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A Method for C2 Acylation of 1,3-Indandiones

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Abstract

The 1,3-indandione scaffold is an important structural motif used in the preparation of a large number of industrial chemical and pharmaceutical compounds. However, few approaches allow for the direct C2 acylation on these building blocks. A method was developed using DMAP and EDCI, which is mild in reactivity, covers a diverse range of carboxylic acid acylating agents, is compatible with electron releasing and withdrawing substituents on the 1,3-indandione partner, and performs well in a polar aprotic solvent (for solubility reasons) This method cleanly afforded twenty five different products in yields of 32–96%.

Graphical abstract

Introduction

1,3-Indandiones are versatile building blocks that have been used in the preparation of a large number of heterocyclic pharmaceutical and industrial chemicals.¹ 2-Acyl 1,3-indandiones are found in the anticoagulant rodenticides valone and diphenadione, best known as “first generation” vitamin K antagonists (Figure 1).² We required compounds with the 2-acyl-1,3-indandione moiety and sought a general synthesis via acylation of 1,3-indandiones but learned that a paucity of reaction conditions were available to us. Note that we draw the 2-acyl-1,3-indandione moiety as the enol form with an exocyclic double bond. X-ray, NMR and computational studies support this form over the tricarbonyl and endocyclic enol forms,^{3–5} and the form as drawn is consistent with our own NMR data.

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Several methods currently exist for the synthesis of 2-acyl-1,3-indandiones (II) from various starting materials (Scheme 1). As mentioned above few methods are reported for the direct 2-acylation of 1,3-indandiones (I), and those that exist are not general, have harsh conditions and result in poor yields (pathway A). These include 1) reaction with *p*-nitrophenol esters as acylating agent,⁶ and 2) reaction with acid chlorides and aluminum chloride.⁷ Since this acylation has been recognized as a common problem, other methods have been developed that bypass an acylation procedure. An example is reaction of *o*-phthalate esters with methyl ketones^{8,9} (pathway B), however conditions are rather harsh since they require high temperatures and strong base. Alternatively reaction of phthalate anhydrides (pathway C) with methyl ketones in base⁹ or with simple alkyl ketones in base^{9,10} gives inconsistent yields and is of limited substrate scope. A recent intramolecular method uses a phenoxy formate as a carbon monoxide source in a palladium catalyzed carbonylation of an *o*-iodophenyl β -diketone to construct II (pathway D).¹¹ Since we sought to prepare a diverse range of acyl moieties appended to a variety of 1,3-indandione containing starting materials, none of these methods were easily adaptable for our purposes. Thus, we decided to re-examine direct acylation using alternative chemistry. We were heartened in that there was a growing body of work on the acylation of other cyclic β -dicarbonyl systems. For instance several investigators described acylation of these systems with different carboxylic acids using dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3-dimethylamino)propyl)-carbodiimide (EDCI) usually with dimethylamino pyridine (DMAP). Ring systems included were meldrums acid^{12,13}, pyrimidine-2,4,6-triones¹⁴, tetramic acids¹⁵ and 1,3-cyclohexandiones.^{16,17} Other acylation methods on 1,3-cyclohexandiones employed samarium trichloride (SmCl₃) with an acid chloride,¹⁸ or cyanogen bromide with an aldehyde.¹⁹ We here describe a simple one-pot C2 acylation of 1,3-indandiones using EDCI and DMAP that achieves yields up to 96%. As starting materials, we explored commercially available 1,3-indandiones with and without electron withdrawing and releasing substituents along with a variety of diverse carboxylic acid building blocks as the acylating agents (Table 1).

Results/Discussion

There are several problems to overcome with any method using a 1,3-indandione analog (I): O-acylation, over-acylation and self-condensation (primarily bindone formation, III in Scheme 1, and other more complex self-condensation products).²⁰ Since the acylation reaction would compete with self-condensation for consumption of the 1,3-indandione starting material, excess acylating agent could minimize the self-condensation route, while using stoichiometric amounts of acylating agent would impede over-acylation. With this in mind we had to strike a balance between these competing factors in determining the number of equivalents of acylating agent to use.

First a series of studies were conducted on the parent 1,3-indandione (R = H in I, Scheme 1) and using benzoic acid, phenylacetic acid and 3-methylbutyric acid or their acid chloride derivatives in attempts to directly functionalize C2. In the process we screened various reagents, solvents, temperatures, concentrations, times, and ratios, monitoring by LCMS to best optimize the reactions. Initially, we tried SmCl₃ to promote a direct C2 functionalization of 1,3-indandiones using acyl chlorides.¹⁸ Only trace amounts of desired

product (II) was observed. The byproducts included O-acylation, over-acylation, and self-condensation to bindone (III). We also attempted acylation methodology using acyl chlorides with other Lewis acids (AlCl_3 or MgCl_2) or with bases such as K_2CO_3 and DMAP. All of these initial attempts resulted in incomplete conversion and/or inseparable mixtures, with formation of bindone (III), over-acylation products and/or other undesirable, unidentified byproducts.

While the use of DCC and DMAP in dichloromethane^{12–17} gave desired products as determined by LCMS, the reaction mixtures were plagued by difficulties in purification (e.g. removal of DCC related urea byproducts). The intended use of any method we developed would be applied to privileged scaffolds that we knew would have low solubility in organic solvents and thus not easily amenable to using chromatographic methods. Thus, our method needed to provide crude reaction mixtures that could be easily purified by trituration, recrystallization or acid-base workup. In order to combat these issues, a switch to the water-soluble coupling reagent EDCI·HCl, which has been widely utilized in the field of peptide coupling reactions in combination with additives, such as hydroxybenzotriazole (HOBT-hydrate). Furthermore, we sought to perform the reactions in polar aprotic solvents such as DMF to overcome any future reaction mixture solubility issues.

We first examined four conditions: either 1.5 equivalents of carboxylic acid, EDCI·HCl and DMAP, or 3.0 equivalents of carboxylic acid, EDCI·HCl and DMAP, both with and without the corresponding equivalent amount of HOBT-hydrate. The HOBT did not show any benefit to reaction composition or rates so it was excluded in further evaluations. Both the 1.5 and 3.0 equivalent regimens gave the desired C2 acylation product, however the 1.5 equivalent format led to greater amounts of bindone (III) formation (5–10% as opposed to 1–5% for the 3.0 equivalent format). Therefore, all remaining reactions proceeded with 3.0 equivalents of coupling agents. Acylation products II are reported in Table 1.

Optimal conditions were found by adding 1,3-indandione (I) to a dilute, room temperature, premixed solution of 3.0 eq of carboxylic acid, DMAP, and EDCI in DMF (9 mL, 0.055M of 1,3-indandione). These reaction conditions were repeated on a variety of substrates varying the R' group on the acid component to explore substrate scope of the reactions (Table 1).

Reaction of sterically unhindered alkyl carboxylic acids with a methylene group adjacent to the carbonyl (IV, $\text{R}' = \text{CH}_2\text{R}''$, entries **1**, **5–7**) were generally unproblematic and gave good yields. This was also true for phenyl acetic acid (entry **17**) and acetic acids with α -heteroatom-based electron withdrawing groups ($\text{R}' = \text{CH}_2\text{R}''$, where R'' is OPh - entry **23**, SO_2Me - entry **25** and $\text{SO}_2(p\text{-tolyl})$ - entry **26**). Compounds with two alkyl or phenyl moieties at the carboxylic acid α -carbon also behaved well ($\text{R}' = \text{CH}(\text{CH}_3)_2$ - entry **8**, $\text{CH}(\text{CH}_3)\text{Ph}$ - entry **21**, and CHPh_2 - entry **22**). However more sterically hindered carboxylic acids that have a tertiary substituted α -carbon were not reactive under these conditions (entries **9–11**). Benzoic acid (entry **12**) was also problematic where less than 20% conversion (by LCMS) occurred with several bi-products including bindone (III) and O-acylation observed. O-Acylation and poor reactivity is also a common problem for aromatic and highly hindered carboxylic acids used as acylating agents on tetramic acids¹⁵ and cyclohexane 1,3 diones¹⁷ using similar conditions to those reported here. However, the

heteroaromatic acid, 2-benzofuran carboxylic acid (entry **13**) gave excellent results. Alternatively, when we tried using acetic acids with basic amine moieties on the α -carbon, we observed either decomposition (entry **27**) or sluggish product formation by LCMS (entry **29**). Boc-protected glycine (entry **28**) also led only to decomposition products. In contrast, the mildly basic pyrazol-1-yl-acetic acid (entry **30**, pKa of conjugate acid = 2.4) did form the desired product in good yield. Of note, is the preparation of valone and diphenadione (**1**^{21,22} and **22**²⁶ in Table 1) using this method. Also, the ¹H and ¹³C NMR spectra of **8** were entirely consistent with the published spectra of same compound synthesized by phenoxy formate palladium catalyzed carbonylation of 1-(2-iodo-phenyl)-4-methylpentane-1,3-dione (compound **3m** in the reference).¹¹

In order to examine the effect of electron releasing (EDG) or electron withdrawing (EWG) substituents on the 1,3-indandione, we reacted substituted 1,3-indandiones containing a 5-methyl substituent (I, R = 5-CH₃, mild EDG), a 5-bromo substituent (I, R = 5-Br, EWG) and a 4-nitro substituent (R = 3-NO₂, strong EWG). We also picked a diverse set of carboxylic acids including 2-methyl butyric acid (entries **2–4**), 2-benzofuran carboxylic acid (entries **14–16**), phenyl acetic acid (entries **18–20**), and pyrazol-1-yl-acetic acid (entries **31–33**). Generally, the electron releasing or withdrawing groups did not affect the yield of the product. The isolated yields for the pyrazole containing compounds (entries **30–33**) tended to be lower because of their high water solubility where a substantial amount dissolved in aqueous phases on triturations and extractions. Since these compounds (**2–4**, **14–16**, **18–20**, **24**, and **30–33**) were substituted on the 1,3 indandione ring they often gave rise to geometric isomers on the NMR time scale, which was particularly evident from the ¹³C spectra.

Through these studies we have shown that direct C2 acylation of various unsubstituted and substituted 1,3-indandiones has been successfully achieved in a single reaction step. The substrate scope was explored via changes to the R' groups on the acid moiety (IV) and with EDG and EWG groups on the 1,3-indandione scaffold (I). Ultimately, we believe this chemical transformation could find wide applications for the rapid synthesis of a variety of related 2-acyl-1,3-indandiones.

EXPERIMENTAL SECTION

General

All reagents used in chemical synthesis were purchased from Aldrich Chemical Co. (Milwaukee, WI), Alfa Aesar (Ward Hill, MA), Thermo Fisher Scientific (Pittsburgh, PA), Enamine-BB or obtained from the Pennsylvania Drug Discovery Institute (PDDI) and were used without further purification. ¹H NMR spectra were obtained on a Varian Mercury 300-MHz NMR spectrometer. Chemical shifts were reported in parts per million (δ) using various solvents as internal standards (CDCl₃, δ 7.26 ppm; DMSO-d₆, δ 2.50 ppm; TMS, δ 0.00 ppm). ¹H NMR splitting patterns were designated as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), or quartet (q). Splitting patterns that could not be interpreted or easily visualized were recorded as multiplet (m). Coupling constants were reported in Hertz (Hz). Low-resolution electrospray mass spectral data (LCMS) were used to monitor reaction progress and were determined using a Waters Alliance 2695 HPLC/MS (Waters Symmetry

C18, 4.6×75 mm, 3.5 μm) with a 2996-diode array detector from 210 to 400 nm using HPLC-grade acetonitrile (w/0.1% TFA) in HPLC-grade H₂O (w/0.1% TFA) acquiring over 9.1 minutes (using 5% to 95% acetonitrile over 7 min, holding at 95% ACN until 8.60 min mark, then going to 5% ACN until the 9.30 min mark). High Resolution Mass spectra (HRMS) were obtained on a Bruker micrOTOF-Q II at the Mass Spectrometry & Proteomics Facility at Notre Dame University.

General Experimental Procedure

In a 20 or 40 mL reaction vial equipped with magnetic stir bar and Teflon-lined cap, a solution of the corresponding carboxylic acid (1.5 mmol, 3.0 eq) and DMAP (183.3 mg, 1.5 mmol, 3.0 eq) in anhydrous DMF (9.0 mL) was homogenized by stirring for 5–10 min. EDCI·HCl (287.6 mg, 1.5 mmol, 3.0 eq) was added, and the resulting mixture was homogenized by stirring for 5–10 min. The corresponding 1,3-indandione (0.5 mmol, 1.0 eq) was added, and the resulting mixture was resealed and stirred for 12–72 h, monitoring by LCMS. When complete, **workup method A, B, or C** was used to isolate the final products.

Workup Method A

The reaction was worked up by diluting with EtOAc (75 mL) and moving into a separatory funnel, then quenching with 2.0 N HCl (40 mL) and shaking vigorously. The separated organic layer was washed with 2.0 N HCl (50 mL), the aqueous layer was back-extracted with EtOAc (50 mL), and the combined organics were washed sequentially with 2.0 N HCl (50 mL) and D.I. H₂O (50 mL). The final organic phase was dried over MgSO₄, filtered, and concentrated *in vacuo*.

Workup Method B

The crude reaction mixture was quenched with 1.0 N HCl (40 mL), and a solid precipitant was filtered as the desired product. The sample was dried overnight *in vacuo* at 30 °C.

Workup Method C

Cold 2.0 N HCl (20 mL) was added to the solution, and the mixture was cooled in an ice bath. The resulting precipitant was filtered, washed with cold 2.0 N HCl (15 mL), water (15 mL), and dried *in vacuo*. The solid was treated with 1.0 N NaOH (10 mL), sonicated for 5–10 min until fully suspended into solution, then treated with DCM (10 mL) and further mixed/sonicated for 5 min. The suspended precipitant was filtered, washed with DCM (5 mL), and dried *in vacuo*. The compound was dissolved in 2N HCl (10 mL) and extracted with DCM (10 mL). The sample was dried and concentrated overnight *in vacuo*.

2-(3-Methylbutanoyl)-1H-indene-1,3(2H)-dione (1).^{21,22}—The title compound was prepared according to the general experimental procedure using isovaleric acid (166 μL, 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup method A as a brown solid (91 mg, 79%); ¹H NMR (300 MHz, CDCl₃) δ 7.89 – 7.80 (m, 2H), 7.79 – 7.64 (m, 2H), 2.94 – 2.76 (m, 2H), 2.32 – 2.12 (m, 1H), 1.04 (d, *J* = 6.67 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 197.3, 188.6, 187.2, 140.9, 138.2, 135.1, 134.2, 122.9, 122.6, 109.2,

40.9, 27.6, 22.6. HRMS (ESI/Q-TOF) m/z : $[M + H]^+$ calcd for $C_{14}H_{15}O_3$, 231.1016; found, 231.1024.

5-Methyl-2-(2-phenylacetyl)-1H-indene-1,3(2H)-dione (2)—The title compound was prepared according to the general experimental procedure using isovaleric acid (166 μ L, 1.5 mmol) and 5-methyl-2,3-dihydro-1*H*-indene-1,3-dione (80 mg, 0.5 mmol). Product was isolated using workup method B as a pink solid (69 mg, 57%). 1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 7.62 Hz, 1H), 7.63 (s, 1H), 7.51 (t, J = 8.20 Hz, 1H), 2.85 (d, J = 7.03 Hz, 2H), 2.51 (s, 3H), 2.21 (td, J = 6.96, 13.62 Hz, 1H), 1.03 (d, J = 6.44 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 188.0, 187.7, 187.7, 186.2, 146.1, 144.9, 144.9, 141.5, 138.9, 138.9, 136.4, 136.1, 135.3, 135.6, 134.8, 134.5, 134.3, 134.2, 123.7, 123.2, 123.1, 122.9, 122.7, 122.5, 122.5, 122.1, 109.4, 68.1, 51.8, 40.8, 27.2, 23.6, 22.6, 22.5, 22.5, 22.4, 22.3, 22.2, 21.6, 21.5. HRMS (ESI/Q-TOF) m/z : $[M + H]^+$ calcd for $C_{15}H_{17}O_3$, 245.1172; found, 245.1190.

5-Bromo-2-(3-methylbutanoyl)-1H-indene-1,3(2H)-dione (3)—The title compound was prepared according to the general experimental procedure using isovaleric acid (166 μ L, 1.5 mmol) and 5-bromo-2,3-dihydro-1*H*-indene-1,3-dione (113 mg, 0.5 mmol). Product was isolated using workup method C as a light pink solid (142 mg, 93%); 1H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.86 – 7.77 (m, 1H), 7.69 (d, J = 7.8 Hz, 1H), 2.84 (dd, J = 7.0, 1.1 Hz, 2H), 2.27 – 2.13 (m, 1H), 1.07 – 0.90 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.2, 138.8, 137.8, 137.6, 137.1, 126.3, 124.7, 124.1, 109.3, 41.4, 29.9, 27.7, 22.6. HRMS (ESI/Q-TOF) m/z : $[M + H]^+$ calcd for $C_{14}H_{14}BrO_3$, 309.0121; found, 309.0113.

2-(3-Methylbutanoyl)-4-nitro-1H-indene-1,3(2H)-dione (4)—The title compound was prepared according to the general experimental procedure using isovaleric acid (166 μ L, 1.5 mmol) and 4-nitro-2,3-dihydro-1*H*-indene-1,3-dione (96 mg, 0.5 mmol). Product was isolated using workup method C as a pink solid (126 mg, 93%); 1H NMR (300 MHz, $CDCl_3$) δ 8.13 – 7.79 (m, 3H), 2.89 (dd, J = 7.90, 7.26 Hz, 2H), 2.23 (dp, J = 13.67, 6.83 Hz, 1H), 1.04 (dd, J = 6.67, 2.70 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 187.3, 182.5, 146.0, 135.7, 134.5, 129.9, 129.1, 128.3, 127.8, 126.2, 108.1, 38.9, 29.9, 22.8. HRMS (ESI/Q-TOF) m/z : $[M + H]^+$ calcd for $C_{14}H_{14}NO_5$, 276.0866; found, 276.0875.

2-(2-Cyclohexylacetyl)-1H-indene-1,3(2H)-dione (5)—The title compound was prepared according to the general experimental procedure using cyclohexylacetic acid (213 mg, 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup method A, followed by column chromatography on a silica gel column using hexanes/ethyl acetate as the eluent to provide a yellow solid (95 mg, 70%). 1H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 2H), 7.78 – 7.66 (m, 2H), 2.87 (d, J = 7.13 Hz, 2H), 1.90 (ddp, J = 10.66, 6.93, 3.57 Hz, 1H), 1.82 – 1.59 (m, 4H), 1.43 – 1.00 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 188.7, 187.3, 140.9, 138.2, 135.1, 134.2, 122.9, 122.6, 109.3, 39.8, 37.0, 33.2, 26.2. HRMS (ESI/Q-TOF) m/z : $[M + H]^+$ calcd for $C_{17}H_{19}O_3$, 271.1329; found, 271.1349.

2-(2-Cyclopentylacetyl)-1H-indene-1,3(2H)-dione (6)—The title compound was prepared according to the general experimental procedure using cyclopentylacetic acid (192 mg, 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup

method A, followed by column chromatography on a silica gel column using hexanes/ethyl acetate as the eluent to provide a yellow solid (45 mg, 35%). ^1H NMR (300 MHz, CDCl_3) δ 7.89 – 7.80 (m, 2H), 7.79 – 7.64 (m, 2H), 2.99 (d, J = 7.49 Hz, 2H), 2.32 (p, J = 7.80 Hz, 1H), 1.89 – 1.24 (m, 8H). ^{13}C NMR (75 MHz, CDCl_3) δ 197.5, 188.7, 187.5, 140.9, 138.3, 135.1, 134.2, 122.9, 122.6, 108.8, 38.2, 37.9, 32.6, 25.0. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{17}\text{O}_3$, 257.1172; found, 257.1171.

2-(4-Methylpentanoyl)-1H-indene-1,3(2H)-dione (7).²³—The title compound was prepared according to the general experimental procedure using 4-methylvaleric acid (189 μL , 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup method A as a brown oil (91 mg, 75%); ^1H NMR (300 MHz, CDCl_3) δ 7.89 – 7.79 (m, 2H), 7.71 (ddd, J = 6.99, 4.65, 1.60 Hz, 2H), 3.03 – 2.92 (m, 2H), 1.79 – 1.51 (m, 3H), 0.97 (d, J = 6.31 Hz, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ 197.4, 188.6, 188.3, 140.8, 138.3, 135.1, 134.1, 122.8, 122.5, 108.4, 35.4, 30.6, 28.2, 22.4. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{17}\text{O}_3$, 245.1172; found, 245.

2-Isobutyryl-1H-indene-1,3(2H)-dione (8).^{11,21}—The title compound was prepared according to the general experimental procedure using isobutyric acid (140 μL , 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup method A as a brown solid (99 mg, 92%); ^1H NMR (300 MHz, CDCl_3) δ 7.87 – 7.80 (m, 2H), 7.76 – 7.65 (m, 2H), 3.90 (p, J = 6.87 Hz, 1H), 1.27 (d, J = 6.91 Hz, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ 197.8, 192.3, 140.8, 138.2, 135.1, 134.1, 122.9, 122.5, 107.1, 30.7, 19.1. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{O}_3$, 217.0859; found, 217.0853.

2-(Benzofuran-2-carbonyl)-1H-indene-1,3(2H)-dione (13)—The title compound was prepared according to the general experimental procedure using 2-benzofurancarboxylic acid (243 mg, 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup method C as a bright yellow solid (133.6 mg, 93%); ^1H NMR (300 MHz, CDCl_3) δ 9.24 (s, 1H), 7.84 – 7.57 (m, 6H), 7.51 – 7.45 (m, 1H), 7.34 – 7.26 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.5, 156.6, 147.2, 134.6, 129.1, 128.1, 124.1, 124.0, 123.8, 122.7, 120.5, 112.4, 107.3, 29.8. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{11}\text{O}_4$, 291.0652; found, 291.0672.

5-Methyl-2-(3-methylbutanoyl)-1H-indene-1,3(2H)-dione (14)—The title compound was prepared according to the general experimental procedure using 2-benzofurancarboxylic acid (243 mg, 1.5 mmol) and 5-methyl-2,3-dihydro-1*H*-indene-1,3-dione (80 mg, 0.5 mmol). Product was isolated using workup method B as a tan solid (146 mg, 96%). ^1H NMR (300 MHz, CDCl_3) δ 9.28 (s, 1H), 7.81 (t, J = 4.31 Hz, 2H), 7.72 – 7.62 (m, 2H), 7.60 – 7.49 (m, 2H), 7.40 – 7.31 (m, 1H), 2.55 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 166.7, 156.2, 146.9, 146.0, 135.1, 128.7, 127.8, 123.8, 123.5, 122.9, 122.4, 120.0, 112.1, 107.4, 34.5, 21.8. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{13}\text{O}_4$, 305.0808; found, 305.0814.

2-(Benzofuran-2-carbonyl)-5-bromo-1H-indene-1,3(2H)-dione (15)—The title compound was prepared according to the general experimental procedure using 2-benzofurancarboxylic acid (243 mg, 1.5 mmol) and 5-bromo-2,3-dihydro-1*H*-indene-1,3-dione (113 mg, 0.5 mmol). Product was isolated using workup method C as a brown solid

(165.2 mg, 90%); ^1H NMR (300 MHz, CDCl_3) δ 9.27 (s, 1H), 7.98 (s, 1H), 7.82 (dd, J = 13.76, 8.17 Hz, 2H), 7.72 (d, J = 8.00 Hz, 1H), 7.64 (d, J = 8.24 Hz, 1H), 7.54 (dd, J = 8.38, 7.09 Hz, 1H), 7.42 – 7.30 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.4, 156.2, 151.7, 146.4, 141.6, 139.0, 138.3, 137.8, 137.1, 130.5, 129.6, 127.6, 127.3, 126.2, 125.7, 124.1, 123.9, 121.5, 121.0, 116.1, 112.3, 107.6, 106.6, 102.9, 77.4, 77.0, 76.6, 73.9, 66.7, 50.2, 29.7, 26.9, 19.8. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{10}\text{BrO}_4$, 368.9757; found, 368.9749. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{10}\text{BrO}_4\text{Na}$, 390.9576; found, 390.9560. HRMS (ESI/Q-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{18}\text{H}_8\text{BrO}_4$, 366.961144; found 366.960341.

2-(Benzofuran-2-carbonyl)-4-nitro-1H-indene-1,3(2H)-dione (16)—The title compound was prepared according to the general experimental procedure using 2-benzofurancarboxylic acid (243 mg, 1.5 mmol) and 4-nitro-2,3-dihydro-1H-indene-1,3-dione (96 mg, 0.5 mmol). Product was isolated using workup method C as a lime-green solid (153 mg, 92%); ^1H NMR (300 MHz, CDCl_3) δ 9.33 (s, 1H), 8.17 – 7.84 (m, 3H), 7.80 (d, J = 8.0 Hz, 1H), 7.69 – 7.61 (m, 1H), 7.60 – 7.50 (m, 1H), 7.36 ppm (t, J = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 196.1, 193.9, 169.1, 156.6, 141.6, 139.4, 136.2, 135.2, 130.3, 128.8, 128.3, 127.7, 126.5, 125.5, 124.6, 124.2, 123.4, 122.8, 121.2, 112.5, 106.1, 29.8. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{10}\text{NO}_6$, 336.0503; found, 336.0516.

2-(2-Phenylacetyl)-1H-indene-1,3(2H)-dione (17).^{24,25}—The title compound was prepared according to the general experimental procedure using phenylacetic acid (204 mg, 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup method C as a reddish-brown solid (102 mg, 78%); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.78 (t, J = 5.93 Hz, 1H), 7.84 (dd, J = 7.43, 1.53 Hz, 1H), 7.60 (d, J = 1.45 Hz, 1H), 7.50 (d, J = 7.45 Hz, 1H), 4.10 (q, J = 7.11 Hz, 2H), 4.02 (d, J = 5.89 Hz, 2H), 1.20 (t, J = 7.11 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 197.3, 188.3, 183.7, 140.8, 138.2, 135.1, 134.8, 134.2, 129.6, 128.8, 127.4, 122.9, 122.5, 108.2, 77.5, 77.0, 76.6, 38.1. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{13}\text{O}_3$, 265.0859; found, 265.0861.

2-(Benzofuran-2-carbonyl)-5-methyl-1H-indene-1,3(2H)-dione (18)—The title compound was prepared according to the general experimental procedure using phenylacetic acid (204 mg, 1.5 mmol) and 5-methyl-2,3-dihydro-1H-indene-1,3-dione (80 mg, 0.5 mmol). Product was isolated using workup method B as a tan solid (113 mg, 81%). ^1H NMR (300 MHz, CDCl_3) δ 7.80 – 7.62 (m, 2H), 7.53 (dd, J = 7.91, 11.42 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.36 – 7.27 (m, 3H), 4.27 (s, 2H), 2.52 (d, J = 4.10 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 196.8, 196.7, 188.1, 188.1, 188.0, 183.1, 146.4, 146.4, 146.3, 145.3, 145.2, 141.5, 138.9, 138.9, 138.8, 136.2, 136.1, 136.0, 135.7, 135.6, 135.0, 134.9, 134.8, 134.7, 130.2, 129.5, 129.4, 128.5, 128.3, 128.0, 127.1, 126.9, 123.3, 123.2, 123.1, 123.0, 122.9, 122.7, 122.5, 122.7, 122.3, 108.7, 78.2, 78.1, 77.7, 77.7, 77.6, 49.0, 38.2, 38.1, 21.9, 21.7. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{15}\text{O}_3$, 279.1016; found, 279.1020.

5-Bromo-2-(2-phenylacetyl)-1H-indene-1,3(2H)-dione (19)—The title compound was prepared according to the general experimental procedure using phenylacetic acid (204 mg, 1.5 mmol) and 5-bromo-2,3-dihydro-1H-indene-1,3-dione (113 mg, 0.5 mmol). Product

was isolated using workup method C as an orange solid (155 mg, 90%); ^1H NMR (300 MHz, CDCl_3) δ 7.98 (d, J = 15.35 Hz, 1H), 7.91 – 7.78 (m, 1H), 7.78 – 7.65 (m, 1H), 7.46 – 7.37 (m, 2H), 7.37 – 7.26 (m, 3H), 4.26 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 186.7, 179.0, 176.5, 175.3, 163.8, 121.2, 120.4, 107.8, 51.7, 46.4. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{12}\text{BrO}_3$, 342.9964; found, 342.9975.

4-Nitro-2-(2-phenylacetyl)-1H-indene-1,3(2H)-dione (20)—The title compound was prepared according to the general experimental procedure using phenylacetic acid (204 mg, 1.5 mmol) and 4-nitro-2,3-dihydro-1*H*-indene-1,3-dione (96 mg, 0.5 mmol). Product was isolated using workup method C as an orange solid (145 mg, 95%); ^1H NMR (300 MHz, CDCl_3) δ 8.14 – 7.82 (m, 3H), 7.48 – 7.26 (m, 5H), 4.28 ppm (d, J = 6.4 Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 194.3, 192.1, 190.5, 185.5, 182.6, 142.4, 140.2, 135.7, 134.9, 131.4, 129.5, 128.5, 128.0, 126.2, 125.5, 108.8, 41.7, 27.8, 23.2, 22.6. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{12}\text{NO}_5$, 310.0710; found, 310.0723.

2-(2-Phenylpropanoyl)-1H-indene-1,3(2H)-dione (21)—The title compound was prepared according to the general experimental procedure using 2-phenylpropanoic acid (225 mg, 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup method B as an orangish-brown solid (103 mg, 68%). ^1H NMR (300 MHz, CDCl_3) δ 7.90 – 7.63 (m, 4H), 7.55 – 7.46 (m, 2H), 7.36 – 7.27 (m, 3H), 5.18 (q, J = 7.14 Hz, 1H), 1.63 (d, J = 7.17 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 197.8, 188.4, 187.9, 140.9, 140.5, 138.2, 135.2, 134.2, 128.8, 128.3, 127.6, 123.0, 122.6, 107.6, 40.8, 17.4. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{15}\text{O}_3$, 279.1016; found, 279.1018.

2-(2,2-Diphenylacetyl)-1H-indene-1,3(2H)-dione (22).²⁶—The title compound was prepared according to the general experimental procedure using diphenylacetic acid (318 mg, 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup method B, followed by column chromatography on a silica gel column using dichloromethane as the eluent to provide a reddish-tan solid (133.1 mg, 78%). ^1H NMR (300 MHz, CDCl_3) δ 7.91 – 7.80 (m, 2H), 7.80 – 7.64 (m, 2H), 7.48 – 7.39 (m, 4H), 7.39 – 7.27 (m, 6H), 6.55 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 197.7, 188.2, 184.8, 140.9, 138.4, 138.2, 135.4, 134.4, 129.4, 128.8, 127.7, 123.1, 122.7, 108.8, 51.9. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{17}\text{O}_3$, 341.1172; found, 341.1184.

2-(2-Phenoxyacetyl)-1H-indene-1,3(2H)-dione (23)—The title compound was prepared according to the general experimental procedure using phenoxyacetic acid (228 mg, 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup method C as a tan solid (124.6 mg, 89%). ^1H NMR (300 MHz, CDCl_3): δ 8.11 – 7.51 (m, 4H), 7.45 – 7.17 (m, 2H), 7.14 – 6.84 (m, 3H), 5.41 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 196.5, 187.9, 180.4, 158.8, 141.1, 139.1, 135.4, 134.5, 129.8, 123.3, 122.9, 122.2, 115.7, 109.0, 65.1. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{13}\text{O}_4$, 281.0797; found, 281.0808.

5-Methyl-2-(2-phenoxyacetyl)-1H-indene-1,3(2H)-dione (24)—The title compound was prepared according to the general experimental procedure using phenoxyacetic acid (228 mg, 1.5 mmol) and 5-methyl-2,3-dihydro-1*H*-indene-1,3-dione (80 mg, 0.5 mmol).

Product was isolated using workup method B as a pink solid (139 mg, 95%). ^1H NMR (300 MHz, CDCl_3) δ 7.78 (d, J = 7.62 Hz, 1H), 7.69 (s, 1H), 7.61 – 7.55 (m, 3H), 6.34 (t, J = 2.98 Hz, 1H), 5.62 – 5.61 (m, 2H), 2.53 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 179.1, 166.1, 158.4, 156.9, 146.3, 146.3, 146.2, 146.1, 140.7, 135.9, 135.8, 135.7, 135.6, 135.4, 135.4, 135.2, 135.2, 135.1, 134.6, 131.0, 129.8, 129.6, 129.4, 129.4, 129.3, 129.2, 125.9, 123.6, 123.1, 123.0, 123.1, 122.7, 121.9, 121.9, 121.8, 121.6, 121.4, 121.1, 116.9, 115.6, 115.4, 115.2, 115.1, 114.9, 108.9, 71.8, 65.8, 65.4, 64.7, 64.5, 64.4, 21.8. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{15}\text{O}_4$, 295.0965; found, 295.0974.

2-(2-(Methylsulfonyl)acetyl)-1H-indene-1,3(2H)-dione (25)—The title compound was prepared according to the general experimental procedure using methylsulfonylacetic acid (207 mg, 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup method C as a yellow solid (113 mg, 85%). ^1H NMR (300 MHz, CDCl_3) δ 8.01 – 7.87 (m, 2H), 7.87 – 7.73 (m, 2H), 4.74 (s, 2H), 3.14 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 196.3, 187.5, 169.2, 141.1, 138.5, 136.1, 135.3, 123.7, 123.3, 111.4, 56.7, 42.9. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{11}\text{O}_5\text{S}$, 267.0322; found, 267.0329.

2-(2-Tosylacetyl)-1H-indene-1,3(2H)-dione (26)—The title compound was prepared according to the general experimental procedure using 4-toluenesulfonylacetic acid (321 mg, 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup method B as a reddish-orange solid (142 mg, 83%). ^1H NMR (300 MHz, CDCl_3) δ 7.92 – 7.84 (m, 3H), 7.84 – 7.72 (m, 3H), 7.32 (dd, J = 8.60, 0.70 Hz, 2H), 4.81 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 196.2, 187.0, 169.5, 145.6, 141.0, 138.4, 136.1, 135.8, 135.0, 130.0, 129.9, 128.7, 128.7, 128.6, 123.4, 123.1, 111.5, 58.2, 21.8, 21.7. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{15}\text{O}_5$, 343.0635; found, 343.0632.

2-(2-(1H-Pyrazol-1-yl)acetyl)-1H-indene-1,3(2H)-dione (30)—The title compound was prepared according to the general experimental procedure using 1-pyrazoleacetic acid (189 mg, 1.5 mmol) and 1,3-indandione (73 mg, 0.5 mmol). Product was isolated using workup method C as a tan solid (116.5 mg, 91%); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.81 (s, 1H), 7.61 – 7.52 (m, 5H), 6.34 (br s, 1H), 5.49 ppm (s, 2H).¹ HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_3$, 255.0764; found, 255.0772.

2-(2-(1H-Pyrazol-1-yl)acetyl)-5-methyl-1H-indene-1,3(2H)-dione (31)—The title compound was prepared according to the general experimental procedure using 1-pyrazoleacetic acid (189 mg, 1.5 mmol) and 5-methyl-2,3-dihydro-1H-indene-1,3-dione (80 mg, 0.5 mmol). Product was isolated using workup method B as a tan solid (59.4 mg, 44%). ^1H NMR (300 MHz, CDCl_3) δ 7.79 – 7.73 (m, 1H), 7.67 (t, J = 3.85 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.33 – 7.28 (m, 2H), 7.03 – 6.89 (m, 3H), 5.39 (s, 2H), 2.52 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 176.2, 146.4, 140.2, 135.5, 130.6, 123.2, 122.8, 109.1, 106.1, 50.7, 21.8. HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_3$, 269.0921; found, 269.0928.

2-(2-(1H-Pyrazol-1-yl)acetyl)-5-bromo-1H-indene-1,3(2H)-dione (32)—The title compound was prepared according to the general experimental procedure using 1-pyrazoleacetic acid (189 mg, 1.5 mmol) and 5-bromo-2,3-dihydro-1H-indene-1,3-dione (113 mg, 0.5 mmol). Product was isolated using workup method C as a purple solid (102.2 mg,

68%); ^1H NMR (300 MHz, DMSO- d_6) δ 7.77 (s, 1H), 7.73 – 7.58 (m, 2H), 7.50 (s, 1H), 7.36 (d, J = 7.7 Hz, 1H), 6.34 (s, 1H), 5.41 ppm (s, 2H).² HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{10}\text{BrN}_2\text{O}_3$, 332.9869; found, 332.9896. Since this compound was not soluble at any practical concentration in a variety of deuterated solvents we were unable to obtain a ^{13}C NMR spectrum of this compound.

2-(2-(1H-Pyrazol-1-yl)acetyl)-4-nitro-1H-indene-1,3(2H)-dione (33)—The title compound was prepared according to the general experimental procedure using 1-pyrazoleacetic acid (189 mg, 1.5 mmol) and 4-nitro-2,3-dihydro-1H-indene-1,3-dione (96 mg, 0.5 mmol). Product was isolated using workup method C as a purple solid (48.8 mg, 32%); ^1H NMR (300 MHz, DMSO- d_6) δ 8.87 (d, J = 7.11 Hz, 1H), 8.01 – 7.35 (m, 6H), 6.66 (s, 1H). HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{10}\text{N}_3\text{O}_5$, 300.0615; found, 300.0615. Since this compound was not soluble at any practical concentration in a variety of deuterated solvents we were unable to obtain a ^{13}C NMR spectrum of this compound.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Valone: $R = \text{CH}_2\text{CH}(\text{CH}_3)_2$
Diphenadione: $R = \text{CH}(\text{Ph})_2$

Figure 1.
First-generation vitamin K antagonists.

Scheme 1.

Various methods for preparing 2-acyl 1,3-indandiones

Table 1

Compilation of acylation results.

Compound II Entry Number	R	R'	Purification Method	% Isolated Yield	Comment
1	H	CH ₂ CH(CH ₃) ₂	A	79	known (refs ^{21,22})
2	5-CH ₃	CH ₂ CH(CH ₃) ₂	B	57	
3	5-Br	CH ₂ CH(CH ₃) ₂	C	93	
4	4-NO ₂	CH ₂ CH(CH ₃) ₂	C	93	
5	H	CH ₂ (cyclohexyl)	A	70 ^a	
6	H	CH ₂ (cyclopentyl)	A	35 ^a	
7	H	CH ₂ CH ₂ CH(CH ₃) ₂	A	75	known (ref ²³)
8	H	CH(CH ₃) ₂	A	92	known (refs ^{11,21})
9	H	C(CH ₃) ₃	-	-	no reaction
10	H	C(CH ₃) ₂ Ph	-	-	no reaction
11	H	CF ₂ Ph	-	-	no reaction
12	H	Ph	-	-	< 20% conversion
13	H	2-benzofuran	C	93	
14	5-CH ₃	2-benzofuran	B	96	
15	5-Br	2-benzofuran	C	90	
16	4-NO ₂	2-benzofuran	C	92	
17	H	CH ₂ Ph	C	78	known (refs ^{24,25})
18	5-CH ₃	CH ₂ Ph	B	81	
19	5-Br	CH ₂ Ph	C	90	
20	4-NO ₂	CH ₂ Ph	C	95	
21	H	CH(CH ₃)Ph	B	68

Compound II Entry Number	R	R'	Purification Method	% Isolated Yield	Comment
22	H	CHPh ₂	B	78 ^a	known (ref ²⁶);
23	H	CH ₂ OPh	C	89	
24	5-CH ₃	CH ₂ OPh	B	95	
25	H	CH ₂ SO ₂ Me	C	85	
26	H	CH ₂ SO ₂ (<i>p</i> -tolyl)	B	83	
27	H	CH ₂ NHPh	-	-	decomposition
28	H	CH ₂ NHBoc	-	-	decomposition
29	H	CH ₂ (N-morpholine)	-	-	<30% conversion
30	H	CH ₂ (1-(<i>lH</i>)-pyrazole)	C	91	
31	5-CH ₃	CH ₂ (1-(<i>lH</i>)-pyrazole)	B	44	
32	5-Br	CH ₂ (1-(<i>lH</i>)-pyrazole)	C	68	
33	4-NO ₂	CH ₂ (1-(<i>lH</i>)-pyrazole)	C	32	

^a After treatment by described method, compound further purified by chromatography