Pergamon

Tetrahedron Letters 40 (1999) 4505–4506

TETRAHEDRON LETTERS

A CONCISE REGIOSPECIFIC SYNTHESIS OF 8,8-DIMETHYL-2*H*, 8*H*-PYRANO [6, 5-*h*]QUINOLIN-2-ONE AND RELATED COMPOUNDS [1]

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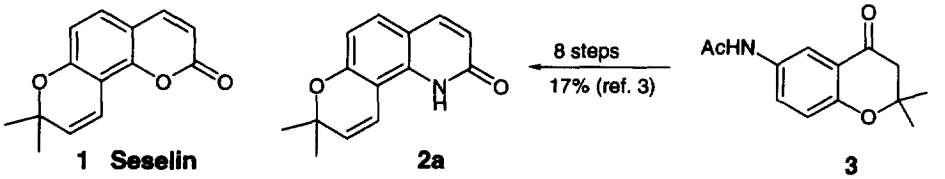
Received 3 March 1999; revised 19 April 1999; accepted 20 April 1999

Abstract: An efficient method for the regiospecific synthesis of 8,8-dimethyl-2*H*,8*H*-pyrano[6,5-*h*]quinolin-2-one and related compounds via a Claisen rearrangement is described.

Seselin (pyranocoumarin) and analogous pyranoquinolin-2-one derivatives possess various useful bioactivities, including anti-HIV activity for the former,[2] and antithrombotic and antiallergic properties for the latter.[3] We recently discovered that 4-methyl substituted pyranoquinolin-2-one (**2b**) also has potent antitumor activity.[4] Its unique substituted angular 8,8-dimethyl-2*H*,8*H*-pyranoquinolin-2-one structure provides an interesting synthetic challenge.



1 Seselin **2a** **3**

One synthetic methodology has been reported for the preparation of unsubstituted 8,8-dimethyl-2*H*, 8*H*-pyrano[6,5-*h*]quinolin-2-one (**2a**),[3] but it requires eight steps and has a 17% overall yield from the synthetic intermediate **3**. In the course of our work, we became interested in making various 4-substituted derivatives, and needed easy access to both unsubstituted (**2a**) and 4-substituted 8,8-dimethyl-2*H*, 8*H*-pyranoquinolin-2-one derivatives (**2b–d**). Herein we describe a simple and efficient four step method to produce such compounds.

We began our study by investigating the synthesis of **2a** (Scheme 1). Following Fujioka's procedures, 3-methoxyaniline (**4**) was reacted with cinnamoyl chloride to give 3-methoxy-cinnamanilide (**5**) in 95% yield. Cyclization of **5** with aluminum chloride as catalyst in chlorobenzene afforded the desired 7-hydroxyquinolin-2-one (**6**).[5] Subsequently, a nucleophilic substitution reaction of **6** with 3-chloro-3-methylbut-1-yne gave **7** in 72% yield. Next, a regiospcific Claisen rearrangement at high temperature provided the desired angular pyranoquinolin-2-one (**2a**) in 96% yield.[6]

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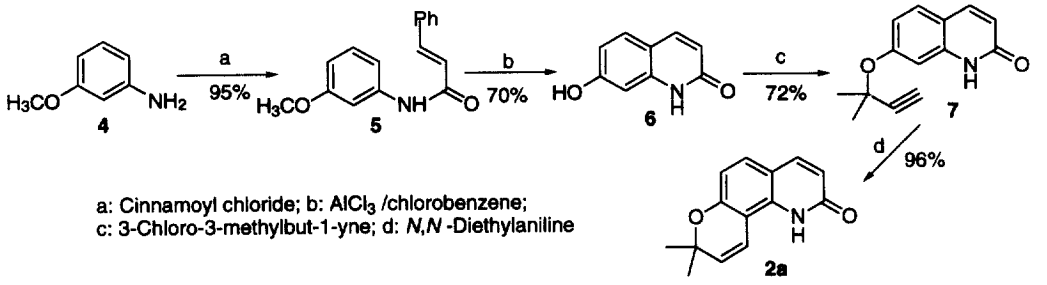
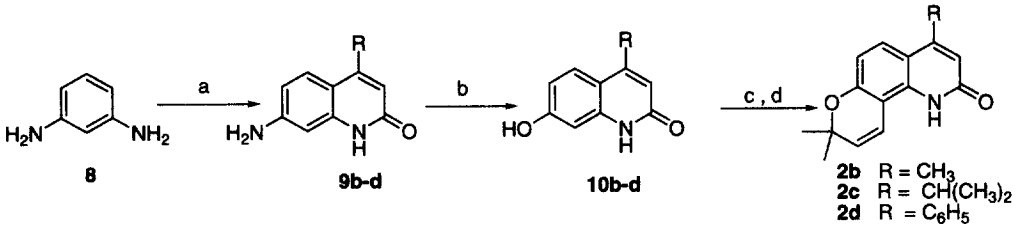
PII: S0040-4039(99)00821-7

Scheme 1



Compounds **2b–d** were prepared by a similar 4-step sequence as illustrated in Scheme 2. First, a Knorr cyclization was used in a similar fashion to procedures of López-Alvarado et al.[7] Treatment of **8** with ethyl acetoacetate, ethyl isobutyrylacetate and ethyl benzoylacetate, respectively, gave 7-amino-quinolin-2-ones (**9b–d**), followed by diazotization and hydrolysis to form 7-hydroxy-quinolin-2-ones (**10b–d**). The next reactions paralleled those for **2a** providing **2b–d** via a regiospecific Claisen rearrangement.[8]

Scheme 2



In conclusion, we have developed a novel 4 step procedure for the general preparation of 8,8-dimethyl-2*H*, 8*H*-pyrano[6,5-*h*]quinolin-2-ones. The procedure is particularly useful because of its efficiency, the ready availability of the starting materials, and ease of operation. It is well-suited to the preparation of analogs for SAR studies.

Acknowledgement: This investigation was supported in part by grant CA 17625 from the Cancer Institute, NIH awarded to K. H. Lee.

References and notes:

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8. All new compounds gave satisfactory analytical and spectroscopic data. Selected spectroscopic data for **4,8,8-Trimethyl-2*H*,8*H*-pyrano[6,5-*h*]quinolin-2-one (2b)**: Yield: 51%; mp: 256–258 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ : 1.46 (s, 6H, 2xCH_3), 2.45 (s, 3H, 4-CH_3), 5.80 (d, J = 9.6Hz, 1H, H-9), 6.40 (s, 1H, H-3), 6.47 (d, J = 8.76 Hz, 1H, H-6), 6.86 (d, J = 9.6 Hz, 1H, H-10), 7.46 (d, J = 8.76 Hz, 1H, H-5), 9.96 (dr, 1H, NH); HRMS calcd for $C_{15}H_{15}NO_2$ 241.1103, Found 241.1110.