Pergamon

*Tetrahedron Letters*, Vol. 38, No. 16, pp. 2795-2798, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00509-1

# A New Synthesis of 8-Methylpsoralen Utilizing a Palladium-Copper Catalyzed Reaction to Generate the Furan Ring and Thus Allowing for the Generation of Novel Analogs in the 5'-Position

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**Abstract:** A rapid synthesis of 8-methylpsoralen is reported that utilizes a palladium-copper catalyzed reaction to generate the furan ring. Since 8-methylpsoralen is considered one of the most photodynamic methylpsoralens known and given the fact that psoralens in general have been shown to have medicinal value against bacteria and viruses, this synthesis allows for the availability to generate new derivatives by supplying a handle in the 5'-position.[1] © 1997 Elsevier Science Ltd.

The beneficial effects of psoralens have been investigated over a vast number of years. The ancient Egyptians recognized the ability of psoralens to treat skin disorders.[2] Psoralens have been utilized to treat psoriasis and vitiligo as well as bacterial and viral infections.[3,4] Since psoralens have achieved medical significance, convenient synthetic routes are needed to generate the parent three ring backbone.

Several synthetic pathways have been developed for the psoralen system, but the majority of these routes employ many steps and often result in very low yields.[5] Kaufman described a synthesis of 8-methylpsoralen using 7-allyloxy coumarin as an intermediate to obtain the final product in a 26% yield.[1] Macleod and Worth reported a four step synthesis that uses a base catalyzed cyclization of 7-acetonylcoumarin to give psoralen in a 30% yield.[6] Nore and Honkanen reported a novel synthesis of 8-methoxypsoralen giving a 12% yield, but the reaction sequence requires seven steps.[7]

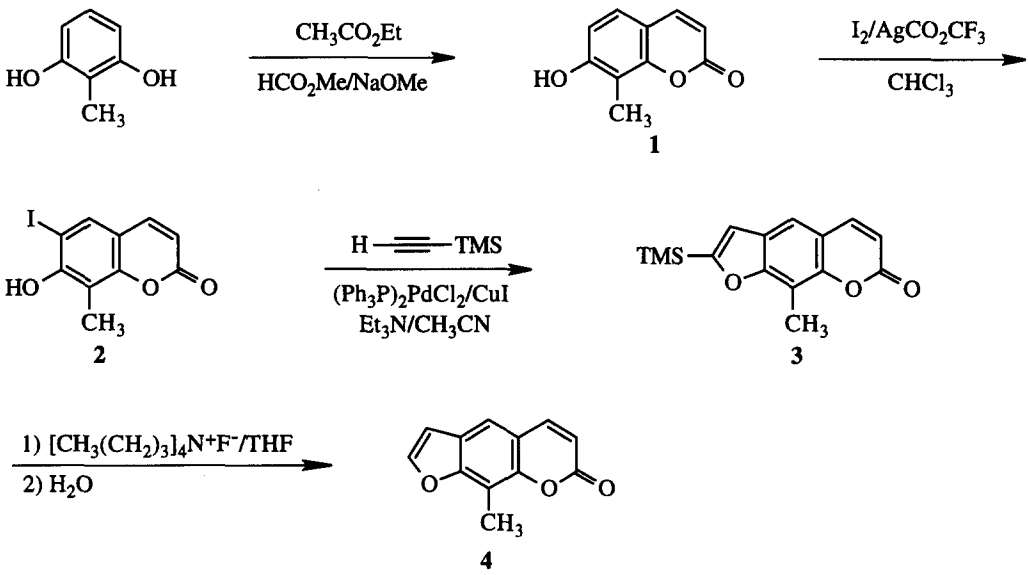
The synthesis of indoles, benzofurans, phthalides, and tolanes utilizing copper(I) acetylides has been developed by Castro and coworkers.[8,9] Thus, Collado's group prepared psoralens from a cyclization reaction utilizing acetylenic reagents and 6-iodo-7-hydroxycoumarin in the presence of $Cu_2O$.[10] Starting with 7-hydroxycoumarin, seven steps were used to generate psoralen in a 23% yield.

Palladium catalyzed syntheses of furans, indoles and other heterocyclic compounds have also been accomplished.[11,12] We now report a four step synthesis for the generation of 8-methylpsoralen utilizing a palladium-copper catalyzed reaction.

Scheme 1 describes the synthesis of 8-methylpsoralen **4**. Coumarin **1** was generated by a Pechmann condensation in a 93% yield.[13,14] The 7-hydroxy-8-methyl coumarin is then iodinated to generate **2** in a 74%

yield.[15,16] Three products were obtained in the reaction: 7-hydroxy-6-iodo-8-methylcoumarin as the major product, and 7-hydroxy-3-iodo-8-methylcoumarin and 7-hydroxy-3,6-diiodo-8-methylcoumarin as minor components.[17]

**Scheme 1**



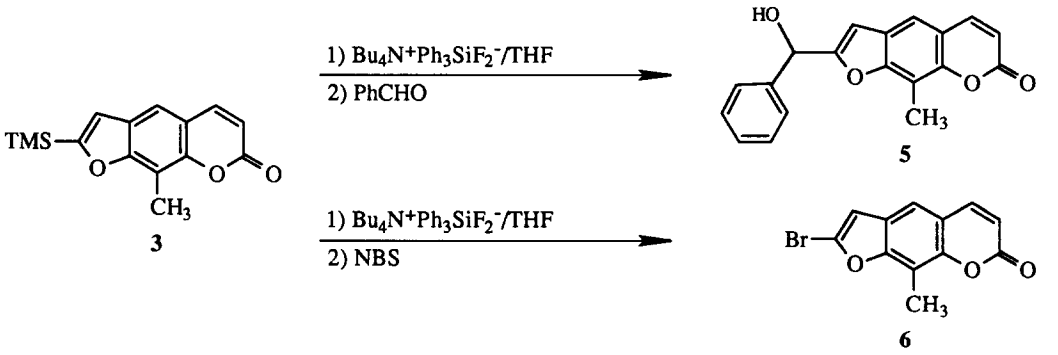

The psoralen backbone was formed by the palladium-copper catalyzed reaction of **2** with trimethylsilylacetylene to give **3** in a 82% yield using the conditions developed by Sonogashira.[18,19] The removal of the trimethylsilyl group by tetrabutylammonium fluoride to give **4** resulted in a 92% yield for 8-methylpsoralen.

The full exploitation of this palladium-copper catalyzed synthesis has not yet been recognized. However, the resulting 52% overall yield of 8-methylpsoralen starting from 2-methylresorcinol shows the power of this synthetic route. Furthermore, utilizing this methodology, starting with different benzene derivatives, new types of psoralen compounds can be formed.

By substituting other electrophilic groups such as bromine or benzaldehyde, after the removal of the trimethylsilyl group, two new psoralen derivatives have been synthesized. Scheme 2 depicts the products that were obtained by utilizing tetrabutylammonium triphenyldifluorosilicate.[20,21] The bromine analog **6** was achieved in a 62% yield while the benzaldehyde analog was obtained in a 68% yield. The new functional

groups added will be excellent handles for coupling other compounds with the psoralen to develop new types of biologically active agents.

**Scheme 2**




Acknowledgment: I thank Dr. Matthew Platz and Dr. David Hart for helpful discussions.

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16. The experimental procedure of **2** is as follows. To a mixture of $AgCO_2CF_3$ (2.89 g, 0.0131 mol) and **1** (0.995 g, 5.65 mmol) in 50 ml of $CHCl_3$ was added an iodine (2.39 g, 9.43 mmol)/$CHCl_3$ (50 ml) via cannula. After stirring 24 h at reflux, the AgI was filtered, and the solvent was removed in vacuo. The residue was chromatographed (silica gel) using $CHCl_3$ as the eluent to give a pale yellow solid **2** (1.26 g, 74%). mp 180-183 °C; $^1$H NMR ($d_6$-DMSO, 200 MHz) δ 2.24 (s, 3 H, $CH_3$), 6.22-6.27 (d, 1 H, ArH), 7.87-7.92 (d, 1 H, ArH), 7.98 (s, 1 H, ArH), 10.19 (s, 1 H, OH); $^{13}$C NMR ($d_6$-DMSO, 62.5 MHz) δ 9.39, 82.42, 112.13, 112.30, 113.96, 134.88, 143.65, 153.03, 157.14, 160.09; HREIMS cacld for $C_{10}H_7IO_3$ ($M^+$): 301.9442, found: 301.9447.

17. Since three iodocoumarins were obtained, the attack of the electrophile could have occurred at the 3-position first and then at the 6-position. Furthermore, since excess $AgCO_2CF_3$ was used, the question could be raised as to whether the excess $AgCO_2CF_3$ was removing the iodine in the 3-position under the reaction conditions. In fact, this was not the case because the 3,6-diiodocoumarin did not react with $AgCO_2CF_3$ under the same conditions as the initial iodination step.

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19. The experimental procedure of **3** is as follows. A mixture of **2** (0.100 g, 0.331 mmol), trimethylsilylacetylene (0.695 g, 7.08 mmol), CuI (0.0148 g, 0.0777 mmol), $(Ph_3P)_2PdCl_2$ (0.0100 g, 0.0142 mmol), $Et_3N$ (5 ml), and $CH_3CN$ (20 ml) were heated at 50 °C for 24 h under Ar. The solvent was removed in vacuo, and the residue was chromatographed (silica gel) using $CH_2Cl_2$ to give an off-white solid (0.074 g, 82%). mp 155-157 °C; $^1$H NMR ($CDCl_3$, 200 MHz) δ 0.37 (s, 9 H, TMS), 2.61 (s, 3 H, $CH_3$), 6.31-6.36 (d, 1 H, ArH), 6.97 (s, 1 H, ArH), 7.47 (s, 1 H, ArH), 7.75-7.80 (d, 1 H, ArH); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) δ -1.92, 8.46, 113.68, 115.01, 115.82, 116.50, 124.58, 144.75, 161.58; HREIMS cacld for $C_{15}H_{16}SiO_3$ ($M^+$): 272.0869, found: 272.0861.

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(*Received in USA* 24 *October* 1996; *revised* 5 *March* 1997; *accepted* 7 *March* 1997)