

ALUMINA-MEDIATED CONDENSATION. A SIMPLE SYNTHESIS OF AURONES

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Abstract: A simple and high yielding synthesis of aurones (2-phenylmethylene-3(2H)-benzofuranones) is described which occurs under mild conditions on alumina surface using readily available benzofuranones and arylaldehydes.

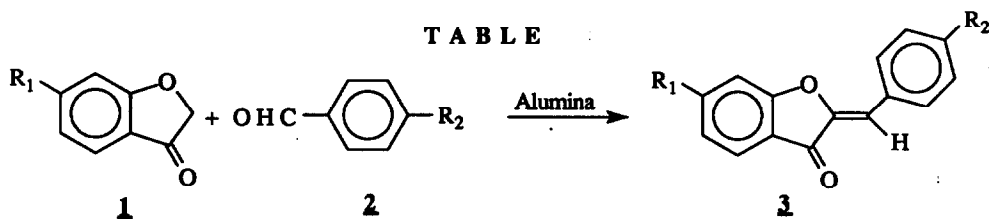
Aurones are important contributors to the pigmentation of the flowers by virtue of their bright golden yellow colors. However, because of their limited occurrence in nature, aurones have received very little attention compared to the related and widely investigated flavones and isoflavones.¹ Though there are a few general methods of synthesis² for aurones, their biological activity³ has not been evaluated, in spite of the fact that their isomeric relations, flavonoids, have displayed a wide spectrum of biological actions⁴ including anti-proliferative activity.⁵⁻⁷

Our continued interest in the chemistry of these minor flavonoid derivatives,⁸⁻¹⁰ and the recent discovery of their potent growth inhibitory properties^{11,12} prompted us to develop a convenient and general method for the synthesis of aurones. This search for an alternative method is necessitated, in part, because of the limitations of the existing procedures which can not accommodate several functional groups. The standard synthesis as applied to naturally occurring hydroxylated aurones involves the condensation of appropriately substituted 3(2H)-benzofuranones (**1**) with arylaldehydes (**2**) in hot alcoholic acidic or basic conditions,^{13,14} an approach which is not compatible with acid or base labile functionalities. The preparation of aurones as byproducts in the Algar-Flynn-Oyamada synthesis of flavonols by the action of chalcones with alkaline hydrogen peroxide¹⁵ and in the Emilewicz-von Kostanecki synthesis of flavones using chalcone dihalides with aqueous alcoholic alkali¹⁶ or cyclohexylamine² did not appeal to us because of the complexity of products formed in these reactions.

Dedicated to Dr. Vernon Knight on the occasion of his 75th birthday

In view of the recent interest of synthetic chemists to accomplish reactions on inorganic solid support¹⁷ and our own success in this general area,^{18,19} we explored the reactions of benzofuranones (**1**) with arylaldehydes (**2**) on basic alumina.

We wish to report that the above reaction results in the high yield and rapid formation (10-15 min) of aurones under mild conditions; the Knoevenagel condensation of active methylene compounds with carbonyl compounds on solid support reagents has literature precedent²⁰. Subsequently, we discovered that the reaction proceeds very well even on ordinary adsorption grade neutral alumina.²¹ The reaction on this solid support is unique in that a variety of functional groups (see table below) including an ester functionality are tolerated; compound such as Z-2-[(4-methoxycarbonylphenyl)methylene]-3(2H)-benzofuranone, **3d**, is readily obtained which may not be an attainable goal using the conventional procedures.^{13,14} Also, the reaction is fast enough that no undesirable byproducts originating from arylaldehyde via a concomitant Cannizzaro reaction²² are observed in the reaction product. Furthermore, the reaction on alumina results in the formation of Z-isomers as confirmed by the analyses of their diagnostic IR²³ and ¹³C-NMR²⁴ spectra (exocyclic olefinic carbon, =CH, resonating ~111ppm). Our results are summarized below with corresponding yields reported for solution reactions in the parenthesis.



Compds ^{a)}	R ₁	R ₂	MP ^{b)} (°C)	Yield ^{c)}
3a	H	H	(110-111) ²³	93% (83)
3b	O Ac (OH)	H	(261-262) ^{25,26}	86%
3c	H	OH	(254-255) ²⁷	93% ^{d)}
3d	H	COOCH ₃	201-202	91%
3e	H	OCH ₃	(138-139) ²³	92% (67)
3f	H	Cl	(166-167) ²³	89% (63)
3g	H	NO ₂	(211-212) ²³	90% (57)
3h	H	N(CH ₃) ₂	(172-173) ³	92%

a) Products exhibited physical and spectral properties in accord with the assigned structures; b) Uncorrected; c) Isolated yields based on 3(2H)-benzofuranones; d) Multiple extractions using ethyl acetate-methanol(1:1,v/v; 5x50ml) are needed for isolation of products bearing hydroxyl groups.

The synthesis of 4'-methoxycarbonylaurone, **3d**, is representative of the general procedure employed. Neutral alumina²¹ (3.25g) is added to a solution of methyl 4-formylbenzoate (0.246g, 1.5mmol) and 3(2H)-benzofuranone (0.134g, 1mmol) dissolved in a minimum amount of dichloromethane (1-2ml) at room temperature and the reaction mixture was thoroughly mixed using an vortex mixer. The product, upon completion of the reaction as followed by TLC examination (~4 hrs), is extracted in to dichloromethane (4x15ml). Removal of the solvent, under reduced pressure, yielded the solid product from which the trace amounts of benzyl alcohol and arylaldehyde are removed by crystallization from dichloromethane-methanol to afford Z-2-[(4-methoxycarbonylphenyl)methylene]-3(2H)-benzofuranone, **3d**, (91%); mp 201-202°C; FT-IR(Nujol): 1715, 1703, 1650, 1643, 1596, 1561, 1428, 1316, 1301, 1276, 1182, 1110, 1017, 886, 759 cm⁻¹; ¹H NMR(400MHz, DMSO-d₆, TMS at 333 K): δ3.90 (s, 3H, COO-CH₃), 6.97(s, 1H, =CH), 7.33-8.11(m, 8H, Ar-H); ¹³C NMR(DMSO-d₆, TMS at 313 K): 851.8, 110.1, 112.9, 120.4, 123.9, 124.1, 129.2, 130.1, 137.5, 147.1, 152.8, 165.4, 169.5, 179.7, 183.3. Anal. Calcd. for C₁₇H₁₂O₄: C, 72.85; H, 4.32 Found: C, 72.80; H, 4.20.

Interestingly, the acetoxy derivative of 6-hydroxy-3(2H)-benzofuranone, **1h** (R=OAc), on alumina undergoes concomitant deacetylation during condensation with benzaldehyde thus affording directly the corresponding 6-hydroxy-2-phenylmethylene-3(2H)-benzofuranone, **3b** (R=OH);²⁵ the deacetylation of acetylated aurones to hydroxyaurones is known to occur poorly under usual alkaline conditions.²⁸

In conclusion, we have developed a simple method for the synthesis of aurones which occurs under mild conditions using inexpensive aluminum oxide.

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