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Mild Conversion of β-Diketones and β-Ketoesters to Carboxylic Acids

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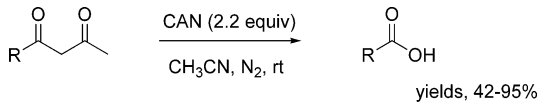

A mild protocol for the conversion of β-ketoesters and β-diketones to carboxylic acids with use of CAN in CH_3CN is described. The method is compatible with a number of functional groups, and can generate carboxylic acids under neutral conditions at room temperature. The reaction is fast and general, providing an alternative method to the commonly used malonic ester acid preparation. Initial mechanistic studies show that initial oxidation of the enol form of the β-dicarbonyl initiates the reaction. The presence of nitrate as an oxidant ligand or as an additive is critical for success of the reaction.

Introduction

Carboxylic acids are ubiquitous and important components of numerous biomolecules and synthetic targets of high pharmaceutical value. Although widespread in nature, organic synthesis has greatly expanded the useful family of carboxylic acids. The traditional methods for preparing carboxylic acids include oxidation of primary alcohols[1−3] and aldehydes,[4−7] reaction of organometallic reagents with carbon dioxide,[8−10] hydrolysis of acid derivatives[11] and nitriles,[12−14] oxidative cleavage of alkenes[15−19] and alkynes,[20,21] haloform type reactions,[22−24] and periodic acid cleavage of vicinal diols and diketones.[25−29] Although many useful methods have been developed for the preparation of carboxylic acids, the procedures usually require strenuous reaction conditions including high temperatures, acidic/basic media, or the use of toxic reagents. These protocols are often incompatible with many functional groups and sometimes are environmentally unfriendly. Taking these points into account, we report a novel, mild, neutral, efficient, and functional group compatible procedure for the synthesis of carboxylic acids through fragmentation of β-ke-

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(22) Fusan, R. C.; Bull, B. A. *Chem. Rev.* **1934**, *15*, 275−309.
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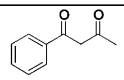
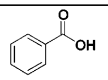
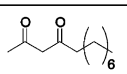
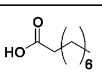
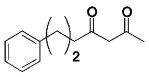
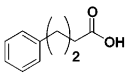
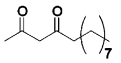
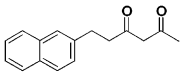
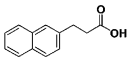
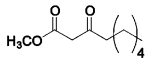
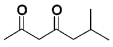
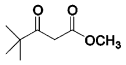
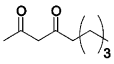
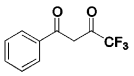
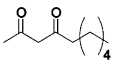
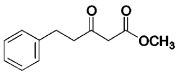
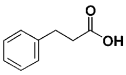
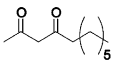
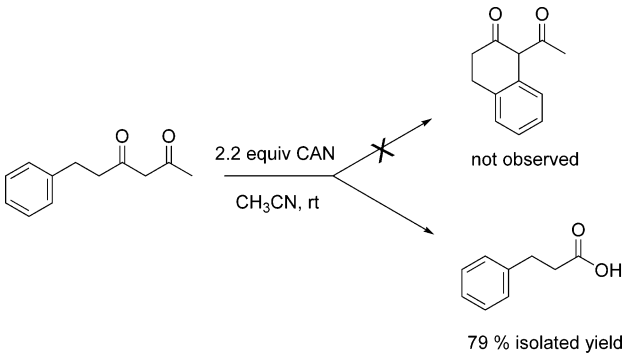
TABLE 1. Reaction of β-Diketones and β-Ketoesters with CAN

Entry	Substrate	Product	Yield	Entry	Substrate	Product	Yield
1		**1** 	42%[a] **1a**	8		**8** 	78%[a] **8a**
2		**2** 	83%[a] **2a**	9		**9** 	75%[a] **9a**
3		**3** 	72%[a] **3a**	10		**10** 	76%[b] **10a**
4		**4** 	67%[a] **4a**	11		**11** 	90%[b] **11a**
5		**5** 	76%[a] **5a**	12		**12** 	80%[b] **12a**
6		**6** 	82%[a] **6a**	13		**13** 	63%[b] **13a**
7		**7** 	88%[a] **7a**	14		**14** 	95%[b] **14a**

[a] Isolated yield. [b] GC yield. Reaction conditions: 1 equiv of substrate was added to 2.2 equiv of CAN in CH_3CN. The reaction was carried out at room temperature under a nitrogen atmosphere for 4 h. Solvent was removed at the completion of the reaction and water was added. The solution was extracted with ether and dried over $MgSO_4$.

SCHEME 1



toester and β-diketone compounds with cerium ammonium nitrate (CAN).

Results and Discussion

While CAN is a useful reagent for intermolecular carbon−carbon bond formation,[30] the application of CAN in intramolecular C−C bond formation is not as prevalent. With this in mind, 6-phenylhexane-2,4-dione was prepared and treated with 2 equiv of CAN in CH_3CN at room temperature. It was expected that an intramolecular reaction would occur to provide the cyclized product shown in Scheme 1. Surprisingly, no cyclization was observed, and instead 3-phenylpropionic acid was obtained as the exclusive product of the reaction. Although oxidative cleavage of β-dicarbonyls and α-hydroxyketones to carboxylic acids with oxone has been reported,[31,32] some of the experiments required elevated temperatures, long reaction times (18 h), basic (Oxone decomposes with pH <5), and aqueous conditions. Considering the neutral and mild conditions with CAN, the generality of the reaction shown in Scheme 1 was examined. The results of reactions of a series of alkylated β-diketones and β-ketoesters with CAN in CH_3CN are summarized in Table 1. The NMR spectra and MS data for all known products were compared to those of authentic samples.

Examination of the results in Table 1 shows that the corresponding acids can be obtained in good to high yields for the substrates examined in this initial study and the results are comparable for β-diketones and β-ketoesters. The relatively low yield from compound **1** is likely due to the higher water solubility of the product compared with others examined. Interestingly the product for 1,3-indanedione (**14**) was the corresponding anhydride formed in nearly quantitative yield.

Since all of the reported yields were obtained utilizing unoptimized conditions described in Scheme 1, a number of reaction conditions were examined to determine if the yields could be further optimized and also to possibly obtain insight into the mechanism of this mild conversion. The data are contained in Table 2. The enol form of 1,3-diketones is readily oxidized by CAN,[33] so initially 3,3-dimethyl-2,4-pentanedione

(30) Nair, V.; Mathew, J.; Prabhakaran, J. *Chem. Soc. Rev.* **1997**, *26*, 127−132.

(31) Ashford, S. W.; Grega, K. C. *J. Org. Chem.* **2001**, *66*, 1523−1524.

(32) Yan, J.; Travis, B. R.; Borhan, B. *J. Org. Chem.* **2004**, *69*, 9299−9302.

(33) Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2004**, *37*, 21−30.

TABLE 2. Examination of Reaction Outcome under a Variety of Conditions

Entry	Substrate	Oxidant, Solvent	Product	Yield[c]
1		CAN, CH_3CN[a]	Starting material	N/A
2	**6**	CAN, CH_3OH[a]		63%
3	**6**	CTAN, CH_2Cl_2[a]	**6a**	80%
4	**6**	CAN, CH_3CN[b]	**6a**	95%
5	**6**	$Ce(OTf)_4$, CH_3CN[a]	Starting material + unidentified products	N/A
6	**6**	$Ce(OTf)_4$, 10 equiv NH_4NO_3, CH_3CN[a]	**6a**	42%
7	**6**	NH_4NO_3, CH_3CN[a]	NR	N/A
8	**6**	HNO_3, CH_3CN[a]	NR	N/A

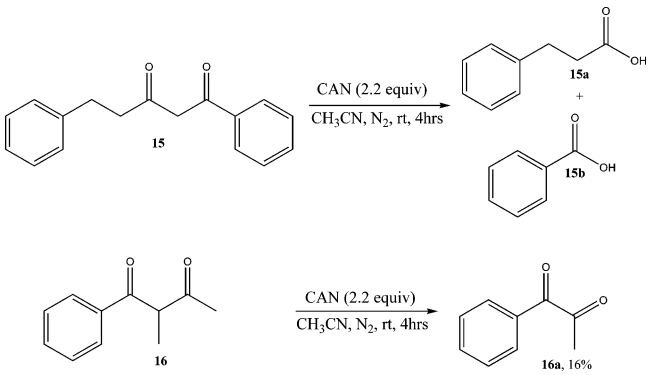
[a] Reaction conditions: see footnote b in Table 1. [b] After reaction, solvent was removed and the products were added to ether (instead of water) and dried over $MgSO_4$ (see optimized procedure in the Experimental Section). [c] Isolated yield.

was examined to determine if reaction through a pathway other than electron transfer was possible (Table 2, entry 1). The lack of reaction with this substrate shows that the first step in the reaction is likely to be oxidation of the enol to a radical cation.[34] Use of methanol (MeOH) as a solvent medium provided the corresponding methyl ester in good yields. Use of ceric tetra-*n*-butylammonium nitrate (CTAN) in CH_2Cl_2 provided comparable yields to reaction of **6** with CAN in CH_3CN (Table 2, entries 2 and 3). Next, the reaction was carried out in a drybox in the absence of O_2 and workup without water addition. Unexpectedly, the product acid was obtained in excellent yield in the absence of these two potential sources of oxygen in the product (Table 2, entry 4). This optimized procedure was used in all subsequent reactions.

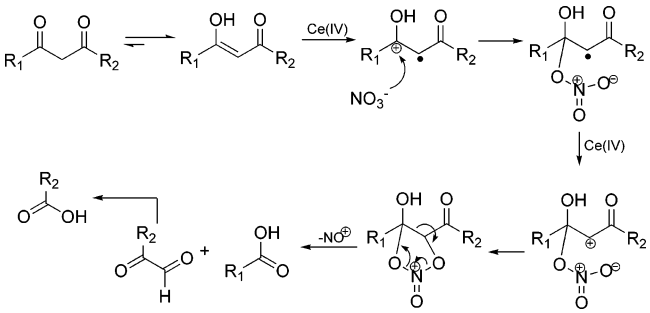
Surprisingly, other Ce(IV) based reagents did not promote this conversion. For instance, when cerium(IV) triflate was employed as the oxidant (Table 2, entry 5), no conversion occurred and only starting material and unidentified side products were obtained. Since internal ligand transfer of nitrate to substrate is common in many reactions of CAN,[35] it is possible that the nitrate ligand played a role in the reaction. The potential role for nitrate was studied by the addition of 10 equiv of ammonium nitrate (based on Ce(IV) concentration) to the reaction with cerium(IV) triflate and this experiment provided a 42% yield of acid product **6a** (Table 2, entry 6). Addition of ammonium nitrate or nitric acid alone to **6** led to recovery of starting material (Table 2, entries 7 and 8). These studies suggest that nitrate along with Ce(IV) are necessary for the success of these reactions.

In all of the reactions studied thus far, cleavage of the chosen 1,3-dicarbonyls provided a carboxylic acid, but the identity of the portion extruded was not found in the reaction mixture likely due to loss through aqueous workup or evaporation during solvent removal. To examine this issue further, a 1,3-dione was

SCHEME 2



SCHEME 3



chosen so that both portions of the molecule were sufficiently lipophilic and nonvolatile under the reaction conditions to allow easy isolation. Reaction of 1,5-diphenylpentane-1,3-dione (**15**) with 2.2 equiv of CAN in acetonitrile followed by the standard workup produced a nearly equimolar amount of 3-phenylpropionic acid (**15a**) and benzoic acid (**15b**) (Scheme 2).

Although the intermediates leading to these products have not been identified with a great degree of certainty, examination of the reaction utilizing React IR (Supporting Information) showed the appearance of bands at 2850 and 2930 cm^{-1}, which are characteristic of the C−H stretch in α-keto aldehydes. Reactions run in CD_3CN within an NMR tube showed a ^1H NMR peak consistent with the aldehydic proton of a α-keto aldehyde along with peaks consistent with the formation of a carboxylic acid. To determine the fate of the central carbon, the α-methylated diketone (**16**) was prepared. Reaction of **16** with 2.2 equiv of CAN in CH_3CN resulted in a 16% isolated yield of 1-phenylpropane-1,2-dione (**16a**) along with unreacted starting material as shown in Scheme 2. A longer reaction time provided a higher yield of **16a**. Examination of the ^1H NMR spectrum of **16** shows that α-methylation of the 1,3-diketone significantly decreases the enol content and this likely contributes to the decreased rate of oxidation by CAN.

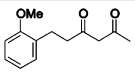
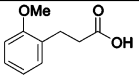
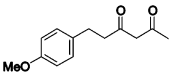
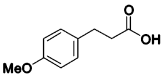
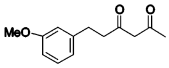
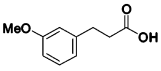
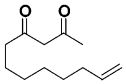
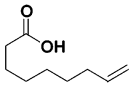
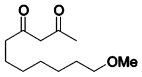
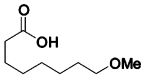
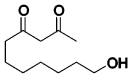
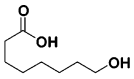
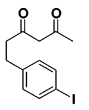
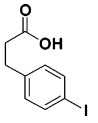
On the basis of the experimental data described to this point, a reasonable mechanism can be proposed. It is likely that after oxidation of the enol form of the 1,3-dicarbonyl by Ce(IV) and internal ligand transfer of nitrate, that rearrangement leads to a carboxylic acid and an α-keto aldehyde which can be further oxidized to a carboxylic acid (Scheme 3).[36] The mechanism in Scheme 3 shows the loss of NO, and attempts to trap it by the addition of anisole to the reaction mixture were inconclusive since the ortho and para nitrated products produced in this

(34) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2550−2589.

(35) (a) Paolobelli, A. B.; Gioacchini, F.; Ruzziconi, R. *Tetrahedron Lett.* **1993**, *34*, 6333−6336. (b) Baciocchi, E.; Civitarese, G.; Ruzziconi, R. *Tetrahedron Lett.* **1987**, *28*, 5357−5360.

(36) (a) Niki, E.; Yamamoto, Y.; Saito, T.; Nagano, K.; Yokoi, S.; Kamiya, Y. *Bull Chem. Soc. Jpn.* **1983**, *56*, 223−228. (b) Antal, M. J., Jr.; Mok, W. S. L.; Richards, G. N. *Carbohydr. Res* **1990**, *199*, 111−115.

TABLE 3. Functional Group Compatibility Studies[b]

Entry	Substrate	Product	Yield[a]
1		**17** 	72%, **17a**
2		**18** 	81%, **18a**
3		**19** 	80%, **19a**
4		**20** 	89%, **20a**
5		**21** 	92%, **21a**
6		**22** 	74%, **22a**
7		**23** 	88%, **23a**

[a] Isolated yield. [b] Reaction conditions: See footnote b in Table 2.

experiment can also be formed by reaction of CAN with anisole alone (albeit at a slower rate).[37]

To be useful in synthesis, it is important to determine the functional group compatibility for this method. A series of different β-dicarbonyl substrates containing oxidizable functional groups were prepared and the results of their reactions with use of the optimized anhydrous procedure are contained in Table 3. The yields of the reactions are very good and phenyl methoxy groups, double bonds, alkyl hydroxy groups, and aryliodides are all compatible with this methodology. Since alcohols and phenyl methoxy groups are known to be oxidized by CAN, these findings indicate that the selectivity is likely due to the fast rate of oxidation of 1,3-dicarbonyls relative to other functional groups.[38]

Conclusions

A mild method for the conversion of β-ketoesters and β-diketones to carboxylic acids with use of CAN in CH_3CN has been developed. The method is compatible with a number of other functional groups and can be carried out under neutral conditions. Aside from functional group compatibility, the procedure can be carried out in a number of solvents as well. Initial studies of the reaction show that the nitrate ligand is necessary for the conversion initiated by Ce(IV). Although Ce is an abundant, nontoxic, and inexpensive metal, one of the major goals of modern chemical research is to develop chemical processes that are environmentally benign. If Ce(IV) is only necessary to initiate oxidation, alternative approaches to this reaction may be possible by initiating the oxidation of β-dicarbonyls electrochemically in the presence of nitrate salts.[39] Further examination of the mechanistic details of the conversion are being explored to determine if this mild procedure can be utilized in other important functional group conversions or bond forming reactions.

Experimental Section

Materials and Experimental Procedures. All solvents were distilled before use. Ceric tetra-*n*-butylammonium nitrate (CTAN)[40] and cerium triflate (CTF)[41] were prepared following reported procedures. β-Dicarbonyl substrates **2**, **3**, **5**, **7**, **8**, **9**, **10**, **13**, **15**, **17**, **18**, **19**, **20**, **21**, **22**, and **23** were prepared by the reaction of 2,4-pentanedione or methyl acetoacetate with corresponding halides under the treatment of NaH and BuLi. Compound **16** was prepared from 1-phenylbutane-1,3-dione, methyl iodide, potassium carbonate, and tetra-*n*-butylammonium bromide in toluene according to the published procedure.[42] All other substrates were purchased and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer. Infrared experiments were performed on a React IR system.

Procedure for Oxidation of β-Dicarbonyls with CAN in CH_3CN. Ceric ammonium nitrate (CAN, 4.4 mmol, in 10 mL CH_3CN) solution was added to a solution of the β-dicarbonyl (2 mmol) in 40 mL of CH_3CN under N_2 over a period of 2 min. After 4 h, CH_3CN was removed at 30 °C by rotary evaporation. Water (75 mL) was poured into the reaction funnel and extracted with 4 × 25 mL of diethyl ether. The organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated via rotary evaporation. The residue was analyzed by GC-MS and purified with column chromatography, using silica gel as the stationary phase.

Optimized Procedure for Oxidation of β-Dicarbonyls with CAN in CH_3CN. Ceric ammonium nitrate (CAN, 4.4 mmol, in 10 mL of CH_3CN) was added to a solution of the β-dicarbonyl (2 mmol) in 40 mL of CH_3CN over a period of 2 min under an inert atmosphere. After 4 h, solvent was removed at 30 °C by rotary evaporation. Ether (40 mL) was poured into the reaction flask and the solution was dried over anhydrous $MgSO_4$, filtered, and concentrated via rotary evaporation. The residue was analyzed by GC-MS and purified via column chromatography, using silica gel as the stationary phase.

6-Naphthalen-2-ylhexane-2,4-dione (3). 6-Naphthalen-2-ylhexane-2,4-dione was prepared by the reaction of 2,4-pentadione and 2-(2-bromoethyl)naphthalene following the general procedure for the preparation of 2,4-dione derivatives. **3**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.03 (s, 3H), 2.67 (t, 2H, J = 7.2 Hz), 2.90 (t, 2H, J = 7.2 Hz), 5.49 (s, 1H), 7.30−7.44 (m, 3H), 7.61−7.79 (m, 4H), 15.46 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.2, 190.4, 138.2, 132.1, 128.1, 127.6, 127.5, 127.0, 126.4, 126.0, 125.3, 100.1, 45.1, 39.9, 31.6, 24.8. MS *m*/*z* (rel intensity) 240 (M^+, 30), 207 (12), 182 (10), 154 (55), 141 (100), 126 (12), 115 (25), 85 (35). HRMS (EI) calcd for $C_{16}H_{16}O_2$ 240.1150, found 240.1162.

6-(2-Methoxyphenyl)hexane-2,4-dione (17). 6-(2-Methoxyphenyl)hexane-2,4-dione was prepared by the reaction of 2,4-pentadione and 1-bromomethyl-2-methoxybenzene following the general procedure for the preparation of 2,4-dione derivatives. **17**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.03 (s, 3H), 2.55 (t, J = 8.2 Hz, 2H), 2.90 (t, J = 8.2 Hz, 2H), 3.53 (s, 0.3H), 3.81 (s, 3H), 5.47 (s, 0.8H), 7.19−7.10 (m, 4H), 15.46 (s, 0.7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.0, 191.0, 157.4, 129.8, 129.0, 127.5, 120.4, 110.2, 99.9, 55.2, 38.3, 26.6, 24.9. MS *m*/*z* (rel intensity) 220 (M^+, 35), 134 (33),

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(42) Choudhary, A.; Baumstark, A. L. *Synthesis* **1989**, *9*, 688−690.

121 (100), 91 (90), 65 (22). HRMS (EI) calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1106.

6-(4-Methoxyphenyl)hexane-2,4-dione (18). 6-(4-Methoxyphenyl)hexane-2,4-dione was prepared by the reaction of 2,4-pentadione and 1-bromomethyl-4-methoxybenzene following the general procedure for the preparation of 2,4-dione derivatives. **18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.54 (t, J = 8.2 Hz, 2H), 2.85 (t, J = 8.2 Hz, 2H), 3.52 (s, 0.3H), 3.76 (s, 3H), 5.45 (s, 0.7H), 7.09−6.79 (m, 4H), 15.45 (s, 0.7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 191.2, 158.0, 132.7, 129.3, 129.2, 113.9, 113.9, 100.0, 55.2, 40.3, 30.7, 24.9. MS *m*/*z* (rel intensity) 220 (M^+, 48), 121 (100), 85 (21). HRMS (EI) calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1099.

6-(3-Methoxyphenyl)hexane-2,4-dione (19). 6-(3-Methoxyphenyl)hexane-2,4-dione was prepared by the reaction of 2,4-pentadione and 1-bromomethyl-3-methoxybenzene following the general procedure for the preparation of 2,4-dione derivatives. **19**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03 (s, 3H), 2.58 (t, J = 8.1 Hz, 2H), 2.89 (t, J = 8.1 Hz, 2H), 3.75 (s, 3H), 4.53 (s, 0.2H), 5.46 (s, 0.9H), 7.24−6.71 (m, 4H), 15.43 (s, 0.7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 190.9, 129.7, 129.0, 127.6, 120.5, 112.3, 111.1, 100.1, 55.2, 40.2, 30.7, 24.9. MS *m*/*z* (rel intensity) 220 (M^+, 67), 135 (100), 121 (68), 85 (70). HRMS (EI) calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1101.

11-Methoxyundecane-2,4-dione (21). 11-Methoxyundecane-2,4-dione was prepared by the reaction of 2,4-pentadione and 1-bromo-6-methoxyhexane following the general procedure for the preparation of 2,4-dione derivatives. **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (m, 6H), 1.53 (m, 4H), 2.03 (s, 3H), 2.23 (t, 2H, J = 7.5 Hz), 3.30 (s, 3H), 3.35 (t, 2H, J = 7.5 Hz), 5.46 (s, 1H), 14.95 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 192.1, 99.8, 72.8, 58.5, 38.4, 38.2, 29.6, 29.2, 29.1, 25.9, 25.6. MS *m*/*z* (rel intensity) 214 (M^+, 1), 182 (1), 164 (3), 138 (5), 100 (65), 85 (100), 55 (30). HRMS (EI) calcd for $C_{12}H_{22}O_3$ 214.1569, found 214.1577.

6-(4-Iodophenyl)hexane-2,4-dione (23). 6-(4-Iodophenyl)hexane-2,4-dione was prepared by the treatment of 2,4-pentadione with 1-bromomethyl-4-iodobenzene hexane following the general procedure for the preparation of 2,4-dione derivatives. **23**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.54 (t, 2H, J = 8.0 Hz), 2.81 (t, 2H, J = 8 Hz), 5.42 (s, 1H), 6.92 (d, 2H, J = 8.2 Hz), 7.58 (d, 2H, J = 8.2 Hz), 15.45 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.2, 192.5, 140.3, 137.5, 130.4, 100.1, 39.7, 30.8, 24.8. MS *m*/*z* (rel intensity) 316 (M^+, 100), 298 (10), 258 (12), 217 (100), 131 (25), 103 (45), 85 (100). HRMS (EI) calcd for $C_{12}H_{13}IO_2$ 315.9960, found 315.9969.

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Supporting Information Available: General methods, experimental protocols, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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