*, CH=), 85.1 (*trans*, furan-C), 84.4 (*cis*, furan-C), 42.8 (*trans*, furan-C), 42.3 (*cis*, furan-C).

*3.2.5. 3-(5-Benzoyl-4-p-tolyl-2-trifluoromethyl-4,5-dihydro-furan-3-yl)-4,4,4-trifluoro-1-phenyl-but-2-en-1-one (**3ca**)*

Yellow oil; IR (film): ν 1693, 1595, 1177, 803, 763, 689 cm^{-1}. HRMS (EI) calcd for $C_{29}H_{20}F_6O_3$ (M^+) m/z 530.1317, found 530.1310. MS m/z 531.0 ($M^+ + 1$). ^{1}H NMR ($CDCl_3$): *cis* 2.35 (s, 3H, CH_3), 5.31 (d, $J = 4.5$, 1H, furan-H), 5.64 (d, $J = 4.5$, 1H, furan-H), 6.18 (s, 1H, CH), 7.25–7.80 (m, 10H, ArH) ppm. *Trans* 2.31 (s, 3H, CH_3), 5.12 (d, $J = 8$, 1H, furan-H), 5.50 (d, $J = 8$, 1H, furan-H), 6.16 (s, 1H, CH), 7.20–7.78 (m, 10H, ArH) ppm. ^{19}F NMR ($CDCl_3$): *cis* −81.9 (s, CF_3), −63.9 (s, CF_3) ppm. *Trans* −84.5 (s, CF_3), −61.9 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$): 193.7, 192.6, 154.7, 154.2, 136.4 (q, 1C, $^2J_{C\text{-}F} = 37.5$), 134.3 (q, 1C, $^2J_{C\text{-}F} = 38$), 134.1, 131.3, 131.2, 130.9, 129.8, 129.7, 129.6, 128.9, 128.7, 127.3, 126.4 (q, 1C, $^1J_{C\text{-}F} = 240$), 123.4 (q, 1C, $^1J_{C\text{-}F} = 245$), 105.9, 95.4 (*trans*, CH=), 94.4 (*cis*, CH=), 89.9 (*trans*, furan-C), 88.6 (*cis*, furan-C), 48.5 (*trans*, furan-C), 46.4 (*cis*, furan-C), 21.3.

*3.2.6. 4-(2-Cyano-1-trifluoromethyl-vinyl)-3-(4-methoxy-phenyl)-5-trifluoromethyl-2,3-dihydrofuran-2-carbonitrile (**3bb**)*

Yellow oil; IR (film): ν 2927, 2216, 1199, 833, 807 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{10}F_6N_2O_2$ (M^+) m/z 388.0646, found 388.0645. MS m/z 388.0 (M^+). ^{1}H NMR ($CDCl_3$): 3.80 (s, 3H, OCH_3), 4.74 (d, $J = 7$, 1H, furan-H), 5.33 (d, $J = 7$, 1H, furan-H), 6.05 (s, 1H, CH), 6.94–7.23 (4H, ArH) ppm. ^{19}F NMR ($CDCl_3$): −67.8 (s, CF_3), −66.7 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$): 162.2, 150.2, 145.3 (q, 1C, $^2J_{C\text{-}F} = 40$), 138.6 (q, 1C, $^2J_{C\text{-}F} = 40$), 129.3, 125.2 (q, 1C, $^1J_{C\text{-}F} = 240$), 115.4 (q, 1C, $^1J_{C\text{-}F} = 240$), 114.8, 114.3, 113.5, 110.8, 93.6, 75.9, 57.7, 55.5.

*3.2.7. 4′-(2-Cyano-1-trifluoromethyl-vinyl)-5′-trifluoromethyl-2′,3-dihydro-[2,3′]-bifluranyl-2′-carbonitrile (**3bc**)*

Yellow oil; IR (film): ν 2925, 2233, 1198, 802 cm^{-1}. HRMS (EI) calcd for $C_{14}H_6F_6N_2O_2$ (M^+) m/z 348.0333, found 348.0331. MS m/z 348.0 (M^+). ^{1}H NMR ($CDCl_3$): 4.94 (d, $J = 8$, 1H, furan-H), 5.59 (d, $J = 7.5$, 1H, furan-H), 6.13 (d, $J = 1$, 1H, furan-H), 6.35 (s, 1H, CH), 6.55 (m, 1H, furan-H), 6.84 (d, $J = 3.5$, 1H, furan-H) ppm. ^{19}F NMR ($CDCl_3$): −67.8 (s, CF_3), −66.0 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$): 168.6, 146.9, 144.9 (q, 1C, $^2J_{C\text{-}F} = 40$), 131.5 (q, 1C, $^2J_{C\text{-}F} = 40$), 120.9 (q, 1C, $^1J_{C\text{-}F} = 240$), 115.0 (q, 1C, $^1J_{C\text{-}F} = 240$), 113.4, 111.5, 114.1, 110.6, 109.0, 105.7, 72.3, 51.6.

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