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HETEROCYCLIC INTRACONVERSION

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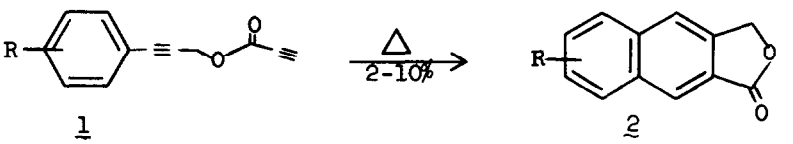
Functionalized naphthalenes are important as intermediates in the synthesis of anthracyclines[1] and in carcinogenicity studies[2]. An attractive route for the construction of such compounds is by intramolecular cycloaddition. Previous work centered around the thermal cyclization of aryl propargyl propiolates 1 to lactone 2. One notable drawback is the very low yields obtained by this procedure[3]. The analogous



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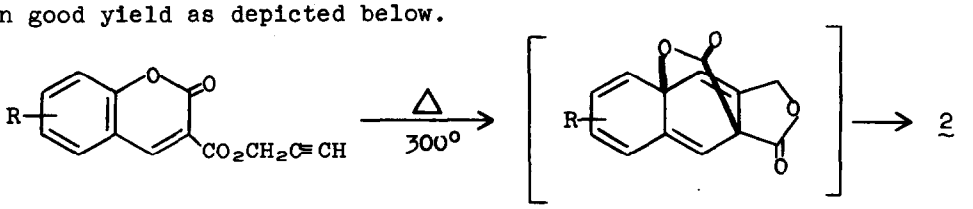
cyclization with trans-cinnamyl phenylpropiolates[4] affords better yields but cannot be extended to simpler systems. Although α-pyrones react with acetylenes to form substituted benzenes by Diels-Alder cycloaddition followed by expulsion of carbon dioxide[5], the corresponding reaction involving coumarins is unknown. We wish to report the intramolecular cycloaddition of coumarin esters 3 to provide naphthoic acid lactones 2 in good yield as depicted below.



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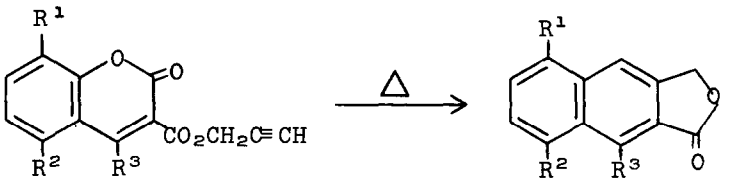
This reaction offers a convenient and regiospecific approach to the synthesis of substituted naphthalenes. Examples illustrating the versatility of our procedure are listed below. The coumarin 4-6 are readily prepared from the requisite salicylaldehyde and dipropargyl malonate using traditional Knoevnagel conditions[6]. Coumarin 7[7] was prepared from dipropargyl sodiomalonate and 2-acetoxybenzoyl chloride followed by methylation with diazomethane. The reaction conditions for the thermal intraconversion were defined after much experimentation and must be closely followed. The intraconversion must be conducted in a sealed tube placed in a 300°C bath[8] for 1.5 to 2 hours. If the reaction time is extended beyond two hours, extensive decomposition occurs. The coumarins are suspended in toluene which has been deoxygenated with argon. Unexpectedly, addition of hydroquinone must be avoided because its presence leads to extensive carbonization and greatly decreased yields. The crude product is chromatographed on silica gel (hexane: ether-1:1) to afford lactones 8[9], 9[10], 10[11], or 11[12].



			yield(%)[a]
4	R^1, R^2, R^3 = H	8	58
5	R^1 = OCH_3, R^2, R^3 = H	9	61
6	R^1 = H, R^2 = OCH_3, R^3 = H	10	51
7	R^1, R^2 = H, R^3 = OCH_3	11	47

a. Yield after chromatography. Conversion was typically 80-90%.

Surprisingly, the analog of 5 in which the acetylenic hydrogen was replaced by a carboethoxy group failed to cyclize under the aforementioned conditions.

Since Kraus[13] and others[14] have described the annelation potential of phthalide anions, lactones 8-11 may represent important intermediates for the synthesis of anthracyclines. This strategy is presently under active investigation.

Acknowledgements

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Footnotes and References

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6) The preparation of 4 is typical. A solution of 3.7g salicylaldehyde, 5.4g dipropargyl malonate and 0.5ml piperidine in 20ml of propargyl alcohol is refluxed for 5 hours. The solution is concentrated in vacuo. The crude product is dissolved in chloroform, washed with dilute HCl and brine followed by drying (Na_2SO_4) and concentration in vacuo. Crude product recrystallized from hexane-ethyl acetate. Yield 65%. 4: mp 114-116; IR (mull) 3235, 2120, 1745, 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (t, J=3Hz, 1H), 4.95 (d, J=3Hz, 2H), 7.5 (m, 4H), 8.6 (s, 1H); MS $C_{13}H_8O_4$ requires 228.0422, measured 228.0420. 5: mp 153-155; IR (mull) 3250, 2135, 1740 (broad) cm^{-1}; NMR ($CDCl_3$) δ 2.55 (t, J=3Hz, 1H), 3.95 (s, 3H), 4.95 (d, J=3Hz, 2H), 7.35 (m, 3H), 8.65 (s, 1H); MS $C_{14}H_{10}O_5$ requires 258.0528, measured 258.0535. 6: mp 138-139; IR (mull) 3280, 2135, 1770, 1715 cm^{-1}; NMR (d_6-acetone) δ 2.8 (t, J=3Hz, 1H), 4.0 (s, 3H), 5.0 (d, J=3Hz, 2H), 7.0 (m, 2H), 7.7 (m, 1H), 8.95 (s, 1H); MS $C_{14}H_{10}O_5$ requires 258.0528, measured 258.0531.

7) To a hexane washed suspension of 1.5g of 50% NaH in 50ml ether is added 4.5g dipropargyl malonate. After hydrogen evolution has ceased, 6.0g of 2-acetoxybenzoyl chloride in 10ml ether is added. The mixture is refluxed for 20 hours, cooled and filtered. The precipitate dissolved in water, treated with concentrated HCl followed by standard ethereal work-up. The crude crystalline enol is stirred with excess ethereal diazomethane until there is no suspended material. The solution is quenched with acetic acid and concentrated. The crude product chromatographed on silica gel with CH_2Cl_2.
7: mp 112-113; IR (mull) 3300, 2140, 1745, 1700, 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (t, J=3H, 1H), 4.2 (s, 3H), 4.95 (d, J=3Hz, 2H), 7-8 (m, 4H); MS $C_{14}H_{10}O_5$ requires 258.0528, measured 258.0519.

8) A refluxing benzophenone bath is used.

9) 8: mp 208-210 (EtOH) Lit. 206[15]; IR (mull) 1750 cm^{-1}; NMR ($CDCl_3$) δ 5.5 (s, 2H), 7.5-8.5 (m, 6H); MS $C_{12}H_8O_2$ requires 184.0524, measured 184.0524.

10) 9: mp 195-196; IR ($CHCl_3$) 1750 cm^{-1}; NMR ($CDCl_3$) δ 4.05 (s, 3H), 5.5 (s, 2H), 7.3-8.3 (m, 5H); MS $C_{13}H_{10}O_3$ requires 214.0630, measured 214.0629.

11) 10: IR (mull) 1750 cm^{-1}; NMR ($CDCl_3$) δ 4.05 (s, 3H), 5.4 (s, 2H), 7-8 (m, 5H); MS $C_{13}H_{10}O_3$ requires 214.0630, measured 214.0620.

12) 11: IR (mull) 1740 cm^{-1}; NMR ($CDCl_3$) δ 3.95 (s, 3H), 5.7 (s, 2H), 7-8 (m, 5H); MS $C_{13}H_{10}O_3$ requires 214.0630, measured 214.0625.

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