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SEQUENTIAL ACETALIZATION-PYROLYSIS OF α-ACETYL BENZALACETONES. A METHOD FOR THE GENERATION OF 6-SUBSTITUTED 2-ACETONAPHTHONES

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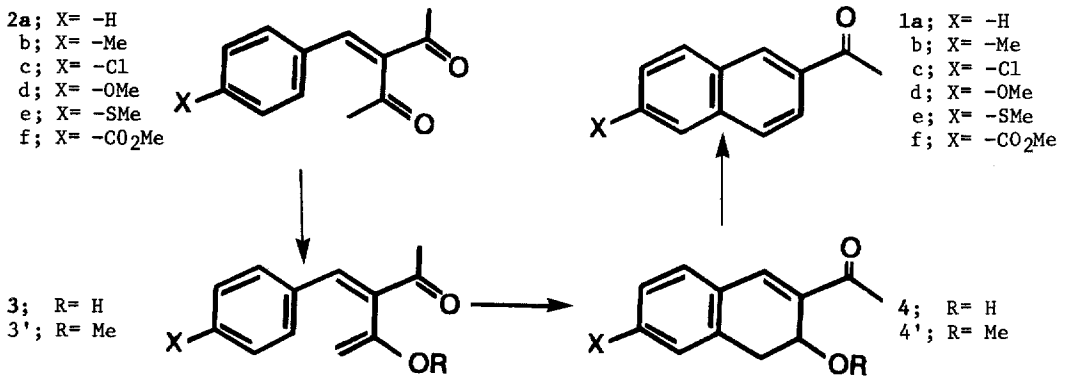
Abstract: 6-Substituted 2-acetonaphthones can be generated from para substituted benzaldehydes and acetylacetone (2,4-pentanedione) in three reactions consisting of condensing the benzaldehyde with acetylacetone, acetalizing the resultant 3-benzylidene 2,4-pentanedione (α-acetyl benzalacetones), with trimethyl orthoformate, pyrolyzing the acetal either in the vapor phase at 475°C or by heating in a high boiling solvent, such as 1-methylnaphthalene.

The 6-substituted 2-acetonapthones (1) are very useful intermediates in the generation of drug formulations[1,2] and naphthanoid polyester monomers[3]. However, the Friedel-Crafts acylations[4,5] presently used to generate these compounds have numerous drawbacks in practice. We sought a method of generating these useful 2-acetonapthones which avoids the use of strongly acidic and corrosive Friedel-Crafts systems, yet might expand the number of available 2-acetonapthones. We directed our attention toward finding a method for the unprecedented annulation of para substituted 3-benzylidene 2,4-pentanediones (**2**) (which have the more trivial name α-acetyl benzalacetone) to the desired 2-acetonapthones. These α-acetyl benzalacetones are well known in the literature and are generally available using the well precedented Knoevenagel condensation of the widely available para substituted benzaldehydes with 2,4-pentanedione (acetylacetone).[6] Our chosen approach to the desired annulation is loosely based upon the thermal ring closures of simple, unsubstituted aryl butadienes [7a-d] to generate 1,2-dihydronaphthalenes. Recently, we have extended this work to demonstrate the more facile ring closure of α-vinyl cinnamates to generate 3,4-dihydro-2-naphthoates.[7e,f] We hoped to perform an analogous thermal cyclization using the enol form of the α-acetyl benzalacetone **3**. The anticipated sequence of events is shown in Scheme 1.

We set out to demonstrate the feasibility of this route and generated a representative series of α-acetyl benzalacetones **2a-f** from the corresponding para substituted benzaldehyde and acetylacetone using very ordinary and well established Knoevenagel conditions[6,8-10] (piperidine/acetic acid catalyst in toluene with azeotropic removal of water). Initial examination of the thermal annulation of **2a** using a quartz filled hot tube[11] at temperatures of 425-525°C revealed that, even at 525°C, the reaction proceeded at very low conversions and the product was complex containing only traces of the desired 2-acetonapthone **1a**.

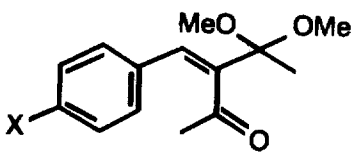
We rationalized that the α-acetyl benzalacetone spent insufficient time in the enol form 3 and therefore the desired reaction was sluggish and side reactions could occur.

We thought that if the enol form was fixed in the system, the ring closure might be enhanced. As a means of achieving this objective we chose to examine the enol ethers, which are generated in situ by pyrolysis of the corresponding acetals.[12]



Scheme 1. Proposed Pathway for the Generation of 2-Acetonaphthones from o-Acetyl Benzalacetones.

The o-acetyl benzalacetones **2a-f** were acetalized[13] by dissolving the diketone in a 1/1 (v/v) solution of trimethyl orthoformate/ methanol in the presence of Amberlyst-15® for 2.5 h at room temperature.[13b] Only the ketone trans to the aryl ring is acetalized in these systems and have been assigned structures **5a-f**[14].



5a; X= -H
b; X= -Me
c; X= -Cl
d; X= -OMe
e; X= -SMe
f; X= $-CO_2Me$

The indicated stereochemistry of the acetals **5a-f** would be expected to lead to enol ethers of the incorrect stereochemistry for the desired ring closure. However, despite our concern about the stereochemistry, we found that these acetals could be sucessfully cyclized to their corresponding 6-substituted 2-acetonapthones **1a-f** by adding the acetal slowly to a drip type pyrolysis unit filled with fine Vycor chips and maintained at a temperature of 470-510°C using an inert gas (Ar) purge to promote passage through the unit.[11] No extensive attempt was made to optimize the process and the results of these cyclizations are summarized in Table 1. (All yields in Table 1 are for the combined acetalization-pyrolysis sequence.)

Table 1. The Sequential Acetalization-Pyrolysis of α-Acetyl Benzalacetones.(a)

Benzal Acetone	X=	Product	Yield(b)	m.p.	lit. m.p.(ref.)
2a	H	1a	64%	49-51°C	52-53°C,53-55°C(c)
2b	Me	1b	66%	64-66°C	66-68°C (5a)
2c	Cl	1c	61%	81-83°C	83-84°C (15a)
2d	OMe	1d	46%	106-107°C	104-105°C (15b)
2e	SMe	1e	56%	118-119°C	120°C (15c)
2f	CO_2Me	1f	45%	144-146°C	147-148°C (15d)

(a) All products were known in the literature as indicated and gave acceptable (1)H nmr, ir, and mass spectra in addition to the melting points listed. (b) All yields are for isolated materials which were spectroscopically and chromatographically homogeneous. Yields were calculated from starting α-acetyl benzalacetone. (c) This compound is available from the Aldrich Chemical Co., Milwaukee, Wisconsin (USA) (cited mp 53-55°C) and Fluka Chemical Corp., Happauge, New York (USA) (cited mp 52-53°C).

The methodology described in this report represents a novel and potentially very useful entry into the naphthalene ring system. The process is a rare example of a electrocyclic reaction involving aromatic bonds and should allow access to any 6-substituted 2-acetonapthone for which a corresponding para substituted benzaldehyde is accessible without the need to resort to corrosive reagents or severely hazardous solvents. In all cases except the annulation of **2e**, the present yield is comparable or superior to the existing aluminum chloride assisted acetylations cited in the literature. Extensions of this technology are under active investigation in these laboratories.

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10. Compounds 2e and 2f are new compositions of matter and have been completely characterized by ^{1}HNMR, IR, MS, and either elemental analysis or exact mass.

11. The pyrolysis apparatus was identical to that described in ref. 7e.

12. Wohl, R. A., Syn., 38 (1974). See also reference 13 and literature cited therein.

13. a) For examples of various acetalization methods see Gaspararrini, F.; Giovannoli, M.; and Misiti, D., Tet., **40**, 1491 (1984) and references cited therein. b) The acetalization method used in this report was a variation of the method described in Patwardhan, S.A. and Dev, S., Syn., 348 (1974).

14. The structural assignment was based on ^{1}HNMR, ^{13}CNMR, IR, and MS. Particularly useful is the IR which clearly indicates the removal of the ketone trans to the aryl ring and retention of the cis ketone (IR(CH_2Cl_2) For **2**: 1645-1655cm^{-1}, 1695-1710cm^{-1}: For 5: 1695-1697cm^{-1}).

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