The Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 22 [1]. An Efficient Synthesis of Leiokinine B

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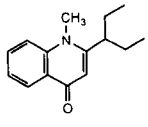
Received October 5, 1992

The alkaloid leiokinine B has been synthesized in one step from the reaction of *N*-methylisatoic anhydride and the enolate derived from 3-ethyl-2-pentanone.

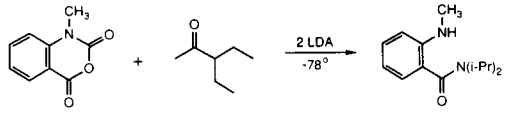
J. Heterocyclic Chem., **29**, 1873 (1992).

The 4-quinolinone alkaloid leiokinine B (**1**), found in the leaves of the Brazilian tree *E. leiocarpa*, possesses moderate antifeedant activity against the pink bollworm *P. gossypiella* [2].



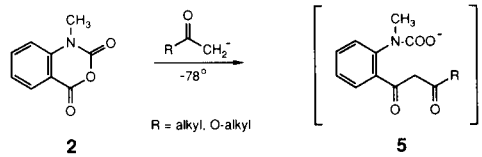
1

The authors who isolated the alkaloid attempted its synthesis by reaction of *N*-methylisatoic anhydride (**2**) with the enolate of 3-ethyl-2-pentanone (**3**). None of the desired alkaloid was formed. Only the diisopropylanthranilamide (**4**) was produced as the sole isolable product due to preferential reaction of lithium diisopropylamide (LDA) rather than the ketone enolate with **2**. The synthesis was subsequently completed by a 6-step sequence starting from 2-nitrobenzoic acid. The observation of the formation of **4** in the reaction of **2** with enolates generated with LDA prompted us to report our experiences in similar systems.



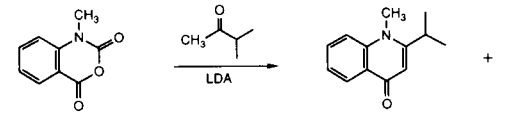
2 **3** **4**

In general, enolates of ketones or esters react with isatoic anhydrides on an equimolar basis provided that an additional equivalent of LDA is present to satisfy partial quenching of the enolate with the highly acidic proton of the initially formed β-diketone intermediates **5** [3]. Under these conditions, the reaction mixture is sometimes accompanied by varying amounts of **4** derived from competitive attack of the excess LDA on **2**.



2 **5**

For instance, reaction of **2** with an equimolar amount of the enolate of 3-methyl-2-butanone, generated with two equivalents of LDA, produced a mixture of the 2-isopropyl-4-quinolinone (**6**) and **4** in a ratio of 7:3. In order to circumvent this situation, the extra equivalent of LDA was replaced with that of enolate. Consequently, when the reaction was performed under identical conditions using two equivalents of enolate, only **6** was formed. None of the anthranilamide **4** could be detected either by thin layer chromatography or by nmr analysis of the crude reaction mixture.



2 **6**

When these conditions were applied to the synthesis of leiokinine B. the reaction proceeded similarly. Thus, when **2** was allowed to react with two equivalents of the lithium enolate derived from 3-ethyl-2-pentanone only the desired alkaloid **1** was produced in 76% yield. All physical properties were identical to those described for the natural product.

In summary, leiokinine B can be synthesized in one step and in high yield from the reaction of *N*-methylisatoic anhydride with the enolate derived from 3-ethyl-2-pentanone both of which are commercially available.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on an Analect FX-6200 spectrometer. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were recorded on a Bruker AC300 spectrometer using tetramethylsilane as the internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

All carbanion generating reactions were conducted under argon atmosphere using tetrahydrofuran which was freshly distilled over lithium aluminum hydride. No attempt has been made to optimize the yields of the described reactions.

N-methylisatoic anhydride was purchased from Aldrich Chemical Company and was recrystallized from methylene chloride/methanol. 3-Ethyl-2-pentanone was purchased from Pfaltz and Bauer.

2-Isopropyl-1-methyl-4(1*H*)-quinolinone (**6**).

To a solution of 2.0 g (0.02 mole) of diisopropylamine in 50 ml of tetrahydrofuran at 0° was added 1.28 g (0.02 mole) of *n*-butyllithium (1.6*M* in hexane). The mixture was cooled to -78° then a solution of 1.8 g (0.021 mole) of 3-methyl-2-butanone in 20 ml of tetrahydrofuran was added dropwise. After the addition was complete the solution was stirred at -78° for 45 minutes then a solution of 1.77 g (0.01 mole) of **2** in 40 ml of tetrahydrofuran was added slowly. The resulting suspension was stirred at -78° for 15 minutes. The mixture was quenched with saturated ammonium chloride to give a bright yellow solution in the organic phase. The mixture was extracted into methyl *t*-butyl ether and the organic solution was dried over sodium sulfate. The solvent was removed under reduced pressure on a rotary evaporator whose water bath was maintained at 70° (to insure complete cyclization of the intermediate β-diketone). The resulting oil was chromatographed on a Waters Prep-500 apparatus using ethyl acetate to elute the product, 1.16 g (58%) of **6** as a solid. An analytical sample was crystallized from methyl *t*-butyl ether/hexane, mp 102-105°; ir (potassium bromide): 1638 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 8.45 (dd, 1H), 7.64 (m, 1H), 7.53 (d, 1H), 7.35 (m, 1H), 6.32 (s, 1H), 3.77 (s, 3H), 3.17 (m, 1H), 1.33 (d, 6H).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.51; H, 7.52; N, 6.98.

Leiokinine B (**1**).

To a solution of 2.0 g (0.02 mole) of diisopropylamine in 50 ml of tetrahydrofuran at 0° was added 1.28 g (0.02 mole) of *n*-butyllithium (1.6*M* in hexane). The mixture was cooled to -78° then a solution of 2.3 g (0.02 mole) of 3-ethyl-2-pentanone (**3**) in 20 ml of tetrahydrofuran was added dropwise. After the addition was complete the solution was stirred at -78° for 45 minutes then a solution of 1.77 g (0.01 mole) of **2** in 40 ml of tetrahydrofuran was added slowly. The resulting suspension was stirred at -78° for 10 minutes then the temperature was allowed to rise until a clear yellow solution formed (at approximately -50°). The mixture was quenched with saturated ammonium chloride and was extracted into methyl *t*-butyl ether. The organic solution was dried over sodium sulfate and the solvent was removed under reduced pressure on a rotary evaporator whose water bath was maintained at 70°. The resulting oil was flash chromatographed using 5% methanol/chloroform to elute the product, 1.75 g (76%) of **1** as a solid. An analytical sample was crystallized from methyl *t*-butyl ether/hexane, mp 134-137°, lit [2] mp 138°; ^{1}H-nmr (deuteriochloroform): δ 8.48 (dd, 1H), 7.67 (m, 1H), 7.56 (d, 1H), 7.38 (m, 1H), 6.30 (s, 1H), 3.80 (s, 3H), 2.85 (m, 1H), 1.76 (m, 4H), 0.93 (t, 6H).

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.42; H, 8.36; N, 6.05.

REFERENCES AND NOTES

[1] Part **21**: G. M. Coppola and H. F. Schuster, *J. Heterocyclic Chem.*, **26**, 957 (1989).

[2] T. Nakatsu, T. Johns, I. Kubo, K. Milton, M. Sakai, K. Chatani, K. Saito, Y. Yamagiwa and T. Kamikawa, *J. Nat. Prod. - Lloydia*, **53**, 1508 (1990).

[3] G. M. Coppola, *J. Heterocyclic Chem.*, **22**, 491 (1985).