Condensation of Homophthalic Anhydrides with Heterocyclic Imines and DMAD under Mild Conditions

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Condensation of 7-methoxyhomophthalic anhydride with 2-imidazoline, 2-thiazoline, 2-oxazoline, 1-pyrroline trimer and DMAD (with triethylamine) occurs rapidly under mild conditions.

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The reaction of homphthalic anhydrides with imines has proven to be a powerful method for the synthesis of a variety of carboxyisoquinolones [1,2]. Coppola has demonstrated that the condensation with imidates occurs with decarboxylation in order to give fused isoquinolones [3].

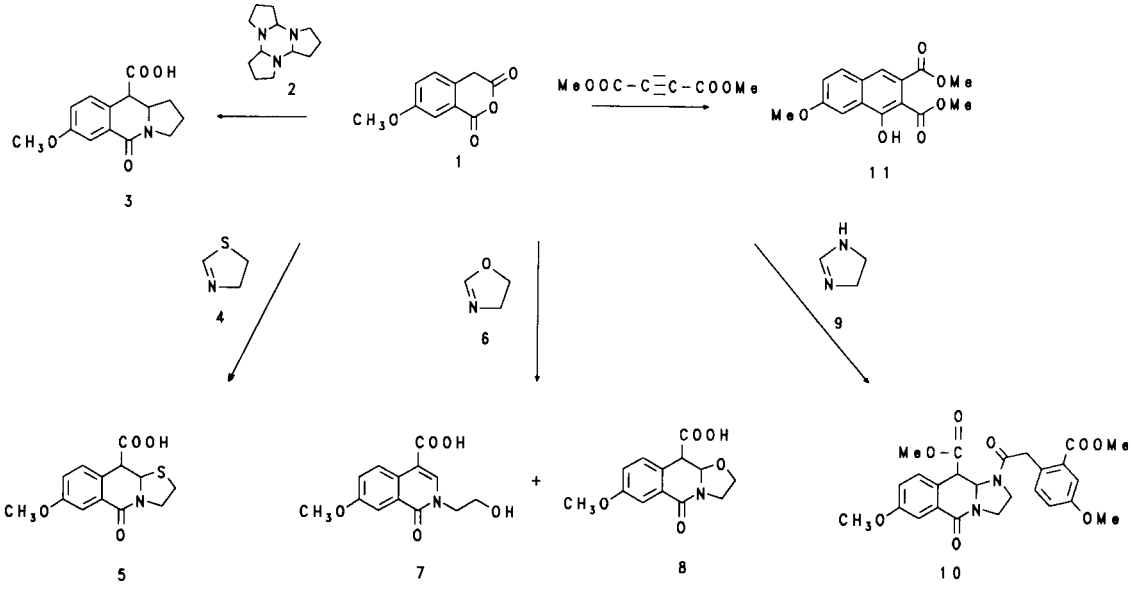
Previous work has also shown that the condensation of 7-methoxyhomophthalic anhydride **1** occurs with 1-pyrroline monomer in order to give 7-methoxy-10-carboxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one **3** [4]. Herein we report that the reaction can be accomplished without prior depolymerization of 1-pyyroline. Simple addition of 1-pyrroline trimer **2** to **1** in dichloromethane gives **3** in quantitative yield as a 50/50 mixture of diastereomers (Scheme I). In this manner the decomposition which normally accompanies depolymerization of the trimer (*via* co-distillation with THF) is avoided.

The condensation of **1** and 2-thiazoline (**4**) also occurs in quantitative yield to give the tricycle **5** as a 2/1:*trans*/*cis* ratio of diastereomers. The ratio of diastereomers was determined from the ^{1}H-nmr spectrum of the mixture which showed a 2/1 ratio for the 10a proton doublets (*cis* $J_{10\text{-}10a}$ = 4.5 Hz, *trans* $J_{10\text{-}10a}$ = 11.7 Hz).

Although the reaction of homophthalic anhydrides with the ethyl imidate of oxazolone occurs with rearrangement and decarboxylation, the reaction with 2-oxazoline (**6**) occurs to give the expected product which undergoes a retro-Michael reaction in order to give the ring opened product **7** in moderate yield (55%) which precipitates from the reaction mixture. This is again evident from the ^{1}H-nmr spectrum which shows a singlet at δ 8.02. Remaining in the mother liquor is the ring closed compound **8** exclusively as the *cis* isomer ($J_{10\text{-}10a}$ = 4.0 Hz). Although the synthesis of 2-oxazoline has been reported previously by Wenker, in our hands this procedure failed to give the desired **6** [5]. Modification involved the treatment of ethanol formamide with a large excess of thionyl chloride for 2 hours, evaporation and treatment of the residue with sodium carbonate, extraction into methylene chloride and distillation from potassium hydroxide.

Reaction of 2 equivalents of **1** with 2-imidazoline **9** gave **10** (90%) after esterification (diazomethane). Here the basic N-1 nitrogen underwent a condensation with a sec-

Scheme I



ond anhydride molecule. The *trans* isomer was the exclusive product ($J_{10\text{-}10a}$ = 10 Hz).

Other azomethine containing heterocycles in which the nitrogen is less basic (*N*-acetylimidazole, oxazole, thiazole, 2-isoxazoline) than those mentioned above fail to react under these conditions.

The reaction of homophthalic anhydride enolates with dienophiles has become a powerful tool which is useful in the synthesis of anthraquinones [6,7]. However, the reaction is reported to require strongly basic conditions. We have found that this reaction does in fact proceed quickly in the presence of a catalytic amount of Et_3N (0.2 equivalent) to give **11** in good yield (72%) at room temperature after 2 hours. Such conditions may involve an alternative mechanism but may be useful with more complex dienophiles which contain base sensitive functionality.

EXPERIMENTAL

Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. The ^1H and ^{13}C-nmr spectra were recorded on a Bruker (400 MHz) or a Varian 360 NMR spectrometer with tetramethylsilane as a internal standard. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia and are with 0.4% of the theoretical percentages. Common reagent grade chemicals were purchased from Aldrich Chemical Company.

7-Methoxy-10-carboxy-1,2,3,5,10,10a-hexahydrothiazolo[3,2-*b*]-isoquinolin-5-one (**5**).

In 5 ml of dry dichloromethane was dissolved 7-methoxyhomophthalic anhydride (**10**) (650 mg, 3.3 mmoles) and to this was added dropwise 2-thiazoline (**4**) (320 mg, 3.6 mmoles) in 2 ml of dichloromethane under a nitrogen atmosphere. The resulting mixture was refluxed for 30 minutes and then allowed to stir at room temperature overnight. The product which precipitates out was collected by filtration and washed well with dichloromethane and dried to give 940 mg of **5** (99%); ms: m/z 279, 235, 218, 192, 175, 164, 158, 149, 135, 117, 103, 88, 77, 55; ^1H-nmr (DMSO-d_6/deuteriochloroform): 7.38 (m, 1H), 7.28 (d, 1H), 7.1 (m, 1H), 5.31 (d, 1H, J = 4.6 Hz), 5.17 (d, 1H, J = 11.6), 4.35-4.30 (m, 1H), 4.02 (d, 1H, J = 11.6), 3.8 (s, 3H), 3.6-3.5 (m, 1H), 3.18-3.02 (m, 2H); ^{13}C-nmr: 171.6, 161.4, 159.0, 129.7, 128.5, 126.2, 118.6, 112.2, 62.0, 55.3, 52.0, 48.9, 28.4.

Anal. Calcd. for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01; S, 11.47. Found: C, 55.86; H, 4.69; N, 5.01; S, 11.55.

2-Oxazoline (**6**).

N-Formylethanolamine (25 g, 280 mmoles) was treated with thionyl chloride (40 ml) with cooling (ice-bath) and after the reaction subsides stirring was continued at room temperature for 1 hour. Excess thionyl chloride was evaporated under reduced pressure and the oily residue was neutralized with sodium carbonate, extracted with dichloromethane, dried (sodium sulfate), and evaporated so that the temperature doesn't rise above 40°. The resulting material was distilled from crushed potassium hydroxide (bp_{100} = 40-45°) to give 13 g of **6** (70%).

2-(2-Hydroxyethyl)-4-carboxy-7-methoxy-1,2-dihydroisoquinolin-5-one (**7**).

In 25 ml of dry dichloromethane was dissolved 7-methoxyhomophthalic anhydride (3.14 g, 16 mmoles) under a nitrogen atmosphere. To this was added dropwise 2-oxazoline (1.27 g, 17 mmoles) and the resulting mixture was refluxed for 3 hours. Upon cooling the product precipitated out and was collected, washed with dichloromethane, and dried to give 2.4 g of **7** (55%); ms: m/z 206, 178, 163, 135, 121, 91, 72, 44; ^1H-nmr (DMSO-d_6): 12.7 (s, 1H), 8.79 (d, 1H, J = 8.9 Hz), 8.25 (s, 1H), 7.69 (d, 1H, J = 2.7 Hz), 7.40 (dd, 1H, J = 2.7, 8.9 Hz), 4.15 (t, 2H, J = 5.0 Hz), 3.9 (s, 3H), 3.75 (t, 3H, J = 5.0 Hz); ^{13}C-nmr: 167.3, 161.5, 158.4, 140.5, 128.9, 127.4, 126.7, 122.8, 108.2, 105.4, 59.3, 55.8, 52.4.

Anal. Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.94; N, 5.32. Found: C, 59.17; H, 5.00; N, 5.31.

1-(2-Methoxycarbonyl-4-methoxyphenylacetyl)-7-methoxy-10-methoxycarbonyl-1,2,3,5,10,10a-hexahydroimidazo[1,2-*b*]isoquinolin-5-one (**10**).

In 15 ml of dry acetonitrile was dissolved 7-methoxyhomophthalic anhydride (**1**) (1.5 g, 7.8 mmoles) and the resulting solution was cooled to 0° in an ice-bath. To this was added dropwise 2-imidazoline (**9**) (277 mg, 3.9 mmoles) dissolved in 5 ml of acetonitrile. A precipitate was noted almost immediately and the resulting mixture was stirred at 0° for an additional 2 hours after which time sufficient methanol was added to dissolve the precipitate and esterification was accomplished with excess diazomethane in ether. The solvents are evaporated and the product was recrystallized from methanol to give 1.7 g of **10** (90%), mp 186-187°; ms: m/z 482, 450, 418, 389, 303, 259, 247, 233, 217, 202, 179, 147, 121, 91, 77; ^1H-nmr (deuteriochloroform): 7.6 (m, 2H), 7.3-7.1 (m, 4H), 5.85 (d, 1H, J = 10 Hz), 4.4-3.5 (m, 19H); C^{13}-nmr: 171.2, 170.3, 167.2, 161.2, 159.5, 158.5, 133.1, 130.0, 129.2, 128.5, 128.4, 125.6, 120.0, 118.3, 116.1, 111.4, 71.2, 55.6, 55.5, 52.5, 52.0, 51.3, 44.8, 43.3, 39.9.

Anal. Calcd. for $C_{25}H_{26}N_2O_8 \cdot H_2O$: C, 60.00; H, 5.60; N, 5.60. Found: C, 59.77; H, 5.28; N, 5.61.

1-Hydroxy-2,3-carboxymethyl-7-methoxynaphthylene (**11**).

In 5 ml of dry dichloromethane was dissolved 7-methoxyhomophthalic anhydride (**1**) (500 mg, 2.6 mmoles) under a nitrogen atmosphere and to this was added 30 mg of triethylamine and the resulting solution was stirred for 5 minutes. To this was added dropwise DMAD (407 mg, 2.8 mmoles) and the reaction was allowed to stir overnight. Analysis (tlc) indicated the reaction was completed after 2 hours. In the morning the organic layer was washed with water, dried (sodium sulfate), and evaporated to give the crude product which was purified by flash chromatography (silica gel, diethyl ether) and the product was then recrystallized from a small amount of ether to give 560 mg of **11** (72%), mp 129-130°; ms: m/z 290, 259, 258, 243, 229, 187, 172, 155, 143, 129, 101, 58; ^1H-nmr (deuteriochloroform): 7.66-7.58 (m, 2H), 7.40 (s, 1H), 7.27 (dd, 1H, J = 2.7, 8.9 Hz), 3.94 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H); ^{13}C-nmr: 170.4, 169.5, 159.3, 159.0, 130.1, 129.5, 127.5, 126.6, 122.3, 119.8, 103.7, 102.4, 55.5, 52.6, 52.3.

Anal. Calcd. for $C_{15}H_{14}O_6$: C, 62.06; H, 4.82. Found: C, 62.08; H, 4.86.

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