

A SIMPLE SYNTHESIS OF 2H-PYRANS; A ONE-STEP SYNTHESIS OF FLINDERSINE

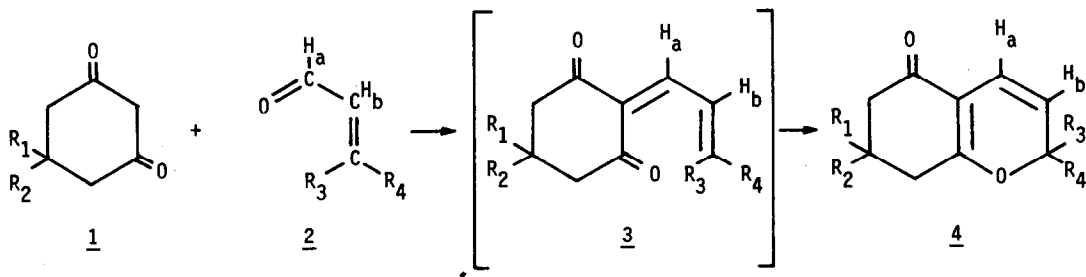
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Valence isomerism between 2H-pyrans and cis-dienones is a well known phenomenon. The influence of substituents on the equilibrium position has been studied<sup>1-4</sup> and several synthetic approaches have been applied<sup>1,3,5</sup>. Especially in the field of the chromenes the synthetic efforts are concentrated on the preparation of the intermediate dienones which in these cases spontaneously and completely cyclize to the desired bicyclic 2H-benzopyrans<sup>5</sup>. When the 2H-pyran ring is not annellated to an aromatic ring the equilibrium usually favors the cis-dienone and only a few exceptions are known<sup>1,7,8</sup>.

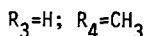
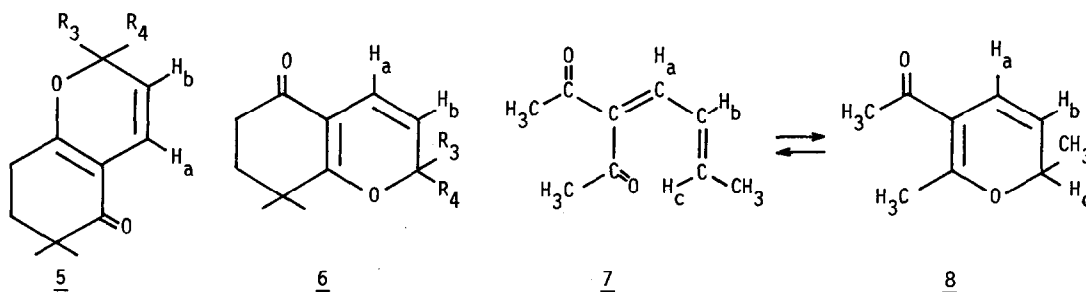
We now present a simple and efficient one-step synthesis of a non-aromatic annellated 2H-pyran-cis-dienone system in which the equilibrium is completely shifted to the cyclized product. The "intermediate" dienones are obtained by condensation of an  $\alpha,\beta$ -unsaturated aldehyde with a 1,3-diketone.



		% yield	
<u>a</u>	R <sub>1</sub> = H ; R <sub>2</sub> = H ; R <sub>3</sub> = CH <sub>3</sub> ; R <sub>4</sub> = H <sub>C</sub>	70	bp 99-100°C (0,01 mm)
<u>b</u>	R <sub>1</sub> = H ; R <sub>2</sub> = H ; R <sub>3</sub> = CH <sub>3</sub> ; R <sub>4</sub> = CH <sub>3</sub>	82	mp 42°C (petr. ether)
<u>c</u>	R <sub>1</sub> = H ; R <sub>2</sub> = H ; R <sub>3</sub> = CH <sub>3</sub> ; R <sub>4</sub> =	70	bp 135-136°C (0,1 mm)
<u>d</u>	R <sub>1</sub> = CH <sub>3</sub> ; R <sub>2</sub> = CH <sub>3</sub> ; R <sub>3</sub> = CH <sub>3</sub> ; R <sub>4</sub> = H <sub>C</sub>	67	bp 110-112°C (0,1 mm)
<u>e</u>	R <sub>1</sub> = CH <sub>3</sub> ; R <sub>2</sub> = CH <sub>3</sub> ; R <sub>3</sub> = CH <sub>3</sub> ; R <sub>4</sub> = CH <sub>3</sub>	70	mp 54-56°C (petr. eth.)
<u>f</u>	R <sub>1</sub> = CH <sub>3</sub> ; R <sub>2</sub> = CH <sub>3</sub> ; R <sub>3</sub> = CH <sub>3</sub> ; R <sub>4</sub> =	80	bp 121-122°C (0,05 mm)

Normally the condensation of aldehydes with 1,3-diketones, for instance dimedone, provides nice crystalline 1 : 2 condensation products which have been used for identification purposes for a long time. When  $\alpha,\beta$ -unsaturated aldehydes are condensed with 1,3-diketones, the first-formed dienones undergo valence isomerism to stable 2H-pyrans which are unsuitable for further condensation. By far the best yields were obtained in boiling pyridine and the addition of anhydrous  $MgSO_4$  gave further yield improvement.

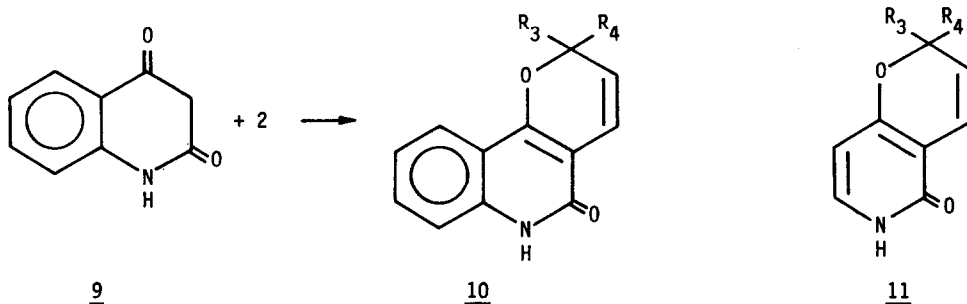
When the reaction was carried out at room temperature a small amount of 1 : 2 condensation product was isolated, together with the 2H-pyran as the major product. The asymmetric 4,4-dimethyl-1,3-cyclohexanedione gave the 2H-pyrans 5 and 6 in 75% and 16% yield respectively. The intermediate dienones could not be detected by nmr or tlc when cyclic 1,3-diketones were used. With 2,4-pentanedione and crotonaldehyde an equilibrium mixture of the dienone 7 (ca 80%) and the 2H-pyran 8 (ca 20%) was obtained.



The protons  $H_a$  and  $H_b$  in 4a-f, 5, 6 and 8 all had chemical shifts around  $\delta$  6.5 (doublets) and  $\delta$  5.3 (doublets or double doublets),  $J(H_a, H_b) = 10$  Hz. The chemical shifts of  $H_c$  in 4a, 4b, 5, 6 and 8 were centered around  $\delta$  5.0,  $J(H_c, CH_3) = 6$  Hz,  $J(H_c, H_b) = 3,5$  Hz and  $J(H_c, H_a) = 1.5$  Hz. The chemical shifts of  $H_a$  in 7 had  $\delta$  7.1 (doublet)  $J=11$  Hz; the chemical shifts of  $H_b$  and  $H_c$  were centered around  $\delta$  6.4 (multiplet)  $J(H_c, CH_3) = 6$  Hz and  $J(H_c, H_b) = 14$  Hz<sup>9</sup>. The coupling constants between  $H_c$  and  $H_b$  in 4a, 4d, 5, 6 and 8 indicate that the 2H-pyran structures were the correct ones. Further evidence was found in i) the comparison of the chemical shifts and coupling constants of 7 with those of the other compounds, ii) in the mass spectra, all showing the large M-15 base peak<sup>10</sup> and iii) in the formation of the two products 5 and 6 when an asymmetric diketone was used. Upon standing at room temperature pure 5 or 6 again gave mixtures of 5 and 6 indicating that isomerisation via the dienone structure is possible.

Especially when the 2H-pyran ring becomes annellated to an aromatic ring the intermediate dienones cyclize very rapidly. This has opened useful synthetic routes for several chromenes<sup>6</sup> and some alkaloids can also be synthesised very

simply and in high yield (86%) in this way, as was demonstrated by us with the synthesis of flindersine<sup>11</sup>. The spectral data were in accord with those reported for 10b in the literature<sup>10,12</sup>. Likewise 9 could be condensed with citral (2c) to 10c and 2,4-dihydropyridine gave 11b in high yield.



		% yield	mp
<u>10b</u>	R <sub>3</sub> = CH <sub>3</sub> ; R <sub>4</sub> = CH <sub>3</sub>	86	197-199°C
<u>10c</u>	R <sub>3</sub> = CH <sub>3</sub> ; R <sub>4</sub> =	89	-
<u>12b</u>	R <sub>3</sub> = CH <sub>3</sub> ; R <sub>4</sub> = CH <sub>3</sub>	85	173-174°C

A general procedure could be described as follows.

A solution of 0.05 mole of 1,3-diketone in 50 ml of pyridine was added in 60 min. to a stirred and boiling mixture of 0.06 mole of  $\alpha,\beta$ -unsaturated aldehyde, 19 g of anhydrous MgSO<sub>4</sub> and 30 ml of pyridine. The mixture was stirred and refluxed for another 15 min. and the pyridine was evaporated. Water and ether were added and the ethereal solution was extracted with dilute acid followed by a dilute NaHCO<sub>3</sub> solution. The ethereal solution was dried and evaporated. The residue was purified by distillation (3a, 3c and 3d), crystallisation (3b and 3e) or column chromatography (3f).

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