SYNTHETIC COMMUNICATIONS, 22(12), 1773-1782 (1992)

SYNTHESIS OF EUPOLAURIDINE AND ITS BENZO-ANNULATED DERIVATIVE

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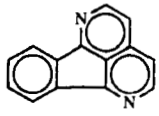
ABSTRACT: The unique diazafluoranthene alkaloid eupolauridine (**1**) was synthesized by a three-step route utilizing as the initial step the thermal rearrangement of the oxime *O*-crotyl ether **12**, which afforded onychine (**2**). Bracher pyridine synthesis procedure subsequently converted **2** into **1**. On the other hand, Friedländer reaction was employed for the synthesis of **3**, which is a benzo-annulated derivative of eupolauridine (**1**).

In the hope of developing a short and economical preparation of eupolauridine (**1**),[1,2] we recently devised a three-step route, employing both the thermal rearrangement of an oxime *O*-crotyl

ether[3,4,5,6] as well as the Bracher pyridine synthesis[7,8] as key steps. Onychine (**2**) was our key intermediate and was therefore our first target.



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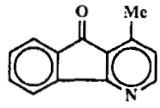

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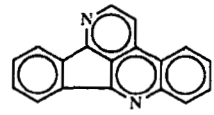

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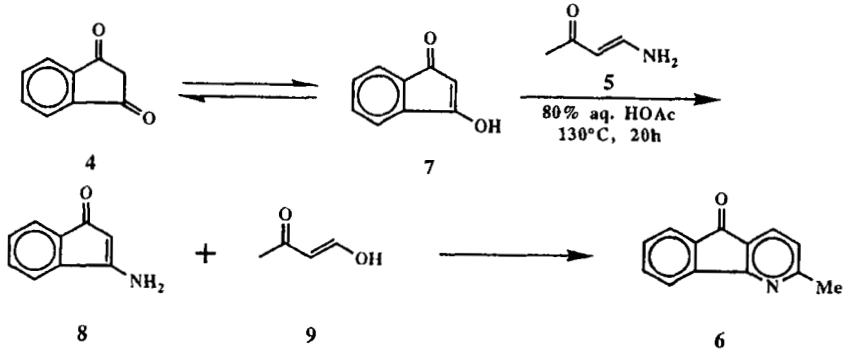
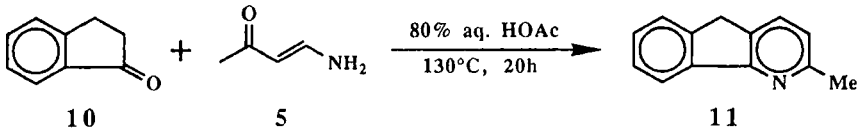
Our preliminary experiments to synthesize **2** was based on the Breitmaier method,[9,10] using 1,3-indanedione (**4**) and 4-aminobut-3-en-2-one[9] (**5**) as the starting materials. Unfortunately, the 3-methyl isomer **6**[4] was obtained (81% yield) instead of onychine (**2**) (Scheme I).

Although other possibilities cannot be ruled out, the formation of **6** is likely due to an exchange of the hydroxyl group of the enolized 1,3-indanedione (**4**) with the amino group of **5** to give **8** prior to cyclization[10] (Scheme I).



4 **7** **8** **9** **6**

Scheme I



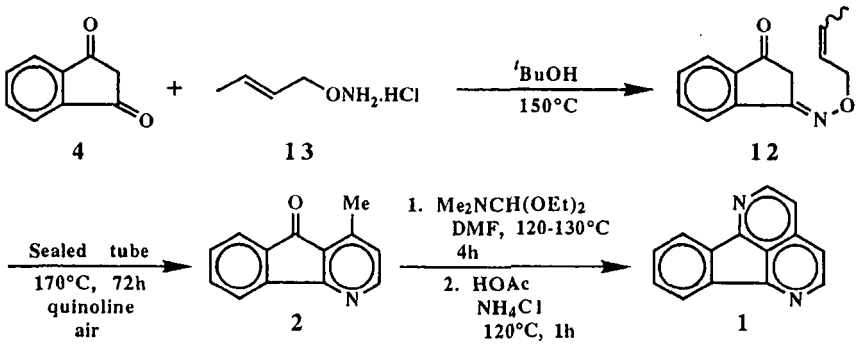
10 5 11

Scheme II

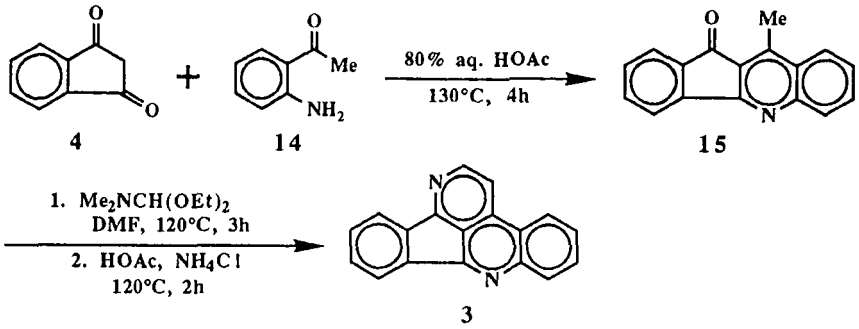
In light of this fact, we sought to use 1-indanone (**10**) as the starting material with the aim that the degree of enolization and hence the exchange process would be reasonably reduced. However, the 3-methyl isomer **11**[4] was likewise obtained in almost quantitative yield (Scheme II).

In order to circumvent the aforementioned difficulties, another approach was developed in which the thermal cyclization of 1,3-indanedione oxime *O*-crotyl ether (**12**) was to serve as the pivotal step.[3,4,5,6] Oxime *O*-crotyl ether **12** was prepared by treatment of **4** with *O*-crotyl hydroxylamine hydrochloride (**13**)[5].

As can be seen in Scheme III, compound **4** condensed with *O*-crotyl hydroxylamine hydrochloride (**13**) to give compound **12** in 50% yield. Thermolysis of **12** in quinoline under air at 170°C resulted in 19% yield of **2**. Onychine (**2**) was eventually converted to eupolauridine (**1**) in 83% yield by the Bracher procedure.[7,8] The NMR spectrum of **1** was in close agreement with that reported earlier.[7]



Scheme III



Scheme IV

In marked contrast to the synthetic failure of onychine (**2**) by the conventional Breitmaier reaction,[3,4] Friedländer condensation[11] of 2-aminoacetophenone (**14**) with **4** in refluxing 80% (v/v) aqueous acetic acid afforded **15** almost quantitatively. Compound **15** was then cyclized with *N*,*N*-dimethyl formamide diethyl acetal in *N*,*N*-dimethyl formamide to furnish the desired **3** in also quantitative yield (Scheme IV).

In conclusion, eupolauridine (**1**) was realized from 1,3-indanedione (**4**) and **13** by a three-step route in 7.8% overall yield. On the other hand, compound **3** was prepared in an almost quantitative yield by a two-step route, starting from **4** and **14**.

Experimental Section

Melting points were measured on a hot-stage microscope and are uncorrected. All NMR spectra were recorded on a Brucker Cryospec WM 250 (250 MHz) spectrometer. Deuterated chloroform ($CDCl_3$) was used as solvent unless stated otherwise and the chemical shift positions were in δ (ppm) downfield from internal tetramethylsilane (TMS). Mass spectra were recorded on a VG Micromass 7070F spectrometer. Elemental analyses were carried out at Shanghai Institute of Organic Chemistry, Academia Sinica, China.

4-Aza-3-methylfluoren-9-one (6). Compounds **4** (1.0 g, 6.8 mmol) and **5** (0.6 g, 7.1 mmol) in aqueous acetic acid (80% v/v, 13 mL) were refluxed at 130°C for 20 hours. The resulting solution was cooled and poured into 2N aqueous sodium hydroxide (100 mL) and was then extracted with chloroform (3 x 40 mL). The organic layer was then dried with anhydrous magnesium sulfate and the solvent was evaporated. Flash column chromatography on silica gel (ethyl acetate/hexanes 1/6, R_f = 0.21) gave the product **6**[4] as yellow solid (0.65 g, 81%), m.p. 131-133°C; ^{13}C NMR: δ 24.96, 120.82, 122.54,

123.92, 125.97, 130.71, 131.44, 134.89, 135.35, 143.73, 164.49, 165.24, 191.61; MS *m/e* 195 (M^+).

4-Aza-3-methylfluorene (11). Compounds **10** (0.50 g, 3.7 mmol) and **5** (0.64 g, 7.5 mmol) in aqueous acetic acid (80% v/v, 10 mL) were refluxed at 120°C for 24 hours. The resulting solution was cooled and neutralized with 2N aqueous sodium hydroxide (80 mL). The resulting mixture was then extracted with chloroform (3 x 40 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The product **11**[4] was separated by flash column chromatography on silica gel (ethyl acetate/hexanes 1/6, R_f = 0.30) as a brown oil (0.67 g, 100%). ^{13}C NMR: δ 24.04, 33.84, 120.41, 120.54, 124.77, 126.79, 128.02, 132.06, 133.34, 140.77, 143.68, 156.62, 159.64; MS *m/e* 181 (M^+).

1,3-Indanedione monooxime *O*-crotyl ether (12). A solution of **4** (0.12 g, 0.82 mmol) in *tert*-butanol (5 mL) was heated at 150°C under nitrogen. A solution of **13** (0.10 g, 0.8 mmol) in *tert*-butanol (40 mL) was added dropwise during 8 hours. The resulting solution was refluxed for 16 hours and was then cooled. The solvent was evaporated. Flash column chromatography on silica gel (ethyl acetate/hexanes 1/12, R_f = 0.18) gave product **12** as yellow solid (90 mg, 50% yield), which can be purified by sublimation at 70°C under vacuum (0.5 mm Hg), m.p. 69-72°C; ^1H NMR δ 1.75-1.77 (d, J = 5.9

Hz, 3H), 3.39 (s, 2H), 4.67-4.69 (d, J = 5.5 Hz, 2H), 5.70-7.89 (m, 2H), 7.50-7.56 (t, J = 7.6 Hz, 1H), 7.65-7.71 (t, J = 7.6 Hz, 1H), 7.80-7.86 (d, J = 7.6 Hz, 1H), 7.93-7.96 (d, J = 7.6 Hz, 1H); MS *m/e* 215 (M^+); Anal. Calcd: C, 72.52; H, 6.10; N, 6.53. Found: C, 72.88; H, 6.08; N, 6.48.

4-Aza-1-methylfluoren-9-one (Onychine) (2). A solution of **12** (0.17 g, 0.79 mmol) in quinoline (1 mL) was placed in a glass tube, which was then sealed under air. It was heated at 170-180°C for 72 hours. The resulting dark brown solution was distilled under vacuum (60°C/4 mm Hg) to remove almost all solvents. The residue was then separated by flash column chromatography on silica gel (ethyl acetate/hexanes 1/12, R_f = 0.11) to give product **2** as yellow solid (29 mg, 18.8% yield), m.p. 132-135°C (lit[1] m.p. 133-135°C); MS *m/e* 195 (M^+).

Eupolauridine (1,6-Diazafluoranthene) (1). A solution of **2** (45 mg, 0.23 mmol) in *N,N*-dimethyl formamide (0.5 mL) was heated under nitrogen at 120°C. *N,N*-dimethylformamide diethyl acetal (0.1 g, 0.6 mmol) was then injected into the solution, the resulting mixture was refluxed for 4 hours until a deep red solution was obtained. Then ammonium chloride (1.5 g) and glacial acetic acid (5 mL) were added and the resulting suspension was heated at 120°C for an additional hour. The resulting mixture was then cooled and poured into water (100 mL). It was extracted with

dichloromethane (4 x 50 mL) and the organic layer was washed successively with saturated sodium hydrogen carbonate solution (3 x 50 mL) and water (50 mL). The organic layer was then dried over anhydrous magnesium sulfate and the solvent was evaporated. Flash column chromatography on silica gel (ethyl acetate/hexanes 1/6, R_f = 0.37) gave **1** (39 mg, 83%) as yellow needles, m.p. 156-157°C (lit[1,2] m.p. 156-157°C); ^{1}H NMR: δ 7.44-7.46 (d, J = 6.0 Hz, 2H), 7.48-7.51, 8.00-8.03 (two 1:1:1:1 quartets, J = 5.4, 3.2 Hz), 8.72-8.74 (d, J = 6.0 Hz, 2H); MS *m/e* 204 (M^+).

2,3-Benzo-4-aza-1-methylfluoren-9-one (15). A solution of **4** (1.0 g, 6.8 mmol) and **14** (1.0 g, 7.4 mmol) in aqueous acetic acid (80% v/v, 10 mL) was refluxed at 130°C for 4 hours and was then allowed to cool. The resulting yellow precipitate was filtered, washed with water and was air-dried to give crude **15** (1.7g, 100%), which was then recrystallized from absolute ethanol to give pure **15** as light yellow needles, m.p. 179-182°C; ^{1}H NMR: δ 3.03 (s, 3H), 7.47-7.57 (m, 2H), 7.63-7.81 (m, 3H), 8.06-8.10 (m, 3H); MS *m/e* 245 (M^+); Anal. Calcd.: C, 83.22; H, 4.52; N, 5.73. Found: C, 83.22, H, 4.28; N, 5.33.

2,3-Benzo-1,6-diazafluoranthene (3). A solution of **15** (0.7 g, 3.2 mmol) in *N,N*-dimethyl formamide (2 mL) was heated under nitrogen at 120°C. *N,N*-dimethyl formamide diethyl acetal (0.56 g, 3.8 mmol) was then injected into the solution, and the resulting

mixture was refluxed for 3 hours until a deep red solution was resulted. Ammonium chloride (1.5 g) and glacial acetic acid (5 mL) were then added and the resulting suspension was heated at 120°C for another 2 hours. It was then cooled and poured into water (100 mL). The solution was extracted with dichloromethane (4 x 50 mL) and the combined organic extract was washed successively with saturated sodium hydrogen carbonate solution (3 x 50 mL) and water (50 mL). The solvent was then evaporated. Flash column chromatography on silica gel (ethyl acetate/hexanes 1/6, R_f = 0.11) gave **3** as yellow solid (0.72 g, 100%), which was purified by recrystallization from ethyl acetate to give yellow needles, m.p. 175-176°C; ^{1}H NMR: δ 7.50-7.54 (m, 2H), 7.66-7.73 (dt, J = 7.8, 1.4 Hz, 1H), 7.80-7.87 (dt, J = 7.8, 1.4 Hz, 1H), 7.93-7.95 (d, J = 5.9 Hz, 1H), 8.02-8.06 (m, 1H), 8.12-8.16 (m, 1H), 8.28-8.32 (dd, J = 7.8, 1.4 Hz, 1H), 8.38-8.42 (dd, J = 7.8, 1.4 Hz, 1H), 8.84-8.86 (d, J = 5.9 Hz, 1H); MS *m/e* 254 (M^+); Anal. Calcd.: C, 84.98; H, 3.96; N, 11.05. Found: C, 84.83; H, 3.82; N, 10.98.

Acknowledgement. This work was partially supported by a UPGC direct grant for small project research (A/C 220300310).

References

1. Bowden, B.F.; Ritchie, E.; Taylor, W.C. *Aust. J. Chem.* **1972**, *25*, 2659; Bowden, B.F.; Picker, K.; Ritchie, E.; Taylor, W.C. *Aust. J. Chem.* **1975**, *28*, 2681.

2. Leboeuf, M.; Cavé, A. *J. Nat. Prod.* **1976**, *39*, 459.
3. Koyama, J.; Sugita, T.; Suzuta, Y.; Irie, H. *Chem. Pharm. Bull.* **1983**, *31*, 2601.
4. Koyama, J.; Sugita, T.; Suzuta, Y.; Irie, H. *Heterocycles* **1979**, *12*, 1017.
5. Koyama, J.; Okatani, T.; Tagahara, K.; Irie, H. *Heterocycles* **1989**, *29*, 1649.
6. Bou-Abdallah, E.; Jossang, A.; Tadic, D.; Leboeuf, M.; Cavé, A. *J. Nat. Prod.* **1989**, *52*, 273.
7. Bracher, F. *Arch. Pharm.* **1989**, *322*, 293.
8. Bracher, F. *Justus Liebigs Ann. Chem.* **1989**, 87.
9. Asinger, F.; Schröder, L.; Hoffmann, S. *Justus Liebigs Ann. Chem.* **1961**, *648*, 83.
10. Breitmaier, E.; Bayer, E. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 765.
11. Cheng, C.C.; Yan, S.J. *Org. React.* **1982**, *28*, 37.

(Received in USA 19 February, 1992)