Tetrahedron Letters 53 (2012) 2837–2841

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot synthesis of unsymmetrical benzils from aryl methyl ketones and arenes in the presence of selenous acid catalysed by *p*-toluenesulfonic acid monohydrate

Icydora Kharkongor, Md. Rumum Rohman, Bekington Myrboh *

Department of Chemistry, North-Eastern Hill University, Shillong 793022, India

A R T I C L E I N F O

Article history:
Received 12 December 2011
Revised 27 March 2012
Accepted 28 March 2012
Available online 1 April 2012

Keywords:
Unsymmetrical benzils
Selenous acid
p-TsOH·H_2O catalyst

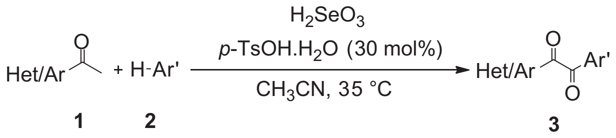
A B S T R A C T

A modified one-pot method for the synthesis of unsymmetrical and heteroaryl benzils from substituted acetophenones and unactivated or weakly activated arenes by the use of H_2SeO_3 and *p*-TsOH·H_2O as catalysts at 35 °C is established. The present method is regioselective and avoids the use of *p*-TsOH·H_2O in stoichiometric amount in the presence of H_2SeO_3 and afforded unsymmetrical benzils in good yields.

The versatility of benzils as organic intermediates is well known as is evidenced by their practical applications, that is as starting materials for the synthesis of heterocycles,[1] and as photosensitive agents.[2] They also exhibit potential for various biological activities like inhibition of mammalian carboxylesterases (CE).[3] The last two decades have seen a lot of efforts directed towards the synthesis of both symmetrical and unsymmetrical benzils.[4,5] The preparation of these 1,2-diketo compounds has been accomplished by several methods such as oxidation of olefins with selenium dioxide,[6,7] or potassium permanganate,[8,9] α-hydroxyketones by atmospheric oxygen,[10,11] acetylenes with potassium permanganate,[12] methylene ketones by selenium dioxide,[13,14] bismuth nitrate–copper(II) acetate,[15] or oxygen in the presence of Fe(III)–EDTA.[16] Although, the reported methods are quite effective, they are often limited to the synthesis of symmetrical benzils in most of the cases with the exception of a few where the preparation of unsymmetrical benzils also requires the use of expensive starting materials.

Based on our earlier work[17] and the ongoing study on the synthetic application of SeO_2 for C–C bond formation,[18] we have further established a modified method for the synthesis of benzils by using selenous acid (H_2SeO_3) and catalytic amount of *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O), in contrast to the previous method where equivalent amount of *p*-TsOH·H_2O is required. The present methodology thus describes the oxidative coupling involving the use of substituted acetophenones and unactivated or weakly activated arenes as the starting materials in the presence of H_2SeO_3, catalysed by *p*-TsOH·H_2O. It may be noted that contrary to the usual pathway where the aryl methyl ketones are oxidized by SeO_2 to glyoxals[17,19] and the reported intramolecular condensation of 2-([1,1′-biphenyl]-2-yl)-2-oxoacetaldehyde to give phenanthrenequinone,[20] we wish to report here a modified one-pot synthesis of unsymmetrical benzils by the oxidative coupling between aryl/heteroaryl methyl ketones and unactivated arenes in the presence of H_2SeO_3 and *p*-TsOH·H_2O as catalysts at 35 °C (Scheme 1).

In the initial reaction, when acetophenone (**1a**) (1.0 mmol) in the presence of H_2SeO_3 (2.00 mmol), and *p*-TsOH·H_2O (10 mol %) in dry benzene (5 mL) was heated at 80 °C for 24 h, the product (**3a**) was obtained in 30% yield. However, after optimization, the same reaction in the presence of 30 mol % of the catalyst proceeded to afford **3a** in 65% within 14 h (Table 1, entry 1). During optimization it was observed that the use of 1 and 1.5 equiv of H_2SeO_3 resulted in the low yields of the product in each case. Evidently H_2SeO_3 is required in both the oxidation step where the ketone



Ar = aryl, Het = heteroaryl; Ar' = benzene, toluene, xylene, anisole, naphthalene, anthracene

Scheme 1. Synthesis of unsymmetrical benzils.

---

* Corresponding author. Tel.: +91 364 272 2612; fax: +91 364 255 0076.
E-mail address: bmyrboh@nehu.ac.in (B. Myrboh).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.03.113

Table 1
One-pot synthesis of unsymmetrical benzils (**3**) via Scheme 1

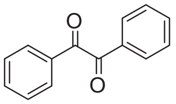
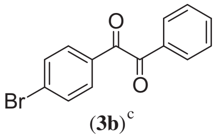
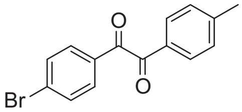
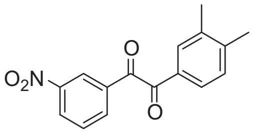
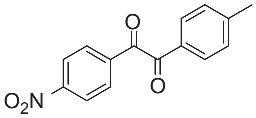
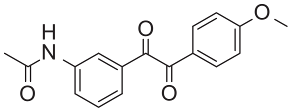
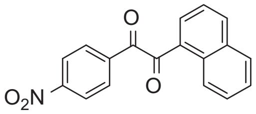
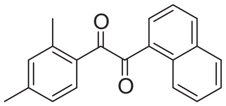
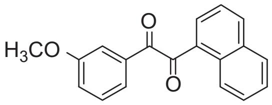
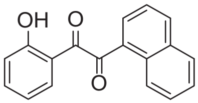
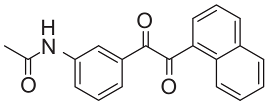
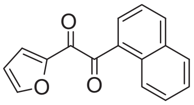
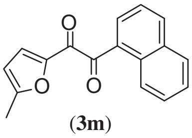
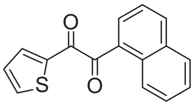
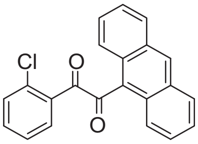
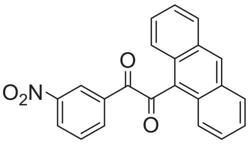
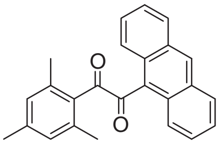
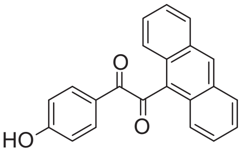
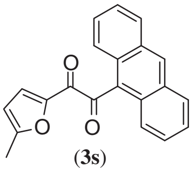
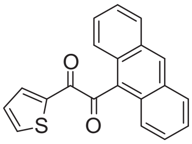
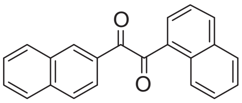
Entry	Substrate **1** (Ar/Het)	Substrate **2** (Ar′)	Time (h)	Product[b,c] **3**	Yield[a] (%)
1	C_6H_5 (**1a**)	C_6H_5 (**2a**)	14	 (**3a**)[c]	65
2	$4\text{-}BrC_6H_4$ (**1b**)	**2a**	14	 (**3b**)[c]	63
3	**1b**	$CH_3C_6H_4$ (**2b**)	14	 (**3c**)[c]	60
4	$3\text{-}NO_2C_6H_4$ (**1c**)	$1,2\text{-}(CH_3)_2C_6H_3$ (**2c**)	14	 (**3d**)[c]	65
5	$4\text{-}NO_2C_6H_4$ (**1d**)	**2b**	14	 (**3e**)[c]	68
6	$3\text{-}NHCOCH_3C_6H_4$ (**1e**)	$CH_3OC_6H_4$ (**2d**)	14	 (**3f**)[c]	70
7	**1d**	1-Naphthyl (**2e**)	12	 (**3g**)[c]	70
8	$2,4\text{-}(CH_3)_2C_6H_3$ (**1f**)	**2e**	12	 (**3h**)[c]	62
9	$3\text{-}CH_3OC_6H_4$ (**1g**)	**2e**	12	 (**3i**)[c]	65
10	$2\text{-}OHC_6H_4$ (**1h**)	**2e**	12	 (**3j**)[c]	69
11	**1e**	**2e**	12	 (**3k**)[c]	75

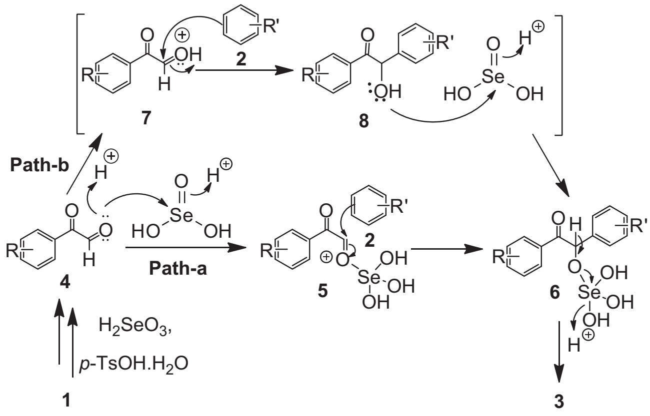
Table 1 (*continued*)

Entry	Substrate **1** (Ar/Het)	Substrate **2** (Ar′)	Time (h)	Product[b,c] **3**	Yield[a] (%)
12	2-Furanyl (**1i**)	**2e**	12	 (**3l**)[c]	57
13	5-Methyl-2-furanyl (**1j**)	**2e**	12	 (**3m**)	61
14	2-Thiophenyl (**1k**)	**2e**	12	 (**3n**)[c]	65
15	2-ClC$_6$H$_4$ (**1l**)	9-Anthracenyl (**2f**)	13	 (**3o**)[c]	63
16	**1c**	**2f**	13	 (**3p**)[c]	64
17	2,4,6-(CH$_3$)$_3$C$_6$H$_2$ (**1m**)	**2f**	13	 (**3q**)[c]	56
18	4-OHC$_6$H$_4$ (**1n**)	**2f**	13	 (**3r**)[c]	54
19	**1j**	**2f**	13	 (**3s**)	56
20	**1k**	**2f**	13	 (**3t**)[c]	58
21	2-Naphthyl (**1o**)	**2e**	12	 (**3u**)[c]	70

[a] Isolated yields.

[b] Products were fully characterized by recording their ^{1}H, ^{13}C NMR, IR spectral and elemental analyses and comparing with the authentic samples.

[c] Literature Ref. 17.



Scheme 2. Plausible mechanism.

is oxidized to the glyoxal and the subsequent arylation step. It was also observed that the use of anhydrous p-TsOH resulted in low yields of the product besides the increase in reaction time. This observation indicates that the presence of water may be necessary to promote the reaction.

Similarly the substrate **1b** furnished the product **3b** in 63% with H_2SeO_3 (2 equiv), and p-TsOH·H_2O (30 mol %) at 80 °C (Table 1, entry 2).

In another trial the reaction of **1b** with toluene (**2b**) afforded the product **3c** in 60% within 14 h at 35 °C without the need to raise the temperature. The methodology was then extended to the reaction of **1c** and **1d** with the weakly activated arenes **2b** and **2c** and in both cases the substituted acetophenones reacted cleanly with the arenes **2b** and **2c** at 35 °C to give the desired benzils (**3c**–**d**) in good yields (Table 1, entries 4 and 5). Notably substituted acetophenones bearing *N*-acetyl groups such as **1e** also undergo the same coupling reaction with stoichiometric amount of anisole (**2d**) in acetonitrile at 35 °C (Table 1, entry 6).

Encouraged by these results the broad scope and limitation of the methodology were studied by the reaction of various substituted acetophenones with polynuclear hydrocarbons such as naphthalene (**2e**) and anthracene (**2f**). Irrespective of the presence of electron withdrawing or donating groups such as chloro, nitro, methyl, methoxy and hydroxy on the *ortho*, *meta* or *para*-positions, the aryl methyl ketones **1c**–**h** and **1l**–**n** reacted smoothly with stoichiometric amount of polynuclear hydrocarbons **2e**–**f** in the presence of H_2SeO_3 (2 equiv) and p-TsOH·H_2O (30 mol %) in acetonitrile at 35 °C (Table 1, entries 7–10 and 15–18) in consistently good yields. Furthermore, the substituted acetophenone **1e** also reacted smoothly with **2e** under the experimental condition to give benzil **3k** in 75% yield in 12 h. [21]

The present method was further extended to the reaction of heteroaryl or fused aromatic methyl ketones with **2e** and **2f**. The same reaction trend was observed for the oxidative coupling of 1-(2-furanyl)ethanone (**1i**), 5-methyl-(2-furanyl)ethanone (**1j**), 1-(2-thiophenyl)ethanone (**1k**) and 1-(2-naphthyl)ethanone (**1o**) with **2e** and **2f** to give the corresponding 1,2-diketone in 56–70% yields (Table 1, entries 12–14 and 19–21)[21]. Notably, the reaction goes to completion in each case as the starting ketone is completely consumed. Besides the isolated product, no other products could be isolated except for several minor impurities which were not further identified. However, the nitrogen containing aromatic methyl ketones, for example, pyran and pyrrole, and the halogenated arenes do not give the desired results. All the unsymmetrical benzils synthesized were fully characterized by ^1H, ^{13}C NMR, IR spectral and elemental analyses and by comparison with authentic samples.[17,22]

It is important to highlight that the use of H_2SeO_3 and catalytic amounts of p-TsOH·H_2O offered a cleaner reaction with perceptible increase in the yield of the products especially in the case of **3l**, **3n** and **3t** where, the isolated yields range between 57%, 65% and 58%, respectively, which is a significant improvement from the earlier procedure (Table 1, entries 12, 14 and 20).[17] The present method also allows for the regioselective formation of the products **3c**–**f** and also afforded the unsymmetrical benzils substituted at C1 and C9 for the reaction of **2e**–**f** as shown in Table 1.

The initial conversion of the aryl methyl ketone **1** to glyoxals (**4**)[17,19] by H_2SeO_3 and the acid catalysed formation of the O–Se bond through carbonyl oxygen of the aldehydic group in the presence of p-TsOH·H_2O generate a strong electrophilic centre at the aldehydic carbon of **5** (path a). The attack of the electron rich arenes **2** to the electrophilic centre presumably resulted in the formation of the selenium intermediate (**6**). Finally, oxidative decomposition of the selenium intermediate (Scheme 2) led to the formation of unsymmetrical benzils (**3**). Alternatively, the glyoxal (**4**) may undergo acid (H^+) catalysed Friedel Craft reaction with arenes to give the intermediate **6** as shown in Scheme 2 (path b).

In summary, we have developed a modified one-pot method for the preparation of unsymmetrical and heteroaryl 1,2-diketones from substituted acetophenones and unactivated or weakly activated arenes by the use of H_2SeO_3 catalysed by p-TsOH·H_2O. The present oxidative coupling process avoids the use of p-TsOH·H_2O in stoichiometric amount in the presence of H_2SeO_3 and in many instances gave better yields of the products. The method is general, regioselective and provides an important alternative for the synthesis of unsymmetrical benzils.

Acknowledgments

I.K. thanks the University Grants Commission (UGC) for Rajiv Gandhi National Fellowship (RGNF) and Sophisticated Analytical Instrument Facility (SAIF), North-Eastern Hill University for NMR and mass spectral analysis and acknowledges the UGC for financial assistance vide Project F. No. 40-83/2011(SR).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.113.

References and notes

1. (a) Vollhardt, K. P. C.; Schore, N. E. *Organic Chemistry* In *2nd ed.*; Freeman: New York, 1994; (b) Gill, G. B. In *Comprehensive Organic Synthesis*; Pattenden, G., Ed.; Pergamon: New York, 1991; Vol. 3, pp 821–838; (c) Kirihara, M.; Ochiai, Y.; Takizawa, S.; Takahata, H.; Nemoto, H. *Chem. Commun.* **1999**, 1387; (d) Wynberg, H.; Kooreman, H. J. *J. Am. Chem. Soc.* **1965**, *87*, 1739; (e) Rothkopf, H. W.; Wohrle, D.; Kossmehl, G. *Chem. Ber.* **1975**, *108*, 875.
2. Matsushita Electric Industrial Co. Ltd., *Jpn. Kokai Tokkyo Koho*, 8198203, **1981**; *Chem. Abstr.*, **1981**, *95*, 188163v.
3. Wadkins, R. M.; Hyatt, J. L.; Wei, X.; Yoon, K. J. P.; Wierdl, M.; Edwards, C. C.; Morton, C. L.; Obennauer, J. C.; Damodaran, K.; Beroza, P.; Danks, M. K.; Potter, P. M. *J. Med. Chem.* **2005**, *48*, 2906.
4. For the synthesis of symmetrical benzils, see: (a) Schraufstatter, E. *Chem. Ber.* **1948**, 239; (b) VanAllan, J. A. *J. Org. Chem.* **1958**, *23*, 1682; (c) Mohr, B.; Enkelmann, V.; Wegner, G. *J. Org. Chem.* **1994**, *59*, 638; (d) Nudelman, N.; Schulz, H. J. *Chem. Res.* **1999**, 423; (e) Kwon, T. W.; Song, S. J.; Kwon, Y. U.; Chung, S. K. *Bull. Korean Chem. Soc.* **2003**, *24*, 231; (f) Yasuike, S.; Kishi, Y.; Kawara, S.-i.; Kurita, J. *Chem. Pharm. Bull.* **2005**, *53*, 427.
5. For the synthesis of unsymmetrical benzils, see: (a) Suginome, H. *J. Org. Chem.* **1958**, *23*, 1046; (b) Yusubov, M. S.; Zholobova, G. A.; Vasilevsky, S. F.; Tretyakov, E. V.; Knight, D. W. *Tetrahedron* **2002**, *58*, 1610; (c) Katritzky, A. R.; Zhang, D.; Kirichenko, K. *J. Org. Chem.* **2005**, *70*, 3274.
6. Fitzi, K. Ger. Patent 2,221,546, 1972; U.S. Patent 3,929,807, 1975; *Chem. Abstr.* **1973**, *78*, 58428.
7. Buehler, C. A.; Harris, J. O.; Arendale, W. F. *J. Am. Chem. Soc.* **1950**, *72*, 4953.
8. Kozlov, N. S.; Shmanal, G. S. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1974**, 974.

9. Barta, T. E.; Stealey, M. A.; Collins, P. W.; Weier, R. M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3443.
10. Cremlyn, R. J.; Lynch, J. M.; Swinbourne, F. J. *Phosphorus Sulfur* **1991**, *57*, 173.
11. (a) Fischer, E. *Justus Liebigs Ann. Chem.* **1882**, *211*, 214; (b) Buehler, C. A.; Harris, J. O. *J. Am. Chem. Soc.* **1950**, *72*, 5015; (c) Katritzky, A. R.; Lang, H.; Wang, Z.; Zhang, Z.; Song, H. *J. Org. Chem.* **1995**, *60*, 7619.
12. Walsh, C. J.; Mandal, B. K. *J. Org. Chem.* **1999**, *64*, 6105.
13. Chang, L. L.; Sidler, K. L.; Cascieri, M. A.; de Laszlo, S.; Koch, G.; Li, B.; MacCoss, M.; Mantlo, N.; O'Keefe, S.; Pang, M.; Rolando, A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2553.
14. Buehler, C. A.; Addleburg, J. W.; Glenn, D. M. *J. Org. Chem.* **1955**, *20*, 1350.
15. Tymonko, S. A.; Nattier, B. A.; Mohan, R. S. *Tetrahedron Lett.* **1999**, *40*, 7657.
16. Rao, T. V.; Dongre, R. S.; Jain, S. L.; Sain, B. *Synth. Commun.* **2002**, *32*, 2637.
17. Rohman, M. R.; Kharkongor, I.; Rajbangshi, M.; Mecadon, H.; Laloo, B. M.; Sahu, P. R.; Kharbangar, I.; Myrboh, B. *Eur. J. Org. Chem.* **2012**, *2012*, 320.
18. Laloo, B. M.; Mecadon, H.; Rohman, M. R.; Kharbangar, I.; Kharkongor, I.; Rajbangshi, M.; Nongkhlaw, R.; Myrboh, B. *J. Org. Chem.* **2012**, *77*, 707.
19. (a) Riley; Morley; Friend *J. Chem. Soc.* **1932**, 1881; (b) Riley; Gray In *Organic Synthesis*; John Wiley and Sons: New York, 1935; Vol. XV,
20. Fuson, R. C.; Talbott, R. L. *J. Org. Chem.* **1961**, *26*, 2674.
21. *General experimental procedure*: To a pre-stirred (stirred at 23 °C for 15 min) mixture of substituted acetophenones (1.0 mmol), arenes (1.0 mmol) and selenous acid (2 mmol) in acetonitrile (5 mL) was added *p*-toluene sulfonic acid monohydrate (*p*-TsOH·H_2O) (30 mol %) at 23 °C. The reaction mixture was allowed to stir at 35 °C for 12–14 h. On completion, the reaction mixture was diluted with ethyl acetate and filtered through a Celite bed. The Celite bed was washed thoroughly with ethyl acetate (3 × 5 mL). The combined filtrate was washed with saturated aqueous sodium bicarbonate solution followed by water (10 mL) and brine (10 mL). The organic layer was separated, dried over anhydrous sodium sulphate (Na_2SO_4) and concentrated under reduced pressure. The crude mass was purified by column chromatography on silica gel (100–200 mesh) using ethyl acetate and hexane as eluent to give the benzyls in pure form.
    In case of arene **2a** (5 mL) the reaction was carried out at 80 °C and for the arene **2b**–**d** (5 mL) at 35 °C without any solvent.
22. *Spectroscopic data for compounds: 1-(5-methylfuran-2-yl)-2-(naphthalen-1-yl)ethane-1,2-dione (**3m**)*: Yellow solid; mp 85–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 3.2 Hz, 1H), 6.20 (d, *J* = 3.2 Hz, 1H), 2.40 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 180.5, 161.2, 149.1, 135.7, 134.6, 134.0, 131.1, 129.2, 128.8, 127.0, 125.8, 124.5, 124.4, 110.1, 14.3 ppm; IR (KBr film) 3162, 3139, 3058, 3045, 2923, 2819, 1645, 1506, 1367, 1201, 1035 cm^{-1}; MS (ES+) Calcd for $C_{16}H_{12}O_3$ 264.1. Found *m*/*z* 287 [M+Na]$^+$. Anal. Calcd for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58. Found: C, 77.38; H, 4.50.
    *1-(Anthracen-9-yl)-2-(5-methylfuran-2-yl)ethane-1,2-dione (**3s**)*: Yellow solid; mp 127–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.99–7.97 (m, 2H), 7.87–7.84 (m, 2H), 7.65 (d, *J* = 3.2 Hz, 1H), 7.43–7.41 (m, 4H), 6.28 (d, *J* = 3.2 Hz, 1H), 2.42 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 176.8, 161.8, 148.1, 131.2, 130.9, 130.6, 129.7, 129.0, 127.6, 126.9, 125.6, 124.5, 110.5, 14.4 ppm; IR (KBr film) 3091, 3052, 3045, 2992, 2859, 1652, 1506, 1446, 1373, 1168, 1035 cm^{-1}; MS (ES+) Calcd for $C_{21}H_{14}O_3$ 314.1. Found *m*/*z* 337 [M+Na]$^+$. Anal. Calcd for $C_{21}H_{14}O_3$: C, 80.24; H, 4.49. Found: C, 80.36; H, 4.41.