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ORIGINAL PAPER

Facile synthesis of 3(2*H*)-furanones

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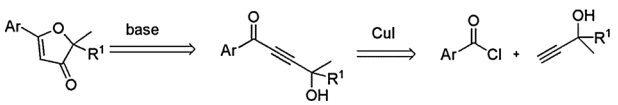
Abstract

A practical method for the synthesis of 3(2*H*)-furanones including the bullatenone was described. Intramolecular cyclization of 4-hydroxyalkynones in the presence of KOH affords the biologically potent furanones in moderate-to-good yield at room temperature. Synthesis of 4-hydroxyalkynones from the reaction of acid chloride and terminal alkyne in the presence of copper iodide at room temperature was also reported.

Graphical abstract



Keywords 3(2*H*)-furanones · 4-Hydroxyalkynone · Annulation · Cu-catalysis · Bullatenone

Introduction

The 3(2*H*)-furanone ring system (Fig. 1) is an interesting class of heterocyclic core that constitutes the central ring of many of the natural products isolated from a variety of sources like sponges, algae, animals, plants, and insects [1–4]. Jatrophone, eremantholides, geiparvarin, and parvifloranine A are some of the natural products of this class that show potent anti-tumor activity [5–7]. The biological property of these complex natural products appears to be associated with their ability to act as alkylating agents by virtue of the conjugate addition of biological nucleophiles to the 3(2*H*)-furanone moiety [8]. Bullatenone, isolated from New Zealand endemic shrub *Lophomyrtus bullata* (Myrtaceae), shows antifungal activity against *Candida albicans* and *Cladosporium resinae* belong to this 3(2*H*)-furanone class [9]. Other compounds having this subunit also show wide spectrum of biological properties, including antiproliferative [10], antiulcer [11], antiallergic [12], selective COX-2 inhibition [13], and selective MAO-B inhibition activities [14].

Synthetic approaches to the 3(2*H*)-furanone ring system which vary in their degree of flexibility have been investigated by several groups. In 1971, Margaretha [15] reported the sodium hydride catalyzed acylation of a hydroxyketone with ethyl formate, followed by an acid-promoted dehydration affords furanone in 50% yield. In 1981, Smith III et al. tried to exploit this strategy to 5-substituted 3(2*H*)-furanones, through utilization of an alkyl ester in place of ethyl formate [16]. However, all attempts in this regard were found to be fruitless. Then, the later author reported an efficient approach involving acid-catalyzed cyclization–dehydration of appropriately substituted α'-hydroxy-1,3-diketone to achieve the 3(2*H*)-furanone ring system [17]. They have also exploited this strategy for the total synthesis of geiparvarine. Since the pioneering work of Parker, Raphael, and Wilkinson [18] on base-catalyzed cyclization of 4-hydroxy-ynones to 3(2*H*)-furanones, several annulation methods have been emerged

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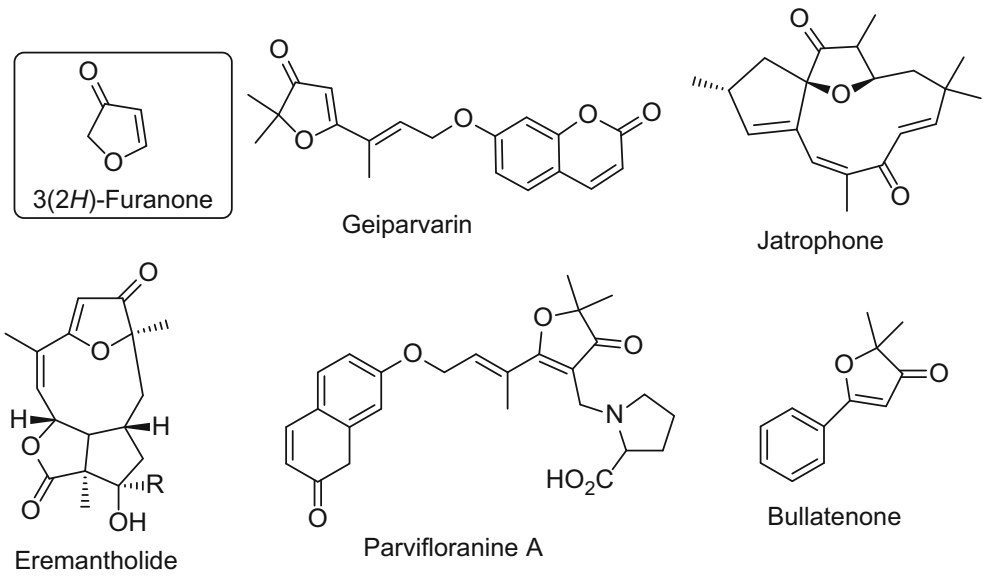
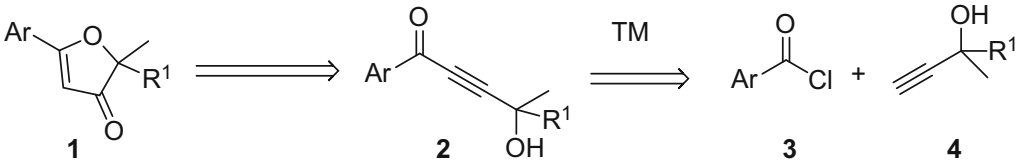


Fig. 1 Examples of biologically potent 3(2*H*)-furanone containing natural products

starting from 4-hydroxy-ynones. For instance, Hiyama and co-workers reported the synthesized of 4-hydroxy-2-alkynones from the oxidation of 2-butyn-1,4-diol using *t*-butyl hydroperoxide and Nafion-H and subsequent transformation to 3(2*H*)-furanones in the presence of polymer reagent Hg/Nafion-H [19]. In 1986, Thomas and Damm reported the sulfuric acid-catalyzed cyclization 4-hydroxy-ynones to enable 3(2*H*)-furanones [20]. Inoue and co-workers synthesized 3(2*H*)-furanones from 4-hydroxy-2-alkyn-1-one derivatives via CO_2-mediated bond reorganization [21–23]. Consequently, Amslinger and Lindner [24] employed diethyl amine in the presence of water to produce 3(2*H*)-furanones from 4-hydroxy-ynones. Notably, the use of potassium hydroxide as well as other harder nucleophiles afforded poor result. The stereoselective aldol reaction of 3-silyloxyfurans with aldehydes in the presence of a Lewis acid to afford furanone derivatives was described by Winkler et al. [25]. In 2011, sodium hydroxide-mediated synthesis of 3(2*H*)-furanones by cycloisomerization of allenic hydroxyl ketones in water medium was achieved by Poonoth and Krause [26]. The reaction of α,β-acetylenic γ-hydroxynitriles with arenecarboxylic acids in the presence of triethylamine leading to 4-cyano-3(2*H*)-furanones was also reported [27–32]. Very recently, Kawano et al. reported an efficient synthesis of 4-halo-3(2*H*)-furanones by halogenative intramolecular cyclization of sulfonium salts [33]. Besides, several other annulation protocols using precious catalysts of transition metals such as Au, Au/Ag, Pt, Pd, and Cu have been developed [34–40]. For instance, Liu et al. described that 2-oxo-3-butynoic esters or disubstituted-1,2-diones react with a range of nucleophiles in the presence of gold catalyst to produce substituted 3(2*H*)-furanones [34]. Akai used the combination of (p-$CF_3C_6H_4)_3$PAuCl and AgOTf as the catalyst for the intramolecular cyclization of γ-hydroxyalkynones [35]. Crone and Krish employed gold-catalyst along with NIS to synthesize iodofunctionalized furans [6]. Cu-catalyzed [4+1] annulation between α-hydroxyketones and nitriles was reported by Jiang and co-workers [36]. Pt-catalyzed activation of alkyne group of 2-hydroxy-2-alkynylcarbonyl compound with a heterocyclization and subsequent 1,2-alkyl shift leading to 3(2*H*)-furanones was described by Krisch et al. [37]. Pd-catalyzed annulation of 4-hydroxyalkynone in the presence of CO_2 was reported by Inoue [38]. Another palladium-catalyzed route for the synthesis of substituted 3(2*H*)-furanones from activated alkenes and 4-chloroacetoacetate was developed by John and Hopf [39]. Undoubtedly, these reported methods have their own merit with several degrees of flexibility. However, the use of expensive transition metal catalyst and limited substrate scope, harsh conditions, and lack of a generality in procedure to achieve the starting materials necessitate further development for the efficient synthesis of functionalized 3(2*H*)-furanones. Here, we report a simple base-catalyzed method for the synthesis of 3(2*H*)-furanones from the easily accessible 4-hydroxyalkynones under metal-free conditions.

Our strategy towards the synthesis of 3(2*H*)-furanone is outlined in Scheme 1. This involves the transition metal-catalyzed coupling of synthetically viable acid chloride **3** and but-3-yn-2-ol (**4**) to produce 4-hydroxyalkynone **2**, which could be transformed to the desired 3(2*H*)-furanones in the presence of base.

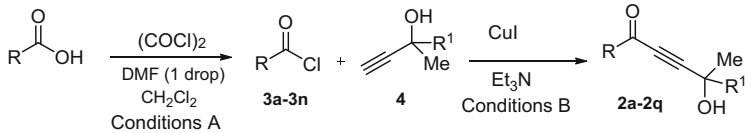
Scheme 1



Results and discussion

We began our study with the synthesis of ynone, i.e., 4-hydroxy-4-methyl-1-phenylpent-2-yn-1-one (**2a**, Ar=Ph) from the reaction of 2-methylbut-3-yn-2-ol (**4a**) and benzoyl chloride (**3a**, Ar=Ph). Notably, the earlier reports 4-hydroxy ynone synthesis (e.g., **2a**) from the reaction of benzoyl chloride and terminal alkyne are mainly populated with the use of expensive Pd catalyst [41–43]. However, the use of a low-cost catalyst such as copper salt is less literature precedent [44–48]. In line with our earlier work on the use of cheaper catalytic system for C–C and C–heteroatom bond formation reaction [49, 50], we planned to synthesize the 4-hydroxy-ynones using less expensive copper catalyst following a similar procedure reported earlier by Kundu et al. [48]. Thus, we treated a series of aryl acid chlorides with 2-methylbut-3-yn-2-ol (**4**) in the presence of 10 mol% of CuI in triethylamine for 30 h to produce a series 4-hydroxyalkynones **2a**–**2m** (Table 1). It may be mentioned here that except benzoyl chloride, the remaining acid chlorides were prepared from the reaction of the corresponding carboxylic acid, oxalyl chloride in dry dichloromethane and used for the next step just after solvent removal without further purification. For entry 13, we are

Table 1 Copper catalyzed ynone synthesis from acid chloride



Entry	R	Acid chloride	R^1	Ynone	Yield/%[a]
1	C_6H_5–	**3a**	CH_3–	**2a** [35]	85
2	4-Me–C_6H_4–	**3b**	CH_3–	**2b** [48]	65
3	2-Me–C_6H_4–	**3c**	CH_3–	**2c**	57
4	2-Cl–C_6H_4–	**3d**	CH_3–	**2d** [51]	45
5	4-Cl–C_6H_4–	**3e**	CH_3–	**2e** [52]	54
6	2-I–C_6H_4–	**3f**	CH_3–	**2f**	48
7	4-I–C_6H_4–	**3g**	CH_3–	**2g**	50
8	4-OMe–C_6H_4–	**3h**	CH_3–	**2h** [53]	72
9	3-OMe–C_6H_4–	**3i**	CH_3–	**2i**	68
10	3,5-$(OMe)_2$–C_6H_3–	**3j**	CH_3–	**2j**	72
11	3,4-$(OMe)_2$–C_6H_3–	**3k**	CH_3–	**2k**	70
12	3,4-$(Cl)_2$–C_6H_3–	**3l**	CH_3–	**2l**	68
13	3,5-$(Cl)_2$–C_6H_3–	**3m**	CH_3–	**2m**	Impure
14	C_6H_5CH=CH–	**3n**	CH_3–	**2n** [35]	37
15	C_6H_5–	**3a**	C_6H_5–	**2o**	70
16	C_6H_5–	**3a**	C_2H_5–	**2p**	79
17	C_6H_5–	**3a**	H–	**2q** [54]	82

[a]Reaction conditions: A: 200 mg acid, 1.5 equiv. $(COCl)_2$, DMF (1 drop); 0 °C—rt, 6 h. B: acid chloride from step 1 in 3 cm^3 Et_3N, 0 °C—rt, N_2 atmosphere, 30 h

unable to isolate the pure ynone **2m**. Besides, this procedure worked nicely for simple or acid chloride having electron-donating groups, unfortunately fails for similar acid chlorides with electron-withdrawing groups. Our efforts to modify the condition using other copper salts and bases were unsuccessful. Although this method is suitable to afford ynone **2n**, we are unable to isolate any ynone from acetyl chloride. On the other hand, terminal alkynes other than 2-methylbut-3-yn-2-ol were also found to be compatible to this reaction condition and afforded the corresponding 4-hydroxy-ynones **2o**, **2p**, and **2q** in good yield.

Next, we turned our attention towards the annulation of 4-hydroxyalkynones **2** to produce 3(2*H*)-furanones. Interestingly, we observed that when 4-hydroxy-4-methyl-1-phenylpent-2-yn-1-one (**2a**) was treated with methanolic KOH, the desired compound **1a** (bullatenone) was produced in 74% yield. Replacing the KOH by an organic base such as diethyl amine also produces the similar yield (70%). To obtain improved yield, screening of different bases and solvents was made by taking 4-hydroxy-4-methyl-1-phenylpent-2-yn-1-one (**2a**) as model substrate (Table 2). To our pleasure, when **2a** was treated with three equiv. of inexpensive potassium hydroxide (KOH) in a mixture of solvent (i.e., toluene: methanol 2 cm^3:0.5 cm^3) at room temperature for 12 h, the desired furanone **1a** was obtained in very good yield (85%). Note worthy that other bases such as pyridine, NaOH, K_2CO_3, K_3PO_4, and *t*-BuOK in similar solvent system were less effective to produce **1a**.

With the optimized reaction condition, next, we subjected the synthesized 4-hydroxyalkynones (**2**) for the annulation (Table 3). Several 3(*H*)-furanones including bullatenone (**1a**) were produced in moderate-to-excellent yield. Functional groups such as Cl, I, and OMe are found to be compatible with reaction condition. Moreover, the presence of an active functional group such as iodo opens the door for further functionalization to biologically potent 3(2*H*)-furanone derivatives.

In line with earlier reports [18, 24], a plausible mechanism for the successful transformation was proposed (Scheme 2). This involves the initial 1,4-addition of the alkynone to produce the corresponding enol **I**, which tautomerizes to the corresponding 1,3-dicarbonyl compound **II**. The preferred intramolecular nucleophilic attack of the tertiary alcoholic OH group to the carbonyl group enables the intermediate **III**, which might be undergoing dehydration to afford the corresponding 3(2*H*)-furanone.

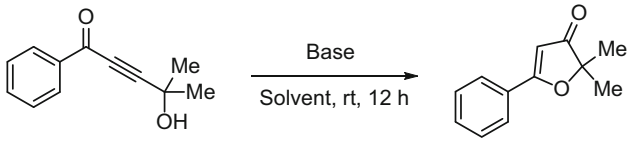
Conclusion

In conclusion, we have developed a simple base-catalyzed route for the synthesis of 3(2*H*)-furanone derivatives from the 4-hydroxy-ynones using the inexpensive potassium hydroxide in toluene and methanol mixture. Our protocol allows to synthesize functionalized 3(2*H*)-furanone, which can be further functionalized by cross-coupling reactions to produce biologically more potent furanone derivatives. Moreover, the synthesis of ynones from the copper-catalyzed acylation of terminal alkyne was also presented.

Experimental

All reactions were carried out in oven dried round bottom flask. Solvents and reagents were used without further purification. The reactions were monitored by TLC and the

Table 2 Optimization of reaction conditions

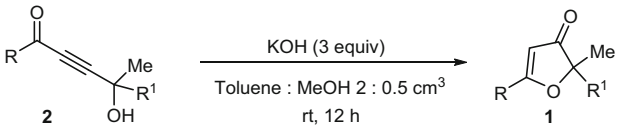


2a **1a**

Entry	Base	Solvent	Yield/%[a]
1	KOH	MeOH (2.5 cm^3)	74
2	$(C_2H_5)_2NH$	MeOH (2.5 cm^3)	70
3	KOH	Toluene (2 cm^3), MeOH (0.5 cm^3)	85
4	NaOH	Toluene (2 cm^3), MeOH (0.5 cm^3)	34
5	K_2CO_3	Toluene (2 cm^3), MeOH (0.5 cm^3)	30
6	K_3PO_4	Toluene (2 cm^3), MeOH (0.5 cm^3)	28
7	*t*-BuOK	Toluene (2 cm^3), MeOH (0.5 cm^3)	46
8	Pyridine	Toluene (2 cm^3), MeOH (0.5 cm^3)	36

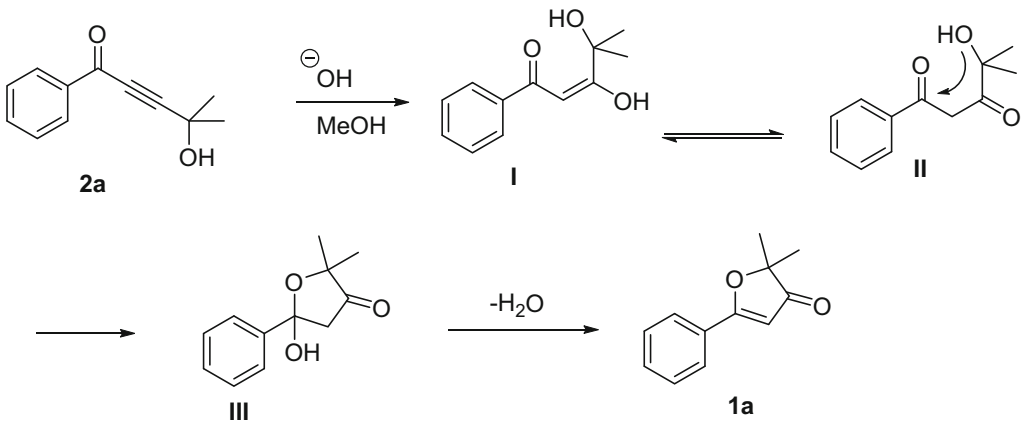
[a]Reaction conditions: 100 mg **2a** and 3 equiv. KOH, 2.5 cm^3 solvent, rt, 12 h

Table 3 Synthesis of 3(2*H*)-furanones



Entry	R, R^1	Ynone	Furanone	Yield/%
1	R=C_6H_5–, R^1=CH_3–	**2a**	**1a** [35]	85
2	R=4-CH_3–C_6H_4–, R^1=CH_3–	**2b**	**1b** [55]	65
3	R=2-CH_3–C_6H_4–, R^1=CH_3–	**2c**	**1c** [55]	61
4	R=2-Cl–C_6H_4–, R^1=CH_3–	**2d**	**1d** [55]	59
5	R=4-Cl–C_6H_4–, R^1=CH_3–	**2e**	**1e** [38]	62
6	R=2-I–C_6H_4–, R^1=CH_3–	**2f**	**1f**	53
7	R=4-I–C_6H_4–, R^1=CH_3–	**2g**	**1g**	50
8	R=3-OMe–C_6H_4–, R^1=CH_3–	**2i**	**1i**	95
9	R=3,5-$(OMe)_2$–C_6H_3–, R^1=CH_3–	**2j**	**1j**	85
10	R=3,4-$(Cl)_2$–C_6H_3–, R^1=CH_3–	**2l**	**1l**	53
11	R=3,5-$(Cl)_2$–C_6H_3–, R^1=CH_3–	**2m**	**1m**	62
12	R=C_6H_5CH=CH–, R^1=CH_3–	**2n**	**1n**	0
13	R=C_6H_5–, R^1=C_6H_5–	**2o**	**1o**	62
14	R=C_6H_5–, R^1=C_2H_5–	**2p**	**1p**	95
15	R=C_6H_5–, R^1=H–	**2q**	**1q**	0

Scheme 2



residue was purified by column chromatography on silica gel (Rankem, India, mess size 60–120), using an ethyl acetate–petroleum ether (60–80 °C) mixture as eluent. Yield of the reactions was calculated with respect to acid chloride presuming that the acid was converted to acid chloride quantitatively. All NMR spectra were recorded on Bruker Avance III (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) spectrometer and chemical shifts were expressed in δ units (ppm). The coupling constants (J values) are expressed in Hz. Mass spectra were recorded on Agilent spectrometer using ESI + mode. FT-IR spectra were recorded by Shimadzu Spectrophotometer (IR Affinity 1S W/L with quest ATR).

General procedure for the synthesis of 4-hydroxy-ynone (2)

To a stirred solution of 200 mg acid in 5 cm^3, dry dichloromethane oxalyl chloride (1.5 equiv.) was added dropwise under nitrogen atmosphere at 0 °C during which

the colour of the solution changes to black. After 6 h, solvent was removed under reduced pressure and the so-formed acid chloride was used for the next reaction without further purification.

To the acid chloride so-formed in situ from acid, nitrogen was purged 2–3 times at 0 °C. Then, 3 cm^3 of triethylamine was added and stirred for 5 min. To the resulting solution, 2-methylbut-3-yn-2-ol (0.8 equiv.) was added slowly and stirred for 30 h under nitrogen atmosphere at room temperature. After completion of the reaction, it was triturated with dichloromethane and water. The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate and petroleum ether mixture as the eluent to afford 4-hydroxy-ynones **2a**–**2q**.

General procedure for the synthesis of 3(2*H*)-furanone (1)

To a stirred solution of 4-hydroxy-ynone (0.53 mmol) in 2 cm^3 toluene, KOH (three equiv.) dissolved in 0.5 cm^3 of methanol was added and the reaction mixture was stirred for 12 h at room temperature. After the completion of the reaction, it was triturated with ethyl acetate and water. The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate and petroleum ether mixture as the eluent to provide **1**.

4-Hydroxy-4-methyl-1-(o-tolyl)pent-2-yn-1-one (2c, $C_{13}H_{14}O_2$) Yield 57%; gummy liquid; IR (KBr): $\bar{\nu}$ = 3587, 2985, 2214, 1647 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, 1H, J = 7.6 Hz), 7.45 (t, 1H, J = 7.6 Hz), 7.32 (t, 1H, J = 7.6 Hz), 7.25 (d, 1H, J = 7.2 Hz), 2.62 (s, 3H), 1.66 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.7, 140.6, 135.1, 133.4, 133.1, 132.1, 125.9, 96.8, 81.3, 65.2, 30.7, 22.0 ppm; HRMS (ESI): *m/z* calcd. for $C_{13}H_{15}O_2^+$ ([M+H]$^+$) 203.1192, found 203.1217.

1-(2-Chlorophenyl)-4-hydroxy-4-methylpent-2-yn-1-one (2d, $C_{12}H_{11}ClO_2$) [51] Yield 45%; gummy liquid; IR (KBr): $\bar{\nu}$ = 3596, 2981, 2224, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.97 (m, 1H), 7.51–7.44 (m, 2H), 7.43–7.35 (m, 1H), 1.65 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 135.3, 133.3, 132.5, 131.4, 129.4, 126.6, 98.3, 81.1, 65.2, 30.4 ppm.

1-(2-Chlorophenyl)-4-hydroxy-4-methylpent-2-yn-1-one (2d, $C_{12}H_{11}ClO_2$) [51] Yield 54%; IR (KBr): $\bar{\nu}$ = 3589, 2978, 2210, 1647 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, 2H, J = 8 Hz), 7.43 (d, 2H, J = 7.2 Hz), 1.67 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 140.9, 134.7, 130.9, 128.9, 98.9, 79.4, 65.2, 30.6 ppm.

4-Hydroxy-1-(2-iodophenyl)-4-methylpent-2-yn-1-one (2f, $C_{12}H_{11}IO_2$) Yield 48%; gummy liquid; IR (KBr): $\bar{\nu}$ = 3586, 2976, 2210, 1652 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–7.96 (m, 2H), 7.43 (t, 1H, J = 7.6 Hz), 7.20–7.12 (m, 1H), 1.62 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 142.2, 138.5, 133.6, 129.9, 128.1, 99.5, 92.8, 79.9, 65.7, 30.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{12}H_{12}IO_2^+$ ([M+H]$^+$) 314.9882, found 314.9875.

4-Hydroxy-1-(4-iodophenyl)-4-methylpent-2-yn-1-one (2g, $C_{12}H_{11}IO_2$) Yield 50%; gummy liquid; IR (KBr): $\bar{\nu}$ = 3587, 2978, 2214, 1652 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.73 (m, 4H), 3.59 (s, 1H), 1.65 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 137.9, 135.7, 130.8, 103.0, 99.2, 95.3, 79.4, 65.1, 30.6 ppm; HRMS (ESI): *m/z* calcd. for $C_{12}H_{12}IO_2^+$ ([M+H]$^+$) 314.9882, found 314.9873.

4-Hydroxy-1-(3-methoxyphenyl)-4-methylpent-2-yn-1-one (2i, $C_{13}H_{14}O_3$) Yield 68%; gummy liquid; IR (KBr): $\bar{\nu}$ = 3587, 2982, 2214, 1646 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, 1H, J = 7.6 Hz), 7.56 (d, 1H, J = 1.6 Hz), 7.36–7.25 (m, 1H), 7.10 (dd, 1H, J = 8.4 Hz, 2.8 Hz), 3.80 (s, 3H), 1.65 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 159.6, 137.8, 129.6, 122.8, 121.0, 112.9, 98.6, 79.8, 65.1, 55.3, 30.6 ppm; HRMS (ESI): *m/z* calcd. for $C_{13}H_{15}O_3^+$ ([M+H]$^+$) 219.1021, found 219.1014.

1-(3,5-Dimethoxyphenyl)-4-hydroxy-4-methylpent-2-yn-1-one (2j, $C_{14}H_{16}O_4$) Yield 72%; gummy liquid; IR (KBr): $\bar{\nu}$ = 3587, 2984, 2218, 1648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 2H), 6.73–6.62 (m, 1H), 3.86 (s, 6H), 1.64 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 160.8, 138.4, 107.2, 106.8, 97.7, 79.9, 65.3, 55.6, 29.7 ppm; HRMS (ESI): *m/z* calcd. for $C_{14}H_{17}O_4^+$ ([M+H]$^+$) 249.1127, found 249.1120.

1-(3,4-Dimethoxyphenyl)-4-hydroxy-4-methylpent-2-yn-1-one (2k, $C_{13}H_{14}O_3$) Yield 70%; gummy liquid; IR (KBr): $\bar{\nu}$ = 3587, 2982, 2210, 1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (dd, 1H, J = 8.4 Hz, 1.6 Hz), 7.58 (d, 1H, J = 1.6 Hz), 6.91 (d, 1H, J = 8.8 Hz), 3.96 (s, 3H), 3.94 (s, 3H), 1.67 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 154.3, 148.8, 129.9, 125.9, 109.9, 97.2, 79.6, 65.1, 56.0, 55.8, 30.6 ppm; HRMS (ESI): *m/z* calcd. for $C_{13}H_{15}O_3^+$ ([M+H]$^+$) 219.1021, found 219.1012.

1-(3,4-Dichlorophenyl)-4-hydroxy-4-methylpent-2-yn-1-one (2l, $C_{12}H_{10}Cl_2O_2$) Yield 68%; gummy liquid; IR (KBr): $\bar{\nu}$ = 3587, 2982, 2214, 1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, 1H, J = 2 Hz), 7.94 (dd, 1H,

J = 8.4 Hz, 2 Hz), 7.58 (d, 1H, J = 8 Hz), 1.68 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 139.0, 135.9, 133.4, 131.2, 130.8, 128.4, 99.3, 79.2, 65.3, 30.6 ppm; HRMS (ESI): *m/z* calcd. for $C_{12}H_{11}Cl_2O_2^+$ ($[M+H]^+$) 257.0136, found 257.0139.

4-Hydroxy-1,4-diphenylpent-2-yn-1-one (2o, $C_{17}H_{14}O_2$) Yield 70%; white solid; m.p.: 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17-8.13 (m, 2H), 7.73–7.70 (m, 2H), 7.66–7.63 (m, 1H), 7.53–7.47 (m, 2H), 7.43–7.39 (m, 2H), 7.38–7.34 (m, 1H), 3.01 (bs, 1H), 1.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.7, 143.7, 136.4, 134.3, 129.6, 128.6, 128.6, 128.4, 128.2, 124.7, 96.4, 82.1, 32.5 ppm; MS (ESI): *m/z* = 251 ($[M+H]^+$, 100%).

4-Hydroxy-4-methyl-1-phenylhex-2-yn-1-one (2p, $C_{13}H_{14}O_2$) Yield 79%; gummy liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, 2H, J = 7.2 Hz), 7.56 (t, 1H, J = 7.2 Hz), 7.42 (t, 2H, J = 7.6 Hz), 3.96 (bs, 1H), 1.90-1.82 (m, 2H), 1.62 (s, 3H), 1.10 (t, 3H, J = 7.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1, 136.3, 134.2, 129.5, 98.1, 80.9, 68.7, 36.0, 28.4, 8.95 ppm; MS (ESI): *m/z* = 203 ($[M+H]^+$, 100%).

4-Hydroxy-1-phenylpent-2-yn-1-one (2q, $C_{11}H_{10}O_2$) [54] Yield 82%; gummy liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, 2H, J = 8.4 Hz), 7.57 (t, 1H, J = 7.2 Hz), 7.45 (t, 2H, J = 7.2 Hz), 5.74–5.67 (m, 1H), 2.53 (d, 1H, J = 2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 133.1, 129.7, 129.4, 128.3, 82.1, 73.1, 60.5, 21.2 ppm; MS (ESI): *m/z* = 175 ($[M+H]^+$, 100%).

5-(2-Iodophenyl)-2,2-dimethylfuran-3(2H)-one (1f, $C_{12}H_{11}IO_2$) Yield 53%; white solid; m.p.: 58–60 °C; IR (KBr): $\bar{\nu}$ = 3015, 2981, 2210, 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (t, 2H, J = 4.2 Hz), 7.55 (dd, 2H, J = 2 Hz, 7.2 Hz), 5.97 (s, 1H), 1.49 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 182.4, 138.1, 128.5, 128.4, 99.7, 98.8, 89.2, 23.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{12}H_{12}IO_2^+$ ($[M+H]^+$) 314.9882, found 314.9873.

5-(4-Iodophenyl)-2,2-dimethylfuran-3-one (1g, $C_{12}H_{11}IO_2$) Yield 50%; white solid; m.p.: 150–152 °C; IR (KBr): $\bar{\nu}$ = 3014, 2982, 2224, 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (dd, 2H, J = 6.8 Hz, 1.6 Hz), 7.55 (dd, 2H, J = 6.4 Hz, 1.8 Hz), 5.98 (s, 1H), 1.5 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 182.4, 138.1, 128.5, 128.4, 99.7, 98.8, 89.2, 23.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{12}H_{12}IO_2^+$ ($[M+H]^+$) 314.9882, found 314.9875.

5-(3-Methoxyphenyl)-2,2-dimethylfuran-3(2H)-one (1i, $C_{13}H_{14}O_3$) Yield 95%; white solid; m.p.: 86–88 °C; IR (KBr): $\bar{\nu}$ = 3015, 2980, 1685, 1597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.45 (m, 2H), 7.34 (t, 1H, J = 1.6 Hz), 7.06-7.13 (m, 1H), 5.96 (s, 1H), 3.88 (s, 3H), 1.49 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.2, 183.4, 159.7, 130.3, 129.9, 119.9, 118.5, 111.8, 98.8, 89.1, 55.5, 23.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{13}H_{15}O_3^+$ ($[M+H]^+$) 219.1021, found 219.1046.

5-(3,5-Dimethoxyphenyl)-2,2-dimethylfuran-3(2H)-one (1j, $C_{14}H_{16}O_4$) Yield 85%; white solid; m.p.: 103–105 °C; IR (KBr): $\bar{\nu}$ = 3007, 2981, 1683, 1602 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (d, 2H, J = 2 Hz), 6.62–6.67 (m, 1H), 5.93 (s, 1H), 3.86 (s, 3H), 1.50 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.0, 183.3, 160.9, 130.9, 105.0, 104.7, 99.0, 89.1, 55.6, 23.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{14}H_{17}O_4^+$ ($[M+H]^+$) 249.1127, found 249.1117.

5-(3,4-Dichlorophenyl)-2,2-dimethylfuran-3(2H)-one (1l, $C_{12}H_{10}Cl_2O_2$) Yield 53%; white solid; m.p.: 128–130 °C; IR (KBr): $\bar{\nu}$ = 3015, 2983, 1685, 1604 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, 1H, J = 2 Hz), 7.62–7.69 (m, 1H), 7.58 (d, 1H, J = 8.4 Hz), 5.97 (s, 1H), 1.50 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.6, 180.7, 136.8, 133.5, 130.9, 129.0, 128.7, 126.3, 99.5, 89.5, 23.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{12}H_{11}Cl_2O_2^+$ ($[M+H]^+$) 257.1036, found 257.1029.

5-(2,4-Dichlorophenyl)-2,2-dimethylfuran-3(2H)-one (1m, $C_{12}H_{10}Cl_2O_2$) **2m** was obtained as an impure product that contaminated with other unidentified impurities starting from 200 mg of 2,4-dichlorobenzoic acid. On treatment of **2m** (impure) with aq. KOH following the general procedure C, **1m** was obtained in 52% yield (with respect to acid) as white crystalline solid; m.p.: 133–135 °C; IR (KBr): $\bar{\nu}$ = 3015, 2983, 1685, 1604 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, 1H, J = 8.4 Hz), 7.55 (d, 1H, J = 2 Hz), 7.39 (dd, 1H, J = 8.4 Hz, 2 Hz), 6.35 (s, 1H), 1.49 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.5, 178.8, 138.2, 134.7, 131.0, 130.3, 127.5, 126.8, 104.4, 87.5, 23.0 ppm; HRMS (ESI): *m/z* calcd. for $C_{12}H_{11}Cl_2O_2^+$ ($[M+H]^+$) 257. 0136, found 257. 0161.

2-Methyl-2,5-diphenylfuran-3(2H)-one (1o, $C_{17}H_{14}O_2$) Yield 62%; gummy liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.94 (m, 2H), 7.63–7.54 (m, 5H), 7.41–7.32 (m, 3H), 6.03 (s, 1H), 1.88 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.3, 183.8, 138.3, 132.8, 128.9, 128.8, 128.5, 128.0, 127.1, 124.5, 98.6, 90.3, 24.4 ppm; MS (ESI): *m/z* = 251 ($[M+H]^+$, 100%).

2-Ethyl-2-methyl-5-phenylfuran-3(2H)-one (1p, $C_{13}H_{14}O_2$) Yield 95%; gummy liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.81 (m, 2H), 7.56–7.52 (m, 1H), 7.51–7.45 (m, 2H), 5.99 (s, 1H), 1.92–1.83 (m, 2H), 1.45 (s, 3H), 0.87 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 184.1, 132.5, 128.9, 128.8, 127.0, 99.9, 91.7, 30.0, 21.7, 7.48 ppm; MS (ESI): *m/z* = 203 ($[M+H]^+$, 100%).

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References

1. Murty SN, Madhav B, Kumar AV, Rao KR, Nageswar YVD (2009) Tetrahedron 65:5251
2. Zhang M, Wang W-L, Fang Y-C, Zhu T-J, Gu Q-Q, Zhu W-M (2008) J Nat Prod 71:985
3. Zhang Y, Wang J-S, Wei D-D, Gu Y-C, Wang X-B, Kong L-Y (2013) J Nat Prod 76:1191
4. Shou Q, Banbury LK, Renshaw DE, Smith JE, He X, Dowell A, Griesser HJ, Heinrich M, Wohlmuth H (2013) J Nat Prod 76:1384
5. Nardini V, Rodrigues SMM, Constantino GVJS (2012) Molecules 17:12151
6. Crone B, Kirsch SF (2007) J Org Chem 72:5435
7. Baraldi PG, Manfredini S, Simoni D, Tabrizi MA, Balzarini J, Clercq ED (1992) J Med Chem 35:1877
8. Marson CM, Edaan E, Morrell JM, Coles SJ, Hursthouse MB, Davies DT (2007) Chem Commun 2494
9. Woollard JMR, Perry NB, Weavers RT, van Klink JW (2008) Phytochem 69:1313
10. Chimichi S, Boccalini M, Cosimelli B, Dall'Acqua F, Viola G (2003) Tetrahedron 59:5215
11. Felman SW, Jirkovsky I, Memoli KA, Borella L, Wells C, Russell J, Ward J (1992) J Med Chem 35:1183
12. Mack RA, Zazulak WI, Radov LA, Baer JE, Stewart JD, Elzer PH, Kinsolving CR, Georgiev VS (1988) J Med Chem 31:1910
13. Shin SS, Byun Y, Lim KM, Choi JK, Lee K-W, Moh JH, Kim JK, Jeong YS, Kim JY, Choi YH, Koh H-J, Park Y-H, Oh YI, Noh M-S, Chung S (2004) J Med Chem 47:792
14. Carotti A, Carrieri A, Chimichi S, Boccalini M, Cosimelli B, Gnerre C, Carotti A, Carrupt P-A, Testa B (2002) Bioorg Med Chem Lett 12:3551
15. Margaretha P (1971) Tetrahedron Lett 4891
16. Smith AB III, Levenberg PA, Jerris PJ, Scarborough RM Jr, Wovkulich PM (1981) J Am Chem Soc 103:1501
17. Jerris PJ, Smith AB III (1981) J Org Chem 46:577
18. Parker W, Raphael RA, Wilkinson DI (1958) J Chem Soc 3871
19. Saimoto H, Shinoda M, Matsubara S, Oshima K, Hiyama T, Nozaki H (1983) Bull Chem Soc Jpn 56:3088
20. Thomas AF, Damm H (1986) Tetrahedron Lett 27:505
21. Inoue Y, Ohuchi K, Imaizumi S, Hagiwara H, Uda H (1990) Synth Commun 20:3063
22. Kawaguchi T, Yasuta S, Inoue Y (1996) Synthesis 1431
23. Inoue Y, Ohuchi K, Imaizumi S (1988) Tetrahedron Lett 29:5941
24. Amslinger S, Lindner SK (2011) Synthesis 2671
25. Winkler JD, Oh K, Asselin SM (2005) Org Lett 7:387
26. Poonoth M, Krause N (2011) J Org Chem 76:1934
27. Trofimov BA, Shemyakina OA, Mal'kina AG, Ushakov IA, Kazheva ON, Alexandrov GG, Dyachenko OA (2010) Org Lett 12:3200
28. Malkina AG, Volostnykh OG, Petrushenko KB, Shemyakina OA, Nosyreva VV, Ushakov IA, Trofimov BA (2013) Tetrahedron 69:3714
29. Shemyakina OA, Stepanov AV, Volostnykh OG, Malkina AG, Ushakov IA, Trofimov BA (2014) Russ J Org Chem 50:1617
30. Malkina AG, Volostnykh OG, Stepanov AV, Ushakov IA, Petrushenko KB, Trofimov BA (2013) Synthesis 45:3435
31. Trofimov BA, Stepanov AV, Malkina AG, Volostnykh OG, Shemyakina OA, Ushakov IA (2015) Synth Commun 45:2718
32. Malkina AG, Shemyakina OA, Stepanov AV, Volostnykh OG, Ushakov IA, Sobenina LN, Borodina TN, Smirnov VI, Trofimov BA (2016) Synthesis 48:271
33. Inagaki S, Nakazato M, Fukuda N, Tamura S, Kawano T (2017) J Org Chem 82:5583
34. Liu Y, Liu M, Guo S, Tu H, Zhou Y, Gao H (2006) Org Lett 8:3445
35. Egi M, Azechi K, Saneto M, Shimizu K, Akai S (2010) J Org Chem 75:2123
36. He H, Qi C, Hu X, Ouyang L, Xiong W, Jiang H (2015) J Org Chem 80:4957
37. Kirsch SF, Binder JT, Liebert C, Menz H (2006) Angew Chem Int Ed 45:5878
38. Inoue Y (1989) Bull Chem Soc Jpn 62:3518
39. John J, Hopf H (2013) Eur J Org Chem 841
40. Bunnelle EM, Smith CR, Lee SK, Singaram SW, Rhodes AJ, Sarpong R (2008) Tetrahedron 64:7008
41. Kawaguchi S-I, Minamida Y, Okuda T, Sato Y, Saeki T, Yoshimura A, Nomoto A, Ogawa A (2015) Adv Synth Catal 357:2509
42. Atobe S, Masuno H, Sonoda M, Suzuki Y, Shinohara H, Shibata S, Ogawa A (2012) Tetrahedron Lett 53:1764
43. Fukuyama T, Yamaura R, Ryu I (2005) Can J Chem 83:711
44. Zanina AS, Shergina SI, Sokolov IE, Kotlyarevskii IL (1981) Izv Akad Nauk SSSR Ser Khim 1158
45. Haung TT, Kirsch SF (2009) In: Attanasi OA, Spinelli D (eds) Targets in heterocyclic systems: chemistry and properties, vol 13. Societa Chemica Italiana, Rome, p 57
46. Gallagher WP, Maleczka RE Jr (2003) J Org Chem 68:6775
47. Ramachandran PV, Teodorovic AV, Rangaishenvi MV, Brown HC (1992) J Org Chem 57:2379
48. Chowdhury C, Kundu NG (1999) Tetrahedron 55:7011
49. Panda N, Mothkuri R, Nayak DK (2014) Eur J Org Chem 1602
50. Panda N, Mothkuri R, Pal A, Paital AR (2013) Adv Synth Catal 355:2809
51. Amegadzie AK, Gardinier KM, Hembre EJ, Hong JE, Jungheim LN, Muehl BS, Remick DM, Robertson MA, Savin KA (2003) Preparation of triazole derivatives as tachykinin receptor antagonists. Patent WO 2003091226 A1, Nov 6, 2003; (2003) Chem Abstr 139:364937
52. Ripka A, Shapiro G, Chesworth R (2009) 1,2-Disubstituted heterocyclic compounds as phosphodiesterase 10 inhibitors and their preparation, pharmaceutical compositions and use in the treatment of CNS disorders and disorders affected by CNS function. Patent WO 2009158393 A1, Dec 30, 2009; (2009) Chem Abstr 152:97491
53. Ahmed MSM, Mori A (2003) Org Lett 5:3057
54. Gree D, Gree R (2007) Tetrahedron Lett 48:5435
55. Sakai T, Yamawaki A, Ito H, Utaka M, Takeda A (1986) J Heterocycl Chem 23:1199