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Transition metal-free cross-coupling of furan ring with haloacetylenes

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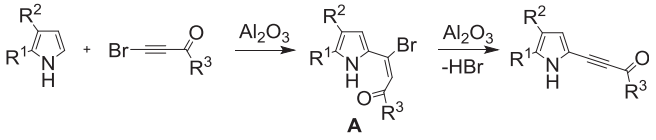
ABSTRACT

On the example of menthofuran, a naturally abundant compound, it has been shown for the first time that the furan ring can be readily cross-coupled with acylhaloacetylenes in the solid Al_2O_3 powder at room temperature to afford the corresponding 2-ethynyl derivatives in up to 88% yield. The reaction represents a ring closing/ring opening process that includes reversible formation of the intermediate cycloadducts further producing acetylene derivatives with elimination of HHal.

1. Introduction

After the pioneering work,[1,2] which showed that pyrroles are cross-coupled with electrophilic acylhaloacetylenes under exceptionally mild conditions (room temperature) in the solid metal oxides and salts media to give 2-acylethynylpyrroles, this methodology has been developed into a general and efficient tool for the synthesis of diverse alkyl-, aryl-, hetaryl-, cycloalkyl-2-ethynylpyrroles, having acyl,[3–5] trifluoroacyl,[6,7] ester,[8,9] aldehyde,[10] phosphonate,[11] ethynyl,[12] and butadiynyl[13] functions at the triple bond.

The mechanism of this ethynylation was proved to involve the addition-elimination sequence (Scheme 1), probably promoted by the coordinately unsaturated center of the used metal oxides and salts (electrophilic assistance) initiated by mechanoactivation (grinding up the reactants). In some cases, intermediates of this reaction, 2-(1-haloethenyl)pyrroles **A**, were isolated and under the same conditions transformed to 2-ethynylpyrroles.[1,2,5]



The development of expedient synthesis of ethynylfurans represents a challenge for heterocyclic chemistry, because such motifs are frequently met in bioactive molecules and natural products,[14,15] for example, in inhibitors of mast cell β-triptase,[16–18] SARS coronavirus main protease,[19] leukocyte calcium uptake,[20] lipoxygenase,[21] and carlina oxide (a natural polyacetylene from Carlina acaulis) with potent antitrypanosomal and antimicrobial activities.[22] They also are prospective building blocks for the synthesis of more complex biomolecules due to the rich chemistry of the triple bond and the furan ring, especially in their combination.[23–31]

A logic development of previous ethynylation of pyrroles with haloacetylenes[1,2,12,13,32] might be translation of this methodology to the furan compounds. In this line, just one short note that 2-(2-furyl)pyrrole[33] was capable of the ethynylating by haloacetylenes was reported. It was mentioned inter alia that the cross-coupled products with furan ethynylated moiety were isolated in small yields (4–5%).

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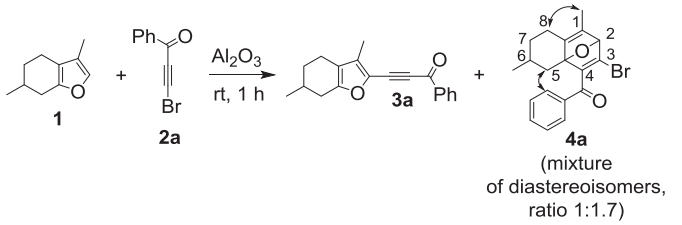


Scheme 1. Reaction of menthofuran **1** with benzoylbromoacetylene **2a** in the Al_2O_3 medium.

2. Results and discussion

Here we report, on the example of natural abundant menthofuran (3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran **1**), first synthetically appropriate results on the transition metal-free cross-coupling of the furan ring with haloacetylenes **2a-g** initiated by their grinding with most common solid oxides and salts (10-fold amount) without solvent and then allowing them to stand at room temperature for 1–72 h. The reaction course (conversion of reactants **1, 2** and the products ratio) was controlled by ^{1}H NMR spectra of the $CDCl_3$ extracts from the reaction mixture.

Menthofuran was chosen as a furan representative, first, due to its higher nucleophilicity (donor effect of the cyclohexane ring and two methyl groups) compared to commonly available furan compounds and, second, because menthofuran is a popular natural product, which is contained in the peppermint and exercises a great effect on the aroma of that oil.[34] Also, it is the precursor of menthofurolactone and dehydromenthofurolactone, two compounds whose sweet and persistent coumarinic odor is the hallmark of premium-quality peppermint oils.[35–37] This well-known fragrance is also a potent hepatotoxin and is obtained from *Mentha pulegium* L., a plant used in folk medicine as an abortifacient.[37]

A preliminary attempt to realize this reaction for furan and 2-methylfuran has shown that only the corresponding cycloadducts are formed instead of the expected ethynylated furans.[38]

We have started to study this reaction for benzoylbromoacetylene **2a** (as acylhaloacetylene representative) using Al_2O_3 as a solid medium.

According to the experiments, after 1 h the reaction results in formation of ethynylfuran **3a** along with the pair of diastereomeric cycloadducts of oxanorbornadiene structure **4a** in 44:56 ratio (Scheme 1). The reaction is strictly regioselective: the bromine atom is neighboring the position 2 of the furan ring exclusively: NOESY interaction between protons of CH_2-5 group and H-*ortho* protons of phenyl ring confirms C-4 location of benzoyl fragment.

After standing reaction mixture for 24 h, 48 h and 72 h the content of ethynylfuran **3a** increased to 64%, 80% and 88%, correspondingly, while cycloadduct content was diminished. These results indicate that cycloadduct **4a** converts to ethynylfuran **3a** with elimination of hydrogen bromide, i.e. the cycloadduct **4a** is kinetic intermediate of the ethynylation. As it was shown on the example of cycloadduct **4a**, such derivatives of menthofuran can be isolated and handled under normal conditions.

We then turned our attention to other oxides and salts (SiO_2, NaCl, K_2CO_3 and K_3PO_4) as solid media to implement the same reaction (Table 1).

In the SiO_2 medium menthofuran was unstable and after 1 h the reaction mixture consisted of mainly the starting acetylene **2a** (60%), content of ethynylfuran **3a** and cycloadduct **4a** being 26% and 13%, correspondingly. If NaCl was used as a solid medium, the main product was cycloadduct **4a** (54%). The other products were ethynylfuran **3a** (16%) and 3,3-bis(3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl)-1-phenylprop-2-en-1-one (**5**) (19%) (Scheme 2). Acetylene **2a** was also present in the reaction mixture (11%), while menthofuran was absent.

Table 1
^{1}H NMR spectroscopic monitoring of reaction menthofuran with benzoylbromoacetylene in the different media.[a]

Solid medium	Composition of the reaction mixture, %			
	2a	**3a**	**4a**	**5**
Al_2O_3	–	44	56	–
SiO_2	60	26	13	1
NaCl	11	16	54	19
K_2CO_3	24	12	63	1
K_3PO_4	–	6	94	–

[a] Reaction conditions: menthofuran **1** (1 mmol), benzoylbromoacetylene **2a** (1 mmol), solid medium (ten-fold mass excess of the total mass of reagents), room temperature, 1 h.

Contrary to the exceptions in the presence of more basic medium (K_2CO_3, K_3PO_4) ethynylation was a minor process, while the major one was cycloaddition (Table 1).

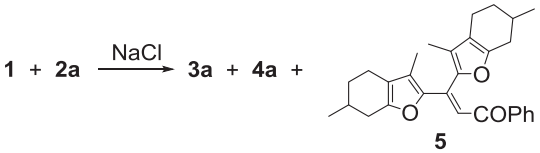
It is important to underline that, when neat reactants (**1** and **2a**) without a solid medium are ground, neither ethynylfuran **3a** nor cycloadduct **4a** are formed, while exothermic reaction take place resulting in resin-like product. Upon dropwise addition of furan **1** to cooled (10 °C) acetylene **2a** the obtained reaction mixture (room temperature, 1 h) consisted of cycloadduct **4a** and propenone **5** in 60:40 ratio, no ethynylfuran **3a** being detected. Interestingly, under these conditions (out of a solid medium) cycloadduct **4a** was not transformed to ethynylfuran **3a**, whereas in $CDCl_3$ it isomerized to 2-bromo-3-hydroxytetrahydronaphthalene **6a** (Scheme 3).

Thus as indicated above, Al_2O_3 has proven to be a medium of choice from the oxides and salts studied for the synthesis of ethynyl derivatives of menthofuran **3a**. Therefore, this oxide was used to evaluate the influence of halogen atom in acylhaloacetylene on the reaction course (Table 2).

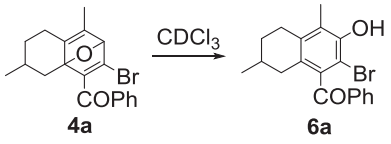
Chlorobenzoylacetylene reacts with furan **1** to afford after 1 h cycloadduct **4a** as major product (**3a**: **4a** ratio is the 36: 62), the reactant conversion being complete. As anticipated, after 3 h, content of ethynylfuran **3a** insignificantly increased and within 72 h the only product was ethynylfuran **3a**. The reaction of furan **1** with iodobenzoylacetylene proceeds slower, after 3 h composition of the reaction mixture being **1**: **2a: 3a**: **4a**: **5** = 9: 17: 28: 11. In 72 h cycloadduct **4a** disappears and the reaction mixture contains ethynylfuran **3a** along with propenone **5** in the ratio of 49: 18 (Table 2).

Thus, in contrast to cross-coupling of pyrroles with acylhaloacetylenes in solid media, ethynylation of the furan moiety with acylhaloacetylenes proceeds through [4 + 2]-cycloaddition followed by ring-opening with elimination of HHal. It is also in keeping with quantitative conversion of isolated cycloadduct **4a**, upon its passing through SiO_2 or Al_2O_3 column, into ethynylfuran **3a**.

As further experiments have shown, this ethynylation is also applicable for bromoacetylenes with formyl (**2b**), acetyl (**2c**), furoyl (**2d**), and thenoyl (**2e**) groups at the triple bond, which react with



Scheme 2. Reaction of menthofuran **1**with benzoylbromoacetylene **2a** in the NaCl medium.



4a 6a

Scheme 3. Isomerization of cycloadduct **4a** to 2-bromo-3-hydroxytetrahydronaphthalene **6a**.

Table 2
^{1}H NMR spectroscopic monitoring of reaction of furan **1** with halobenzoylacetylenes in the Al_2O_3 medium.[a]

Haloacetylene	Composition of the reaction mixture, %											
	1 h				3 h				72 h			
	1	**3a**	**4a**	**5**	**1**	**3a**	**4a**	**5**	**1**	**3a**	**4a**	**5**
Cl–C≡C–C(=O)–Ph	–	36	62	2	–	38	61	1	–	100	–	–
Br–C≡C–C(=O)–Ph	–	44	56	–	–	49	51	–	–	88	12	–
I–C≡C–C(=O)–Ph [b]	17	15	25	6	9	17	28	11	–	49	–	18

[b] Content of iodobenzoylacetylene for 1 h, 3 h and 72 h was 37%, 35% and 33% correspondingly.
[a] Reaction conditions: **1** (1 mmol), halobenzoylacetylene (1 mmol), Al_2O_3 (ten-fold mass excess of the total mass of reagents), room temperature.

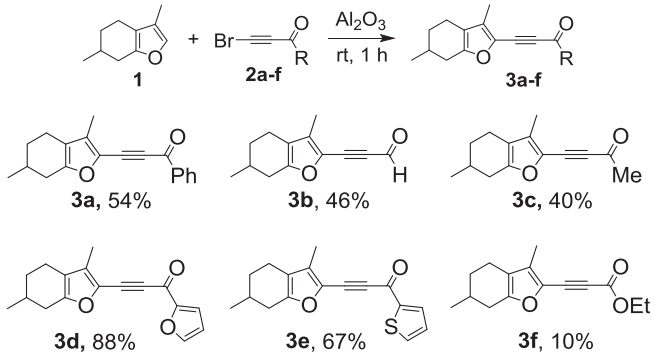
menthofuran **1** in the solid Al_2O_3 to afford the acetylenic derivatives **3b-e** in 40–88% yields (Scheme 4).

For bromopropiolate **2f**, the major reaction product was cycloadduct **4f**, which in the $CDCl_3$ solution was isomerized to 2-bromo-3-hydroxynaphthalene **6f**. Ethynylfuran **3f** in this case was minor product, its isolated yield being just ca. 10% (Schemes 4 and 5).

In the case of bromodiacetylene **2g**, the only isolated product was bicyclic propiolate **6g**, the isomer of the expected cycloadduct **4g** (Scheme 6).

Thus, it appears likely that the oxanorbornadiene intermediates such as **4a**, reversibly generated on the first reaction step, transform to the ethynyl derivatives of menthofuran *via* zwitterion **B** with the positive charge distributed over the whole furan moiety. The latter eliminates hydrogen bromide in the concerted process (hydrogen releases from the position 2 of the furan moiety, Scheme 7).

An experimental evidence for the proposed mechanism is the observation that cycloadducts **4** are gradually transformed to ethynylated products **3**. The formation of the intermediate zwitterion **B** is supported by isolation of propenone **5** resulted from



Scheme 4. Reaction of menthofuran **1** with haloacetylenes **2a-f** in the Al_2O_3 medium.

substitution of bromine atom either in zwitterion **B** or bromovinyl intermediate **7** (Scheme 8).

An alternative route to propenone **5** might be the nucleophilic addition of the second molecule of menthofuran to ethynyl derivative of menthofuran **3a** (Scheme 8). However, as shown by a special experiment, ethynylfuran **3a** did not add furan **1** under the reaction conditions.

The mechanistic rationalizations here considered are supported by the fact that the furan derivatives, having no donor substituents, like furan-2-carbaldehyde and its acetals as well as 6-methoxybenzofuran, happened to be reluctant in the reaction with haloacetylenes under the conditions studied (Fig. 1).

Indeed, the initial [4 + 2]-cycloaddition is a typical Diels-Alder condensation with inverse electronic demand, i.e., diene (in this case furan moiety) should be electron-rich compound, correspondingly the opened form of cycloadduct, the zwitterion **B**, should be the more stable the stronger donor substituent are in the furan moiety.

3. Conclusion

In summary, on the example of menthofuran, it has been shown for the first time that furans bearing electron-donating substituents are capable of cross-coupling with haloacetylenes in solid media of oxides or salts under mild conditions in the absence of transition metals to afford acetylenic derivatives. Thus, it was found that a naturally abundant furan compound, menthofuran, is readily cross-coupled with haloacetylenes under transition metal-free conditions in the solid Al_2O_3 powder at room temperature to give 2-ethynyl derivatives in up to 88% yield. In contrast to the ethynylation of pyrroles under similar conditions, the reaction studied involves reversible [4 + 2]-cycloaddition of the furan ring to form the isolable intermediated cycloadducts, which then further transform to the acetylenic derivatives. The novel menthofuran derivatives, thus obtained, represent promising bioactive compounds and rewarding precursors for drug design.

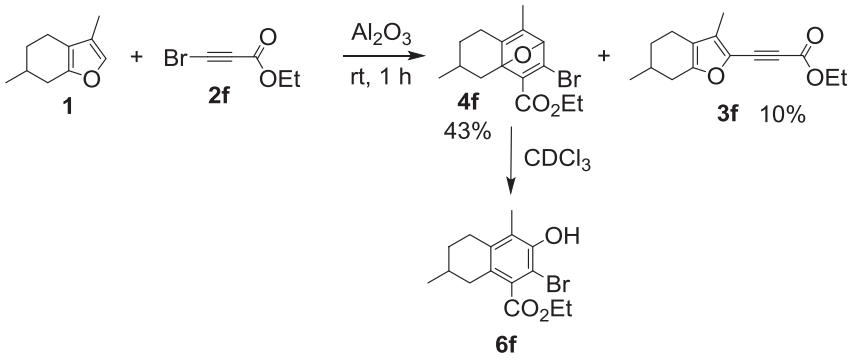
4. Experimental

4.1. General information

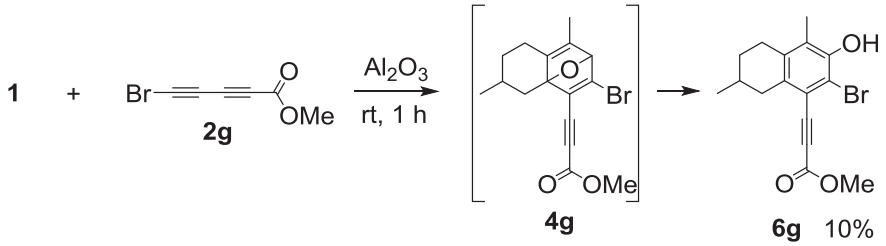
IR spectra were obtained with a Bruker Vertex 70 spectrometer (400–4000 cm^{-1}, films). ^{1}H (400.1 MHz), ^{13}C (100.6 MHz) spectra were recorded on a Bruker DPX-400 spectrometer at ambient temperature in $CDCl_3$ solutions and referenced to $CDCl_3$ (residual protons of $CDCl_3$ in ^{1}H NMR $\delta = 7.26$ ppm; ^{13}C NMR $\delta = 77.16$ ppm). The C, H, S microanalyses were performed on a Flash EA 1112 CHNS-O/MAS analyzer. Br content was determined by combustion method. Melting point (uncorrected) was determined on a Kofler micro hot stage apparatus. 3,6-Dimethyl-4,5,6,7-tetrahydrobenzofuran is commercial product. Acylhaloacetylenes are obtained accordingly to procedures.[39,40]

4.2. General procedure for synthesis of 3-(3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl)-1-prop-2-yn-1-ones *3a-e*

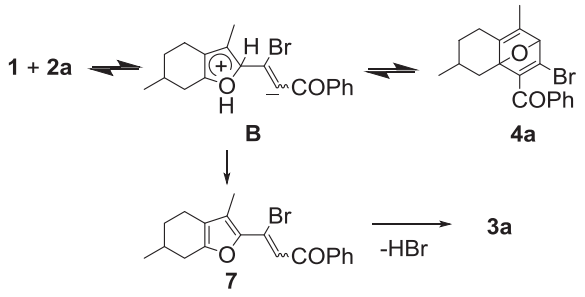
Equimolar amounts of 3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran (0.150 g, 1 mmol) and haloacetylenes **2a-e** (1 mmol) were ground at room temperature with a 10-fold amount (by weight) of Al_2O_3 in a porcelain mortar for 10 min and allowed to stay at room temperature for 60 min. ^{1}H NMR analysis showed that in all cases reaction mixtures contain cycloadduct **4a-e** and acetylene **3a-e** in average ratio 1: 1. Slow column chromatography (SiO_2, eluent *n*-hexane) of the reaction mixture leads to the transformation of cycloadduct **4a-e** to acetylene **3a-e**, which was



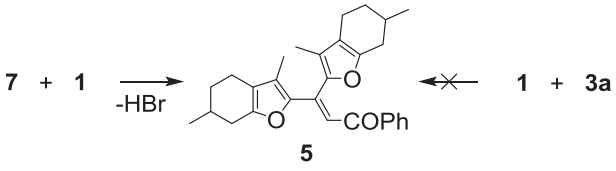
Scheme 5. Reaction of menthofuran **1** with bromopropiolate **2f** in the Al_2O_3 medium.



Scheme 6. Reaction of menthofuran **1** with bromodiacetylene **2g** in the Al_2O_3 medium.



Scheme 7. Possible reaction pathway.



Scheme 8. Possible pathway of propenone **5** formation.

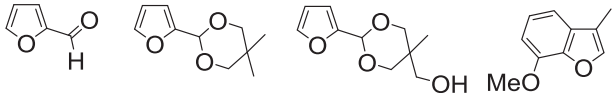


Fig. 1. The furan derivatives, having no donor substituents.

isolated in pure state. The cycloadduct **4a** was isolated according to the procedure presented below.

*4.2.1. 3-(3,6-Dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl)-1-phenylprop-2-yn-1-one (**3a**)*

Yield 150 mg (54%), yellow crystals, *Rf* 0.5 (*n*-hexane-diethyl ether, 2:1), mp 132–134°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20–8.18 (m, 2H, H*o*-Ph), 7.62–7.58 (m, 1H, H*p*-Ph), 7.52–7.48 (m, 2H, H*m*-Ph), 2.76–2.70 (m, 1H, C<u>H</u>CH$_3$), 2.46–2.31 (m, 2H, CH$_2$), 2.28–2.20 (m, 1H, CH$_2$), 2.17 (s, 3H, CCH$_3$), 2.00–1.85 (m, 2H, CH$_2$), 1.44–1.34 (m, 1H, CH$_2$), 1.10 (d, 3H, J = 8.0 Hz, CH<u>CH</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 156.4, 137.0, 134.7, 133.8, 130.6, 129.3, 128.6, 120.0, 97.4, 85.9, 31.8, 30.9, 29.4, 21.3, 19.9, 9.6; IR ν_{max} 3062, 2953, 2921, 2158, 1625, 1542, 1450, 1292, 1223, 1166, 1007, 834, 791, 751, 704, 660; Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52%; Found: C, 82.21; H, 6.88%.

*4.2.2. 3-(3,6-Dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl) propiolaldehyde (**3b**)*

Yield 93 mg (46%), yellow oil, *Rf* 0.5 (*n*-hexane-diethyl ether, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (s, 1H, CHO), 2.72–2.66 (m, 1H, C<u>H</u>CH$_3$), 2.42–2.30 (m, 2H, CH$_2$), 2.22–2.16 (m, 1H, CH$_2$), 2.08 (s, 3H, CH$_3$), 1.97–1.84 (m, 2H, CH$_2$), 1.41–1.33 (m, 1H, CH$_2$), 1.08 (d, 3H, J = 8.0 Hz, CH<u>CH</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 157.4, 136.0, 130.2, 120.3, 99.5, 88.2, 31.9, 30.8, 29.3, 21.3, 19.9, 9.6; IR ν_{max} 3024, 2951, 2920, 2847, 2163, 1649, 1546, 1451, 1435, 1381, 1290, 1216, 1162, 1139, 1099, 987, 812, 719, 678; Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98%; Found: C, 77.38; H, 7.23%.

*4.2.3. 4-(3,6-Dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl)but-3-yn-2-one (**3c**)*

Yield 86 mg (40%), yellow crystals, *Rf* 0.65 (*n*-hexane-diethyl ether, 2:1), mp 84–86°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71–2.65 (m, 1H, C<u>H</u>CH$_3$), 2.41 (s, 3H, CO<u>CH</u>$_3$), 2.37–2.28 (m, 2H, CH$_2$), 2.22–2.15 (m, 1H, CH$_2$), 2.06 (s, 3H, CCH$_3$), 1.96–1.83 (m, 2H, CH$_2$), 1.38–1.33 (m, 1H, CH$_2$), 1.08 (d, 3H, J = 8.0 Hz, CH<u>CH</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.6, 156.3, 134.6, 130.2, 119.9, 98.4, 83.2, 32.2, 31.8, 30.8, 29.3, 21.4, 19.8, 9.5; IR ν_{max} 2952, 2919, 2850, 2164, 1653, 1619, 1453, 1436, 1359, 1295, 1189, 1093, 1069, 1021, 911, 733, 576; Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46%; Found: C, 77.96; H, 7.78%.

*4.2.4. 3-(3,6-Dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl)-1-(furan-2-yl)prop-2-yn-1-one (**3d**)*

Yield 236 mg (88%), yellow crystals, *Rf* 0.4 (*n*-hexane-diethyl ether, 2:1), mp 131–133°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.66 (m, 1H, H-5 furan), 7.38–7.37 (m, 1H, H-3, furan), 6.58–6.57 (m, 1H, H-4, furan), 2.74–2.70 (m, 1H, CHCH$_3$), 2.44–2.31 (m, 2H, CH$_2$), 2.25–2.18 (m, 1H, CH$_2$), 2.14 (s, 3H, CCH$_3$), 2.00–1.84 (m, 2H, CH$_2$), 1.43–1.33 (m, 1H, CH$_2$), 1.10 (d, 3H, *J* = 8.0 Hz, CHCH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 156.5, 153.3, 147.7, 134.9, 130.5, 120.1, 119.9, 112.6, 96.5, 84.8, 31.9, 30.9, 29.4, 21.4, 19.9, 9.6; IR ν_{max} 3120, 2923, 2847, 2173, 1617, 1544, 1458, 1394, 1297, 1271, 1165, 1044, 1006, 789, 732; Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01%; Found: C, 76.32; H, 6.27%.

*4.2.5. 3-(3,6-Dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl)-1-(thiophen-2-yl)prop-2-yn-1-one (**3e**)*

Yield 190 mg (67%), yellow crystals, *Rf* 0.37 (*n*-hexane-diethyl ether, 2:1), mp 143–145°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96–7.95 (m, 1H, H-5, thiophene), 7.69–7.68 (m, 1H, H-3, thiophene), 7.18–7.16 (m, 1H, H-4, thiophene), 2.75–2.69 (m, 1H, CHCH$_3$), 2.43–2.31 (m, 2H, CH$_2$), 2.25–2.19 (m, 1H, CH$_2$), 2.15 (s, 3H, CCH$_3$), 2.00–1.86 (m, 2H, CH$_2$), 1.43–1.34 (m, 1H, CH$_2$), 1.10 (d, 3H, *J* = 8.0 Hz, CHCH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 156.5, 145.0, 134.7, 134.6, 134.4, 130.5, 128.4, 120.0, 96.6, 84.6, 31.9, 30.9, 29.4, 21.4, 19.9, 9.6; IR ν_{max} 3095, 2949, 2920, 2846, 2166, 1595, 1543, 1407, 1348, 1294, 1238, 1046, 970, 858, 722; Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; S, 11.28%; Found: C, 71.67; H, 5.93; S, 11.34%.

*4.3. (3-Bromo-1,6-dimethyl-5,6,7,8-tetrahydro-2H-2,4a-epoxynaphthalen-4-yl)(phenyl)methanone (**4a**)*

Equimolar amounts of 3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran (0.150 g, 1 mmol) and benzoylbromoacetylene (0.209 g, 1 mmol) were ground at room temperature with a 10-fold amount (by weight) of Al_2O_3 in a porcelain mortar for 10 min and allowed to stay at room temperature for 60 min. Reaction mixture was placed on the glass filter and washed with *n*-hexane, solvent removed and oily residue recrystallized from 5 to 7 ml of *n*-hexane to give acetylene **3a.** Mother liquor was evaporated to give cycloadduct **4a** as yellow oil, *Rf* 0.63 (*n*-hexane-diethyl ether, 2:1), yield 144 mg (40%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (m, 2H, H*o*-Ph'), 7.84 (m, 2H, H*o*-Ph), 7.56 (m, 2H, H*p*-Ph, H*p*-Ph'), 7.45 (m, 4H, H*m*-Ph, H*m*-Ph'), 4.99 (s, 1H, H-2′), 4.97 (s, 1H, H-2), 2.58 (m, 1H, H-8), 2.45 (m, 2H, H-8′), 2.33 (m, 1H, H-5), 2.27 (m, 1H, H-8), 2.19 (m, 1H, H-6), 2.07 (m, 1H, H-5′), 1.93 (m, 1H, H-5′), 1.85 (m, 1H, H-7), 1.83 (d, *J* = 2.8 Hz, 3H, CCH$_3$), 1.82 (dd, *J* = 1.2, 2.0 Hz, 3H, CCH$_3$′), 1.77 (m, 1H, H-7′), 1.68 (m, 1H, H-6′), 1.64 (m, 1H, H-7′), 1.51 (m, 1H, H-5), 1.08 (m, 1H, H-7), 0.93 (d, *J* = 6.0 Hz, 3H, CHCH$_3$′), 0.92 (d, *J* = 6.60 Hz, 3H, CHCH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0 (C=O), 192.7 (C=O′), 152.6 (C-4), 152.0 (C-4′), 146.8 (C-8a'), 146.5 (C-8a), 143.5 (C-3′), 143.2 (C-3), 140.4 (C-1′), 139.5 (C-1), 136.8 (C-*i*), 136.6 (C-*i*'), 133.7 (C-*p,* C-*p*'), 129.7 (C-*o,* C-*o*'), 128.7 (C-*m*, C-*m*'), 98.2 (C-4a'), 96.7 (C-4a), 91.6 (C-2′), 91.0 (C-2), 38.1 (C-5), 35.4 (C-5′), 32.6 (C-7), 30.0 (C-7′), 29.1 (C-6), 28.1 (C-6′), 23.6 (C-8), 22.6 (CHCH$_3$), 21.7 (CHCH$_3$′), 19.4 (C-8′), 12.1 (CCH$_3$′), 11.9 (CCH$_3$); IR ν_{max} 3060, 3032, 2922, 2871, 1673, 1591, 1446, 1409, 1334, 1282, 1223, 1089, 1007, 906, 723, 690; Anal. Calcd for $C_{19}H_{19}BrO_2$: C, 63.52; H, 5.33; Br, 22.24; Found: C, 63.80; H, 5.11; Br, 22.56%.

*4.4. (2-Bromo-3-hydroxy-4,7-dimethyl-5,6,7,8-tetrahydronaphthalen-1-yl)(phenyl) methanone (**6a**)*

This product was formed (0.230 g, 64%) as yellow crystals (*Rf* 0.56 (*n*-hexane-diethyl ether, 2:1), mp 68–70 °C) from 0.359 g of cycloadducts **4a** under storage in *n*-hexane solution and purified by flash chromatography (SiO_2, *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85–7.83 (m, 2H, H*o*-Ph), 7.61–7.59 (m, 1H, H*p*-Ph), 7.47–7.45 (m, 2H, H*m*-Ph), 5.53 (br s, 1H, OH), 2.81 (m, 1H, H-5), 2.77 (m, 1H, H-8), 2.59 (m, 1H, H-5), 2.31 (m, 1H, H-8), 2.25 (s, 3H, CCH$_3$), 1.90 (m, 1H, H-6), 1.70 (m, 1H, CHCH$_3$), 1.35 (m, 1H, H-6), 0.91 (d, 3H, *J* = 5.8 Hz, CHCH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 147.9, 137.0, 136.1, 134.0 (two signals), 129.8, 129.0 (two signals), 124.5, 104.4, 35.5, 30.9, 28.7, 27.5, 21.7, 12.5; IR ν_{max} 2921, 2873, 1671, 1589, 1446, 1409, 1336, 1283, 1225, 1087, 1007, 908, 832, 729, 690; Anal. Calcd for $C_{19}H_{19}BrO_2$: C, 63.52; H, 5.33; Br, 22.24%; Found: C, 63.84; H, 5.51; Br, 22.51%.

*4.5. 3,3-Bis(3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl)-1-phenylprop-2-en-1-one (**5**)*

This product was isolated from the reaction of 3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran (0.150 g, 1 mmol) and benzoylbromoacetylene (0.209 g, 1 mmol) when NaCl was used instead of Al_2O_3 (See 4.2. general procedure); Yield 0.043 g (10%), yellow oil, *Rf* 0.4 (*n*-hexane-diethyl ether, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.74 (m, 2H, H*o*-Ph), 7.39–7.36 (m, 1H, H*p*-Ph), 7.31–7.29 (m, 2H, H*m*-Ph), 6.84 (s, 1H, =CH), 2.76–2.71 (m, 1H, CHCH$_3$), 2.57–2.52 (m, 1H, CHCH$_3$), 2.36–1.84 (m, 12H, 6CH$_2$), 1.68 (s, 3H, CCH$_3$), 1.59 (s, 3H, CCH$_3$), 1.10 (d, 3H, *J* = 6.6 Hz, CHCH$_3$), 1.01 (d, 3H, *J* = 6.6 Hz, CHCH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 153.2, 151.5, 145.8, 142.8, 139.9, 132.9, 131.3, 128.2, 127.8, 125.6, 123.8, 121.4, 119.5, 119.2, 31.7, 31.5, 31.2, 31.1, 29.6, 29.5, 21.5, 21.4, 20.1, 19.9, 9.5, 9.2; IR ν_{max} 3060, 2921, 2853, 1634, 1545, 1446, 1378, 1271, 1218, 1108, 1071, 1021, 913, 858, 732, 702, 647; Anal. Calcd for $C_{29}H_{32}O_3$: C, 81.27; H, 7.53%; Found: C, 81.42; H, 7.85%.

*4.6. Reaction of furan **1** with ethyl 3-bromopropiolate **1f***

Equimolar amounts of 3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran (0.150 g, 1 mmol) and ethyl 3-bromopropiolate (0.177 g, 1 mmol) were ground at room temperature with a 10-fold amount (by weight) of Al_2O_3 in a porcelain mortar for 10 min and allowed to stay at room temperature for 60 min. ^{1}H NMR analysis of crude reaction mixture shows that it contains both isomeric cycloadducts **4f** and ethynylfuran **3f** in 2:1 ratio. Fractionating (SiO_2, eluent *n*-hexane + 0.5% of diethyl ether) of the reaction mixture gives pure acetylene as white crystals (**3f**) and cycloadducts mixture (**4f**) as colorless oil.

*4.6.1. Ethyl-3-(3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl) propiolate (**3f**)*

Yield 25 mg (10%), white crystals, *Rf* 0.62 (*n*-hexane-diethyl ether, 2:1), mp 46–48°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (q, 2H, *J* = 16 Hz, CH$_2$CH$_3$), 2.69–2.64 (m, 1H, CHCH$_3$), 2.41–2.30 (m, 2H, CH$_2$), 2.20–2.14 (m, 1H, CH$_2$), 2.06 (s, 3H, CCH$_3$), 1.94–1.82 (m, 2H, CH$_2$), 1.40–1.35 (m, 1H, CH$_2$), 1.33 (t, 3H, *J* = 8.0 Hz, CH$_2$CH$_3$), 1.07 (d, 3H, *J* = 8.0 Hz, CHCH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 154.5, 133.5, 130.3, 119.5, 89.7, 78.5, 61.9, 31.8, 31.0, 29.4, 21.4, 19.9, 14.3, 9.4; IR ν_{max} 2951, 2924, 2873, 2855, 2192, 1706, 1549, 1455, 1371, 1293, 1210, 1025, 862, 742; Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37%; Found: C, 73.36; H, 7.62%.

*4.6.2. Ethyl-3-bromo-1,6-dimethyl-5,6,7,8-tetrahydro-2H-2,4a-epoxynaphthalene-4-carboxylate (**4f**) (the pair of diastereoisomers)*

Yield 141 mg (43%), colorless oil, *Rf* 0.55 (*n*-hexane-diethyl ether, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.90 (s, 1H, CH′), 4.88 (s, 1H, CH), 4.26–4.24 (m, 2H, CH$_2$CH$_3$), 2.63–2.61 (m, 1H, CH$_2$), 2.60–2.58 (m, 1H, CH$_2$), 2.20–2.18 (m, 1H, CHCH$_3$), 1.92–1.88 (m, 1H, CH$_2$), 1.85–1.83 (m, 3H, CCH$_3$), 1.84–1.80 (m, 1H, CH$_2$), 1.51–1.47 (m, 1H,

CH_2), 1.35–1.31 (m, 3H, $CH_2\underline{CH_3}$), 1.12–1.10 (m, 1H, CH_2), 1.05–1.01 (m, 3H, $\underline{CH}CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7 (C=O′), 163.1 (C=O), 149.8 (C-3), 148.2 (C-3′), 146.9 (C-8a, C-8a'), 144.9 (C-4′), 144.3 (C-4), 141.1 (C-1′), 139.7 (C-1), 96.1 (C-4a'), 94.7 (C-4a), 91.3 (C-2′), 90.9 (C-2), 60.6 ($\underline{C}H_2CH_3$, $\underline{C}H_2CH_3$′), 38.1 (C-5), 35.5 (C-5′), 32.5 (C-7), 30.0 (C-7′), 29.2 (C-6), 28.0 (C-6′), 24.3 (C-8), 22.4 ($CH\underline{C}H_3$), 21.7 ($CH\underline{C}H_3$′), 19.8 (C-8′), 14.2 ($CH_2\underline{C}H_3$, $CH_2\underline{C}H_3$′), 12.1 (C-Me'), 11.8 (C-Me); IR ν_{max} 2950, 2926, 2873, 1725, 1588, 1446, 1416, 1374, 1293, 1213, 1080, 1023, 1014, 913, 860, 733, 650; Anal. Calcd for $C_{15}H_{19}BrO_3$: C, 55.06; H, 5.85; Br, 24.42%; Found: C, 55.28; H, 6.03; Br, 24.74%.

4.7. *Ethyl-2-bromo-3-hydroxy-4,7-dimethyl-5,6,7,8-tetrahydronaphthalene-1-carboxylate (**6f**)*

This product was formed (196 mg, 60%) as yellow crystals (*Rf* 0.7 (*n*-hexane-diethyl ether, 2:1), mp 105–107 °C) from 0.327 g of cycloadducts **4f** under storage and purified by flash chromatography (SiO_2, *n*-hexane);

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.51 (br s, 1H, OH), 4.41 (q, 2H, J = 16 Hz, $\underline{CH_2}CH_3$), 2.76–2.72 (m, 1H, H-5), 2.68–2.64 (m, 1H, H-8), 2.54–2.52 (m, 1H, H-5), 2.32–2.26 (m, 1H, H-8), 2.18 (s, 3H, $C\underline{CH_3}$), 1.93–1.90 (m, 1H, H-6), 1.75–1.73 (m, 1H, $C\underline{H}CH_3$), 1.40 (t, 3H, J = 8.0 Hz, $CH_2\underline{CH_3}$), 1.36–1.32 (m, 1H, H-6), 1.03 (d, 3H, J = 8.0 Hz, $CH\underline{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 147.9, 137.0, 133.0, 127.0, 125.0, 104.7, 61.8, 35.7, 31.0, 28.6, 27.5, 21.8, 14.3, 12.4; IR ν_{max} 2923, 2873, 1726, 1583, 1442, 1413, 1373, 1333, 1289, 1212, 1074, 1036, 861, 816, 765, 710; Anal. Calcd for $C_{15}H_{19}BrO_3$: C, 55.06; H, 5.85; Br, 24.42%; Found: C, 55.29; H, 6.08; Br, 24.80%.

4.8. *Methyl-3-(2-bromo-3-hydroxy-4,7-dimethyl-decahydronaphthalen-1-yl)propiolate (**6g**)*

Equimolar amounts of 3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran (0.150 g, 1 mmol) and methyl-5-bromopenta-2,4-diynoate (**2g**) (0.177 g, 1 mmol) were ground at room temperature with a 10-fold amount (by weight) of Al_2O_3 in a porcelain mortar for 10 min and allowed to stay at room temperature for 60 min. ^{1}H NMR analysis of crude reaction mixture shows that it contains only both isomeric cycloadducts **4g**. TLC (SiO_2, eluent - *n*-hexane: diethyl ether 1: 1) of the reaction mixture give bicyclic phenol **6g** as light yellow oil, *Rf* 0.7 (*n*-hexane-diethyl ether, 1:1); Yield 34 mg (10%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.56 (br, 1H, OH), 3.86 (s, 3H, $O\underline{CH_3}$), 3.08–3.02 (m, 1H, $\underline{CH}CH_3$), 2.74–2.70 (m, 1H, CH_2), 2.57–2.48 (m, 2H, CH_2), 2.40–2.33 (m, 1H, CH_2), 2.21 (s, 3H, $C\underline{CH_3}$), 1.95–1.74 (m, 2H, CH_2), 1.08 (d, 3H, J = 4.0 Hz, $CH\underline{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 148.3, 136.8, 135.4, 127.5, 118.1, 111.8, 88.0, 84.0, 53.0, 37.3, 30.9, 28.6, 27.3, 21.7, 12.8; IR ν_{max} 3012, 2949, 2924, 2857, 2216, 1712, 1648, 1440, 1237, 1106, 1074, 1022, 765; Anal. Calcd for $C_{16}H_{17}BrO_3$: C, 56.99; H, 5.08; Br, 23.70%; Found: C, 57.20; H, 5.31; Br, 24.02%.

Conflicts of interest

There are no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.02.024.

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