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Synthesis of 4-Aryl-2(5*H*)-furanones by Gold(I)-Catalyzed Intramolecular Annulation

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Abstract: A novel method that involves intramolecular annulation and a new type of rearrangement has been developed for the synthesis of 4-aryl-2(5*H*)-furanones. A variety of prop-2-ynyl 3-oxo-3-phenylpropanoates undergo annulation cyclization in the presence of chloro(triphenylphosphine)gold and trifluoromethanesulfonic to afford the desired products in moderate to high yields.

Keywords: 4-aryl-2(5*H*)-furanones; gold(I) catalysts; intramolecular annulations; prop-2-ynyl 3-oxo-3-phenylpropanoates

4-Aryl-2(5*H*)-furanones constitute an important class of heterocyclic compounds that have substantial biological activity. This furanone unit is found in many naturally occurring products[1] such as cadiolide A and pinusolide, as well as in synthetic pharmaceuticals such as rofecoxib,[2] eucilat,[3] and L-784512 (Figure 1).[4]

In addition, 4-aryl-2(5*H*)-furanones are valuable intermediates in the total synthesis of natural products.[5] There are a number of synthetic approaches to these interesting intermediates, including tandem cyclohydrocarbonylation/CO insertion of α-ketoalkynes,[6] Rh(I)-catalyzed CO gas-free cyclohydrocarbonylation of alkynes with formaldehyde,[7] coupling-cyclization of polymer-supported aryl iodides with 1,2-allenylcarboxylic acids,[8] Au-catalyzed isomerization of cyclopropenes,[9] rhodium-catalyzed reaction of internal alkynes with organoborons in a CO atmosphere,[10] and metal-halogen exchange of 3-bromo-2-silyloxyfurans.[11] Unfortunately, these methods have several disadvantages, including difficulty in handling gaseous CO, which is toxic, low product yields and poor regioselectivity.

Recently, the application of intramolecular cyclization of 1,3-dicarbonyl compounds has been significantly expanded by the use of metal catalysts or Brønsted acids, and it has been found that this reaction can be carried out at lower temperatures with a wide variety of substrates.[12] The aforementioned intramolecular cyclization has been shown to be a

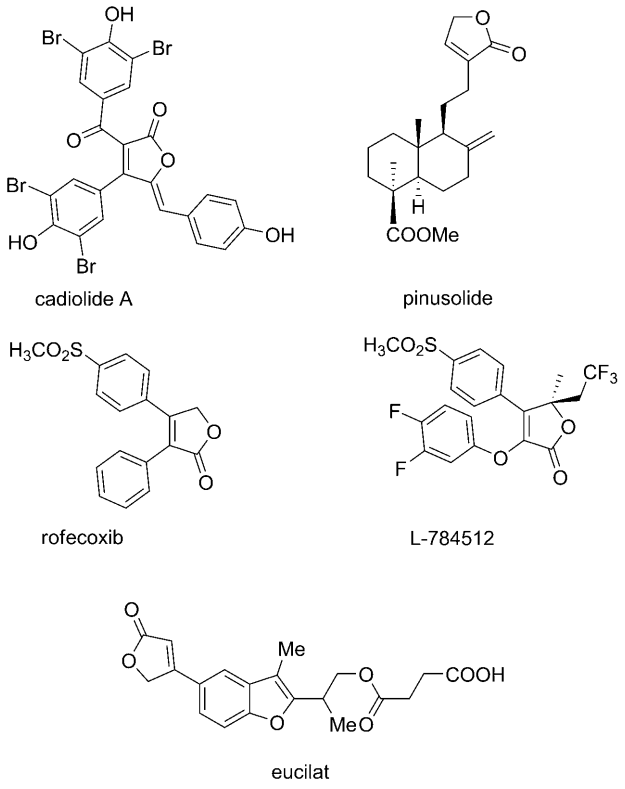
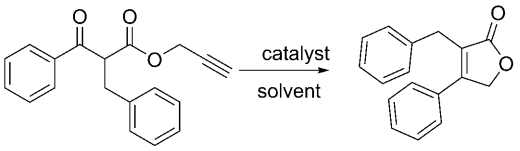


Figure 1. Examples of natural products and synthetic pharmaceutical drugs.

Table 1. Optimization of the reaction conditions for the synthesis of **2a**.[a]



1a **2a**

Entry	Catalyst/Additive	Acid	Solvent	Yield[b]
1	$AuCl(PPh_3)$, AgOTf/–	–	DCE	0%
2	$AuCl(PPh_3)$/–	HOTf	DCE	45%
3	$AuCl(PPh_3)/H_2O$	HOTf	DCE	85%
4	$AuCl(PPh_3)/H_2O$[c]	HOTf	DCE	82%
5	$AuCl(PPh_3)/H_2O$[d]	HOTf	DCE	65%
6	$AuCl(PPh_3)/H_2O$	HOTf[e]	DCE	61%
7[f]	$C1/H_2O$	HOTf	DCE	75%
8[g]	$C2/H_2O$	HOTf	DCE	78%
9	$AuBr_3/H_2O$	HOTf	DCE	77%
10	$–/H_2O$	HOTf	DCE	40%
11	$AgOTf/H_2O$	HOTf	DCE	76%
12	$AgBF_4/H_2O$	HOTf	DCE	40%
13	$AgSbF_6/H_2O$	HOTf	DCE	64%
14	$Cu(OTf)_2/H_2O$	HOTf	DCE	23%
15	$CuOTf/H_2O$	HOTf	DCE	17%
16	$AuCl(PPh_3)/H_2O$	HOTf	CH_3CN	24%
17	$AuCl(PPh_3)/H_2O$	HOTf	toluene	61%
18	$AuCl(PPh_3)/H_2O$	HOTf	DCM	62%
19	$AuCl(PPh_3)/H_2O$	HOTf	THF	0%
20	$AuCl(PPh_3)/H_2O$	TFA	DCE	33%
21	$AuCl(PPh_3)/H_2O$	$AlCl_3$	DCE	0%
22[h]	$AuCl(PPh_3)/H_2O$	HOTf	DCE	40%

[a] Unless otherwise noted, reaction conditions are as follows: 60 mg **1a**, 5% $AuCl(PPh_3)$, 10.0 equiv. H_2O, 10.0 equiv. HOTf and 2.5 mL 1,2-dichloroethane were added at room temperature and the reaction mixture was stirred for 12 h.

[b] Isolated yield.

[c] 5.0 equiv. H_2O were added.

[d] 15.0 equiv. H_2O were added.

[e] 5.0 equiv. HOTf were added.

[f] C1 is chloro[(1,1′-biphenyl-2-yl)di-*tert*-butylphosphine]-gold(I).

[g] C2 is (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]-gold(I) hexafluoroantimonate. DCE is dichloroethane and HOTf is trifluoromethanesulfonic acid.

[h] Reaction was conducted at 40 °C.

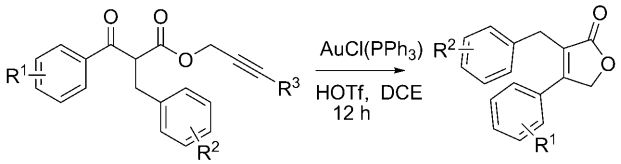
useful tool for the synthesis of five-membered rings.[12b,13] However, very few methods have been developed for the synthesis of 4-aryl-2(5*H*)-furanones through cyclization of 1,3-dicarbonyl compounds.[14] In this research we have developed a novel approach that involves the use of a phosphine-Au(I) complex and a Brønsted acid for the synthesis of 4-aryl-2(5*H*)-furanones and carried out preliminary mechanistic studies.

In our initial study, treatment of prop-2-ynyl 2-benzyl-3-oxo-3-phenylpropanoate (**1a**) with 5% $AuCl(PPh_3)$ [(triphenylphosphine)gold(I) chloride] and 5% AgOTf (trifluoromethanesulfonic acid silver salt) at room temperature failed to give any of the cyclization product (entry 1, Table 1). However, the cyclization product was obtained in moderate yield when 10.0 equivalents of HOTf (a Brønsted acid) were used instead of AgOTf (entry 2, Table 1). Interestingly, the yield of **2a** increased to 85% when 10.0 equivalents of H_2O were added to the reaction mixture (entry 3, Table 1). Therefore, the water concentration was concluded to be an important factor that affected the reaction yield. For example, further increase or decrease of the added water loading did not obviously compromise the yield (entries 4 and 5, Table 1). The amount of HOTf also played a key role in increasing the yield of the cyclization product (entry 6, Table 1). Other gold catalysts such as chloro[(1,1′-biphenyl-2-yl)di-*tert*-butylphosphine]gold(I), (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I), and $AuBr_3$, were less effective (entries 7-9, Table 1). The yield of the product decreased when the reaction was carried out in the absence of $AuCl(PPh_3)$ (entry 10, Table 1).

Ag and Cu catalysts could also be used in the reaction, but the product yields were lower than that achieved with $AuCl(PPh_3)$ (entries 11–15, Table 1). There was no improvement in the yield of **2a** when the solvent was changed from 1,1-dichloroethane to toluene, acetonitrile, or dichloromethane (entries 16–18, Table 1). In fact, no conversion was observed when the reaction was carried out in THF (entry 19, Table 1). Several Brønsted and Lewis acids were also investigated (entries 20 and 21, Table 1) and the yields were reduced drastically to 33% and 0% when HOTf was replaced with CF_3COOH or $AlCl_3$, respectively. When the temperature was increased, the reaction was accelerated: the reaction proceeded to completion in 1 h at 40 °C. However, in this case, the cyclization product was obtained in a low (40%) yield (entry 22, Table 1).

After identifying the optimum reaction conditions, we proceeded to explore the scope and generality of our method. As shown in Table 2, several functional groups were tolerated in the reaction, including halogens, electron-donating groups, and electron-withdrawing substituents on the aryl ring, and the desired products were isolated in moderate to high yields. Generally, the yield was 80–88% when the benzyl group had neutral (entry 1, Table 2) or electron-rich substituents, such as *tert*-butyl (entry 2, Table 2), methyl (entries 3–5, Table 2), and phenyl (entry 6, Table 2). Interestingly, reactions involving substrates with weakly electron-withdrawing substituents such as chloride proceeded smoothly to afford the desired products (entries 7–9, Table 2); on the other hand, substrates with ester groups gave the products in satisfactory yields [entries 10 and 11 (77% and 78% yields, respectively), Table 2]. Substrates with the

Table 2. Gold(I)-catalyzed cyclization of prop-2-ynyl 2-benzyl-3-oxo-3-phenylpropanoates mediated by HOTf.[a]



1 2

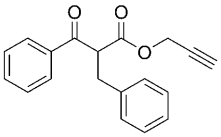
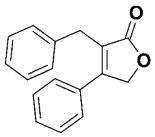
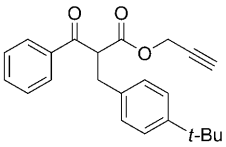
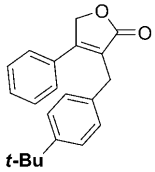
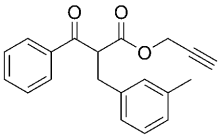
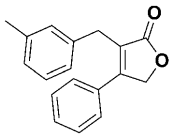
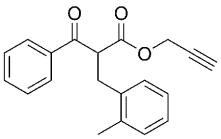
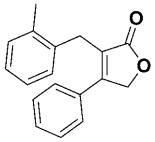
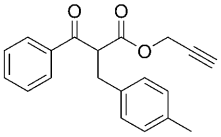
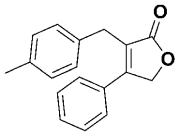
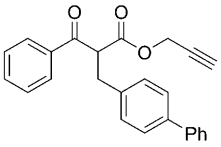
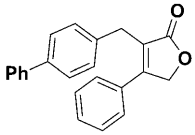
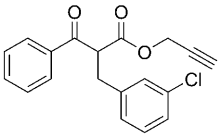
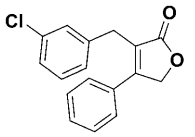
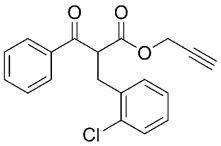
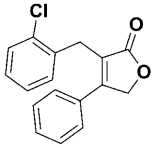
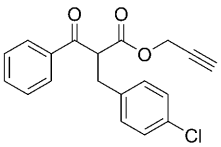
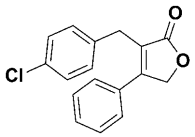
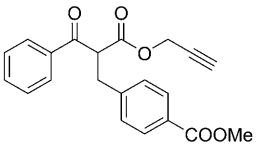
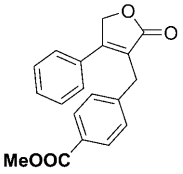
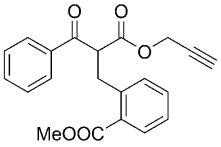
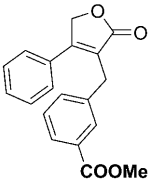
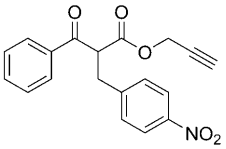
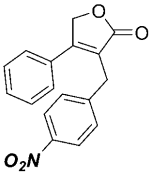
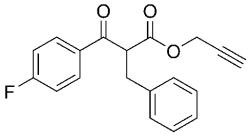
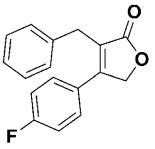
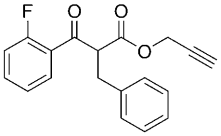
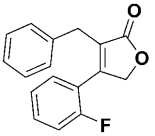
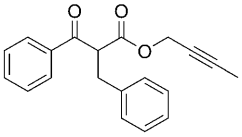
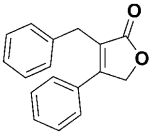
Entry	Substrate	Product		Yield
1			**2a**	85%
2			**2b**	81%
3			**2c**	81%
4			**2d**	85%
5			**2e**	88%
6			**2f**	80%
7			**2g**	80%
8			**2h**	84%
9			**2i**	85%

Table 2. (Continued)

Entry	Substrate	Product		Yield
10			**2j**	78%
11			**2k**	77%
12			**2l**	0%
13			**2m**	68%
14			**2n**	65%
15			**2o**	0%

[a] Unless otherwise noted, 0.2 mmol substrates, 10.0 equiv. H_2O, 5% $AuCl(PPh_3)$, 10.0 equiv. HOTf and 2.5 mL DCE were added at room temperature.

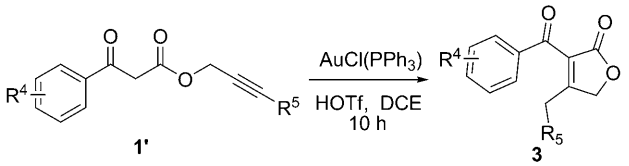
strongly electron-withdrawing nitro group did not afford the cyclization product (entry 12, Table 2). Moreover, compounds with a fluoro substituent at the 4- or 2-position of the 3-phenyl ring afforded the cyclization product in 65% and 68% yields, respectively (entries 13 and 14, Table 2). When an internal alkyne substrate was treated with the standard condition, no product was observed (entry 15, Table 2).

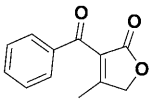
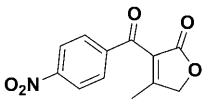
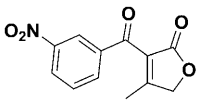
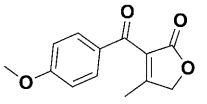
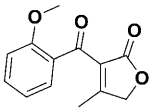
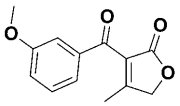
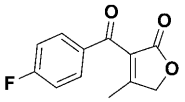
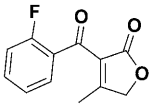
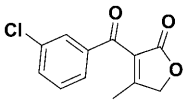
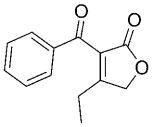
We also observed that the present protocol could be used for the direct cyclization of prop-2-ynyl 3-oxo-3-phenylpropanoates (Table 3). More importantly, the product yields were high in this case, and the reaction time was reduced to 10 h. As reported in the previous studies, electron-neutral (entry 1, Table 3), electron-donating, and electron-withdrawing groups such as nitro (entries 2 and 3, Table 3), methoxy (entries 4–6, Table 3), fluoro (entries 7 and 8, Table 3), and chloro groups (entry 9, Table 3) were well tolerated in the reaction. Substrates with an internal alkyne did not give any cyclization product (entry 10, Table 3).

The structure of **2a** was confirmed by ^1H NMR, ^{13}C NMR, mass spectrometry and X-ray crystallography (Figure 2).

On the basis of our previous knowledge and the results of our present studies, a plausible mechanism as shown in Scheme 1 is proposed for this process. Reaction of substrate **1a** under the catalysis of $AuCl(PPh_3)$ catalysis affords intermediate **4** in the presence of water. The protonation of the ketone (**4**, Scheme 1) would therefore facilitate the regioselective intramolecular cyclization, leading to the formation of species **5**. Subsequently, an AcOH was removed by an intramolecular synergic effect. Finally the target product **2a** would be formed through a double bond transfer.

Table 3. Gold(I)-catalyzed cyclization of prop-2-ynyl 3-oxo-3-phenylpropanoates mediated by HOTf.[a]



Entry	R^4	R^5	Product		Yield[b]
1	H	H		**3a**	92%
2	*p*-NO_2	H		**3b**	87%
3	*m*-NO_2	H		**3c**	80%
4	*p*-CH_3O	H		**3d**	85%
5	*o*-CH_3O	H		**3e**	87%
6	*m*-CH_3O	H		**3f**	91%
7	*p*-F	H		**3g**	93%
8	*o*-F	H		**3h**	91%
9	*m*-Cl	H		**3i**	88%
10	H	CH_3		**3j**	0%

[a] Unless otherwise noted, 0.2 mmol substrate, 10.0 equiv. H_2O, 5% $AuCl(PPh_3)$, 10.0 equiv. HOTf and 2.5 mL DCE were added at room temperature.
[b] Isolated yield.

To probe the reaction mechanism, we performed labeling studies using the deuterated additive and starting materials (Scheme 2). A non-deuterated product was obtained under standard conditions using deuterated terminal alkyne [Eq. (1)], which demonstrated that the alkyne group may undergo degradation in the process. The reaction of **1a** under the standard reaction conditions with D_2O as additive afforded the deuterated cyclization product on 5-position [Eq. (2)]. The non-deuterated product was observed when the deuterated substrate on 2-position reacted with H_2O as additive [Eq. (3)]. These results indicated that the water may also participate in the reaction in the double bond transfer process. These deuterium labeling experiments could support our mechanistic hypotheses.

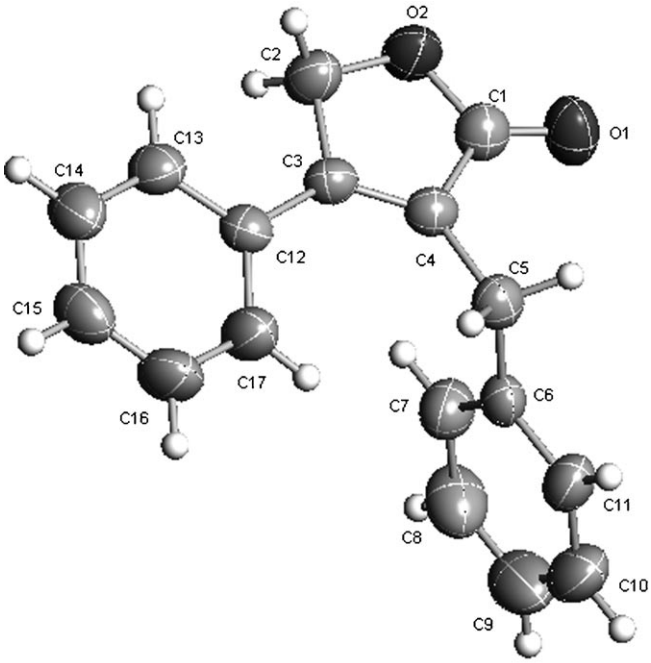


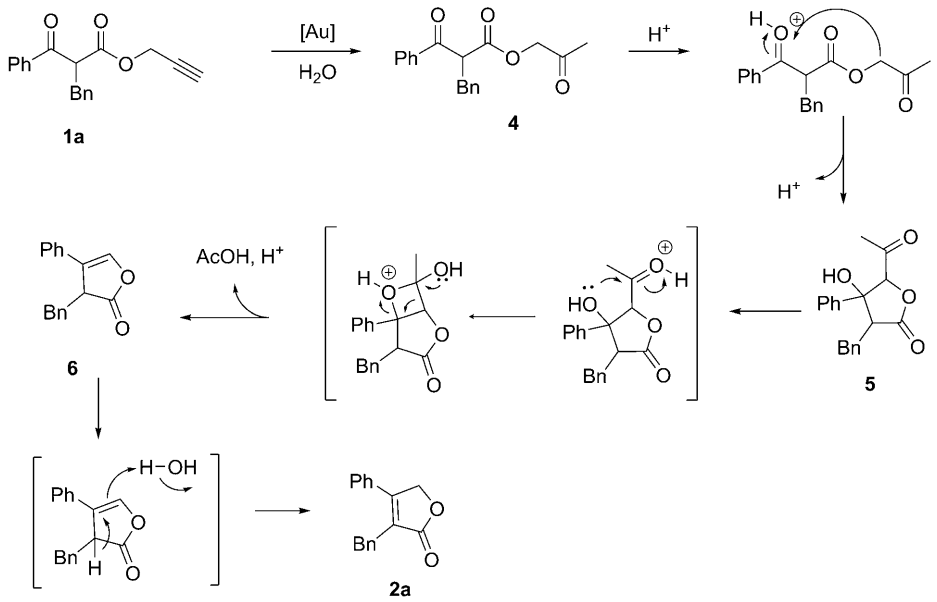
Figure 2. X-ray crystallographic structure of **2a**.

In summary, we have developed a novel Au(I)-catalyzed, HOTf-mediated reaction for the synthesis of 4-aryl-2(5*H*)-furanones. The reaction can be carried out under ambient temperature conditions, and it shows excellent tolerance to various functional groups; furthermore, the desired products are obtained in good to excellent yields. The high regioselectivity and mild reaction conditions are expected to make this method a valuable tool for the synthesis of 2(5*H*)-furanone frameworks.

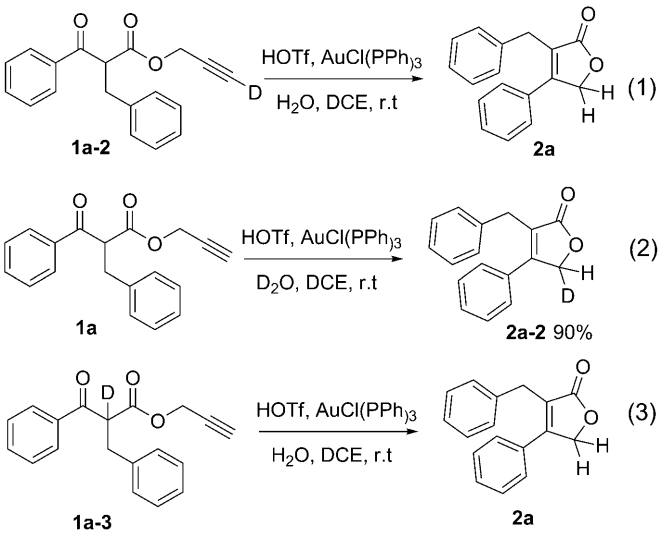
Experimental Section

General Procedure for the Synthesis of 3-Benzyl-4-phenyl-2(5*H*)-furanone (2a) as an Example

A mixture of **1a** (0.2 mmol, 58.4 mg), 10.0 equiv. H_2O (2 mmol, 36 mg), $AuCl(PPh_3)$ (0.01 mmol, 5 mg) and HOTf (2 mmol, 300 mg) in 1,2-dichloroethane (2.5 mL) was stirred at room temperature in a sealed tube under argon protec-



Scheme 1. A plausible mechanism.



Scheme 2. Experiments with deuterated substrates.

tion for 12 h. After the reaction was completed as monitored by TLC, the solvent was removed under reduced pressure, and the residue was purified by column chromatography. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.45$ (m, 5H), 7.26 (m, 5H), 5.12 (s, 2H), 3.90 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 157.0$, 137.6, 131.0, 130.5, 129.1, 128.7, 128.2, 127.2, 126.6, 125.8, 70.8, 30.0; HR-MS (EI): $m/z = 250.0991$, calcd. for $C_{17}H_{14}O_2$ $[M]^+$: 250.0994.

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[15] CCDC 803457 contains the supplementary crystallographic data for **2a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

