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A Sequential Anionic [4+2] Cycloaddition And Thermal [4+2] Cycloreversion Strategy to Furocoumarins : A Concise Synthesis of Methoxsalen

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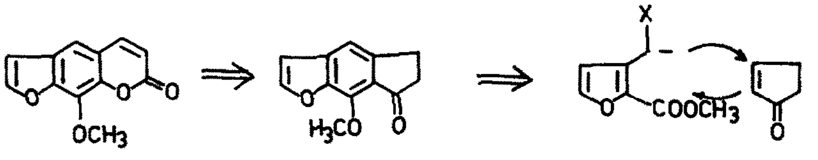
Abstract : The synthesis and utility of unprecedented fluorenofurans **7** and oxa-*s*-indacenones **8** as key intermediates for synthesis of methoxsalen **1** is described, illustrating a novel synthetic approach to furocoumarins.

The interest in the chemistry of furocoumarins continues to be unabated due to their wide therapeutic applications in skin ailments and ever complex photobiology.[1] Despite a long history of synthetic efforts[2] in this field, the commercial availability[3] of methoxsalen **1**, the most active member of the family, relies upon its natural sources. Elaboration of either coumarins or benzofurans for the synthesis of furocoumarins has been of limited scope.[2] Similarly, the only report[4] on exploitation of monosubstituted furans through intramolecular Diels-Alder reaction is demerited by lengthiness of reaction sequence and its inapplicability to methoxsalen **1**.



1

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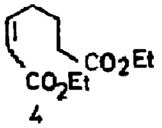
3a: X = $SO_2C_6H_4CH_3$-p
b: X = SOC_6H_5

Scheme 1

With an aim to evolve a general and efficient synthesis of furocoumarins, we began to work on the retrosynthesis of methoxsalen **1** shown in Scheme 1. But, the plan was thwarted by total failure in crucial annulation[5] of furo-1,4-dipolar reagents **3a**[6a] or **3b**[6b] with cyclopentenone or diester **4** in the presence of ^{t}BuOLi or LDA, possibly due to base-catalysed polymerisation of the Michael acceptors. Alternatively, furan-annulation onto bicyclopentadienone **5** (likely to be resistant to base-catalysed polymerisation due to its rigidity) and retrocycloaddition of **7** to generate oxaindacenones **8** were contemplated. The reaction between furosulfone **3a** and enone **5** in the presence of ^{t}BuOLi, expectedly provided the annulated products **6** (~ 88%). However, all the attempts to effect dehydrosulfonation of **6** proved futile, due to the cis-orientation of the sulfone group and the indicated hydrogen in **6**. On the other hand, furosulfoxide **3b** underwent smooth annulation (^{t}BuOLi) with **5** to furnish B-ring aromatized product **7a**[7] (77%) in one-pot. But, the objective to accomplish Baeyer-Villiger (B.V.) oxidation of **7b**, followed by retro Diels-Alder reaction to obtain methoxsalen **1** was not fulfilled, because of strong resistance of compound **7b** to oxidation (H_2O_2-Ac_2O, m-CPBA, MMPP) under a variety of conditions.[8] Subsequently, retrocycloaddition of **7** was examined under different conditions. Flash vacuum pyrolysis (500° C / 0.1 mm) of **7a** and **7b** cleanly provided novel oxaindacenones **8a** and **8b** respectively in quantitative yields. It may be noted that 2,3-unsubstituted indenones are difficult to prepare. Similarly as for compound **7**, B.V. oxidation of **8a** or **8b** was also unsuccessful, despite our austere experimentation. Finally, a circuitous path was followed to complete the synthesis of **1** from **8**. Treatment of **8b** with thiophenol in the presence of triethylamine gave **9a** (98%). B.V. oxidation of sulfide **9a** yielded methoxsalen **1** (20%) along with **9b** (40%). Although the sulfone **9b** was inert to B.V. oxidation, it could be converted to **8b** (90%) on DBU treatment, in effect, increasing the yield of methoxsalen **1** to ~ 50%. In summary, the present synthesis of methoxsalen **1** represents a new synthetic route to furocoumarins. The applicability of this route to the synthesis of other members of furocoumarin family and the chemistry of the novel oxaindacenones **8a, b** are under active investigation.



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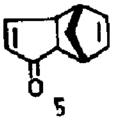

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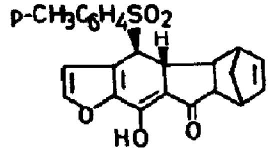

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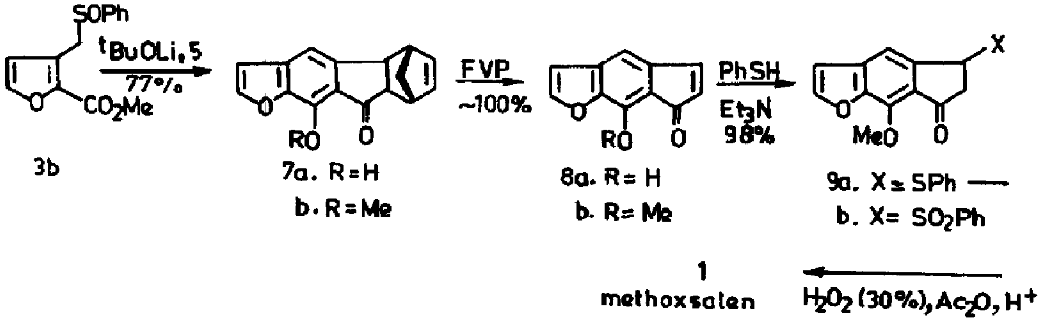

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6) (a) Majumdar, G.; Murty, K. V. S. N.; Mal, D. *Tetrahedron Lett.* **1994** (in press). mp of **3a** : 119-120° C. (b) Compound **3b**, an oil, was prepared in two steps (~ CH_2Br → ~ CH_2SPh → ~ CH_2SOPh) from methyl 2-bromomethylfuroate.
7) Physical data of selected compounds : **7a**, mp. 170-171° C; ^1H NMR ($CDCl_3$) δ 9.55 (bs, 1H), 7.70 (d, 1H, J = 2), 7.00 (s, 1H), 6.71 (d, 1H, J = 2), 5.93-5.88 (m, 1H), 5.53-5.48 (m, 1H), 3.90-3.84 (m, 1H), 3.30-3.20 (m, 3H), 1.81-1.67 (m, 2H). **8a**, mp. 163° C; ^1H NMR ($CDCl_3$) δ 7.66 (d, 1H, J = 2), 7.43 (d, 1H, J = 5.8), 6.80 (s, 1H), 6.71 (d, 1H, J = 2), 5.90 (d, 1H, J = 5.8); **8b**, mp. 83° C; ^1H NMR ($CDCl_3$) δ 7.63 (d, 1H, J = 2), 7.39 (d, 1H, J = 5.8), 6.82 (s, 1H), 6.70 (d, 1H, J = 2), 5.84 (d, 1H, J = 5.8), 4.38 (s, 3H).
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