Sequential Acetalization–Pyrolysis of α-Acetylcinnamates and α-Acetylbenzalacetones. A Method for the Generation of 2-Carbonyl-Substituted Naphthalenes[1]

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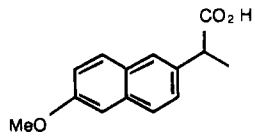
Substituted 2-acetonaphthones and 2-naphthoate methyl esters can be generated from benzaldehydes in a sequence of three reaction steps. Knoevenagel condensation of a benzaldehyde with 2,4-pentanedione or methyl acetoacetate yields α-carbonyl-substituted benzalacetones. The α-carbonyl-substituted benzalacetones are then cyclized to generate the α-carbonyl-substituted naphthalenes by a sequential acetalization with trimethyl orthoformate followed by subsequent pyrolysis of the dimethyl acetal either in the vapor phase at 475 °C or by being heated in boiling 1-methylnaphthalene. 2-Acetonaphthones are obtained when 2,4-pentanedione is used and 2-naphthoate methyl esters are obtained from methyl acetoacetate.

Introduction

Naphthalenes containing carbonyl substituents in the 2-position, and particularly those having an additional substituent in the 6-position, have been found to be extremely useful in the pharmaceutical[1] and polymer industry.[2,3] For example, 6-hydroxy-2-naphthoic acid and 2,6-naphthalenedicarboxylic acid represent important components of several commercial liquid crystal polymers and 6-methoxy-2-acetonaphthone has been used to generate the commercially important drug naproxen (1).



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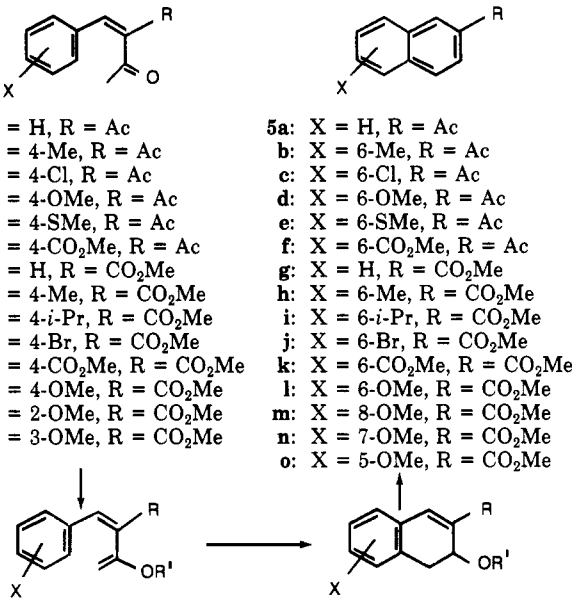
Scheme I. Anticipated Pathway for the Generation of 2-Carbonyl-Substituted Naphthalenes from α-Carbonyl-Substituted Benzalacetones



2a: X = H, R = Ac
b: X = 4-Me, R = Ac
c: X = 4-Cl, R = Ac
d: X = 4-OMe, R = Ac
e: X = 4-SMe, R = Ac
f: X = 4-CO_2Me, R = Ac
g: X = H, R = CO_2Me
h: X = 4-Me, R = CO_2Me
i: X = 4-*i*-Pr, R = CO_2Me
j: X = 4-Br, R = CO_2Me
k: X = 4-CO_2Me, R = CO_2Me
l: X = 4-OMe, R = CO_2Me
m: X = 2-OMe, R = CO_2Me
n: X = 3-OMe, R = CO_2Me

5a: X = H, R = Ac
b: X = 6-Me, R = Ac
c: X = 6-Cl, R = Ac
d: X = 6-OMe, R = Ac
e: X = 6-SMe, R = Ac
f: X = 6-CO_2Me, R = Ac
g: X = H, R = CO_2Me
h: X = 6-Me, R = CO_2Me
i: X = 6-*i*-Pr, R = CO_2Me
j: X = 6-Br, R = CO_2Me
k: X = 6-CO_2Me, R = CO_2Me
l: X = 6-OMe, R = CO_2Me
m: X = 8-OMe, R = CO_2Me
n: X = 7-OMe, R = CO_2Me
o: X = 5-OMe, R = CO_2Me

3: R′ = H
3′: R′ = Me

4: R′ = H
4′: R′ = Me

Presently, the most common method of generating the 2-acetonaphthones has been via a Friedel–Crafts acylation using either aluminum chloride in nitrobenzene[2,3,5a] or, in more recent reports, boron trifluoride in liquid HF.[5] These processes suffer from numerous drawbacks in actual practice, including sometimes unpredictable regioselectivity, the extremely corrosive nature of the systems, the requirement of extremely hazardous solvent systems, and the large amount of Lewis acid required. (These Friedel–Crafts acylations require at least 2 mol of Lewis acid to generate 1 mol of product, posing an enormous disposal problem.) Further limiting the application of this process is the limited availability of the requisite, pure 2-substituted naphthalenes on an industrial scale.

The corresponding 2-naphthoates are often derived by subsequent oxidation of the 2-acetonaphthones or related Friedel–Crafts acylation products.[3] Few additional general

(1) Portions of this paper have appeared in the form of patents and as a preliminary communication. See: (a) Zoeller, J. R.; Sumner, C. E. U.S. Pat. 4,761,496, 1988. (b) Zoeller, J. R.; Sumner, C. E. U.S. Pat. 4,761,497, 1988. (c) Sumner, C. E.; Zoeller, J. R. U.S. Pat. 4,786,748, 1988. (d) Zoeller, J. R. U.S. Pat. 4,788,341, 1988. (e) Zoeller, J. R. *Tetrahedron Lett.* **1989**, *30*, 1457.

(2) (a) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203. (b) Crenshaw, R. R.; Luke, G. M.; Baily, G. *J. Med. Chem.* **1972**, *15*, 1179. (c) Gaudie, A. C.; Gaster, L. M.; Lake, A. W.; Rose, C. J.; Freeman, P. C.; Hughes, B. O.; Miller, D. *J. Med. Chem.* **1978**, *21*, 1260. (d) Fouqney, C.; Jacques, J.; Azadian-Boulanger, G. *Eur. J. Med. Chem., Chem.-Chim. Ther.* **1978**, *13*, 303. (e) Kametani, T.; Kigasawa, K.; Hiirigi, M.; Ishimaru, H.; Haga, S.; Shirayama, K. *Yakugaku Zasshi* **1978**, *98*, 146. (f) Fisnerova, L.; Grimova, J.; Nemecek, O. *Cesk. Farm.* **1981**, *30*, 300. (g) Walker, K. A. M.; Wallach, M. B.; Hirschfield, D. R. *J. Med. Chem.* **1981**, *24*, 67. (h) Eriguchi, A.; Takegoshi, T. *Chem. Pharm. Bull.* **1982**, *30*, 428. (i) Cavrini, V.; Roveri, P.; Gatti, R.; Feruzzi, C.; Panico, A. M.; Pappalardo, M. S. *Farmaco, Ed. Sci.* **1982**, *37*, 171. (j) Middleton, W. J.; Bingham, E. M. *J. Flour. Chem.* **1983**, *22*, 561. (k) Saint-Marie Descours, D. A.; Pacheo, H.; Venco, D.; Yavordis, D. *Eur. J. Med. Chem., Chem.-Chim. Ther.* **1984**, *19*, 5. (l) Lukes, G. E.; Williamson, T. B. U.S. Pat. 3,184,379, 1965. (m) Nelson, P. H. U.S. Pat. 3,651,148, 19–72. (m) Galanty, E. E. Germ. Offen. 2,258,349, 1973. (n) Moreau, M.; Risse, C. Germ. Offen. 2,329,298, 1973. (o) Anderson, P. L.; Brittain, D. A. U.S. Pat. 3,973,257, 1973. (p) Galanty, E. E. U.S. Pat. 3,969,415, 1976. (q) Anderson, P. L.; Brittain, D. A. U.S. Pat. 4,035,406, 1977. (r) Goudie, A. C. Brit. Pat. 1,581,598, 1980). (s) Kohda, A.; Kurosaki, U.S. Pat. 4,277,474, 1981. (t) Nenci, P.; Anania, M. C.; Malorana, S.; Alemega, A.; Licandro, E.; Mainola, L. Eur. Pat. Appl. 176,049, 1986.

(3) For uses of 2-acetonaphthones in generating polymer intermediates, see: (a) Feld, M., Germ. Offen. 3,529,381, 1987. (b) Maki, T., Asahi, Y. Japan Kokai 62 61,947, 1987; *Chem. Abstr.* **1987**, *107*, 115377y. (c) Maki, T.; Asahi, Y. Japan Kokai 62 61,946, 1987; *Chem. Abstr.* **1987**, *107*, 115378z. (d) Naito, S.; Suzuki, Y.; Koga, H.; Onda, Y. Japan Kokai 61 286,342, 1986; *Chem. Abstr.* **1987**, *107*, 39449f.

(4) There are innumerable applications of the use of 2,6-naphthalenedicarboxylic acid and 2-hydroxy-6-naphthanoic acids and their esters in the generation of polyesters, particularly as liquid crystal polymers, to be found in the patent literature. Exemplary of their applications are the following: (a) Jackson, W. J., Jr. *Macromolecules* **1983**, *16*, 1027 and references cited therein. (b) Calundann, G. W.; Jaffe, M. *Proc. Robert A. Welch Found., Conf. Chem. Res., XXVI. Synth. Polym., Houston, TX* **1982**, 247 and references cited therein.

(5) (a) Davenport, K. G.; Linstead, H. C., III. U.S. Pat. 4,593,125, 1986. This reference offers an excellent and concise review of the entire technology as well as presenting a version using HF–BF_3. (b) Hyatt, J. A.; Raynolds, P. W. *J. Org. Chem.* **1984**, *49*, 384. (c) Steinbach, R.; Ruppert, I.; Schlich, K. Germ. Offen. 3,519,009, 1986; (d) Germ. Offen. 3,518,668, 1986. (e) Fujiyama, S.; Matsumoto, S.; Yanagawa, T. Eur. Pat. Appl. 215,351, 1987.

0022-3263/90/1955-0319$02.50/0

methods exist for generating either the 2-acetonaphthones or the 2-naphthoates.[6]

We have been seeking new methods of generating the useful 2-carbonyl-substituted naphthalenes that avoid the use of strongly acidic and corrosive Friedel–Crafts systems and might expand the range of readily available 2-acetonaphthones and 2-naphthoates. Recently, we reported the thermal ring closure of a series of methyl α-vinylcinnamates to generate methyl 3,4-dihydro-2-naphthoates.[7a,b] (This represented a significant extension of the earlier work with very simple 1-aryl-1,3-butadienes.[7c-f]) Encouraged by our results with these systems, we chose to examine the ring closure of the analogous α-acetylcinnamates **2g–n** and the related α-acetylbenzalacetones **2a–f** in the hope of utilizing the enolic form of these compounds to accomplish a similar transformation. Attainment of this objective would represent an unprecedented method for the intramolecular arylation of benzalacetone derivatives and a unique entry into the naphthalene ring system. We have depicted our anticipated sequence of events in Scheme I.

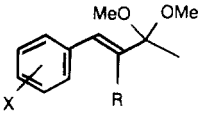
Although the direct pyrolytic ring closure of the α-acetylcinnamates and α-acetylbenzalacetones proved to be synthetically untenable, we have found that the desired reaction can be accomplished effectively using a modification of the anticipated route, which entails using the enol ether of benzalacetones **2a–n** (structure **3′**) instead. In this report we would like to communicate the details of our investigation into these successful ring closures of the α-acetylbenzalacetones and -cinnamates.

Results and Discussion

The starting α-acetylbenzalacetones **2a–f** and α-acetylcinnamates **2g–n** were readily accessible by using the very well established Knoevenagel condensation[8,9] of benzaldehydes with either 2,4-pentanedione or methyl acetoacetate, respectively. When we attempted to pyrolyze the α-acetylbenzalacetone **2a** at temperatures of up to 525 °C using a simple drip-type pyrolysis unit, GC analyses revealed that the vast majority of the starting material was recovered intact. Of the small quantities of product obtained, there was, in addition to a host of minor components, six major components. The desired 2-acetonaphthone **5a** constituted <17% of these six major components. When the same examination was performed with α-acetylcinnamate **2h**, none of the desired 2-naphthoate **5h** was obtained within our detection limits.

We rationalized that the reason we failed to observe efficient conversion of the α-acetylbenzalacetones and α-acetylcinnamates to the desired naphthalenes was that these substances spent insufficient time in the desired enol form **3**. We believed that if we could fix the acetyl group in the α-acetylcinnamates and -benzalacetones in the enol form, this approach might still prove to be successful. We chose to examine the enol ethers that are generated in situ from the pyrolysis of the corresponding acetals[10,11] as a means of achieving this objective.

Although the interesting and crucial step in our synthesis of the 2-carbonyl-substituted naphthalenes is the pyrolysis of the acetals, the acetalization of the α-acetylbenzalacetones and α-acetylcinnamates proved to require somewhat different conditions and resulted in some observations worthy of detailed discussion. With α-acetylbenzalacetones **2a–f**, the acetalization occurred under somewhat ordinary conditions (room temperature, 1:1 $HC(OMe)_3$/MeOH, Amberlyst-15).[11b] However, only the ketone trans to the aryl ring proved to be reactive and we have assigned these compounds structures **6a–f**.



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e: X = 4-SMe, R = Ac
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j: X = 4-Br, R = CO_2Me
k: X = 4-CO_2Me, R = CO_2Me
l: X = 4-OMe, R = CO_2Me
m: X = 2-OMe, R = CO_2Me
n: X = 3-OMe, R = CO_2Me

The stereochemistry of the structural assignment of these acetals, which generally contain varying amounts of the enol ethers as an impurity, is strongly supported by the spectroscopic data. The infrared spectrum of the starting α-acetylbenzalacetones display two infrared bands at 1645–1655 cm^{-1} (assigned as the ketone trans to the aryl ring) and at 1695–1710 cm^{-1} (assigned to the aryl cis to the aryl ring.) Upon acetalization, these bands are replaced by a single carbonyl peak at 1696–1697 cm^{-1}, which is a strong indication that the cis carbonyl is retained.

The GC-MS of the materials yielded very good molecular ions for each of the acetals **6a–f** but also displayed varying levels of the corresponding enol ethers. The gross proton NMR spectra of these materials were in agreement with structures **6a–f** but indicated the presence of varying amounts of the enol ethers as an impurity. Focusing on **6c**, which appeared to be the most stable (had the least amount of enol ether evident upon solvent removal), we measured the H–^{13}C coupling constants between the allylic carbons and the olefinic hydrogen and found these coupling constants to be 10 Hz for ketonic carbon and 4 Hz for the acetal carbon, providing further confirmatory evidence of our structural assignment.

In retrospect, the monoacetalization of the α-acetylbenzalacetones should not be surprising. First, nucleophilic access to the cis ketone is sterically hindered. Second, the acetalization of the cis ketone, even if it is accomplished, would result in a very sterically crowded situation in which the aryl ring and the acetal, which is likely to be comparable to or perhaps larger than a *tert*-butyl group, must

(6) A description of the synthesis of a variety of naphthoates by several methods is described in Adcock, W.; Wells, P. R. *Aust. J. Chem.* **1965**, *18*, 1351. Also see ref 7.

(7) (a) Zoeller, J. R. *J. Org. Chem.* **1988**, *53*, 4716. (b) Zoeller, J. R. U.S. Pat. 4,783,548, 1988. (c) Volkovitch, P. B.; Conger, J. L.; Castiello, F. A.; Brodie, T. D.; Weber, W. P. *J. Am. Chem. Soc.* **1975**, *97*, 901. (d) Rosen, B. I.; Weber, W. P. *Tetrahedron Lett.* **1977**, 151. (e) Rosen, B. I.; Weber, W. P. *J. Org. Chem.* **1977**, *42*, 47. (f) Radcliffe, M. M.; Weber, W. P. *J. Org. Chem.* **1977**, *42*, 297.

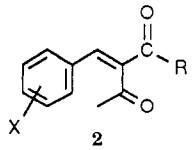
(8) (a) For a review, see: Jones, G. *Org. React.* **1967**, *15*, 204. (b) Additional references may be found in House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin, Inc.; Reading, MA, 1972; p 632.

(9) (a) Robinson, C. N.; Slater, C. D.; Covington, J. S., III; Chang, C. R.; Dewey, L. S.; Franceschini, J. M.; Fritzsche, J. L.; Hamilton, J. E.; Irving, C. C., Jr.; Morris, J. M.; Norris, D. W.; Rodman, L. E.; Smith, V. I.; Stablein, G. E.; Ward, F. C. *J. Magn. Reson.* **1980**, *41*, 293. (b) Horning, E. C.; Koo, J.; Fish, M. S.; Walker, G. N. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, p 408. (c) Weinberger, M. A.; Meppelder, F. H.; Nicholson, G. G.; Holmes, H. L. *Appl. Spectrosc.* **1974**, *28*, 146.

(10) Wohl, R. A. *Synthesis* **1974**, 38. See also ref 11 and references cited therein.

(11) For examples of various acetalization methods, see: (a) Gasparrini, F.; Giovannoli, M.; Misiti, D. *Tetrahedron* **1984**, *40*, 1491 and references cited therein. (b) Patwarden, S. A.; Dev, S. *Synthesis* **1974**, 348.

Table I. Sequential Acetalization–Pyrolysis of α-Acetylbenzalacetones and α-Acetylcinnamates to 2-Carbonyl-Substituted Naphthalenes



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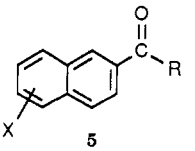

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entry	starting material compd	X	R	Acetalization[a] method	pyrolysis[b] method	product compd	X	R	isolated[c,d] yield, %	mp (lit. mp),[e] °C	ref
1	**2a**	H	Me	A	A	**5a**	H	Me	64	49–51 (52–53)	16
2	**2b**	4-Me	Me	A	A	**5b**	6-Me	Me	66	64–66 (66–68)	5b
3	**2c**	4-Cl	Me	A	A	**5c**	6-Cl	Me	61	81–83 (83–84)	17
4	**2d**	4-OMe	Me	A	A	**5d**	6-OMe	Me	46	106–107 (104–105)	18
5	**2d**	4-OMe	Me	A	B	**5d**	6-OMe	Me	40	106–107 (104–105)	18
6	**2e**	4-SMe	Me	A	A	**5e**	6-SMe	Me	56	118–119 (120)	19
7	**2f**	4-CO_2Me	Me	A	A	**5f**	6-CO_2	Me	45	144–146 (147–148)	20
8	**2f**	4-CO_2Me	Me	A	B	**5f**	6-CO_2	Me	20	144–146 (147–148)	20
9	**2g**	H	OMe	B	A	**5g**	H	OMe	60	75–76 (76)	21
10	**2h**	4-Me	OMe	B	A	**5h**	6-Me	OMe	52	121–123 (123.5–124.5)	6, 7
11	**2h**	4-Me	OMe	B	B	**5h**	6-Me	OMe	43	121–123 (123.5–124.5)	6, 7
12	**2i**	4-i-Pr	OMe	B	A	**5i**	6-i-Pr	OMe	63	62–64 (68–69)	22
13	**2j**	4-Br	OMe	C	A	**5j**	6-Br	OMe	45	123–125 (123.5–124.5)	6
14	**2k**	4-CO_2Me	OMe	C	A	**5k**	6-CO_2Me	OMe	49	193–193.5 (188–190)	16
15	**2l**	4-OMe	OMe	B	A	**5l**	6-OMe	OMe	27	125–127 (128–129)	6
16	**2m**	2-OMe	OMe	B	A	**5m**	8-OMe	OMe	34	(liquid)	23
17	**2n**	3-OMe	OMe	B	A	**5n**	5-OMe + 7-OMe	OMe	19	67–69[f]	*f*
								OMe	24	87–88 (91–92)	6

[a] Acetalization methods: A = 1/1 (v/v) $HC(OMe)_3$/MeOH, Amberlyst-15 (cat.), room temperature, 5–16 h; B = 1/1 (v/v) $HC(OMe)_3$/MeOH, Amberlyst-15 (cat.), $HRh(CO)(PPh_3)_3$ (cat.), room temperature, 5–7 h; C = 1/1 (v/v) $HC(OMe)_3$/MeOH, Amberlyst-15 (cat.), 55 °C, N_2 purge 3–6 h. [b] Pyrolysis methods: A = 475–505 °C in the vapor phase; B = 1-methylnaphthalene (bp 241 °C), reflux, 10 h. [c] All yields are for the conversion of **2** to **5** through the sequential acetalization–pyrolysis and represent isolated pure products. [d] All products were isolated by chromatography except example 13, which was isolated by crystallization. [e] All melting points are uncorrected. [f] New compound. See ref 29 in the text for complete characterization.

share the same side of an olefin. In an equilibrium process such as these acetalizations, the introduction of this much steric encumbrance would be expected to inhibit or preclude the reaction.

This selectivity for the acetalization of the ketone trans to the aryl ring is mirrored in the acetalizations of the α-acetylcinnamates **2g–n**. The Knoevenagel condensation of methyl acetoacetate with benzaldehydes results in a mixture of olefinic isomers, generally with an *E*:*Z* ratio of ca. 3:7 as determined by NMR integration.[12] When we attempted to acetalize these compounds, only one of the two isomers was reactive under the same conditions utilized for the acetalization of benzalacetones **2a–f**. By analogy to the α-acetylbenzalacetones, we surmised that the reactive isomer was the *Z* olefin but were able to clearly verify this conjecture by examination of the NMR spectrum from a typical reaction mixture.

When the olefinic mixture of **2h** was stirred in a 1:1 $HC(OMe)_3$/MeOH solution in the presence of Amberlyst-15 catalyst at room temperature, the peak at 7.55 ppm assignable to the *Z* isomer is replaced by a peak at 6.81 ppm in several hours. However, the peak at 7.66 ppm assigned to the *E* isomer remains.[13] These observations again demonstrate the lack of reactivity of the cis ketones toward acetalization in these systems. Unless an alternative method was found, this would have left ca. 30% of the material unreacted and presumably useless in the subsequent pyrolysis. Fortunately, we were able to identify two alternative procedures for the acetalization of these α-acetylcinnamates that allowed for their complete conversion to the desired acetals.

If a small quantity of the metal hydride, $HRh(CO)(PPh_3)$, was included (typical mole ratios of α-acetylcinnamate:catalyst = 10^3–10^4:1) the reaction goes readily to completion in 5–7 h.[14] Alternatively, particularly in the case of the bromo derivative **6j** in which the bromo group could be potentially removed by hydrogenation in the presence of the transition-metal catalyst, the acetalization was accomplished in 1:1 $HC(OMe)_3$/MeOH by using an Amberlyst-15 resin at 60 °C with a continuous nitrogen purge to remove methyl formate (bp 34 °C) as it is generated.

The acetals **6a–n** are not obtained as pure compounds, but the GC-MS indicated that the enol ethers were the only significant impurity. (The enol ethers are also observed in the ^1H NMR and appear to represent both the *E* and the *Z* isomers.) The propensity of these acetals to eliminate methanol and their extreme sensitivity to water

(12) (a) Marshall has briefly discussed the problem of attaining *E*:*Z* mixtures upon condensing benzaldehyde with methyl acetoacetate to generate **2g**. He assigned the spectrum for the *E* and *Z* isomers in the olefinic mixture of **2g** on the basis of the $H-^{13}C$ coupling constants and determined that the predominant isomer was the *Z* isomer. The two isomers of **2g** were reported to be inseparable. We concentrated on the separation of **2h** using medium pressure liquid chromatography[12b] with an 8% ethyl acetate in hexane eluant and were able to separate sufficient quantities of the pure *E* and *Z* isomers (albeit with a significant overlap fraction) to permit us to obtain coupled ^{13}C NMR spectra. This exercise only served to verify Marshall's original conclusions as the $H-^{13}C$ coupling constants of isolated *E* and *Z* isomers of **2h** were identical with those reported by Marshall for the isomers of **2g** and, as reported by Marshall, the *Z* isomer was the predominant isomer. The ^1H NMR spectra of the remaining α-acetylcinnamates (reported in Table II in the supplementary material) were assigned by analogy to these two materials. Integration of the ^1H NMR was used to determine the *E*:*Z* ratios. See: Marshall, J. L. *Carbon-Carbon and Carbon-Proton NMR Couplings*; Verlag Chemie International: Deerfield Beach, FL, 1983; p 37. (Also see ref 13.) (b) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

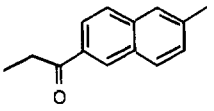
(13) It is noteworthy that GC is not a viable analytical tool for determining the isomer distribution. Separated isomers of **2h** both indicate a mixture of isomers on GC, indicating a ready isomerization. TLC on silica gel leads to extensive hydrolysis of the acetal and is therefore also a poor technique for following these reactions.

(14) We have found that the ruthenium hydride, $HRu(Cl)(CO)(PPh_3)_3$, (available from Alfa-Ventron, Danvers, MA) is equally effective in this reaction. We presume that these metal hydrides promote olefin isomerization, thus providing a renewed source of the reactive olefin.

made it undesirable to attempt extensive purification of these materials. Since the enol ethers are required intermediates in the subsequent pyrolysis, the most convenient method of pyrolyzing these acetals was to simply use the acetals as obtained.

There was one obvious potential difficulty resulting from these acetalizations. The acetals obtained by the methods we described would be expected to generate enol ethers possessing the incorrect stereochemistry for the subsequent pyrolytic ring closure that we anticipated in Scheme I. Despite this concern, we found that the acetals **6a–n** could be successfully cyclyzed at atmospheric pressure in fair to good overall yields by adding the acetal slowly to a drip-type pyrolysis unit filled with fine Vycor chips while maintaining a temperature of between 475 and 510 °C and an inert gas purge to promote passage through the pyrolysis unit. Apparently the temperature was sufficient to overcome the barrier of rotation about the olefinic bond. We have summarized the results in Table I. (All yields listed in Table I are for the combined acetalization–pyrolysis.)

The major yield loss in the vapor-phase reaction appears to be due to the formation of tars in the vaporization portion of the reactor. We generally have not attempted a rigorous examination of the minor byproducts, but in the case of the cyclization of **2b** (entry 2 in Table I), we did attempt to rigorously define all the byproducts. The only identifiable, nonvolatile byproduct that was isolated and identified after chromatography was 6-methyl-2-propionaphthone (**7**), which was obtained in about 3% yield.



7

Some interesting features of the cyclization should be emphasized. The acetalization–pyrolysis of 4-substituted α-acetyl-substituted cinnamates and benzalacetones, which represent the most useful compounds and therefore the majority of the examples, results in the selective generation of 2,6-disubstituted products since the two potential reactive sites are degenerate. Likewise, with a 2-substituted α-acetylcinnamate, where one potential reaction site is blocked, we obtained exclusively the 2,8-substituted product. (See entry 16 in Table I.)

When methyl 3-methoxy-α-acetylcinnamate was examined as our example of a 3-substituted α-acetylcinnamate (entry 17 in Table I), we obtained mixtures of the 5-methoxy- and the 7-methoxy-2-naphthoate, as expected. The exceptional observation is that the 7-isomer was favored. This contrasts with earlier studies using the *m*-methoxy-substituted arylbutadienes[15] and *m*-methoxy-substituted α-vinylcinnamates,[7] in which the 5-methoxy substitution predominates.

As demonstrated in entries 5, 8, and 11, of Table I, the reaction can also be performed in the liquid phase (although the yields seem to be slightly reduced) by heating a 1-methylnaphthalene (bp 241 °C) solution of the acetals at reflux for 6–10 h. The drawback to this version of the process, besides the slightly lower yields, is the difficulty encountered in removing the high boiling solvent. However, this feature may help extend the usefulness of this reaction.

Summary and Conclusion

2-Carbonyl-substituted naphthalenes may be generated by sequentially acetalizing and pyrolyzing the appropriate α-acetylbenzalacetones and α-acetylcinnamate. This methodology represents a novel and potentially useful entry into the naphthalene ring system. The process avoids the use of corrosive and hazardous solvents and reagents and should allow access to any 6- or 8-substituted 2-acetonaphthone or 2-naphthoate for which a corresponding para- or ortho-substituted benzaldehyde is available or readily accessible. It further represents a rare example of an electrocyclic reaction involving an aromatic bond and a unique method for the internal arylation of an enol equivalent. The methodology presented in this paper should represent a potentially useful new synthetic method with potential applications in the pharmaceutical and polymer industries.

Experimental Section

NMR spectra were recorded on a JEOL JMN-GX 400 FT NMR spectrometer, infrared spectra were recorded on a Nicolet 5DX infrared spectrometer, mass spectra were recorded on a VG Micromass ZAB-2F mass spectrometer, and melting points were determined on a Fischer-Johns hot stage melting point apparatus and are uncorrected. Elemental analyses were performed in our analytical laboratories.

Synthesis of α-Acetylbenzalacetones 2a–f. All the starting α-acetylbenzalacetones **2a–f** were prepared by the Knoevenagel condensation as described in the procedure of Robinson et al.,[9a] with the exception that we substituted toluene for benzene in the procedure for safety considerations. The required benzaldehydes were all purchased from Aldrich Chemical Co., Milwaukee, WI, with the exception of methyl 4-formylbenzoate, which was purchased from Fluka Chemical Co., Happuage, NY. The required 2,4-pentanedione was purchased from Eastman Chemicals, Rochester, NY. With the exception of compound **2e**, all the compounds were previously known and fully characterized materials.[9a,c]

3-(4′-(Methylthio)benzylidene)-2,4-pentanedione (2e). Following the procedure of Robinson et al.,[9a] α-acetylbenzalacetone **2e** was obtained in 62% yield after a single recrystallization from toluene–hexane. An analytical sample was obtained by a second crystallization from methanol. 400-MHz ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3 H), 2.42 (s, 3 H), 2.51 (s, 3 H), 7.22 (d, 2 H, J = 13 Hz), 7.31 (d, 2 H, J = 13 Hz), 7.41 (s, 1 H). IR (film): 1709, 1690 (shoulder), 1655 cm^{-1}. MS (50 eV) M^+ = 234. Anal. Calcd for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.06. Found: C, 66.70; H, 6.06. Mp 64–65 °C.

General Procedure for the Synthesis of α-Acetylcinnamates 2g–n. All the starting α-acetylbenzalacetones **2g–n**

(15) Radcliffe, M. M.; Weber, W. P. *J. Org. Chem.* **1977**, *42*, 297.
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(21) Fitzgerald, P.; Packer, J.; Vaughn, J.; Wilson, A. F. *J. Chem. Soc.* **1956**, 170.
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(24) The reaction can be run without the neutralization step if the material is used immediately. Failure to neutralize the solution has led to very viscous materials and losses in yield in several cases (presumably due to polymerization) if the material is stored for even 24 h prior to its use.
(25) The reactions were generally complete in 5–7 h and the longer reaction periods were used generally out of convenience than necessity.
(26) There is a considerable quantity of tar generated at the inlet where vaporization occurs. This tar limits the amount of material that can be passed through the pyrolysis tube before it has to be removed and cleaned. Generally, we have found that the tubes described in the literature were adequate for a run at the 0.050-mol scales described in this report. The amount of tar was variable but worst with methoxy groups on the aromatic ring. In our hands, a single tube could generally handle between 20 and 30 g of crude acetal **2h** before plugging occurred.

were prepared by a Knoevenagel condensation.[8,9] Methyl acetoacetate was purchased from Eastman Chemicals, Rochester, NY. This reaction has been carried out innumerable times in the literature using ethyl or methyl acetoacetates in combination with a wide variety of benzaldehydes under a wide diversity of conditions and compounds **2g**,[27a] **2h**,[27b] **2i**,[27c,d] **2m**,[27a] and **2n**[27f] have been previously synthesized by this method. However, due to the common nature of this reaction, the characterization is generally lacking or incomplete. Therefore we have summarized the analytical data for all these materials in Table II in the supplementary material. The following procedure, which describes the preparation of α-acetylcinnamate **2i**, is exemplary of our syntheses of these materials. (Yields for the various condensations are listed in Table II in the supplementary material.)

A solution of 162 g (1.10 mol) of *p*-isopropylbenzaldehyde and 108 mL (116 g, 1.00 mol) was prepared in 200 mL of methanol. To this solution were added 2 mL of piperidine and 4 mL of acetic acid. The mixture was heated to a slow reflux for 45–60 min and then cooled to room temperature. The piperidine was removed by adding 10–15 g of Amberlyst-15 and swirling the mixture for 5 min and then filtering the solution to remove the solid resin. After the resin was washed with a small amount of methanol, the solution was reduced in volume as far as possible on a rotary evaporator. The residue was distilled, yielding a fraction boiling between 158 and 160 °C at 1.8 mmHg (yield: 202.8 g, 0.824 mol, 82%).[28] Analytical data appears in Table II in the supplementary material.

Acetalization Procedures. Three slightly different procedures were used to acetalize compounds **2a–n**. These procedures are described below and correspond to the method designations in Table I. All the compounds are obtained with varying degrees of enol ethers as impurities and were used in the subsequent pyrolysis step as obtained. Analytical data are summarized in Table III in the supplementary material. (The required Amberlyst resins are available from Aldrich Chemical Co.)

Acetalization Procedure A. This procedure was used to acetalize α-acetylbenzalacetones **2a–f** and is very similar to the method of Patwarden and Dev.[11b] The following acetalization of α-acetylbenzalacetone **2b** may be regarded as exemplary.

A solution of 10.10 g (0.050 mol) of α-acetylbenzalacetone **2b** in 60 mL of 1/1 (v/v) trimethyl orthoformate/methanol was prepared and to this solution was added 2–2.2 g of Amberlyst-15 resin. The reaction mixture was magnetically stirred under an Ar atmosphere for 2.5 h at ambient temperature. (The reaction can be monitored by GC analysis until essentially all the starting material is consumed. The hot injection port does lead to measurable quantities of enol ether generation.) The solution was then filtered to remove the acidic resin and the resin washed with a small quantity of 1/1 trimethyl orthoformate/methanol. To neutralize any residual acid, the solution was swirled briefly with 1–1.5 g of Amberlyst-21 resin and filtered again.[24] The intermediate monoacetal **6b** was isolated by solvent removal in vacuo. Crude yield: 11.90 g. (All the α-acetylbenzalacetones **2a–f** were acetalized by this method, requiring about the same time interval except **2f**, which required 16 h to reach completion.)

Acetalization Procedure B. This procedure was utilized to acetalize α-acetylcinnamates **2g–i,l–n** and differs primarily in the addition of $HRh(CO)(PPh_3)_3$ (Available from Alfa-Ventron, Danvers, MA). The acetalization of α-acetylcinnamate **2g** may be regarded as exemplary.

A solution of 10.20 g (0.050 mol) of α-acetylcinnamate **2g** in 30 mL of 1/1 (v/v) trimethyl orthoformate/methanol was prepared and to this solution was added 1–1.2 g of Amberlyst-15 resin and 10 mg (11 μmol) of $HRh(CO)(PPh_3)_3$.[14] The reaction mixture was magnetically stirred under an Ar atmosphere for 5–16 h[25] at ambient temperature. (The reaction can be monitored by GC analysis until essentially all the starting material is consumed. The hot injection port does lead to measurable quantities of enol ether generation). The solution was then filtered to remove the acidic resin. To neutralize any residual acid, the solution was swirled briefly with 1–1.5 g of Amberlyst-21 resin and filtered again.[24] The intermediate monoketal **6g** was isolated by solvent removal in vacuo. Crude yield: 12.84 g.

Acetalization Procedure C. This procedure was used to acetalize α-acetylcinnamates **2j** and **2k**. In these cases higher temperatures and continuous removal of methyl formate were used to force the reaction to completion. The acetalization of α-acetylcinnamate **2j** can be regarded as exemplary of the procedure.

A solution of 14.15 g (0.050 mol) of α-acetylcinnamate **2j** in 30 mL of 1/1 (v/v) trimethyl orthoformate/methanol was prepared and to this solution was added 1.2 g of Amberlyst-15 resin. A slow constant purge of nitrogen was established through the solution and the solution was heated to 55 °C and maintained at this temperature while magnetically stirring the mixture for 5.5 h. (If the nitrogen purge is too vigorous additional 1/1 trimethyl orthoformate/methanol might be required to compensate for the loss of solvent volume.) The solution was cooled and then filtered to remove the acidic resin. To neutralize any residual acid, the solution was swirled briefly with 1–1.5 g of Amberlyst-21 resin and filtered again.[24] The intermediate monoketal **6j** was isolated by solvent removal in vacuo. Crude yield: 16.42 g.

Pyrolysis Methods. Two different pyrolysis procedures were examined in this study. The first was a vapor-phase process (method A in Table I) and the second was a liquid-phase process (method B in Table I). Both processes are described in detail below and are lettered to correspond to Table I. All the naphthalene products are known in the literature with the exception of methyl 5-methoxy-2-naphthoate (**5o**)[29] and were characterized on the basis of their ^1H NMR, infrared, and mass spectral properties, as well as the melting point comparison shown in Table I.

Pyrolysis Procedure A. Vapor-Phase Pyrolysis. A simple drip-type pyrolysis unit identical with that previously described in the literature[7a] was operated by maintaining the reactor zone in the range of 475–500 °C and maintaining an argon purge of 50 mL/min. The crude acetals generated by any of the acetalization processes were added as neat liquids with the notable exception of acetal **2k**, which was a solid and added as a 33% solution by weight in methyl acetate. The rate of addition was maintained at a consistent 2 mL/h using a syringe drive. The resultant dark mixture is added to a 50-mm medium pressure liquid chromatography column;[12b] the material was separated by using ethyl acetate–hexane as eluent. Yields for the overall process appear in Table I.[26]

Pyrolysis Procedure B. Liquid-Phase Pyrolysis in 1-Methylnaphthalene. Several examples of a liquid-phase pyrolysis appear in Table I. The thermal ring closure of α-acetylcinnamate acetal **6h** may be considered as exemplary. A 1.02-g (3.86 mmol) sample of crude α-acetylcinnamate acetal **6h** was dissolved in 50 mL of 1-methylnaphthalene (bp 241 °C) (obtained from the Aldrich Chemical Co., Milwaukee, WI, and redistilled prior to use). The mixture was heated at reflux for 6 h and then allowed to cool. The entire contents of the flask were added to a 50-mm diameter medium pressure liquid chromatography column.[12b] The 1-methylnaphthalene is subsequently removed by elution with pure hexane until no more 1-methylnaphthalene is dectected. (The completion of this elution is easily screened by simply applying a spot to a TLC plate containing a fluorescent indicator and examining with a UV lamp. Elution is not necessary prior to this screening.) The product was subsequently eluted by using 5% ethyl acetate in hexane to give 0.330 g (1.65 mmol, 43% yield) of pure methyl 6-methyl-2-naphthoate (**5h**).

Registry No. 1, 123-54-6; **2a**, 4335-90-4; **2b**, 15818-09-4; **2c**, 19411-75-7; **2d**, 15725-17-4; **2e**, 119757-22-1; **2f**, 52287-60-2; **2g**,

(27) (a) There are innumerable references to **2g**. For examples, see ref 27c and 27d. (b) Karnail, S. A. Eur. Pat. Appl. 208,964, 1987. (c) Danion, R.; Carrier, R. *Bull. Soc. Chim. Fr.* **1968**, 2526. (d) Atwal, K. S.; Bergy, J. L.; Hedburg, A.; Moreland, S. *J. Med. Chem.* **1987**, *30*, 635. (e) Ohno, S.; Komatsu, O.; Morishima, T.; Sumita, K. *Chem. Pharm. Bull.* **1986**, *34*, 1589. (f) Fossheim, R.; Joslyn, A.; Solo, A. J.; Luchowski, E.; Rutledge, A.; Triggle, D. J. *J. Med. Chem.* **1988**, *31*, 300.

(28) All the α-acetylcinnamates were isolated by distillation with the exception of the carbomethoxy derivative **2k**, which was isolated by crystallization in an ice bath.

(29) Analytical data for methyl 5-methoxy-2-naphthoate. 400-MHz ^1H NMR ($CDCl_3$): δ 3.98 (s, 3 H), 4.02 (s, 3 H), 6.92 (d, 1 H, J = 8 Hz), 7.45 (t, 1 H, J = 8 Hz), 7.53 (d, 1 H, J = 8 Hz), 8.04 (dd, 1 H, J = 1, 9 Hz), 8.30 (d, 1 H, J = 9 Hz), 8.56 (d, 1 H, J = 1 Hz). IR (CH_2Cl_2): 1715 cm^{-1}. FDMS: 216. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.63; H, 5.70. MP 67–69 °C.

20048-05-9; **2h**, 120634-43-7; **2i**, 123206-98-4; **2j**, 123206-99-5; **2k**, 123207-00-1; **2l**, 20048-01-5; **2m**, 123207-02-3; **2n**, 123207-03-4; **5a**, 93-08-3; **5b**, 5156-83-2; **5c**, 42036-59-9; **5d**, 3900-45-6; **5e**, 62759-49-3; **5f**, 33627-00-8; **5g**, 2459-25-8; **5h**, 6162-30-7; **5i**, 101513-13-7; **5j**, 33626-98-1; **5k**, 840-65-3; **5l**, 5043-02-7; **5m**, 33295-54-4; **5n**, 5088-92-6; **5o**, 117745-72-9; **6a**, 123207-04-5; **6b**, 119757-21-0; **6c**, 123207-05-6; **6d**, 123207-06-7; **6e**, 123207-07-8; **6f**, 123207-08-9; **6g**, 123207-09-0; **6h**, 120634-45-9; **6i**, 123207-10-3; **6j**, 123207-11-4; **6k**, 123207-12-5; **6l**, 123207-13-6; **6m**, 123207-14-7; **6n**, 123207-15-8; **7**, 69750-34-1; $HRh(CO)(PPh_3)_3$, 17185-29-4; 4-(methylthio)-benzaldehyde, 3446-89-7.

Supplementary Material Available: Tables of spectroscopic data for acetals **6a-n** (Table III) and spectroscopic and analytical data for α-acetylcinnamates **2g-n** (Table II) (3 pages). Ordering information is given on any current masthead page.

Sequential Wittig-Oxyanion Accelerated Cope Reactions of 2,2,2-Triphenyl-5-vinyl-1,2λ⁵-oxaphospholane

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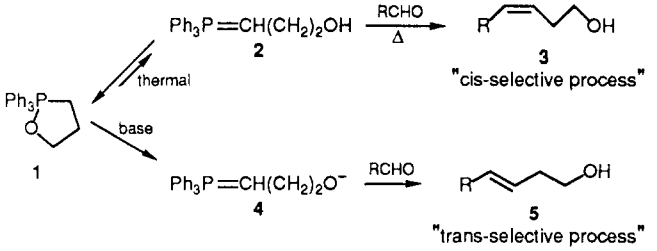
2,2,2-Triphenyl-5-vinyl-1,2λ⁵-oxaphospholane was prepared and condensed with a variety of aldehydes and ketones in a Wittig reaction to produce 3-hydroxy 1,5-dienes. These compounds were next subjected to an oxyanion accelerated Cope rearrangement. In the two-step process, the carbonyl was replaced with a difunctionalized carbon bearing a vinyl moiety and a three-carbon pendant aldehyde.

Introduction

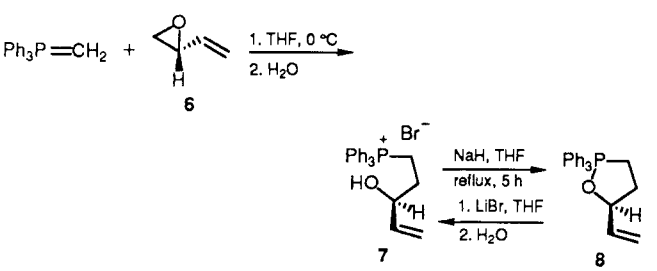
The Cope rearrangement remains one of the most useful tools in the synthetic chemists arsenal.[1] Recent interest in the oxyanion accelerated version[2] of this [3,3]sigmatropic rearrangement in its application to total synthesis[3] and new synthetic methodology[4] easily serve to demonstrate that utility. Our concern with this reaction focuses on the synthetic applications of 2,2,2-triphenyl-5-vinyl-1,2λ⁵-oxaphospholane, a compound which functions as a novel reagent for use in a Wittig-oxyanion accelerated Cope process (vide infra).

In 1967, Hands and Mercer reported the first isolation[5] of a 1,2λ⁵-oxaphospholane when they prepared 2,2,2-triphenyl-1,2λ⁵-oxaphospholane (1) shown in Scheme I. The authors found that this structurally interesting heterocycle reacted more readily with aldehydes than with ketones under thermally mediated conditions (90-120 °C) to afford Wittig products.[6] Although this compound has been the subject of only a few synthetic studies since this report,[7]

Scheme I



Scheme II



Maryanoff and co-workers[8d] have more recently indicated that reactions of the parent 1,2λ⁵-oxaphospholane can also be promoted by base at much lower reaction temperatures.[8] It has also been demonstrated that the olefin geometry in the homoallyl alcohol products is dependent on the dichotomy of reactivity illustrated in Scheme I. In the presence of base or in the "trans-selective process", the trans product **5** can predominate over the cis in ratios

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(2) For a review of the oxyanion accelerated Cope rearrangement, see: Swaminathan, S. *J. Ind. Chem. Soc.* **1984**, *61*, 99.

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