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First nucleophilic addition of acetylide to 1,3-diketonate anions: reaction of 1-aryl-4,4,4-trifluorobutane-1,3-diones with sodium acetylide

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ABSTRACT

The nucleophilic addition of sodium acetylide to 1,3-diketonates derived from 1-aryl-4,4,4-trifluorobutane-1,3-diones is reported. Tertiary 1,4-alkynediols containing CF_3 and aroylmethyl groups are synthesized. 5,5′-Diaryl-3,3′-bis(trifluoromethyl)-2,2′-bifurans are prepared via a novel double cyclization of these alkynediols.

Trifluoromethylated propargylic compounds have attracted significant attention mainly due to their biological activity[1] and as excellent building blocks for the preparation of a variety of complex CF_3-containing acyclic and heterocyclic compounds.[2] The most common method for the synthesis of propargylic alcohols and their derivatives is based on the reactions of metal acetylides and ketones.[1e,3] However, there is no data in the literature on the use of 2-unsubstituted 1,3-diketones in similar reactions.

According to the literature,[4] β-diketones (acetylacetones) react with sodium acetylide to give sodium diketonates. Formation of nonelectrophilic enolates is the main reason which prevents nucleophilic addition of the acetylide anion to the 1,3-dicarbonyl compound.

In this Letter, a novel reaction of such β-diketones (1-aryl-4,4,4-trifluorobutane-1,3-diones **1a–d**) with sodium acetylide is described (Scheme 1). It was found that reaction of diketones **1** with excess sodium acetylide proceeded under moderate heating via regioselective nucleophilic addition of the acetylide anion at C-3 (the carbon connected to the CF_3 group). The reaction was conducted by adding a solution of **1** in THF to a suspension of sodium acetylide in a mixture of THF and xylene. After acetylene evolution had ceased (due to the acid–base reaction), the mixture was stirred at ambient temperature for 2 h, then heated at 70–90 °C for 2 h, and quenched with dilute H_2SO_4 to give highly functionalized symmetric tertiary alkynediols, 1,8-diaryl-3,6-dihydroxy-3,6-bis(trifluoromethyl)-oct-4-yne-1,8-diones **2** as novel, interesting CF_3-containing propargylic building blocks (47–71% yield).

The structures of alkynediols **2** were confirmed by ^1H, ^{19}F, ^{13}C NMR and IR spectroscopy, and elemental analysis. Thus, in the ^1H NMR spectrum of alkynediol **2a** two doublets due to the methylene protons appeared at δ 3.30 and 3.63 (^2J = 17.0 Hz).

A singlet due to the two equivalent OH groups at δ 5.35 was observed. Signals due to ten aromatic protons appeared in the range δ 7.47–7.84. In the ^{13}C NMR spectrum of compound **2a**, besides signals of the aromatic carbons, singlets due to the methylene (δ 41.3), alkyne (δ 81.7), and carbonyl (δ 198.1) carbons were observed. The carbinol and trifluoromethyl carbons appeared as characteristic quartets at δ 70.1 ($^2J_{C,F}$ = 32.9 Hz) and δ 122.8 ($^1J_{C,F}$ = 283.8 Hz), respectively.[5]

A high-field singlet in the ^{19}F NMR spectrum of **2a** ($CDCl_3$, C_6F_6) at δ 80.2 confirmed that the CF_3 groups were connected to the sp^3 hybridized carbons. Diastereomeric pairs of **2** were indistinguishable in the NMR spectra due to the long distance between the asymmetric centres (carbons C-3 and C-6), which have a negligibly small mutual asymmetric influence.

A possible mechanism for the reaction involves addition of the acetylide anion to the activated C-3 carbon of diketonate anion **A**. The resulting dianionic intermediate **B** undergoes deprotonation to give trianion **C**. The acetylide anion of **C** attacks a second diketonate anion **A** leading to the formation of tetraionic intermediate **D**. Quenching the reaction with aqueous H_2SO_4 affords alkynediols **2**. No monoaddition products derived from intermediates **B** were found in the crude product. This finding can be explained by the good solubility of disodium diolates **B** in the reaction medium

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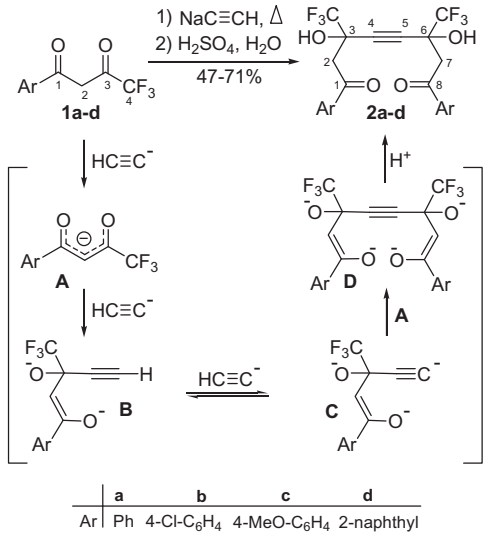
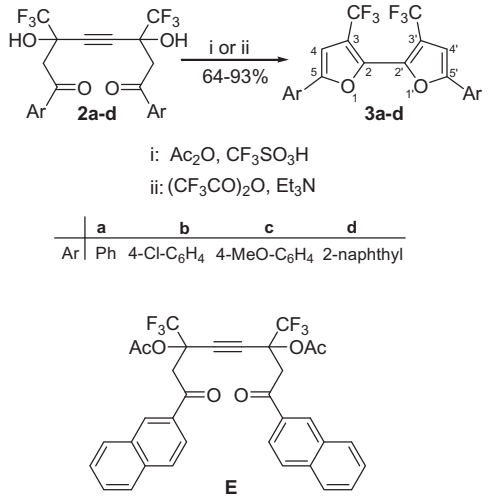


Scheme 1. Synthesis of CF_3-containing alkynediols **2a–d**.



Scheme 2. Synthesis of 5,5′-diaryl-3,3′-bis(trifluoromethyl)-2,2′-bifurans **3a–d**.

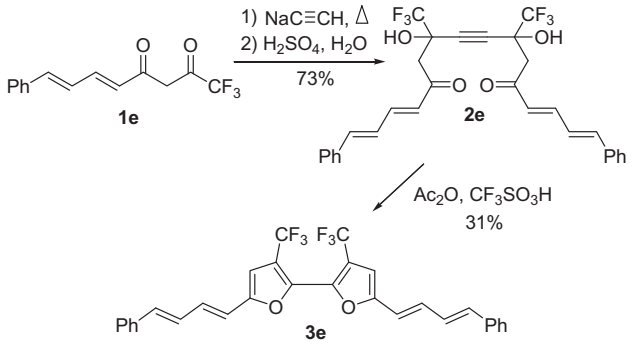
Table 1
Compounds **2** and **3** produced via Schemes 1–3[5,9]

Entry	Ar	Product	Yield (%)	Mp (°C)
1	Ph	**2a**	71	126–128
2	4-Cl–C_6H_4	**2b**	48	132–134
3	4-MeO–C_6H_4	**2c**	47	162–164
4	2-Naphthyl	**2d**	60	174–175
5	$Ph(CH)_4$	**2e**	73	147–149
6	Ph	**3a**	93,[a] 73[b]	168–170
7	4-Cl–C_6H_4	**3b**	93[a]	227–228
8	4-MeO–C_6H_4	**3c**	82[a]	220–222
9	2-Naphthyl	**3d**	64,[a] 68[b]	242–244
10	$Ph(CH)_4$	**3e**	31[a]	227–229

[a] Prepared by treatment with Ac_2O/CF_3SO_3H.
[b] Prepared by treatment with $(CF_3CO)_2O/Et_3N$.

(THF-xylene) in contrast to sodium acetylide. Therefore, the reaction **C** → **D** proceeds much faster than reaction **A** → **B** to give alkynediols **2** as the major products.

It is known, that anionic[6a–c] and palladium-catalyzed[6c] cyclization of several pent-4-ynones leads to the formation of the



Scheme 3. Synthesis of highly conjugated CF_3-containing alkynediol **2e** and 2,2′-bifuran **3e**.

corresponding furan derivatives.[6] It was found that treatment of compounds **2a–d** with acetic anhydride in the presence of trifluoromethanesulfonic acid at ambient temperature was followed by double intramolecular cyclization and resulted in the formation of 5,5′-diaryl-3,3′-bis(trifluoromethyl)-2,2′-bifurans **3a–d** (64–93%), the first representatives of 3,3′-bis(trifluoromethyl)-2,2′-bifurans (Scheme 2).

Alternatively, bifurans **3** could be prepared in good yields (Table 1) by treatment of **2** with trifluoroacetic anhydride in triethylamine (Scheme 2).

Solutions of **3** in organic solvents possess visible fluorescence (a characteristic property of 5,5′-diaryl-2,2′-bifurans[7]). This approach should enrich considerably the class of 5,5′-diaryl-2,2′-bifurans, some derivatives of which are antiprotozoal agents and prodrugs thereof.[8]

The structures of compounds **3** were confirmed by ^1H, ^{19}F, ^{13}C NMR and IR spectroscopy, and elemental analysis. Thus, in the ^1H NMR spectrum of bifuran **3a**, besides signals due to the 10 aromatic protons, a singlet due to 2 equiv furan potons (H-4 and H-4′) at δ 6.95 was observed. In the ^{13}C NMR spectrum of **3a** three characteristic quartets due to the C-4, C-4′ (δ 105.1, $^3J_{C,F}$ = 3.3 Hz), C-3, C-3′ (δ 117.1, $^2J_{C,F}$ = 38.9 Hz), and CF_3, CF_3' (δ 122.0, $^1J_{C,F}$ = 268.0 Hz) carbons were observed, confirming the CF_3-furan structure. Carbons C-5, C-5′ appeared as a singlet at δ 154.8. The characteristic quartet of quartets (coupling to two CF_3 groups) due to C-2, C-2′ (δ 140.7, $^3J_{C,F}$ = 4.4 Hz, $^4J_{C,F}$ = 1.5 Hz) proved unambiguously the 2,2′-bifuran structure. In the ^{19}F NMR spectra of compounds **3** ($CDCl_3$, C_6F_6) the trifluoromethyl group appeared as a singlet at about δ 104.0.[9]

No signals from any intermediates were found in the ^1H NMR spectra of crude bifurans **3**. Nevertheless, extraction of traces of possible intermediates from a portion (~30 mg) of a crude sample of **3d** with $CDCl_3$ (~1 mL) (solubility of **3d** in chloroform was low) gave, according to ^1H and ^{19}F NMR spectra, a mixture of **3d** and the corresponding intermediate diacetate **E** (Scheme 2) in the ratio 1:1. The characteristic signals of this intermediate in the ^1H NMR spectrum included a singlet at δ 2.11 (6H, 2Me), two doublets due to the methylene protons at δ 3.77 and 3.94 (^2J = 15.4 Hz). In the ^{19}F NMR spectrum of the extract the trifluoromethyl groups appeared as singlets at δ 83.8 (**E**) and δ 104.0 (**3d**).

Vinylogs of CF_3-diketones **1** can also be used in the reaction with sodium acetylide. Thus, 7,10-dihydroxy-1,16-diphenyl-7,10-bis(trifluoromethyl)hexadeca-1,3,13,15-tetraen-8-yne-5,12-dione (**2e**) (73%) and 5,5′-bis(4-phenylbuta-1,3-dienyl)-3,3′-bis(trifluoromethyl)-2,2′-bifuran (**3e**) (31%) were synthesized from 1,1,1-trifluoro-8-phenylocta-5,7-diene-2,4-dione (**1e**) via the approaches described above (Scheme 3, Table 1). The structures of **2e** and **3e** were confirmed by ^1H, ^{19}F, ^{13}C NMR and IR spectroscopy, and elemental analysis.

The starting CF_3-diketones **1** are commercially available or easily obtainable.[10]

In summary, regioselective nucleophilic addition of the acetylide anion to 1,3-diketonate anions derived from 1-aryl-4,4,4-trifluorobutane-1,3-diones has been demonstrated for the first time. This reaction is of significant interest for the development of the chemistry of trifluoromethylated 1,3-diketones concerning their possible reactions with *C*-nucleophiles. A novel double cyclization of 1,8-diaryl-3,6-dihydroxy-3,6-bis(trifluoromethyl)oct-4-yne-1,8-diones into 5,5′-diaryl-3,3′-bis(trifluoromethyl)-2,2′-bifurans was also discovered.

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5. *3,6-Bis(trifluoromethyl)-3,6-dihydroxy-1,8-diphenyloct-4-yne-1,8-dione* (**2a**): The reaction was conducted under an argon atmosphere. A solution of 4,4,4-trifluoro-1-phenylbutane-1,3-dione (**1a**) (11.3 g, 52.3 mmol) in dry THF (15 mL) was added gradually to a cooled (−10 °C) mixture of sodium acetylide suspension 18 wt% slurry in xylene (60 mL) and dry THF (50 mL). The mixture was stirred at ambient temperature for 2 h, at 70 °C for 30 min, and at 90 °C for 1.5 h (the low-boiling solvent THF partially distilled off during heating the reaction mixture in the range 70–90 °C). The mixture was cooled to ambient temperature and quenched with cold (0 °C) 10% aqueous H_2SO_4 (200 mL). Hexane (250 mL) was added, and the resulting mixture stirred at 0 °C for 30 min. The residue was filtered, washed with H_2O and hexane, and dried. The dry residue was dissolved in a minimum volume of a hot mixture of hexane–toluene (1:1), the hot solution was passed through a layer of silica gel (5 cm^3), and the layer washed with a hot mixture of hexane–toluene (1:1) (20 mL). The resulting residue was filtered, washed with hexane (5 mL) and dried to give compound **2a** as a white solid. Yield 8.52 g (71%), mp 126–128 °C; IR (KBr) 3429, 1698, 1658, 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.30 (2H, d, *J* = 17.0 Hz, 2 C*H*H), 3.63 (2H, d, *J* = 17.0 Hz, 2 CH*H*), 5.35 (2H, s, 2 OH), 7.47 (4H, t, *J* = 7.3 Hz, 2 Ar–H), 7.63 (2H, t, *J* = 7.3 Hz, 2 Ar–H), 7.84 (4H, d, 2 Ar–H); ^{19}F NMR (376.5 MHz, $CDCl_3$, C_6F_6) δ 80.2 (s, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.3 (CH_2), 70.1 (C-3, C-6, q, $^2J_{C,F}$ = 32.9 Hz), 81.7 (C-4, C-5), 122.8 (CF_3, q, $^1J_{C,F}$ = 283.8 Hz), 128.4 (Ph), 130.0 (Ph), 134.6 (Ph), 136.0 (Ph), 198.1 (CO); Anal. Calcd for $C_{22}H_{16}F_6O_4$: C, 57.65; H, 3.52. Found: C, 57.90; H, 3.45.
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9. *5,5′-Diphenyl-3,3′-bis(trifluoromethyl)-2,2′-bifuran* (**3a**).
   Method A. Alkynediol **2a** (3.00 g, 6.55 mmol) was added with stirring to a mixture of Ac_2O (20 mL) and CF_3SO_3H (0.5 mL). The mixture was kept at ambient temperature for 8 h and then cooled to −30 °C. The residue was filtered, washed with cold Ac_2O (5 mL) and EtOH (5 mL), and dried to give compound **3a** as cream needles. Yield 2.58 g (93%), mp 168–170 °C; IR (ATR) 1586, 1571, 1516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (2H, s, H-4, H-4′), 7.37 (2H, t, *J* = 7.4 Hz, 2 Ar–H), 7.45 (4H, t, *J* = 7.4 Hz, 2 Ar–H), 7.74 (4H, d, *J* = 7.4 Hz, 2 Ar–H); ^{19}F NMR (376.5 MHz, $CDCl_3$, C_6F_6) δ 104.0 (s, CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) 105.1 (C-4, C-4′, q, $^3J_{C,F}$ = 3.3 Hz), 117.1 (C-3, C-3′, q, $^2J_{C,F}$ = 38.9 Hz), 122.0 (CF_3, CF_3', $^1J_{C,F}$ = 268.0 Hz), 124.2 (Ph), 128.7 (Ph), 129.01 (Ph), 129.04 (Ph), 140.7 (C-2, C-2′, qq, $^3J_{C,F}$ = 4.4 Hz, $^4J_{C,F}$ = 1.5 Hz); 154.8 (C-5, C-5′); Anal. Calcd for $C_{22}H_{12}F_6O_2$: C, 62.57; H, 2.86. Found: C, 62.53; H, 2.77.
   Method B. Alkynediol **2a** (0.200 g, 0.44 mmol) was added to dry Et_3N (3 mL). The mixture was cooled to 0 °C, and $(CF_3CO)_2O$ (1.0 mL) was added gradually over 2 min. The mixture was stirred at 0 °C for 20 min and at ambient temperature for 20 min. Then the mixture was carefully diluted with AcOH (3 mL) and H_2O (1 mL). The residue was filtered, washed with EtOH, and crystallized from a mixture of EtOH and isoamyl alcohol (1:1) to give compound **3a** as cream needles. Yield 0.135 g (73%), mp 168–170 °C.
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