Notes

Synthesis of Trichonine via Double Elimination Reaction and Its Structural Reinvestigation

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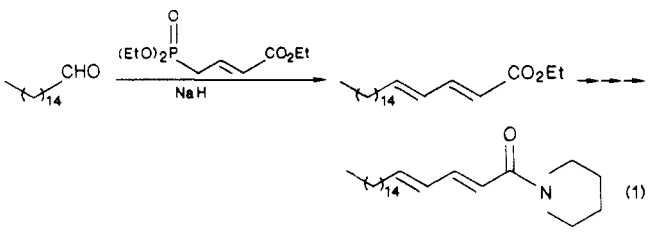
Trichonine (1) is an alkaloid isolated from the petroleum ether extract of *P. trichostachyon* leaves, and its structure was assigned to be (*E,E*)-1-(2,4-eicosadienoyl)pyrrolidine by Singh et al.[2] Later Vig et al. supported this assignment on the basis of the separate synthesis according to eq 1.[3]



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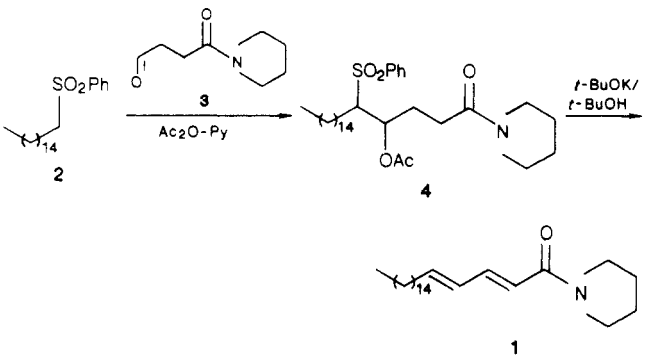
More recently, one of the present authors (B.M.T.) has achieved molybdenum-catalyzed synthesis of 1 in a 12:1 *E,E*:*E,Z* diene ratio.[4]

Previously, we have disclosed that the double elimination reaction of β-substituted sulfones[5] was successfully applied to a stereoselective synthesis of (2*E*,4*E*)-dienamides.[6] Here we wish to describe a simple route for synthesizing 1 in good yield. Moreover, we have found that the physical and spectral properties of the pure *E,E* isomer were different from those reported previously.[2,3] Thus, isolation and elucidation of pure isomers will be discussed in detail in this paper as well.

Our procedure is illustrated in Scheme I. Since the sulfone **2** is sparingly soluble in tetrahydrofuran (THF) below 0 °C, **2** was exposed to *n*-BuLi at 0 °C. An attempt to lithiate the suspenson of **2** at −20 °C failed. Subsequent reaction of the lithiated sulfone with the aldehyde **3** at −78 °C followed by acetylation of the resulting β-hydroxy sulfone without purification afforded β-acetoxy sulfone **4** in 64% yield based on **2**. The somewhat low yield is ascribable to the instability of the lithiated sulfone at 0 °C. Treatment of **4** with *t*-BuOK in *t*-BuOH furnished 1-(2,4-eicosadienoyl)pyrrolidine in 82% yield. Thin layer chromatography (TLC) (silica gel, 1:1 hexane–ethyl acetate) of this product exhibited three spots (R_f value 0.34, 0.46, and 0.55). On chromatography with a short activated alumina column, three isomers were separated in a 85:10:5 ratio. On the basis of 500-MHz ^{1}H NMR spectra, each species was unambiguously assigned to the *E,E*, *E,Z*, and *Z,E* isomers in the order of increasing R_f values. The distinguishing NMR values were the coupling constants for the olefinic protons. *E,E*: $J_{1,2}$ = 14.4, $J_{3,4}$ = 15.1 Hz; *E,Z*: $J_{1,2}$ = 14.7, $J_{3,4}$ = 9.9 Hz; *Z,E*: $J_{1,2}$ = 11.4, $J_{3,4}$ = 15.4 Hz. Melting points of these isomers were found to be 74–75 °C, 49–51 °C, and 45–49 °C, respectively. Obviously, the present *E,E* isomer gave rise to the melting point higher than the reported value (65–67 °C).[2,3] The structural assignment of the latter case was based on a 60-MHz ^{1}H NMR spectrum which exhibited two broad signals for the allylic (2.05–3.32 ppm) and olefinic (5.82–6.52 ppm) protons. Although no such unusual signal was detected for allylic protons in our compounds, the broad olefinic proton signal is suggestive of contamination of stereoisomers. Actually, we have observed the isomerization of the *E,E* isomer to the *Z,E* counterpart on prolonged column chromatography. The α,β-double bond is easy to isomerize because of facile enolization under chromatographic conditions. Therefore, the basis for the conclusion of the previous workers is apparent. As expected, the mixtures of isomers experienced depression of melting points, the degree of which was dependent on the ratio of geometric isomers.

Scheme I



In order to confirm these results, we have reinvestigated Vig's method (eq 1). In our experiment, the *E,E*, *E,Z*, and *Z,E* isomers resulted in a 88:10:2 ratio (mp 65–68 °C) and their properties were completely consistent with the results described above.

In conclusion, the double elimination reaction of the β-substituted sulfone proved to be effective for synthesis of trichonine and pure stereoisomers have been fully characterized.

Experimental Section

All reactions were conducted under a nitrogen or argon atmosphere. ^{1}H NMR spectra were recorded on Hitachi R-24B (60 MHz) and Jeolco JNM GX-500 (500 MHz) spectrometers. Mass spectra were measured with a Jeolco JMS D-300 spectrometer. Melting points were determined by using a Yanaco micro melting point apparatus and were not corrected. Column chromatography was performed on silica gel (Wako gel C-200) or on activated alumina (Wako 200 mesh). THF was distilled from sodium

(1) (a) Okayama University of Science. (b) University of Wisconsin.
(2) Singh, J.; Dhar, K. L.; Atal, C. K. *Tetrahedron Lett.* **1971**, 2119.
(3) Vig, B.; Mahajan, A. C. *Indian J. Chem.* **1972**, *10*, 564.
(4) Trost, B. M.; Lautens, M.; Peterson, B. *Tetrahedron Lett.* **1983**, *24*, 4525.
(5) Mandai, T.; Yanagi, T.; Araki, K.; Morisaki, Y.; Kawada, M.; Otera, J. *J. Am. Chem. Soc.* **1984**, *106*, 3670.
(6) Mandai, T.; Moriyama, T.; Tsujimoto, K.; Kawada, M.; Otera, J. *Tetrahedron Lett.* **1986**, *27*, 603.

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benzophenone ketyl. t-BuOH and pyridine were distilled from calcium hydride. 1-(4-Formylbutanoyl)pyrrolidine (3) was prepared by the Swern oxidation[7] of 1-(4-hydroxybutanoyl)pyrrolidine which was readily obtained from γ-butyrolactone and pyrrolidine.

1-(4-Acetoxy-5-(phenylsulfonyl)eicosanoyl)pyrrolidine (4). To a THF solution (10 mL) of the sulfone **2** (689 mg, 1.88 mmol) was added *n*-BuLi (1.5 N hexane solution, 1.50 mL, 2.25 mmol) at 0 °C. After being stirred for 1 h at this temperature, the solution was cooled to −78 °C. To the resulting pale yellow suspension was added the aldehyde **3** (378 mg, 2.44 mmol) in THF (5 mL). The color of the suspension turned white after the reaction mixture had been stirred for 30 min at −78 °C. The reaction mixture was extracted with 0.3 N HCl–ethyl acetate. The organic layer was dried ($MgSO_4$) and evaporated to give a crude oil of 1-(4-hydroxy-5-(phenylsulfonyl)eicosanoyl)pyrrolidine (939 mg), which was subjected to acetylation with acetic anhydride (3 mL)–pyridine (3 mL) at room temperature. Usual workup and column chromatography on silica gel (5:1 hexane–ethyl acetate) afforded **4** (677 mg, 64%): ^1H NMR (60 MHz) (CCl_4) δ 0.70–2.32 (m, 39 H), 1.78, 1.83 (s, 3 H), 2.99–3.52 (m, 5 H), 4.88–5.22 (m, 1 H), 7.38–7.97 (m, 5 H).

Synthesis of Trichonine (1). To a t-BuOH solution (15 mL) of **4** (360 mg, 0.65 mmol) was added t-BuOK (220 mg, 1.95 mmol) in t-BuOH (4 mL) at room temperature. After being stirred for 12 h, the reaction mixture was combined with water and ethyl acetate. The separated organic layer was dried ($MgSO_4$) and evaporated. Column chromatography of the residue on activated alumina gave the following three isomers. (2*Z*,4*E*)-**1** (eluent 20:1 hexane–ethyl acetate): 10 mg (4%); mp 45–49 °C; ^1H NMR (500 MHz) ($CDCl_3$) δ 0.79 (m, 3 H), 0.98–1.50 (m, 26 H), 1.77–1.89 (m, 4 H), 2.04–2.26 (m, 2 H), 3.37–3.40 (m, 4 H), 5.68 (d, 1 H, *J* = 11.4 Hz), 5.88 (dt, 1 H, *J* = 15.4 and 7.0 Hz), 6.30 (dd, 1 H, *J* = 11.4 and 11.0 Hz), 7.20 (dd, 1 H, *J* = 15.4 and 11.0 Hz); HRMS calcd for $C_{24}H_{43}NO$ 361.3345, obsd 361.3348. (2*E*,4*Z*)-**1** (eluent 10:1 hexane–ethyl acetate): 20 mg (8%); mp 49–51 °C; ^1H NMR (500 MHz) ($CDCl_3$) δ 0.80 (m, 3 H), 0.95–1.64 (m, 26 H), 1.67–1.87 (m, 4 H), 2.11–2.29 (m, 2 H), 3.28–3.48 (m, 4 H), 5.69 (dt, 1 H, *J* = 9.9 and 7.7 Hz), 6.04 (dd, 1 H, *J* = 12.1 and 9.9 Hz), 6.08 (d, 1 H, *J* = 14.7 Hz), 7.52 (dd, 1 H, *J* = 14.7 and 12.1 Hz); HRMS calcd for $C_{24}H_{43}NO$ 361.3345, obsd 361.3345. (2*E*,4*E*)-**1** (eluent 10:1 hexane–ethyl acetate): 165 mg (70%); mp 74–75 °C; ^1H NMR (500 MHz) ($CDCl_3$) δ 0.80 (t, 3 H, *J* = 11.6 Hz), 1.15–1.35 (m, 26 H), 1.84 (br s, 4 H), 2.04–2.10 (m, 2 H), 3.45 (br s, 4 H), 6.00 (dt, 1 H, 15.1 and 7.1 Hz), 6.01 (d, 1 H, 14.4 Hz), 6.11 (dd, 1 H, *J* = 15.1 and 11.5 Hz), 7.20 (dd, 1 H, *J* = 14.4 and 11.5 Hz; HRMS calcd for $C_{24}H_{43}NO$ 361.3345, obsd 361.3346.

Registry No. (2*E*,4*E*)-**1**, 33169-28-7; (2*Z*,4*E*)-**1**, 104035-11-2; (2*E*,4*Z*)-**1**, 104035-14-5; **2**, 104035-13-4; **3**, 41193-97-9; **4**, 104035-12-3; 1-(4-hydroxy-5-(phenylsulfonyl)eicosanoyl)pyrrolidine, 104035-15-6.

(7) Mancuso, A.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

Fluoride- or Alkoxide-Induced Reaction of 1-[(Trimethylsilyl)methyl]azoles with Carbonyl Compounds

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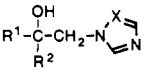
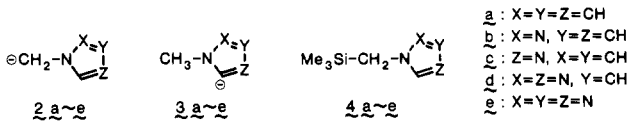
Synthetic routes to (imidazol-1-yl)- or (1,2,4-triazol-1-yl)ethanols **1** have received considerable attention recently because of the importance of their general structure in orally active antifungal azole moieties.[1] In the course of our synthetic project on orally active antifungal azoles, this structure prompted us to study the reaction of carbonyl compounds with azolylmethyl carbanions **2**.

Lithiation of 1-alkylazoles occurs at ring positions,[2] exceptionally at N-C_α of the alkyl radical.[3-10] 1-Methylpyrazole was lithiated at the N-methyl group in competition with the 5-position; however, 1,5-dimethylpyrazole was lithiated at the N-methyl group.[4] Katritzky et al.[7] reported that lithiation of 1-benzylpyrazole originally occurred at the CH_2 group and then the lithio derivative was isomerized to the thermodynamically more stable 5-isomer. Thus, if lithiation of a 1-methylazole leads to the azolylmethyl anion **2**, generation of **2** from 1-methylazoles cannot occur because of isomerization toward the thermodynamically more stable ring carbanion **3**.



1: X=N or CH



a: X=Y=Z=CH
b: X=N, Y=Z=CH
c: Z=N, X=Y=CH
d: X=Z=N, Y=CH
e: X=Y=Z=N

2a–e **3a–e** **4a–e**

With these points in mind, we attempted to generate carbanion **2** by fluoride- or alkoxide-induced desilylation of the corresponding 1-[(trimethylsilyl)methyl]azoles **4**. Although Tsuge et al.[11] demonstrated fluoride-induced desilylation of dimethyl 1-[(trimethylsilyl)methyl]-1,2,3-triazole-4,5-dicarboxylate to generate 1,2,3-triazolyl-1-ylmethyl anion, there had been no example of unsubstituted azolylmethyl anion **2** being generated from the corresponding **4**. We now report the fluoride- or alkoxide-induced reaction of 1-[(trimethylsilyl)methyl]azoles **4** with carbonyl compounds, with focus on the reactivities of **2** generated in this reaction.

Results and Discussion

Preparation of 1-[(Trimethylsilyl)methyl]azoles 4a–e. 1-[(Trimethylsilyl)methyl]pyrrole (**4a**)[12] and 1-[(trimethylsilyl)methyl]imidazole (**4c**)[13] were prepared as described in the literature. Treatment of pyrazole and 1,2,4-triazole with (chloromethyl)trimethylsilane in the presence of potassium carbonate in dry Me_2SO afforded 1-[(trimethylsilyl)methyl]pyrazole (**4b**, 51%) and 1-[(trimethylsilyl)methyl]-1,2,4-triazole (**4d**, 77%), respectively. In a similar manner, the reaction of tetrazole with (chloromethyl)trimethylsilane afforded a mixture of 1-[(trimethylsilyl)methyl]tetrazole (**4e**, 25%) and 2-[(trimethylsilyl)methyl]tetrazole (15%). The structures of these compounds were confirmed by ^1H NMR spectroscopy.[14]

(1) (a) Gravestock, M. B.; Ryley, J. F. *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic Press: Orlando, 1984; p 127 and references cited therein. (b) Ogata, M.; Matsumoto, H.; Hamada, Y.; Takehara, M.; Tawara, K. *J. Med. Chem.* **1983**, *26*, 768.

(2) Gschwend, H. W.; Rodriguez, H. R. *Org. React (N.Y)* **1979**, *26*, 1.
(3) Micetich, R. G. *Can. J. Chem.* **1970**, *48*, 2006.
(4) Butler, D. E.; Alexander, S. M. *J. Org. Chem.* **1972**, *37*, 215.
(5) Julia, M.; Schouteeten, A.; Baillarge, M. M. *Tetrahedron Lett.* **1974**, 3433.
(6) Katritzky, A. R.; Grzeskowiak, N. E.; Siddiqui, T.; Jayaram, C.; Vassilatos, S. N. *J. Chem. Res. Synap.* **1982**, 26.
(7) Katritzky, A. R.; Jayaram, C.; Vassilatos, S. N. *Tetrahedron* **1983**, *39*, 2023.
(8) Katritzky, A. R.; Abdel-Rahman, A. E.; Leahy, D. E.; Schwarz, O. A. *Tetrahedron* **1983**, *39*, 4133.
(9) Katritzky, A. R.; Sączewski, F.; Marson, C. M. *J. Org. Chem.* **1985**, *50*, 1351.
(10) Cuberes, M. R.; Moreno-Mañas, M.; Trius, A. *Synthesis* **1985**, 302.
(11) Tsuge, O.; Kanemasa, S.; Matsuda, K. *Chem. Lett.* **1983**, 1131.
(12) Ashby, B. A. U.S. Patent 3 346 588, 1967; *Chem. Abstr.* **1968**, *68*, 78131s.
(13) Barcza, S. U.S. Patent 3 692 798, 1972; *Chem. Abstr.* **1973**, *78*, 43692e.
(14) Butler, R. N. *Adv. Heterocycl. Chem.* **1977**, *21*, 327.

0022-3263/86/1951-3897$01.50/0