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A three-component procedure for the synthesis of 5-(1-aryl-3-arylprop-2-yn-1-yl)-2,2-butylidene-1,3-dioxane-4,6-dione derivatives

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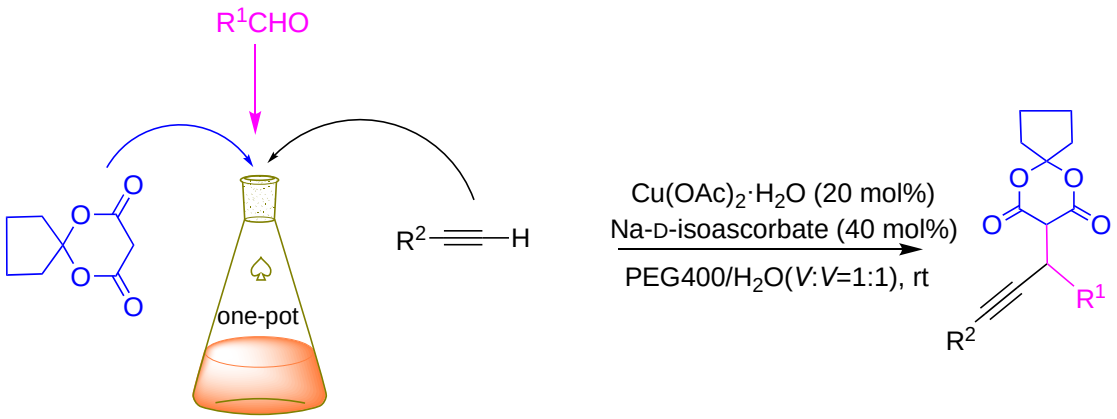
Abstract

A simple and efficient procedure for the synthesis of 5-(1-aryl-3-arylprop-2-yn-1-yl)-2,2-butylidene-1,3-dioxane-4,6-dione derivatives through one-pot reactions of araldehydes, 2,2-butylidene-1,3-dioxane-4,6-dione and an arylethyne in the presence of $Cu(OAc)_2 \cdot H_2O$/Na-D-isoascorbate, is described. The procedure involves initial Knoevenagel reaction, followed by conjugate addition. The high isolated yields, broad substrate scope, mild conditions, and easy operation are the main advantages of the protocol.



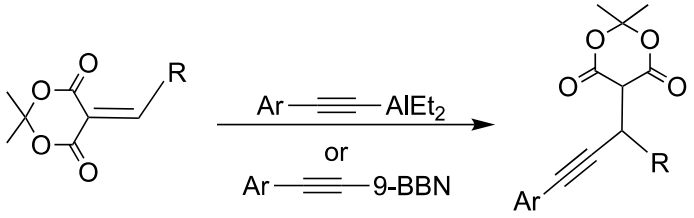
Keywords: *β*-alkynyl Meldrum's acid analogues, one-pot reaction, $Cu(OAc)_2 \cdot H_2O$/Na-D-isoascorbate, 2,2-butylidene-1,3-dioxane-4,6-dione

Introduction

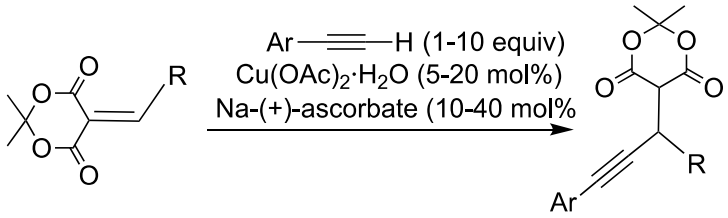
β-Alkynyl Meldrum's acid analogues have exhibited an amazingly wide spectrum of biological properties including as PDE IV inhibitors, TNF inhibitors, GPR40 receptor agonists, and GRP receptor antagonists.[1,2] They are also important building blocks in organic synthesis performed to access diverse *β*-alkynyl carbonyl compounds,[3] γ-butyrolactones[4-6] and clausenamide alkaloids.[7] Therefore, the development of a simple and efficient methology for the synthesis of *β*-alkynyl Meldrum's acids has attracted the attention of synthetic as well as medicinal chemists.

5-(1-aryl-3-arylprop-2-ynyl)-2,2-methyl-1,3-dioxane-4,6-diones are commonly synthesized employing one of three methods involving conjugate addition of metalated teminal alkynes, *in situ* generated copper alkynylides or *in situ* generated zinc alkynylides to Meldrum's acid derived acceptors (Scheme 1).

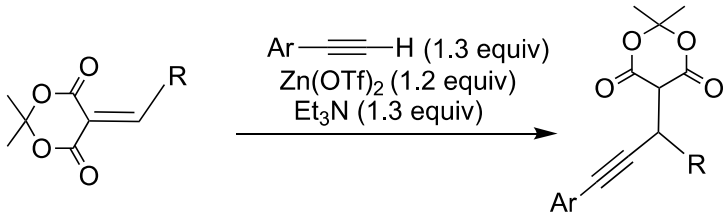
(a) The conjugate addition of metalated teminal alkynes with Meldrum' s acid derived acceptors



(b)The conjugate addition of *in situ* generated Cu-alkynylides with Meldrum' s acid derived acceptors



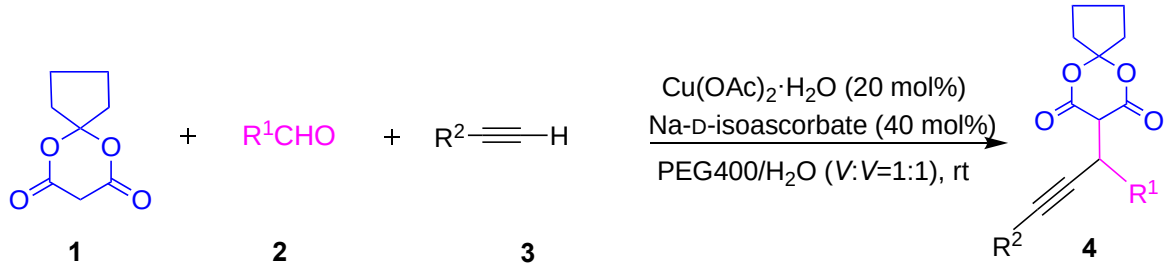
(c) Zinc-mediated conjugate addition of Alkynes to Meldrum' s acid derived acceptors



Scheme 1. Reported conjugate additions of alkyne-based metal salts and Meldrum's acid derived acceptors.

The first known method for the conjugate addition of alkynes includes the use of boron[8,9] or aluminum alkynylides [10,11] in the presence of *t*-BuMe$_2$SiOTf [12-14] as an activator under conditions of rigorous exclusion of oxygen and moisture. From a practical point of view, the second method of *in situ* generated metal alkynylides is attractive, as it can be completed in a single synthetic operation. A series of elegant papers[15-19] reported the direct conjugate addition of *in situ* generated Cu-acetylides to Meldrum's acids in the presence of copper acetate, based on Na-(+)-ascorbate as a reductant. This method was optimal only for addition of aylacetylenes to γ-branched alkylidene acceptors. The third method disclosed[20] the diastereoselective alkynylation of chiral oxazepanedione acceptors with Zn(OTf)$_2$ and an amine base. The substituents were limited to alkyl groups of Meldrum's acids derived receptors. Hence, the development of a simple, wide substrate and efficient procedure for the synthesis of new *β*-alkynyl Meldrum's acids is still needed.

In continuation of our efforts toward the development of novel *β*-alkynyl Meldrum's acid compounds,[21] herein we report the use of $Cu(OAc)_2·H_2O$/Na-D-isoascorbate as a catalytic system for the synthesis of 5-(1-aryl-3-arylprop-2-yn-1-yl)-2,2-butylidene-1,3-dioxane-4,6-dione derivatives through three-component reactions of an araldehyde, 2,2-butylidene-1,3-dioxane-4,6-dione and an arylacetylene (Scheme 2).



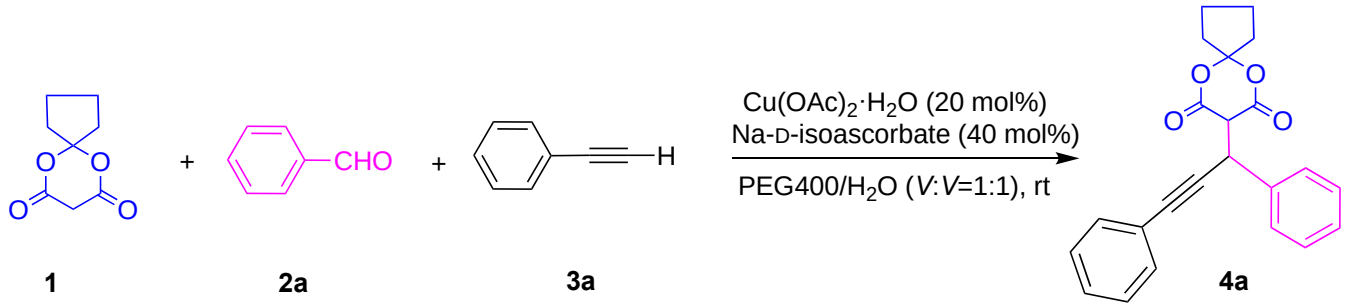
1 **2** **3** **4**

Scheme 2. The three-component synthesis of 5-(1-aryl-3-arylprop-2-yn-1-yl)-2,2-butylidene-1,3-dioxane-4,6-diones

Results and Discussion

For optimizing the reaction conditions, the three-component reaction of 2,2-butylidene-1,3-dioxane-4,6-dione (**1**), benzaldehyde (**2a**) and phenylacetylene (**3a**) was chosen (Table 1). In our initial screening experiments, examination of various copper salts was undertaken. Various copper salts including $CuSO_4·5H_2O$, $Cu_2(CO_3)(OH)_2$, $Cu(acac)_2$, $Cu_3(PO_4)_2·2H_2O$, CuI, CuCl and $Cu(OAc)_2·H_2O$ were examined (Table 1, entries 1-7). Results showed that the yield reached 81% in the presence of $Cu(OAc)_2·H_2O$/Na-D-isoascorbate (Table 1, entry 7). Encouraged by this result, different reductants such as sodium ascorbate, Na_2SO_3 and $NH_2OH·HCl$ were examined and sodium ascorbate displayed the best efficiency (Table 1, Entries 7-9). We also investigated the effect of reaction time and found that 5.0 hours gave the best result (Table 1, entry 7). Thus, the optimal reaction conditions for 2,2-butylidene-1,3-dioxane-4,6-dione (**1,** 1 mmol), benzaldehyde (**2a,** 2 mmol) and phenylacetylene (**3a**, 1.5 equiv) involved $Cu(OAc)_2·H_2O$ (20 mol%) Na-D-isoascorbate (40 mol%) in PEG/H_2O (*V*:*V*=1:1, 4 mL), furnishing **4a** in 81% yield.

Table 1. Optimization of reaction conditions for the synthesis of **4a**[a]



1 **2a** **3a** **4a**

Entry	Copper source	Reductant	Time(h)	Yield (%)[b]
1	$CuSO_4·5H_2O$	Na-D-iso ascorbate	12	43
2	$Cu_2(CO_3)(OH)_2$	Na-D-iso ascorbate	12	14

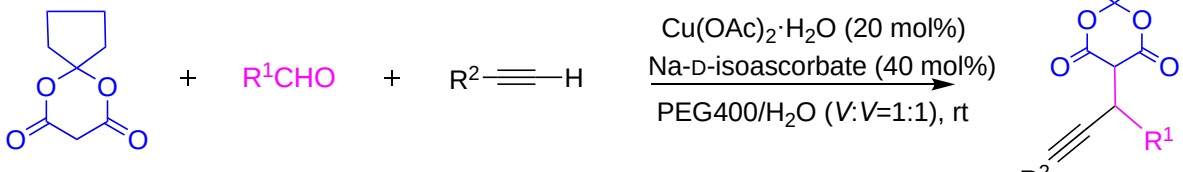
Table 1. Continued

Entry	Copper source	Reductant	Time(h)	Yield (%)[b]
3	$Cu(acac)_2$	Na-D-iso ascorbate	12	38
4	$Cu_3(PO_4)_2·2H_2O$	Na-D-iso ascorbate	12	8
5	CuCl	-	20	0
6	CuI	-	20	0
7	$Cu(OAc)_2·H_2O$	Na-D-iso ascorbate	5.0	81
8	$Cu(OAc)_2·H_2O$	$NH_2OH·HCl$	5.0	0
9	$Cu(OAc)_2·H_2O$	Na_2SO_3	5.0	51
10	$Cu(OAc)_2·H_2O$	Na-D-iso ascorbate	4.0	70
11	$Cu(OAc)_2·H_2O$	Na-D-iso ascorbate	6.0	81

[a] Reaction conditions: 2,2-butylidene-1,3-dioxane-4,6-dione (**1**, 1 mmol), benzaldehyde (**2a**, 2 mmol), Cu salt (20 mol%), PhC≡CH (1.5 equiv), reductant (40 mol%), PEG400/H_2O (*V*:*V*=1:1) (4 mL, rt; [b] Isolated yield.

Using the optimized conditions, a number of substrates were investigated (Table 2). A variety of substituents, electron-rich and -poor aromatic groups, heteroaromatic (Table 2, entries 1-7), branched (Table 2, entry 11), and unbranched (Table 2 entries 9-11) aliphatic, as well as alkenes (Table 2, entry 8), can be tolerated on the aldehydes. 4-Chlorophenylacetylene also participated in this reaction effectively (Table 2 entries 12, 13).

Table 2. Synthesis of products **4** promoted by $Cu(OAc)_2·H_2O$/Na-D-isoascorbate[a]



1 **2a-k** **3a-b** **4a-m**

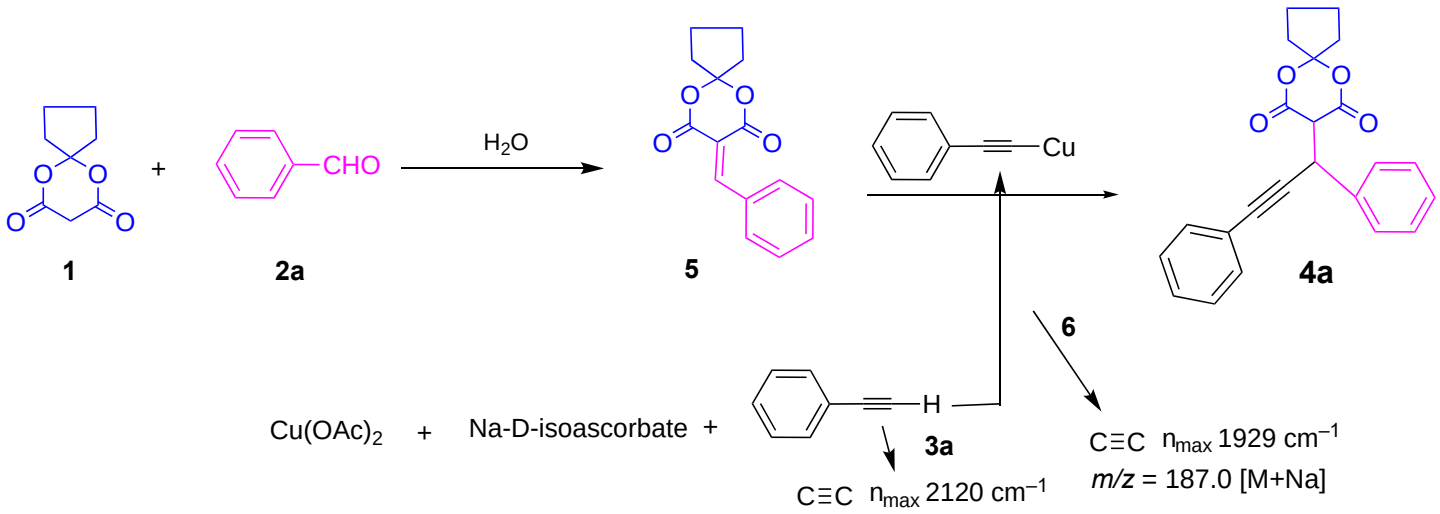
Entry	R^1	R^2	Time(h)	Product	Yields (%)[b]
1	**2a** (C_6H_5)	**3a** (C_6H_5)	5	**4a**	81
2	**2b** (4-FC_6H_4)	**3a** (C_6H_5)	3	**4b**	71
3	**2c** (4-ClC_6H_4)	**3a** (C_6H_5)	5	**4c**	76
4	**2d** (4-$CH_3C_6H_4$)	**3a** (C_6H_5)	9	**4d**	64
5	**2e** (4-$NO_2C_6H_4$)	**3a** (C_6H_5)	6	**4e**	55
6	**2f** (4-$CH_3OC_6H_4$)	**3a** (C_6H_5)	14	**4f**	87
7	**2g** (2-furyl)	**3a** (C_6H_5)	20	**4g**	80
8	**2h (**PhCH=CH)	**3a** (C_6H_5)	24	**4h**	86
9	**2i** (CH_3)	**3a** (C_6H_5)	20	**4i**	54

Table 2. Continued

Entry	R^1	R^2	Time(h)	Product	Yields (%)[b]
10	**2j** ($CH_3(CH_2)_2$)	**3a** (C_6H_5)	20	**4j**	67
11	**2k** ($(CH_3)_2CH$))	**3a** (C_6H_5)	20	**4k**	64
12	**2a** (C_6H_5)	**3b** (4-ClC_6H_4)	8	**4l**	72
13	**2j**($CH_3(CH_2)_2$)	**3b** (4-ClC_6H_4)	16	**4m**	68

[a]Reaction conditions: 2,2-butylidene-1,3-dioxane-4,6-dione (**1**, 1 mmol), aldehyde (**2**, 2 mmol), ArC≡CH (1.5 equiv), $Cu(OAc)_2{\cdot}H_2O$ (20 mol%), Na-D-isoascorbate (40 mol%), PEG400/H_2O (*V*:*V*=1:1) (4 mL), rt ; [b]Isolated yield

In order to gain further information on the intermediate formation of the phenylethynyl-Cu(I) **6**, After reduction of $Cu(OAc)_2{\cdot}H_2O$ (20 mol%) with Na-D-isoascorbate (40 mol%) in PEG400/H_2O, phenylacetylene (1.5 equiv) was added. The resulting mixture was stirred for 5.0 h, then the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, concentrated under reduced pressure. The yellow residue obtained was washed with absolute EtOH and dried in a vacuum. The yellow powder was subjected to infra-red and mass spectroscopic analysis. In the high-resolution MALDI-TOF mass spectrum, the major peak corresponded to (PhC≡CCu+Na) *m/z* 187.0. The stretching frequencies of the C≡C bond decreased from 2120 cm^{-1} for phenylacetylene to 1929 cm^{-1} for the copper alkynylide. Based on the above results, a reasonable mechanism for the one-pot synthesis of 5-(1-phenyl-3-phenylprop-2-yn-1-yl)-2,2-butylidene-1,3-dioxane-4,6-dione **4a** is depicted in Scheme 3. The terminal C-H of phenylacetylene **3a** is activated by Cu(I) prepared from $Cu(OAc)_2{\cdot}H_2O$ in the presence of Na-D-isoascorbate, and thence phenylethynyl-Cu(I) **6** is formed. Subsequently, the product **4a** is obtained by the conjugate addition reaction of phenylethynyl-Cu(I) **6** and 5-phenylmethylene-2,2-butylidene-1,3-dioxane-4,6-dione **5** (resulting from a Knoevenagel reaction of the benzaldehyde and 2,2-butylidene-1,3-dioxane-4,6-dione **1**).



Scheme 3. Proposed mechanism for the formation of **4a**.

Conclusions

A three-component synthetic procedure of 5-(1-phenyl-3-phenylprop-2-yn-1-yl)-2,2-butylidene-1,3-dioxane-4,6-dione derivatives catalyzed by a combination of $Cu(OAc)_2·(H_2O)$ and Na-D-isoascorbate, has been developed. The operation and work-up procedures were very simple and no column chrommatography purification was
needed. This provides an effective method for the synthesis of new β-arylalkynyl Meldrum's acid analogues.

Experimental Section

General. 2,2-Butylidene-1,3-dioxane-4,6-dione was prepared according to the literature.[22-24] The other chemicals were purchased from Aladdin, Aldrich and Fluka Chemical Companies and used without further purification. Melting points were measured on XT-4 digital micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a BRUKER AVANCE 400 MHz spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard. ^{13}C NMR data were collected on a BRUKER AVANCE 100 MHz instrument with $CDCl_3$ as the solvent and TMS as the internal standard. The analytical mass spectrometry was performed on an Agilent LC-MSD Trap VL Apparatus.

Typical one-pot procedure for the synthesis of 4a. To a 25 mL tube equipped with a stirring bar were added PEG400/H_2O (*V*:*V*=1:1, 4.0 mL), $Cu(OAc)_2·H_2O$ (0.2 mmol, 20 mol%), phenylacetylene (**3a**, 1.5 mmol), Na-D-iso ascorbate (0.4 mmol, 40 mol%), 2,2-butylidene-1,3-dioxane-4,6-dione (**1**, 1 mmol) and benzaldehyde (**2a**, 2 mmol). The reaction mixture was stirred vigorously for 5.0 h, treated with CH_2Cl_2 and sat aq. NH_4Cl soln. The organic layer was separated and the water phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by recrytallization from absolute EtOH to afford the pure product.

5-(1,3-Diphenylprop-2-yn-1-yl)-2,2-butylidene-1,3-dioxane-4,6-dione (4a). White solid, mp 156-158 °C (Yield: 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.78-1.93 (4H, m, $2CH_2$), 2.09-2.19 (4H, m, $2CH_2$), 4.01 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 5.11 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 7.27-7.38 (6H, m, HAr), 7.45-7.51 (2H, m, HAr), 7.65 (2H, d, $^3J_{HH}$ 7.2 Hz, 2CH, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 22.6, 24.2, 35.9, 38.5, 38.9, 53.9, 85.1, 86.3, 114.2, 122.9, 127.7, 128.2, 128.3, 128.5, 128.8, 131.9, 137.3, 163.0, 164.0. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{20}NaO_4$, 383.1259; found, 383.1247.

5-[1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-yl]-2,2-butylidene-1,3-dioxane-4,6-dione (4b). White solid, mp 125-127 °C (Yield: 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.79-1.93 (4H, m, $2CH_2$), 2.09-2.20 (4H, m, $2CH_2$), 3.98 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 5.10 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 7.04 (2H, t, $^3J_{HH}$ 8.4 Hz, HAr), 7.28-7.34 (3H, m, HAr), 7.47(2H, dd, $^4J_{HF}$ 2.0 Hz, $^3J_{HH}$ 5.2 Hz, HAr), 7.64 (2H, dd, $^3J_{HF}$ 8.4 Hz, $^3J_{HH}$ 5.2 Hz, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 22.5, 24.4, 35.2, 38.5, 38.9, 53.8, 85.1, 86.2, 114.3, 115.2, 115.4, 122.7, 128.3, 128.4, 130.7(d, $^2J_{CF}$ 8.0 Hz), 131.9, 132.8(d, $^3J_{CF}$ 3.1 Hz), 161.0(d, $^1J_{CF}$ 245.1 Hz), 163.1, 163.7. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{19}FNaO_4$, 401.1165; found, 401.1182.

5-[1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-yl]-2,2-butylidene-1,3-dioxane-4,6-dione (4c). White solid, mp 126-128 °C (Yield: 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.79-1.93 (4H, m, $2CH_2$), 2.09-2.21 (4H, m, $2CH_2$), 3.99(1H, d, $^3J_{HH}$ 2.8 Hz, CH), 5.08 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 7.28-7.33 (5H, m, HAr), 7.45-7.49 (2H, m, HAr), 7.61 (2H, d, $^3J_{HH}$ 8.4 Hz, 2CH, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 22.5, 24.2, 35.3, 38.5, 38.9, 53.7, 85.3, 85.9,

114.3, 122.6, 128.3, 128.5, 128.6, 130.4, 131.9, 133.7, 135.7, 163.0, 163.7. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{19}ClNaO_4$, 417.0870; found, 417.0882.

5-[1-(4-Methylphenyl)-3-phenylprop-2-yn-1-yl]-2,2-butylidene-1,3-dioxane-4,6-dione (4d). White solid, mp 139-141 °C (Yield: 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.77-1.91 (4H, m, $2CH_2$), 2.07-2.19 (4H, m, $2CH_2$), 2.33 (3H, s, CH_3), 3.99 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 5.08 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 7.16 (2H, d, $^3J_{HH}$ 8.0 Hz, 2CH, HAr), 7.26-7.32 (3H, m, HAr), 7.44-7.49 (2H, m, HAr), 7.54 (2H, d, $^3J_{HH}$ 8.0 Hz, 2CH, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 21.1, 22.5, 24.2, 35.6, 38.5, 38.9, 53.9, 84.9, 86.6, 114.2, 123.0, 128.2, 128.3, 128.7, 129.2, 131.9, 134.3, 137.4, 163.1, 164.1; HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{22}NaO_4$, 397.1416; found, 397.1408.

5-[1-(4-Nitrophenyl)-3-phenylprop-2-yn-1-yl]-2,2-butylidene-1,3-dioxane-4,6-dione (4e). White solid, mp 136-138 °C (Yield: 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.81-1.96 (4H, m, $2CH_2$), 2.12-2.25 (4H, m, $2CH_2$), 4.05(1H, d, $^3J_{HH}$ 2.8 Hz, CH), 5.20 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 7.30-7.37 (3H, m, HAr), 7.47-7.52 (2H, m, HAr), 7.87(2H, d, $^3J_{HH}$ 8.8 Hz, 2CH, HAr), 8.22 (2H, d, $^3J_{HH}$ 8.8 Hz, 2CH, HAr). ^{13}C NMR (100 MHz, $CDCl_3$)*:* δ (ppm): 22.5, 24.3, 35.6, 38.6, 38.9, 53.6, 84.5, 85.8, 114.5, 123.6, 128.4, 128.8, 130.1, 132.0, 144.4, 147.4, 162.9, 164.1. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{19}NNaO_6$, 428.1110; found, 428.1116.

5-[1-(4-Methoxylphenyl)-3-phenylprop-2-yn-1-yl]-2,2-butylidene-1,3-dioxane-4,6-dione (4f). Light yellow solid, mp 125-127 °C (Yield: 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.78-1.92 (4H, m, $2CH_2$), 2.08-2.20 (4H, m, $2CH_2$), 3.80 (3H, s, CH_3O), 3.98 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 5.06 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 6.88 (2H, d, $^3J_{HH}$ 8.4 Hz, 2CH, HAr), 7.28-7.31 (3H, m, HAr), 7.44-7.49 (2H, m, HAr), 7.58 (2H, d, $^3J_{HH}$ 8.4 Hz, 2CH, HAr). ^{13}C NMR (100 MHz, $CDCl_3$)*:* δ (ppm): 22.6, 24.2, 35.2, 38.6, 38.9, 53.9, 55.3, 84.8, 86.8, 113.8, 114.2, 123.0, 128.2, 128.3, 129.1, 130.1, 131.9, 159.1, 163.2, 163.9. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{22}NaO_5$, 413.1365; found, 413.1381.

5-(1-(Furan-2-yl)-3-phenylprop-2-yn-1-yl)-2,2-butylidene-1,3-dioxane-4,6-dione (**4g**). Off-white solid, mp 130-131 °C (Yield: 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.82-1.96 (4H, m, $2CH_2$), 2.17-2.28 (4H, m, $2CH_2$), 4.22 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 5.11 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 6.38 (1H, dd, $^3J_{HH}$ 3.2, 2.0 Hz, CH, H_{furan}), 6.55 (1H, dd, $^3J_{HH}$ 3.2, 0.8 Hz, CH, H_{furan}), 7.27-7.32 (3H, m, HAr), 7.33 (1H, t, $^3J_{HH}$ 2.0, 0.8 Hz, CH, H_{furan}), 7.43-7.47 (2H, m, HAr). ^{13}C NMR (100 MHz, $CDCl_3$)*:* δ (ppm): 22.6, 24.3, 30.4, 38.6, 38.9, 50.6, 83.9, 84.1, 108.4, 111.0, 114.3, 122.5, 128.2, 128.5, 132.0, 141.8, 150.1, 162.7, 163.6. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{21}H_{18}NaO_5$, 373.1052; found, 373.1064.

(*E*)-5-[3-phenyl-1-(phenylethynyl)prop-2-en-1-yl]-2,2-butylidene-1,3-dioxane-4,6-dione (**4h**). White solid, mp 135-137 °C (Yield: 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.81-1.96 (4H, m, $2CH_2$), 2.18-2.27 (4H, m, $2CH_2$), 3.91 (1H, d, $^3J_{HH}$ 2.8 Hz, CH), 4.54 (1H, ddd, $^3J_{HH}$ 2.8 , 3.6 Hz, $^4J_{HH}$ 0.8 Hz, CH), 6.51 (1H, dd, $^3J_{HH}$ 15.6, 8.0 Hz, CH, $H_{C=C}$), 6.81 (1H, d, $^3J_{HH}$ 15.6 Hz, CH, $H_{C=C}$), 7.22-7.33 (6H, m, HAr), 7.41-7.47 (4H, m, HAr). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 22.6, 24.3, 33.7, 38.5, 39.0, 52.6, 84.2, 86.4, 114.3, 122.9, 124.8, 126.7, 128.0, 128.2, 128.3, 128.6, 131.9, 134.1, 136.3, 163.4, 163.5. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{25}H_{22}NaO_4$, 409.1416; found, 409.1421.

5-(1-Methyl-3-phenylprop-2-yn-1-yl)-2,2-butylidene-1,3-dioxane-4,6-dione (**4i**). White solid, mp125-126 °C (Yield: 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.55 (3H, d, $^3J_{HH}$ 7.2 Hz, CH_3), 1.82-1.96 (4H, m, $2CH_2$), 2.17-2.27 (4H, m, $2CH_2$), 3.72 (1H, d, $^3J_{HH}$ 3.2 Hz, CH), 3.79 (1H, ddd, $^3J_{HH}$ 2.8, 7.2 Hz, CH), 7.27-7.31 (3H, m, HAr), 7.38-7.42 (2H, m, HAr). ^{13}C NMR (100 MHz, $CDCl_3$)*:* δ (ppm): 17.7, 22.6, 24.3, 25.0, 38.4, 39.1, 51.9, 82.1, 89.4, 114.1, 123.1, 128.0, 128.1, 131.8, 163.6, 163.8; HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{18}NaO_4$, 321.1103; found, 321.1095.

5-(1-Propyl-3-phenylprop-2-yn-1-yl)-2,2-butylidene-1,3-dioxane-4,6-dione (**4j**). White solid, mp 105-106 °C (Yield: 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 0.99 (3H, t, $^3J_{HH}$ 7.2 Hz, CH_3), 1.44-1.61 (2H, m, H_{CH2}), 1.64-1.75 (1H, m, H_{CH2}), 1.81-1.96 (4H, m, $2CH_2$), 2.10-2.16 (1H, m, H_{CH2}), 2.18-2.27 (4H, m, $2CH_2$), 3.62 (1H, ddd, $^3J_{HH}$

2.8, 4.4, 7.2 Hz, CH), 3.71(d, $^3J_{HH}$ 2.8 Hz, 1 H), 7.25-7.28(3H, m, HAr), 7.38-7.42(2H, m, HAr). ^{13}C NMR (100 MHz, $CDCl_3$)*:* δ (ppm): 13.6, 21.3, 22.6, 24.3, 30.7, 34.1, 38.5, 39.0, 51.2, 83.1, 88.3, 114.1, 123.2, 128.0, 128.1, 131.8, 163.8, 164.1. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{22}NaO_4$, 349.1416; found, 349.1429.

5-(1-Isopropyl-3-phenylprop-2-yn-1-yl)-2,2-butylidene-1,3-dioxane-4,6-dione (**4k**). White solid, mp 106-107 °C (Yield: 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.01 (3H, d, $^3J_{HH}$ 6.4 Hz, CH_3), 1.23 (3H, d, $^3J_{HH}$ 6.4 Hz, CH_3), 1.81-1.95 (4H, m, $2CH_2$), 2.16-2.27 (4H, m, $2CH_2$), 2.48-2.61 (1H, m, CH), 3.25 (1H, dd, $^3J_{HH}$ 2.8, 10.4 Hz, CH), 3.78(1H, d, $^3J_{HH}$ 2.8 Hz, CH), 7.23-7.27 (3H, m, HAr), 7.36-7.40 (2H, m, HAr). ^{13}C NMR (100 MHz, $CDCl_3$)*:* δ (ppm): 20.4, 21.9, 22.7, 24.2, 30.0, 38.7, 39.0, 39.2, 48.7, 83.7, 87.9, 114.2, 123.1, 128.0, 128.1, 131.8, 163.8, 165.4; HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{22}NaO_4$, 349.1416; found, 349.1408.

5-[1-Phenyl-3-(4-chlorophenyl)-prop-2-yn-1-yl)-2,2-butylidene-1,3-dioxane-4,6-dione (4l). White solid, mp 139-140 °C (Yield: 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.79-1.92 (4H, m, $2CH_2$), 2.09-2.21 (4H, m, $2CH_2$), 4.01 (1H, d, $^3J_{HH}$ 2.8 Hz, CH_3), 5.09 (1H, d, $^3J_{HH}$ 2.8 Hz, CH_3), 7.26-7.32 (3H, m, HAr), 7.36(2H, d, $^3J_{HH}$ 7.6 Hz, HAr), 7.40(2H, d, $^3J_{HH}$ 8.8 Hz, HAr), 7.6.4(2H, d, $^3J_{HH}$ 7.6 Hz, HAr); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 22.6, 24.2, 35.8, 38.5, 38.9, 53.8, 83.9, 87.3, 114.3, 121.3, 127.8, 128.6, 128.8, 133.2, 134.3, 137.0, 162.9, 164.0. HRMS calcd for $C_{23}H_{19}ClNaO_4$ $[M+Na]^+$ 417.0870, found *m/z* 417.0862.

5-[1-*n*-Propyl-3-(4-Chlorophenyl)-prop-2-yn-1-yl]-2,2-butylidene-1,3-dioxane-4,6-dione (4m). White solid, mp 121-122 °C (Yield: 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 0.99 (3H, t, $^3J_{HH}$ 7.2 Hz, CH_3), 1.48-1.61 (2H, m, CH_2), 1.65-1.70 (1H, m, CH_2), 1.84-1.95 (4H, m, $2CH_2$, butylidene), 2.09-2.15 (1H, m, CH_2), 2.18-2.27 (4H, m, $2CH_2$, butylidene), 3.60-3.63 (1H, m, CH), 3.72 (1H, d, $^3J_{HH}$ 2.4 Hz, CH), 7.24(2H, d, $^3J_{HH}$ 8.0 Hz, 2CH, HAr), 7.32 (2H, d, $^3J_{HH}$ 8.0 Hz, 2CH, HAr). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 13.6, 21.3, 22.6, 24.3, 30.6, 34.0, 38.4, 39.0, 51.2, 82.0, 89.3, 114.2, 121.6, 128.5, 133.1, 134.0, 163.8, 164.1. HRMS calcd for $C_{21}H_{23}ClNaO_4$ $[M+Na]^+$ 383.1026; found, 383.1022.

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