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A CONVENIENT ONE-POT SYNTHESIS OF 3-NITRO-2H-CHROMENES BY ULTRASONIC AGITATION ON BASIC ALUMINA

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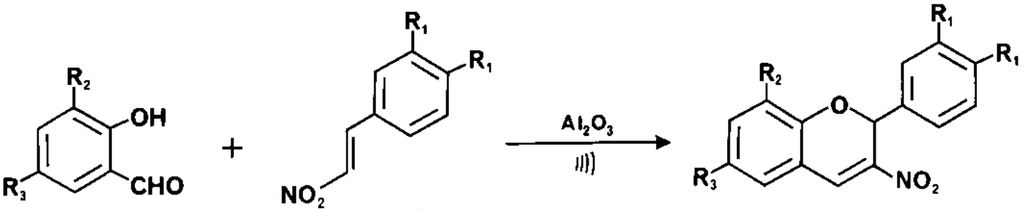
Abstract - The condensation of o-hydroxybenzaldehydes with β-nitrostyrene derivatives was carried out on basic alumina. Sonic acceleration of this condensation provides a convenient synthesis of 2-phenyl-3-nitro-2H-1-benzopyrans in good yields.

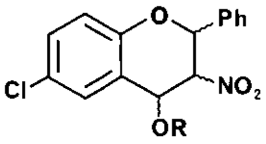
3-Nitrochromenes are an important class of biologically active oxygen heterocycles.[1-4] In view of the reported radioprotecting effects of Δ^3-chromenes containing electron attracting substituents[5] and our continuous interest in the chemistry of conjugated nitroalkenes[6], we became interested in the synthesis of 2-phenyl-3-nitro-2H-chromenes. Conventional synthesis[3,7,8] of these compounds involve the condensation of β-nitrostyrene derivatives with the corresponding o-hydroxybenzaldehydes in pyridine[3], and triethylamine[7,8]. Unfortunately, the yields are modest, reaction times are long, and isolation of the desired product is tedious.

Aluminum oxide is known to be an effective catalyst for a number of condensation reactions[9], including the Knoevenagel reaction[10,11] and the synthesis of 4H-chromenes[12]. Consequently, we explored the application of basic alumina[13] in the syntheses of Δ^3-chromenes. Preliminary studies involved the reactions of salicylaldehyde with β-nitrostyrene adsorbed on basic alumina in the absence of solvent. The highest yields (82%) of 3-nitro-2-phenylchromene were obtained when the molar ratio of aldehyde to nitrostyrene was 2:1. Nearly pure 2-phenyl-3-nitrochromene was obtained by simply extracting the reaction mixture with acetone. Unfortunately, we found that the reaction yields decreased in the presence of solvents, thus jeopardizing the use of solid reactants. However, we soon discovered that solid reagents could be dissolved in an appropriate solvent, mixed with alumina, the solvent removed, and the reaction allowed to proceed. The reaction time was relatively long but was decreased through the use of sonification;[14] such sonic acceleration is rapidly gaining recognition in heterogeneous reaction systems.[15,16]



1 2 3

3	R_1	R_2	R_3
a	H	H	H
b	H	OCH_3	H
c	OEt	H	H
d	OEt	OCH_3	H
e	H	H	Cl



4 a R = H
b R = $COCH_3$

We wish to report that ultrasonic agitation of a variety of *o*-hydroxybenzaldehydes and β-nitrostyrene derivatives on basic alumina provides a rapid and simple procedure for the syntheses of 2-phenyl-3-nitro-2H-1-benzopyrans, 3. The results are summarized in Table I.

TABLE I

Compound No	Time (h)	Yield[a] %	Mp[b] °C	Lit. Mp	Ref.
3a	2.0	85	92-93	92.5-93.5	7
3b	2.5	76	121-122	120	3
3c	2.5	68	89-90	-	17
3d	3.5	42	129-130	-	18
3e	4.0	47	117-118	116	3
4a	4.0	36	210-211	-	-
4b	-	-	169-170	-	19

a - isolated and unoptimized yields based on β-nitrostyrene

b - uncorrected

In a typical experiment, basic alumina[13] (13-15 g) was added to a mixture of *o*-hydroxybenzaldehyde (10 mmol) and β-nitrostyrene (5 mmol) at room temperature and stirred for 1 min. [When the reactants were solid, a minimum amount (4-5 ml) of diethyl ether or dichloromethane was used to dissolve them prior to the addition of the alumina and then the solvent was removed under reduced pressure]. The reaction mixture was then subjected to sonic agitation[14] at 30-35°C for the time indicated in Table I. The product was extracted into acetone or dichloromethane (5x15 ml). Removal of the solvent under reduced pressure afforded the 2H-chromenes. Further purification (removal of traces of aldehyde) was carried out by passing a solution (CH_2Cl_2) of the chromene through a small column of basic alumina. The products exhibited physical and spectral characteristics in accord with the assigned structures.

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17. ^{1}H-NMR ($CDCl_3$) δ : 8.01(s,1H,C_4-H), 7.4-6.8(m,7H,Ar-H), 6.48(s,1H,C_2-H), 4.01(q,4H,2x-OCH_2), 1.38(t,3H,CH_3) and 1.36(t,3H,CH_3); ^{13}C-NMR ($CDCl_3$) δ : 74.15(C_2), 64.6(OCH_2), 64.4(OCH_2), 14.75 and 14.69(CH_3); Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.86; H, 5.57; N, 4.10. Found: C, 66.99; H, 5.85; N, 4.10.
18. ^{1}H-NMR ($CDCl_3$ δ : 8.02(s,1H,C_4-H), 7.26-6.75(m,6H,Ar-H), 6.58(s,1H,C_2-H), 4.03(q,4H,2x-OCH_2), 3.8(s,3H,-OCH_3), 1.39(t,6H,2xCH_3); ^{13}C-NMR($CDCl_3$) δ : 74.12(C_2), 64.6 and 64.5(-OCH_2), 56.4(-OCH_3) and 14.8(CH_3); Anal. Calcd. for $C_{20}H_{21}NO_6$; C, 64.69; H, 5.66; N, 3.77. Found: C, 64.51; H,5.37; N,3.66.
19. ^{1}H-NMR($CDCl_3$) δ : 7.42-7.18(m,8H,Ar-H), 6.9(d,1H,C_4-H), 5.4(d,$J_{2,3}$ = 10Hz,1H,C_2-H), 5.18(d,$J_{3,4}$ = 8.6Hz,1H,C_3-H), 2.15(-OAc); Anal. Calcd. for $C_{17}H_{14}ClNO_5$: C, 58.70; H, 4.03; N, 4.03. Found: C, 58.52; H, 4.05; N, 3.98.

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