# A Novel High Yield γ-Chromone Synthesis

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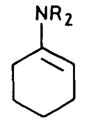
Substituted γ-chromones are rapidly produced in high (>90%) yield by reaction of morpholino (or piperidino)-methylene malonyl urethanes with 2-hydroxybenzaldehydes in hot ethanol solution.

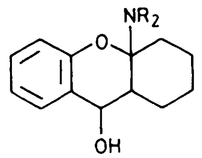
The reaction of salicylaldehyde and nuclear substituted derivatives with enamines *e.g.* cyclohexanone enamines (**1**), is well documented[1] and shown to produce adducts of type (**2**). The mechanism of the reaction is purported to involve reaction of the aldehydic carbon of the 2-hydroxybenzaldehyde with the β-carbon atom of the enamine in the dipolar form to produce the intermediate dipolar species which then cyclises to give (**2**).

In an attempt to duplicate this reaction, equimolar amounts of 5-chlorosalicylaldehyde, the enamine (**3**) derived from the ethoxymethylenemalonylurethane (**4**),† and morpholine in ethanol were heated on a steam bath. After 2—3 min the γ-chromone (**6**), m.p. >220 °C, crystallised from the solution in near (>90%) quantitative yield. The structure assigned to the compound was confirmed by elemental analysis, mass, high resolution mass, $^1$H and $^{13}$C n.m.r. spectra.

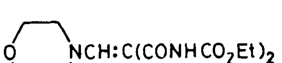
The same compound was similarly obtained using the corresponding piperidine imine. In the same way, reaction of salicylaldehyde, 3-methoxy-, 3-ethoxy-, and 3,5-dibromo-salicylaldehydes, and 1-hydroxy-2-napthaldehyde produced analogous chromones (**7**)—(**11**) respectively, in high yield. The mother liquor obtained from the initial reaction was evaporated and the residue heated *in vacuo* to give a crystalline sublimate of urethane identical with an authentic specimen. The mechanism of the reaction may be as outlined in Scheme 1 although the precise sequence is uncertain.



**(1)**



**(2)**



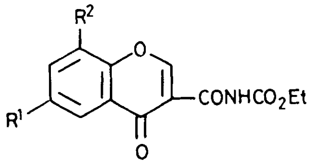
**(3)**

$\mathrm{EtOCH{:}C(CONHCO_2Et)_2}$

**(4)**

$\mathrm{CH_2(CONHCO_2Et)_2}$

**(5)**



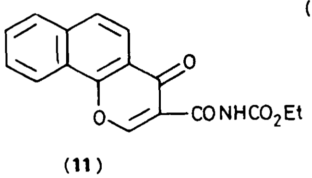
**(6)** $R^1$ = Cl, $R^2$ = H

**(7)** $R^1$ = $R^2$ = H

**(8)** $R^1$ = H, $R^2$ = OMe

**(9)** $R^1$ = H, $R^2$ = OEt

**(10)** $R^1$ = $R^2$ = Br



**(11)**

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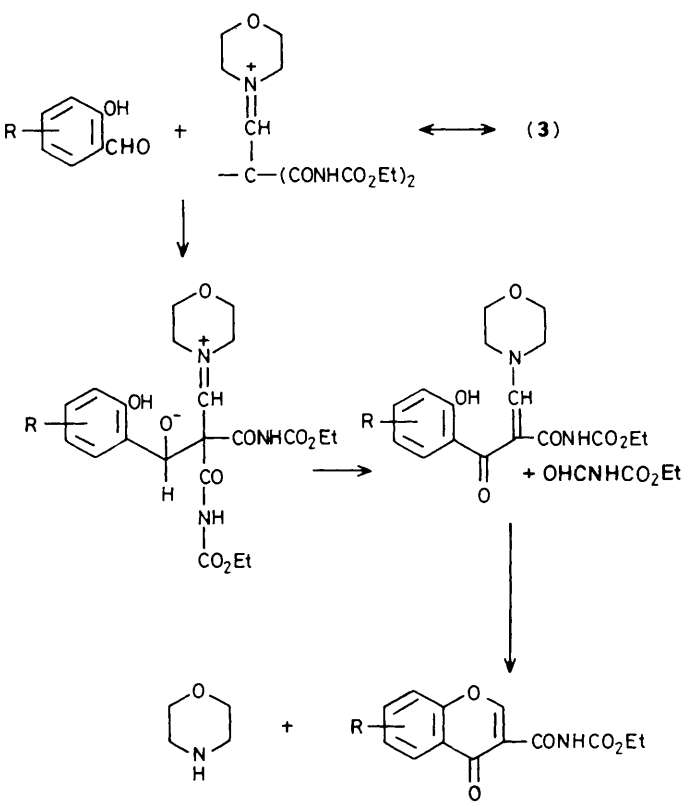
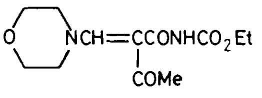
† Prepared by boiling a mixture of malonylurethane[2] (50 g), triethyl orthoformate (36 g) and acetic anhydride (66 ml) under reflux for 1.5 h, followed by evaporation of volatile material *in vacuo*, giving the pure crystalline ethoxymethylene derivative (42 g) m.p. 122 °C, which was separated and washed with ether.



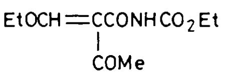
**Scheme 1**

Urethane is presumably derived from the postulated formylurethane by alcoholysis.

The use of enamine in this reaction has also been found not to be essential. Thus when the ethoxymethylene derivative (**4**) was treated with 3-ethoxysalicylaldehyde in hot ethanol chromone (**9**) was produced, though in somewhat lower yield than that obtained using either the corresponding morpholine or piperidine imine. The generality of the reaction was further confirmed by reaction of the morpholine imine (**12**) [derived from the ethoxymethylene derivative (**13**)] with 5-bromosalicylaldehyde in ethanol, which rapidly produced 3-acetylchromone (**14**) in high yield and crystallised from the solution on addition of water.

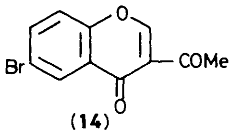


(**12**)



$EtOCH{=}C(COMe)CONHCO_2Et$

(**13**)



(**14**)

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