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4-(Dimethylamino)pyridine as a Catalyst for Carbon Acylation. 2. Control of Carbon vs. Oxygen Acylation in Benzofuranones[1]

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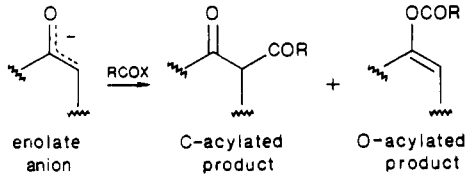
3-Phenylbenzofuranone (1), when deprotonated with sodium hydride and treated with excess chloroformates, generally affords products arising from oxygen acylation (enol carbonates 4). Such molecules, when treated with a catalytic quantity of 4-(dimethylamino)pyridine (DMAP, 6) in halogenated solvents, rearrange to the carbon-acylated isomers 3. These migrations are proposed to involve the intermediacy of an acylated (dimethylamino)pyridinium species (10), which transfers the ester functionality from oxygen to carbon. Inclusion of DMAP in the acylation reaction mixture, however, leads to direct carbon acylation. Thus, complete regiocontrolled acylation of these substrates is attainable.

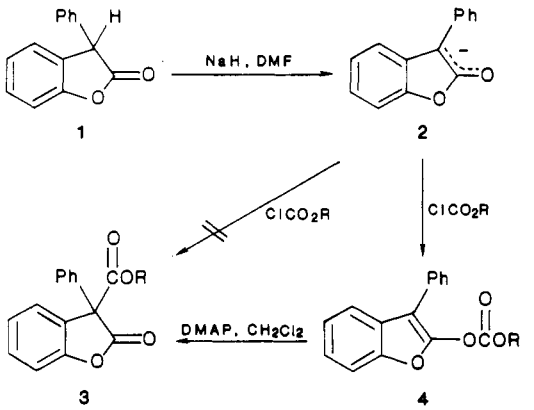
Introduction

A long-standing challenge in organic synthetic chemistry involves the regioselective acylation of enolate anions, and a large amount of work has been devoted to the exploration of conditions designed to effect preferential carbon or oxygen acylation.[2] In general, carbon acylation is favored



by acid chlorides (vs. anhydrides),[3] divalent countercations (vs. alkali metals),[4] diethyl ether as solvent (vs. dimethoxyethane),[5] low temperature,[5] and inverse addition of enolate to acid chloride.[6] However, although these guidelines are useful for many molecules, the regioselectivity of enolate acylation is known to be extremely substrate-dependent, and it is known that with certain substrates, O-acylation competes or even predominates despite the use of conditions conducive to reaction at carbon.[7] In particular, delocalized enolates, such as those derived from malonates and similar compounds, diaryl acetic acid esters, etc., tend toward oxygen acylation as a consequence of the greater electron density on that atom.[8] This kinetic acylation often affords the O-acylated isomer as the sole isolable product, despite utilization of the above-mentioned techniques that typically aid in guiding the incoming electrophile to carbon. On the other hand, even highly carbon-selective acylation reactions are frequently contaminated with the oxygen-functionalized isomer,[9] often posing serious separation problems and always reducing reaction yields.

Scheme I[a]



[a] *a*, R = CH_3; *b*, R = CH_2CH_3; *c*, R = $CH_2CH_2CH_3$; *d*, R = $CH_2CH_2CH_2CH_3$; *e*, R = $CH(CH_3)CH_2CH_3$; *f*, R = $CH_2C_6H_5$; *g*, R = C_6H_5; *h*, R = $CH_2CH{=}CH_2$; *i*, R = $CH{=}CH_2$.

We recently reported a novel oxygen-to-carbon ester migration in the benzofuranone ring system mediated by 4-(dimethylamino)pyridine (DMAP).[10] Enol carbonates derived from oxygen acylation with alkyl chloroformates were found to rearrange quantitatively to the corresponding carbon-acylated isomers upon treatment with a catalytic amount of DMAP; the conversions were accompanied by a transient, very deep blue coloration. Since that time, we have embarked upon a project aimed at probing the mechanism and extending the scope of this potentially very useful reaction. Benzofuranones comprise an important class of natural products[11] with a wide spectrum of biological activity,[12] and so are frequent synthetic targets. Thus, they have been the focus of our attention to

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date, and we herein report the details of this investigation.

Results and Discussion

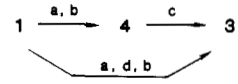
This unique reaction was discovered during a synthetic program aimed at the preparation of various compounds for testing as potential antineoplastic agents. Our specific target compound was the ester lactone **3b**, which we initially envisioned as the product of treating the enolate derived from 3-phenylbenzofuranone (1) with excess ethyl chloroformate. In fact, only the enol carbonate **4b** arising from kinetic oxygen acylation was isolated, although a more polar trace impurity, later identified as the desired carbon-acylated isomer **3b**, was detectable via thin-layer chromatography. Many reaction parameters, as outlined in the Introduction, were manipulated in an attempt to affect this propensity for oxygen acylation. Although in some cases the proportion of carbon-acylated product was raised to approximately 20–30%, we sought to define conditions wherein formation of the desired ester lactone was the predominant reaction pathway. These attempts all met with failure.

We were therefore delighted to discover that exposure of enol carbonate **4b** in dichloromethane solution to a catalytic amount of DMAP resulted in the instantaneous production of an inky blue/purple coloration which spontaneously disappeared within a few minutes; workup revealed that a *quantitative* rearrangement to the desired isomer **3b** had occurred. These observations are summarized in Scheme I.

DMAP is well-established in synthetic chemistry as an extremely useful "hyper-nucleophilic" acylation catalyst, and thus is routinely employed to accelerate the acylation of oxygen, nitrogen, and other nucleophilic atoms.[13] However, its potential utility in carbanion acylation reactions is essentially unexplored.[14]

Our examination of this intriguing transformation indicates the rearrangement to be completely general in the benzofuranone system for ester functionalities introduced via chloroformates. For these molecules, with only one exception, oxygen acylation was the predominant reaction when carried out under all tested conditions; however, each resulting enol carbonate **4** isomerized rapidly to the carbon-acylated isomer **3** when treated with DMAP. In order to maximize the potential synthetic utility of the reaction, however, we also deemed it important to ascertain whether it was in fact necessary to effect such an isomerization as a separate step or if inclusion of DMAP in the acylation reaction mixture would lead directly to carbon acylation via a one-pot procedure. Our ultimate aim was, if the latter scenario were feasible, to develop conditions that would produce exclusive oxygen acylation (e.g., polar aprotic solvent, alkali metal cation), since the resulting enol carbonates are useful synthetic intermediates in their own right,[15] but that would exhibit a complete reversal of regioselectivity upon inclusion of (dimethylamino)pyridine. We were thus extremely gratified to discover that not only can carbon acylation can be effected in a single step by simply incorporating DMAP into a reaction mixture, which alone promotes nearly exclusive oxygen acylation, but the chemical yield is higher than that obtained for the two-step process. The increase in chemical yield for these conversions was not particularly surprising in view of the reputation for enhancing most typical acylation reactions currently enjoyed by DMAP and its derivatives. It was most satisfying, however, to ascertain that DMAP retained its catalytic efficacy even in the highly polar, basic medium necessary to produce enolate anions and that complete regioselectivity was realized. Thus, true carbon vs. oxygen acylation selectivity has been achieved wherein either transformation requires only a single step.

Scheme II[a]



[a] (a) NaH, DMF, 25 °C; (b) $ClCO_2R$; (c) DMAP, CH_2Cl_2, 25 °C; (d) DMAP.

The general reaction sequences that comprised the current study are outlined in Scheme II. In all cases, both the one-step and two-step conversions were examined. The primary goals of this aspect of the investigation were to compare the efficiency of the two sequences in producing carbon-acylated products, to verify that the rearrangement reaction as a separate manipulation was viable for all substrates, and to determine if the blue color characteristic of alkyl ester migrations was a general phenomenon and would thus provide some insight into the mechanistic course of the migratory process.

3-Phenylbenzofuranone (1)[16] was deprotonated with sodium hydride in dimethylformamide (DMF), according to a literature procedure.[17] For the two-step reactions, the green-brown enolate was treated directly with an excess of the appropriate chloroformate. Following aqueous workup, the resulting enol carbonate **4** was purified via distillation and/or recrystallization and fully characterized. Dissolution in dichloromethane followed by treatment with DMAP effected the oxygen-to-carbon ester transfer reaction. The rearrangements were routinely monitored by TLC, the carbon-acylated compound being significantly more polar than the enol carbonate isomer. In some cases, reaction progress was followed by using NMR spectrometry by carrying out the rearrangement in an NMR tube with deuteriochloroform as the solvent and recording the spectrum at short intervals. The methyl derivative **4a** provided the clearest profile, as the time required for reaction completion could be accurately determined by observing the simultaneous disappearance of the enol carbonate methyl group (3.80 ppm) and appearance of the ester methyl group (3.72 ppm). FT-IR spectrophotometry also provided unambiguous differentiation of carbon- vs. oxygen-acylated roducts. The enol carbonates **4** typically exhibited a single characteristic carbonyl stretching band at ca. 1800 cm^{-1},[18] while the corresponding carbon-acylated isomers **3** exhibited two peaks at ca. 1815 (corresponding to the benzofuranone carbonyl) and 1745 (arising from the ester functionality) cm^{-1}.[19] The single-step procedures entailed adding a catalytic amount of DMAP to the above enolate solution prior treatment with the chloroformate. Significantly, for the substrates exhibiting the transitory blue color upon rearrangement during a separate step (which was observed for all but one), a blue color was also visible at this point in spite of the brownish turbidity of

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(16) Prepared via a modification of the procedure outlined in ref 11a.

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Table I.[a] Chemical Yields for Scheme II, Including a Comparison of the Efficiency of the One-Step vs. Two-Step Carbon Acylation Reactions

entry	chloroformate	1 → 4 yield	4 → 3[b]	overall yield: two-step (1 → 4 → 3)	overall yield: one-step (1 → 3)
1 (a)	methyl	77.6	87.5	67.9	72.7
2 (b)	ethyl	89.0	90.0	80.1	88.3
3 (c)	*n*-propyl	87.5	83.0	72.6	76.5
4 (d)	*n*-butyl	74.9	96.0	71.9	76.8
5 (e)	*sec*-butyl	88.2	91.3	80.5	92.2
6 (f)	benzyl	85.2	86.4	73.6	81.3
7 (g)	phenyl	64.0	89.5[c]	29.5	79.4
8 (h)	allyl	94.0	63.5	60.0	74.8
9 (i)	vinyl	*d*	*d*	*d*	55.0

[a] All yields refer to purified material. [b] Accompanied by blue coloration except where noted. [c] Rearrangement was coloreless. [d] Direct carbon acylation was observed.

the reaction mixture. The obvious conclusion is that the same reactive intermediate is functioning here as in the rearrangement portion of our two-step procedure. This point will be addressed in more detail shortly.

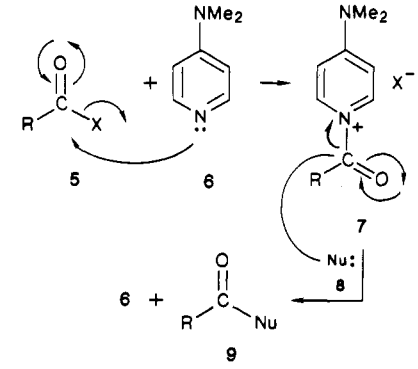
The results of these experiments are summarized in Table I. With one exception, all of the chloroformates tested gave essentially exclusive oxygen acylation when DMAP was not employed. The corresponding C-acylated isomers were detectable via TLC; however, attempts to employ NMR analysis to quantify the isomer ratio failed due to the extremely minute amounts of carbon-acylated material formed. Vinyl chloroformate (entry 9) was anomalous in that nearly exclusive carbon acylation occurred directly without the intervention of DMAP catalysis, although a trace of enol carbonate was visible upon TLC analysis. The identity of the impurity as the O-acylated isomer **4i** was surmised from the observation that treatment of the product mixture in dichloromethane solution with DMAP caused the disappearance of the trace spot on TLC with an accompanying marked increase in resolution of the infrared and NMR spectra.

The rearrangement reactions typically required less than 2 min, and in no case could residual enol carbonate be detected. Interestingly, the appearance of color during these reactions was not a prerequisite for success. The enol carbonate formed by using phenyl chloroformate developed no color at all when treated with DMAP, although the reaction proceeded to completion in a timeframe consistent with our other rearrangements.

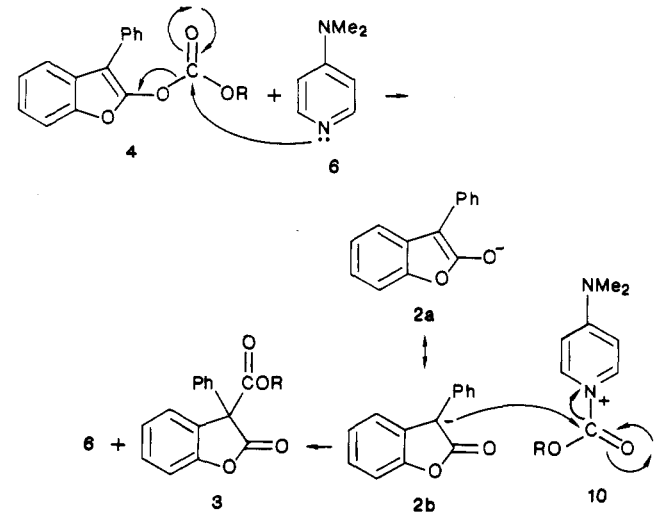
The possible identity of the transient species responsible for the blue color observed in the majority of these rearrangements is intriguing. Acylation reactions employing acid chlorides (**5**, X = Cl) or anhydrides (**5**, X = O_2CR) and catalyzed by DMAP (as well as by pyridine or other derivatives such as the commercially available 4-pyrrolidinopyridine) are known to proceed via acylation of the pyridine ring in **6** to afford a highly reactive pyridinium species (e.g., **7**), as outlined in Scheme III.[13a] This entity then undergoes facile nucleophilic attack (8 = O, S, N, etc.), affording the acylated product **9** and regenerating the catalyst.

We propose that a similar species is operative in our rearrangement reaction; the overall sequence of events is depicted in Scheme IV. Although oxygen acylation (affording enol carbonate **4**) is kinetically favored as a consequence of the greater electron density on and thus greater nucleophilicity of that atom, equilibrating conditions should favor carbon functionalization due to the greater exothermicity associated with the formation of a carbon–carbon bond (the conjugative stability typically associated with β-diesters is obviated by the presence of

Scheme III



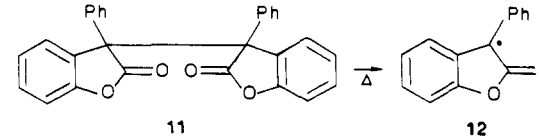
Scheme IV



the 3-phenyl substituent in the current cases). Nucleophilic attack by DMAP (**6**) on the enol carbonate **4** carbonyl group would afford the acylated pyridinium ion **10**, expelling the highly delocalized 3-phenylbenzofuranone enolate anion **2** in the process. Subsequent attack by the enolate carbon atom (cf. structure **2b**) would afford the carbon-functionalized isomer **3**.

The characteristic coloration is rationalized as follows. From our experiments, we know that the enolate **2** derived from 3-phenylbenzofuranone is greenish. Since 1-(ethoxycarbonyl)-4-(dimethylamino)pyridinium chloride (**10**, R = Et) is known to be colorless,[20] the obvious implication is that the deep blue color observed during the rearrangement reaction must be due to an interaction between these two entities, probably through the formation of a charge-transfer (or donor–acceptor) complex. Such complexes between electron-rich and electron-deficient aromatic systems are well-precedented.[21]

Interestingly, the free radical generated via thermolysis of the dimer of **1** (2,2′-dioxo-3,3′-diphenyl-2,2′,3,3′-tetrahydrobibenzo[*b*]furan-3-yl, **11**) is also deep blue.[22] How-



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(21) (a) Banthorpe, D. V. *Chem. Rev.* **1970**, *70*, 295. (b) Bent, H. A. *Ibid.* **1968**, *68*, 587.
(22) Karafiloglou, P.; Catteau, J.-P.; Lablache-Combier, A.; Ofenberg, H. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1545.

Table II. Solvent Dependency of the DMAP-Mediated Rearrangement of Enol Carbonate 4a to 3a

solvent	dielectric constant[a]	reaction time	reaction color	precipitate color
dimethylformamide	37	2.50 min	deep purple	no ppt
dichloromethane	9.1	1.00 min	purple	no ppt
chloroform	4.8	0.50 min	purple	no ppt
diethyl ether	4.3	no reactn	no reactn[b]	purple
hexane	1.9	no reactn	no reactn[b]	purple

[a] Obtained from Riddick, J. A., Bunger, W. B., Eds. in *Organic Solvents*, Vol. II of *Techniques of Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1970. [b] Colorless supernatant.

ever, the intermediacy of any free radical species in the 4 to 3 rearrangement reactions is doubtful in light of the proven involvement of DMAP and the accompanying lack of any literature documentation for its utilization in radical reactions.[23,24] Additionally, no CIDNP effects were encountered in the experiments wherein the rearrangement reactions were monitored via nuclear magnetic resonance.[25]

The intermediacy of a polar donor–acceptor ion pair is also supported by the marked solvent-dependence of the rearrangement. Solutions of methyl enol carbonate **4a** were prepared in several solvents (10% w/v) and treated with a catalytic amount (ca. 10 mol %) of DMAP. Reaction time was measured by disappearance of the blue color, while TLC was employed to verify reaction completion. The results are outlined in Table II and indicate an interesting trend. The halogenated solvents performed most satisfactorily, with chloroform allowing a substantially faster rearrangement than the more polar dichloromethane. Dimethylformamide slowed the reaction considerably, consistent with solvation and thus partial separation of the ion pair (although evidently insufficient to negate the charge-transfer phenomenon). Examination of nonpolar solvents relatively incapable of maintaining ionic species in solution (diethyl ether, hexane) provided the most conclusive evidence. In both cases, addition of DMAP resulted in the precipitation of a purple, highly crystalline material, with the supernatant liquid remaining clear and colorless. Intrigued that this precipitate might consist of the actual ion pair **2**–**10**[26] (Scheme IV), we combined equimolar amounts of enol carbonate **4a** and DMAP in hexane and isolated the precipitated material under anhydrous conditions. Dissolution of the crystals in chloroform afforded a deep blue solution that quickly decolorized and was found to contain solely the carbon-acylated isomer **3a** (in addition to DMAP). This precipitate proved to be extraordinarily air-sensitive; attempts at rigorous analysis are in progress and will be reported elsewhere when complete.

Conclusion

In summary, we have developed a new method for regioselective acylation in the benzofuranone ring system. Whereas conventional acylation techniques afford mainly oxygen-functionalized products, exposure of these materials to a catalytic amount of DMAP in halogenated solvents effects a quantitative rearrangement reaction wherein the ester group is transferred to the adjacent carbon atom. Alternatively, inclusion of DMAP directly in the reaction mixture causes exclusive carbon acylation with an accompanying increase in yield. This technique should be applicable to other extended enolate systems where carbon acylation is desired but complicated by a tendency for reaction at oxygen. We are extending our investigation to incorporate a variety of such substrates.

Experimental Section

All reactions were carried out under an atmosphere of nitrogen, unless otherwise specified. Glassware was routinely oven-dried at 120 °C for a minimum of 4 h and then was assembled under a nitrogen stream. Anhydrous solvents were obtained by distillation, immediately prior to use, from sodium benzophenone ketyl (tetrahydrofuran), barium oxide (diisopropylamine, dimethylformamide), or sodium (toluene). Infrared spectra were obtained on either a Nicolet Model 20 DXB Fourier transform or a Perkin-Elmer Model 700 spectrophotometer; absorption maxima are reported in wavenumbers (cm^{-1}) and, in the case of the latter instrument, were standardized by reference to the 1601-cm^{-1} peak of polystyrene. Proton nuclear magnetic resonance spectra were recorded on a Varian T-60 instrument. All samples were measured as solutions in deuteriochloroform ($CDCl_3$) or dimethyl-d_6 sulfoxide (DMSO). Chemical shifts are reported downfield from tetramethylsilane (TMS) in parts per million of the applied field. Peak multiplicities are abbreviated as follows: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m; envelope, e. Coupling constants (J) are reported in hertz (Hz). Thin-layer chromatographic anayses were carried out on Analtech silica gel G (250 μm) plates by using the specified solvent as eluent; visualization was effected by either ultraviolet light or by charring with phosphomolybdic acid. Preparative column chromatography employed Merck silica gel 60 (230–400-mesh ASTM). Combustion microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

General Procedure for O-Acylation of 3-Phenylbenzofuranone. To a 50-mL, three-necked flask, fitted with a magnetic stirring bar, rubber septum, thermometer, and nitrogen inlet, was charged 0.8 g (27 mmol) of sodium hydride (80% dispersion in oil) that was washed with three 5-mL portions of hexane. A 13-mL portion of dimethylformamide (DMF) was added with stirring and cooling in an ice bath. To the stirring suspension was added 4.2 g (20 mmol) of 3-phenylbenzofuranone in small portions at 20–30 °C as foaming allowed. The slurry was stirred for 90 min, becoming turbid and green, and a chloroformate (22 mmol) was added over a period of several minutes. The heterogeneous mixture was stirred overnight at room temperature and poured into 200 mL of water, and the mixture was thoroughly extracted with ether. The consolidated extracted were washed with 100 mL of water and brine, dried over anhydrous magnesium sulfate, and filtered, and the filtrate was concentrated in vacuo. The products were distilled to remove nonvolatile impurities but were not rigorously purified prior to rearrangement.

Carbonic acid, methyl 3-phenylbenzofur-2-yl ester (4a) was prepared from methyl chloroformate and was isolated in 77.6% yield following bulb-to-bulb distillation (145–150 °C/0.05 mm) as a viscous, clear, colorless oil: IR (neat) 2970, 1795, 1755, 1642, 1481, 1204, 1199 cm^{-1}; NMR ($CDCl_3$) δ 8.00–7.20 (m, 9 H, Ar H), 3.80 (s, 3 H, CH_3); TLC (silica gel; CH_2Cl_2) R_f 0.66.

Carbonic acid, ethyl 3-phenylbenzofur-2-yl ester (4b) was prepared from ethyl chloroformate and was isolated in 89.0% yield following bulb-to-bulb distillation (115–123 °C/0.02 mm) as a viscous, clear, colorless oil: IR (neat) 2972, 1794, 1618, 1455, 1380, 1301 cm^{-1}; NMR ($CDCl_3$) δ 7.78–7.12 (m, 9 H, Ar H), 4.25 (q, 2 H, -OCH_2-), 1.28 (t, 3 H, CH_3); TLC (silica gel; CH_2Cl_2) R_f 0.76.

Carbonic acid, *n*-propyl 3-phenylbenzofur-2-yl ester (4c) was prepared from *n*-propyl chloroformate and was isolated in 87.5% yield following bulb-to-bulb distillation (120–128 °C/0.02 mm) as a viscous, clear, light yellow oil: IR (neat) 2970, 1800, 1650, 1475, 1220, 1200 cm^{-1}; NMR ($CDCl_3$) δ 8.05–7.19 (m, 9 H, Ar H), 4.18 (t, 2 H, -OCH_2-), 1.15 (m, 2 H, -CH_2-), 0.83 (t, 3 H, CH_3); TLC (silica gel; CH_2Cl_2) R_f 0.66.

(23) Ward, H. R. In *Free Radicals*; Kochi, J. K., Ed.; John Wiley and Sons: New York, 1973; Vol. I, p 241.

(24) A referee has suggested that the blue color could be due to an equilibrium mixture of the pyridinium cation/enolate anion salt and a radical pair formed by the complete transfer of an electron from the anion to the cation. This possibility will be considered as our investigation into the phenomenon continues.

(25) The absence of a CIDNP effect does not conclusively rule out free-radical involvement, but such cases are very unusual. See: Glarum, S. H. In *Chemically Induced Magnetic Polarization*; Lepley, A. R., Closs, G. L., Eds.; John Wiley and Sons: New York, 1973.

(26) Such molecular complexes have been isolated previously. See: Prout, C. K.; Wright, J. D. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 659.

Carbonic acid, *n*-butyl 3-phenylbenzofur-2-yl ester (4d) was prepared from *n*-butyl chloroformate and was isolated in 74.9% yield following bulb-to-bulb distillation (132–141 °C/0.03 mm) as a viscous, clear, colorless oil: IR (neat) 2970, 1800, 1660, 1518, 1498, 1380 cm^{-1}; NMR ($CDCl_3$) δ 8.00–7.20 (m, 9 H, Ar H), 3.92 (t, 2 H, $-OCH_2-$), 2.00–1.40 (m, 4 H, $-CH_2CH_2-$), 1.03 (t, 3 H, CH_3); TLC (silica gel; CH_2Cl_2) R_f 0.68.

Carbonic acid, *sec*-butyl 3-phenylbenzofur-2-yl ester (4e) was prepared from *sec*-butyl chloroformate and was isolated in 88.2% yield following bulb-to-bulb distillation (130–140 °C/0.03 mm) as a viscous, clear, colorless oil: IR (neat) 2968, 1805, 1663, 1515, 1500, 1373 cm^{-1}; NMR ($CDCl_3$) δ 8.00–7.20 (m, 9 H, Ar H), 3.99 (d, 2 H, $-OCH_2-$), 2.24–1.65 (m, 1 H, $CHMe_2$), 1.11 (d, 6 H, CH_3); TLC (silica gel; CH_2Cl_2) R_f 0.74.

Carbonic acid, benzyl 3-phenylbenzofur-2-yl ester (4f) was prepared from benzyl chloroformate and was isolated in 85.2% yield following bulb-to-bulb distillation (190–196 °C/0.08 mm) as a viscous, clear, colorless oil: IR (neat) 2972, 1805, 1379 cm^{-1}; NMR ($CDCl_3$) δ 8.00–7.20 (m, 14 H, Ar H), 4.95 (s, 2 H, $-CH_2-$); TLC (silica gel; CH_2Cl_2) R_f 0.80.

Carbonic acid, phenyl 3-phenylbenzofur-2-yl ester (4g) was prepared from phenyl chloroformate and was isolated in 64.0% yield following bulb-to-bulb distillation (115 °C/0.35 mm) as a light orange oil: IR (neat) 1771, 1258, 1241, 1229, 1180, 1161 cm^{-1}; NMR ($CDCl_3$) 7.00–7.50 (m, 14 H, Ar H); TLC (silica gel, CH_2Cl_2) R_f 0.75.

Carbonic acid, allyl 3-phenylbenzofur-2-yl ester (4h) was prepared from allyl chloroformate and was isolated in 94.1% yield following bulb-to-bulb distillation (125–130 °C/0.02 mm) as a viscous, clear, colorless oil: IR (neat) 3100, 1800, 1640, 1620, 1460, 1220, 1190, 1060 cm^{-1}; NMR ($CDCl_3$) δ 8.09–7.18 (m, 9 H, Ar H), 5.81 (m, 1 H, —CH=), 5.28 (m, 2 H, $=CH_2$), 4.61 (br d, 2 H, $-OCH_2$); TLC (silica gel; CH_2Cl_2) R_f 0.68.

Attempted Preparation of Carbonic Acid, Vinyl 3-Phenylbenzofur-2-yl Ester (4i). Utilization of the above procedure employing vinyl chloroformate afforded nearly exclusive carbon acylation to produce **2,3-dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, vinyl ester (3i)** in 55% yield following bulb-to-bulb distillation (147–150 °C/0.05 mm) as a yellow solid: mp 63–64 °C; IR (KBr) 1818, 1745, 1646, 1615 cm^{-1}; NMR ($CDCl_3$) δ 7.60–7.10 (m, 9 H, Ar H), 5.20–4.60 (m, 3 H, vinyl H); TLC (silica gel; CH_2Cl_2) R_f 0.69 Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.31. Found: C, 72.86; H, 4.47.

General Procedure for the Rearrangement of Enol Carbonates to C-Acylated Isomers via DMAP Catalysis. To a 125-mL separatory funnel was charged 1 g of enol carbonate along with 20 mL of dichloromethane; solution was effected by swirling. To this solution was added about 40 mg of DMAP, and the mixture was briefly shaken. In all cases except the phenyl derivative (**4g**), a deep blue/purple color developed immediately which then, after about 1 min, disappeared over the course of about 15 s. The reaction solution was washes successively with three 20-mL portions of 5% hydrochloric acid and then with 100 mL of water. The organic layer was finally dried over anhydrous magnesium sulfate and concentrated in vacuo to afford the crude product. Purification was effected as noted.

2,3-Dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, methyl ester (3a) was prepared from **4a** as outlined above and was isolated in 87.5% yield following bulb-to-bulb distillation (140–147 °C/0.05 mm) as a clear, colorless oil which solidified after standing for several days to a white, crystalline solid: mp 68–70 °C; IR (KBr) 1813, 1744, 1477, 1463, 1230, 1129, 1062 cm^{-1}; NMR ($CDCl_3$) δ 7.60–7.00 (m, 9 H, Ar H), 3.72 (s, 3 H, CH_3); TLC (silica gel; CH_2Cl_2) R_f 0.79. Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.58; H, 4.47. Found: C, 71.92; H, 4.64.

2,3-Dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester (3b) was prepared from **4b** as outlined above and was isolated in 90.0% yield following bulb-to-bulb distillation (99–101 °C/0.01 mm) as a clear, colorless oil which solidified after standing for several days to a white, crystalline solid: mp 69–71.5 °C; IR (KBr) 1815, 1739, 1617, 1482, 1227, 1177, 1121 cm^{-1}; NMR ($CDCl_3$) δ 7.80–7.20 (m, 9 H, Ar H), 4.43 (q, 2 H, $-OCH_2-$), 1.25 (t, 3 H, CH_3); TLC (silica gel; CH_2Cl_2) R_f 0.63. Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 4.99. Found: C, 72.26; H, 5.06.

2,3-Dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, *n*-propyl ester (3c) was prepared from **4c** as outlined above and was isolated in 83.0% yield following bulb-to-bulb distillation (92–94 °C/0.05 mm) as a clear, colorless oil which solidified after standing for several days to a white, crystalline solid: mp 114–117 °C; IR (KBr) 1816, 1735, 1615, 1597, 1477, 1461 cm^{-1}; NMR ($CDCl_3$) δ 7.63–7.11 (m, 9 H, Ar H), 4.35 (t, 2 H, OCH_2), 1.67 (m, 2 H, CH_2), 1.00 (t, 3 H, CH_3); TLC (silica gel; CH_2Cl_2) R_f 0.77. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.29; H, 5.75.

2,3-Dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, *n*-butyl ester (3d) was prepared from **4d** as outlined above and was isolated in 96.0% yield following bulb-to-bulb distillation (134–136 °C/0.04 mm) as a clear, colorless oil which solidified after standing for several days to a pale yellow, waxy solid: IR (neat) 1817, 1745, 1483, 1233, 1129, 1064 cm^{-1}; NMR ($CDCl_3$) δ 7.60–7.00 (m, 9 H, Ar H), 4.15 (t, 2 H, OCH_3), 1.32 (m, 4 H, CH_2CH_2), 0.83 (t, 3 H, CH_3); TLC (silica gel; CH_2Cl_2) F_r 0.79. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.82; H, 5.70.

2,3-Dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, *sec*-butyl ester (3e) was prepared from **4e** as outlined above and was isolated in 91.3% yield following bulb-to-bulb distillation (129–135 °C/0.40 mm) as a clear, colorless oil: IR (neat) 1811, 1798, 1744, 1390, 1220, 1066 cm^{-1}; NMR ($CDCl_3$) 8.02–7.21 (m, 9 H, Ar H), 4.12 (d, 2 H, OCH_2), 2.21–1.71 (m, 1 H, $CHMe_2$), 1.05 (d, 6 H, CH_3); TLC (silica gel; CH_2Cl_2) R_f 0.59. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.45; H, 5.75.

2,3-Dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, benzyl ester (3f) was prepared from **4f** as outlined above and was isolated in 86.4% yield following bulb-to-bulb distillation (173–176 °C/0.05 mm) as a clear, colorless oil which solidified after standing for several days to a white, crystalline solid: mp 88–90 °C; IR (KBr) 1816, 1747, 1463, 1383, 1233, 1065 cm^{-1}; NMR ($CDCl_3$) δ 7.52–7.31 (m, 14 H, Ar H) 5.32 (s, 2 H, CH_2); TLC (silica gel; CH_2Cl_2) R_f 0.71. Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68. Found: C, 76.81; H, 4.96.

2,3-Dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, phenyl ester (3g) was prepared from **4g** as outlined above and was isolated in 89.5% yield following bulb-to-bulb distillation (157–160 °C/0.05 mm) as a clear, colorless oil: IR (neat) 1817, 1763, 1493, 1463, 1384, 1232, 1065 cm^{-1}; NMR ($CDCl_3$) δ 7.60–6.82 (m, 14 H, Ar H); TLC (silica gel; CH_2Cl_2) R_f 0.76. Anal. Calcd for $C_{21}H_{14}O_4$: C, 76.35; H, 4.27. Found: C, 76.23; H, 4.36.

2,3-Dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, allyl ester (3h) was prepared from **4h** as outlined above and was isolated in 63.5% yield following bulb-to-bulb distillation (156–160 °C/0.06 mm) as a pale yellow oil which solidified after standing for several days to a white, crystalline solid: mp 69–71 °C; IR (KBr) 1800, 1780, 1450, 1300 cm^{-1}; NMR ($CDCl_3$) δ 7.95–7.11 (m, 9 H, Ar H), 5.64 (m, 1 H, —CH=), 5.08 (m, 2 H, $=CH_2$), 4.56 (br d, 2 H, $-OCH_2$); TLC (silica gel; CH_2Cl_2) R_f 0.66. Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 5.22. Found: C, 73.81; H, 4.91.

General Procedure for C-Acylation of 3-Phenylbenzofuranone. To a 50-mL, three-necked flask, fitted with a magnetic stirring bar, rubber septum, thermometer, and nitrogen inlet was charged 0.8 g (27 mmol) of sodium hydride (80% dispersion in oil) which was washed with three 5-mL portions of hexane. A 13-mL portion of dimethylformamide (DMF) was added with stirring and cooling in an ice bath. To the stirring suspension was added 4.2 g (20 mmol) of 3-phenylbenzofuranone in small portions at 20–30 °C as foaming allowed. The slurry was stirred for 90 min, becoming turbid and green, whereupon ca. 40 mg of DMAP was added. After 5 min, chloroformate (22 mmol) was added over a period of several minutes. The heterogeneous mixture was stirred overnight at room temperature and poured into 200 mL of water, and the mixture was thoroughly extracted with ether. The consolidated extracts were washed with 100 mL of water, 100 mL of 5% hydrochloric acid, and brine, dried over anhydrous magnesium sulfate, and filtered, and the filtrate was concentrated in vacuo.

Compounds **3a** through **3h** were prepared in the above manner, with physical constants, spectral parameters, and chromatographic data identical with those observed for material produced via the two-step (1 to 4 to 3) procedure. The yields are collected in Table I.

Solvent-Dependency Studies. To a dry 10-mL test tube was added 100 mg (0.37 mmol) of carbonic acid, methyl 3-phenylbenzofur-2-yl ester (**4a**) along with 1.0 mL of the appropriate

solvent; dissolution was effected by swirling. A 10-mg portion of DMAP was added and the test tube was shaken. The time necessary for complete dissipation of color was recorded and the appearance of any precipitate noted.

Isolation of the 2-10 Ion Pair. To a 50-mL, three-necked flask, fitted with a magnetic stirring bar, rubber septum, and nitrogen inlet, was charged 400 mg (1.50 mmol) of carbonic acid, methyl 3-phenylbenzofur-2-yl ester (**4a**) and 30 mL of hexane. To the stirring solution was added 183 mg (1.50 mmol) of 4-(dimethylamino)pyridine, resulting in the immediate precipitation of a purple, highly crystalline solid (the hexane supernatant remained clear and colorless). The hexane was removed via syringe while maintaining a nitrogen atmosphere, leaving 550 mg (94%) of the purple product. Exposure of this material to air resulted in immediate decolorization, deliquescence, and consequential decomposition to an unidentifiable product mixture.

The above experiment was repeated, except that after aspiration of the hexane, 30 mL of chloroform was added via syringe with stirring. A deep blue color formed immediately which dissipated after ca. 30 s. TLC analysis indicated the presence of DMAP and the C-acylated isomer **3a**. The clear, pale yellow solution was worked up as in the general procedure for rearrangement reactions (see above) to afford 364 mg (94%) of 2,3-dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, methyl ester (**3a**), exhibiting identical physical and spectral characteristics as material prepared in earlier experiments.

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Registry No. 1, 3117-37-1; **3a**, 108139-61-3; **3b**, 108139-62-4; **3c**, 108139-63-5; **3d**, 108139-64-6; **3e**, 110745-15-8; **3f**, 110745-16-9; **3g**, 110745-17-0; **3h**, 110745-18-1; **3i**, 110745-19-2; **4a**, 108139-58-8; **4b**, 108139-57-7; **4c**, 108139-59-9; **4d**, 108139-60-2; **4e**, 110745-20-5; **4f**, 110745-21-6; **4g**, 110745-22-7; **4h**, 110745-23-8; DMAP, 1122-58-3; ethyl chloroformate, 541-41-3; propyl chloroformate, 109-61-5; butyl chloroformate, 592-34-7; *sec*-butyl chloroformate, 17462-58-7; benzyl chloroformate, 501-53-1; allyl chloroformate, 2937-50-0; vinyl chloroformate, 5130-24-5; methyl chloroformate, 79-22-1; phenyl chloroformate, 1885-14-9.

Stereoselective Synthesis of Vinylcyclopropanes via Palladium-Catalyzed Reactions

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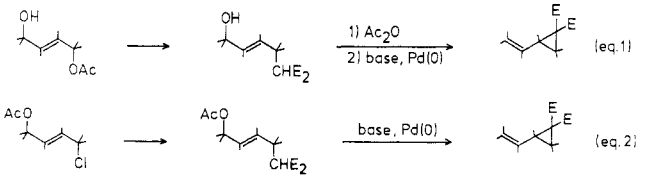
Vinylcyclopropanes were synthesized in a stereocontrolled manner from 1-acetoxy-4-chloro-2-alkenes. A stereospecific palladium-catalyzed substitution of the chloro group by dimethyl malonate anion and subsequent palladium-catalyzed cyclization afforded the vinylcyclopropanes in about 70% overall yield. In the cyclization $Pd(dppe)_2$, $Pd(dba)_2$/dppe, or $Pd(OAc)_2$/dppe was used as catalyst. The best result was obtained with $Pd(OAc)_2$/dppe. It was found that the cyclization to vinylcyclopropane is reversible and under prolonged reaction time dienylmalonates are formed.

Vinylcyclopropanes are a class of compounds that has attracted considerable interest among organic chemists. There are many naturally occuring vinylic cyclopropanes, e.g., carenes, sesquicarenes, sirenine, dictyopterenes, pyrethroids, etc.[2] In addition, vinylcyclopropanes are important synthetic intermediates.[3] As a consequence a number of methods for their preparation have been developed.[2c,d,4]

One of us has recently developed a method for the preparation vinylcyclopropanes from 2-alkene-1,4-diol monoacetates utilizing palladium catalysis (eq 1).[4] We would now like to extend this methodolgy by utilizing 1-acetoxy-4-chloro-2-alkenes[5] as starting materials (eq 2).



This allows control of the relative stereochemistry between the cyclopropane ring and the double bond. In addition, bicyclic vinylcyclopropanes are available by this approach.

In the original approach (eq 1)[4] the starting material was obtained either from hydrogenation of a 2-alkyne-1,4-diol or from condensation of an 1-alkyn-3-ol derivative with an aldehyde (or ketone) and subsequent hydrogenation. Thus, when both carbons bearing the oxygen atoms are chiral, a mixture of two diastereomers is formed. By the use of chloro acetates as starting materials (eq 2) this problem can be overcome. These chloro acetates are prepared from the appropriate conjugated diene in a ste-

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