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An Efficient Synthesis of Alnustone, a Naturally Occurring Compound

Süleyman GÖKSU, Hülya ÇELİK, Hasan SEÇEN
Department of Chemistry, Faculty of Arts and Sciences, Atatürk University, 25240 Erzurum-TURKEY
e-mail: hsecen@atauni.edu.tr

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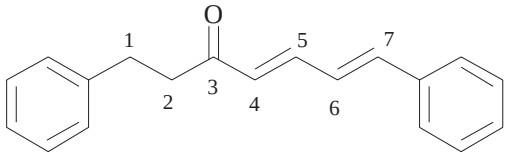
Alnustone, 4(E),6(E)-1,7-diphenyl-hepta-4,6-dien-3-one, was synthesized starting from benzaldehyde in three steps with an overall yield of 57%. The condensation of benzaldehyde with acetone gave benzalacetone. The Pd-C catalyzed hydrogenation of benzalacetone afforded benzylacetone. The in situ enamination of benzylacetone with pyrrolidine and acetic acid followed by cinnamaldehyde treatment gave alnustone.

Key Words: alnustone, 4(E),6(E)-1,7-diphenyl-hepta-4,6-dien-3-one, diarylheptanoid, benzaldehyde, benzalacetone, benzylacetone, cinnamaldehyde.

Introduction

The diarylheptanoids having an aryl-C_7-aryl skeleton are a broad class of naturally occurring compounds. So far, over 100 diarylheptanoid compounds have been discovered, isolated and identified in nature[1−3]. Suga et al.[4−6] isolated and identified alnustone **1,** a non-phenolic diarylheptanoid, from the male flower of *Alnus pendula* (Betulaceae). Kuroyanagi et al.[7] isolated alnustone **1** from the seeds of *Alpinia katsumadai* Hayata (Zingiberaceae), which is used as an aromatic stomachic. Claeson et al.[8,9] isolated alnustone **1** from the rhizomes of *Curcuma xanthorrhiza* Roxb. (Zingiberaceae) and reported its significant anti-inflammatory activity. Studies by Hikino et al.[10] revealed the antihepatotoxic action of alnustone **1** similar to many diarylheptanoids. Yang et al.[11,12] reported the anti-emetic activity of alnustone **1** isolated from *Alpinia katsumadai*.



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Sakakibara et al.[13] starting from β-phenyl propionylchloride and in five steps performed the first synthesis of alnustone **1**. Vig et al. developed two procedures for the synthesis of alnustone **1** starting from

benzaldehyde[14] and benzyl alcohol[15] in five steps. Kato et al.[16] also described a preparation method for alnustone **1** starting from 3-phenyl-propionic acid in seven steps. In the literature synthesis of alnustone **1** overall yields changes from 13% to 27%. In this paper, we report an easy three-step efficient synthesis of alnustone **1** starting from benzaldehyde using cheaper reagents.

Experimental

General. The ^{1}H and ^{13}C-NMR spectra were recorded on 200 (50) MHz Varian spectrometers. Column chromatography experiments were performed on silica gel 60 (ASTM). Benzaldehyde, cinnamaldehyde, acetone, pyrrolidine and Pd-C are commercially available (Merck, Fluka) and were used without further purification.

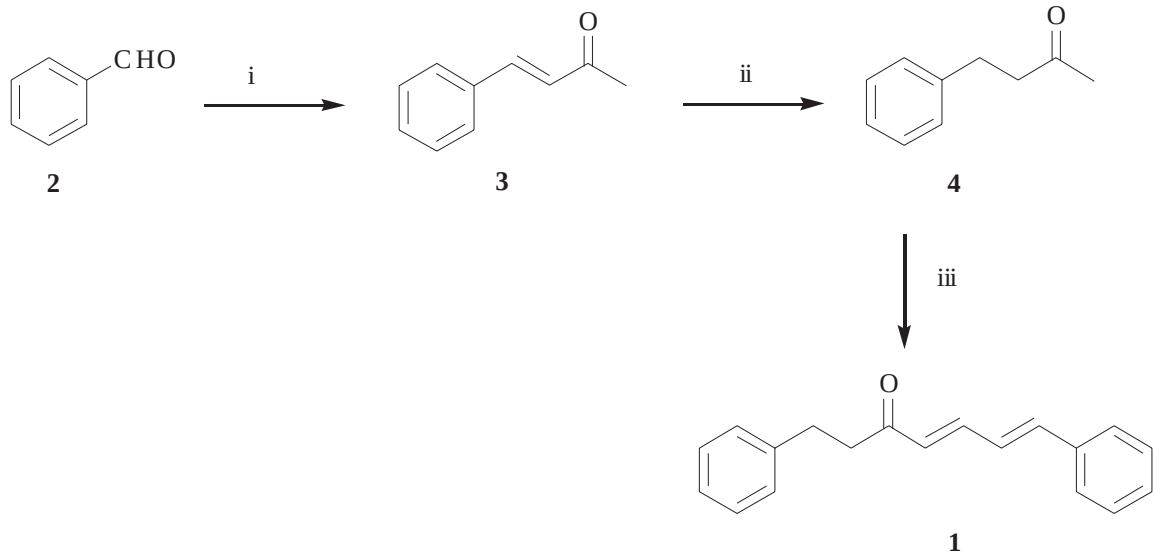
3(E)-4-Phenyl-3-buten-2-one (3). The reported procedure[18] was used for the synthesis of 3(E)-4-phenyl-3-buten-2-one (**3**) at an 82% yield. Yellow needless, m.p. 40-42°C, recrystallized from hexane-ethyl acetate (9:1) (lit[18] m.p. 40-42°C solidified). **^{1}H-NMR** (200 MHz, $CDCl_3$) δ (ppm): 7.50-7.30 (6H, five protons of phenyl group and H_4, m), 6.66 (1H, H_3, d, J = 16.3 Hz), 2.30 (3H, methyl, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ (ppm): 199.7 (C_2), 145.1 (C_4), 136.6 (*ipso*-carbon at phenyl), 132.3 ($p-$carbon at phenyl), 130.9 (o- and o'-carbons at phenyl), 130.2 (m- and m'-carbons at phenyl), 129.2 (C_3), 29.3 (C_1).

4-Phenyl-2-butanone (4). the Pd-C catalyzed hydrogenation of **3** in EtOH following the published literature procedure[12] afforded 4-phenyl-2-butanone (**4**) (96%). Yellow oil (lit[19]b.p. 235°C). **^{1}H-NMR** (200 MHz, $CDCl_3$) δ (ppm): 7.34-7.18 (5H, five protons of phenyl group, m), 2.90 (2H, at C_3 or C_4,A_2 part of A_2B_2 system), 2.76 (2H, at C_3 or C_4,B_2 part of A_2B_2 system), 2.14 (3H, methyl, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ (ppm) 209.4 (C_2), 143.0 (*ipso*-carbon at phenyl), 130.4 ($o-$ and o'-carbons at phenyl), 130.2 ($m-$ and m'-carbons at phenyl), 128.1 (p-carbon at phenyl), 47.0 (C_4), 31.8 (C_1 and C_3).

4(E),6(E)-1,7-Diphenyl-hepta-4,6-dien-3-one (Alnustone) (1). To a solution of pyrrolidine (2.64 g, 37.1 mmol) and acetic acid (2.23 g, 37.1 mmol) in ether (20 ml) prepared at 0°C was added dropwise a solution of **4** (5.00 g, 33.7 mmol) in ether (25 ml) over 10 min at the same temperature. After additional stirring for 30 min, a solution of cinnamaldehyde (4.46 g, 33.8 mmol) in ether (25 ml) was added dropwise over 30 min and stirred over 60 h at room temperature. Dilute HCl was added to the reaction mixture. The organic phase was extracted with ether (2 × 50 ml), then washed with water (2 × 30 ml) and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue on a silica gel (70-230 mesh) column eluting with 9:1 hexane-ethyl acetate gave alnustone **1** (6.46 g, 73%). Yellow needless, m.p. 60-62°C, recrystallized from EtOH (lit[4] m.p. 61.0-62.5°C from EtOH; lit[13] m.p. 60.5-62.5°C solidified; lit[16] m.p. 64-65°C from MeOH). **^{1}H-NMR** (200 MHz, $CDCl_3$) δ (ppm): 7.50-7.18 (11H, ten protons of two phenyl groups and H_5, m), 6.99-6.79 (2H, H_6 and H_7, m), 6.30 (1H, H_4, d, J = 15.5 Hz), 3.07-2.89 (4H, at C_1 and C_2,A_2B_2system). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ (ppm): 200.9 (C_3), 144.4, 143.3, 143.2, 138.2, 131.6, 131.1, 130.8, 130.5, 130.3, 129.2, 128.8, 128.1, 44.3 (C_1), 32.3 (C_2). **EI-MS** (m/e) 262.0 (M^+, 75), 261.0 (98), 171.0 (45), 170.0 (85), 158.0 (20), 157.0 (87), 156.0 (100), 131.0 (20), 130.0 (74), 129.0 (92), 128.0 (96), 127.0 (98), 126.0 (84), 115 (38), 114.0 (60), 105 (56), 91.0 (56), 90.0 (82), 77 (65), 76 (75). ^{1}H-NMR, ^{13}C-NMR and EI-MS are in agreement with data given in the literature[7].

Results and Discussion

Itokawa et al.[17] synthesized a series of diarylheptanoids by the condensation of simple aromatic aldehydes with 6-phenyl-2-hexanone. By following their study in our approach, we focused on the condensation of benzylacetone **4** and cinnamaldehyde. The first step of our synthesis was the preparation of benzalacetone **3** by condensing benzaldehyde **2** and acetone by means of aqueous NaOH at a yield of 82%. Pd-C catalyzed hydrogenation of benzalacetone **3** in ethanol afforded benzylacetone **4** at a yield of 96%. In situ enamination of benzylacetone **4** with pyrrolidine in the presence of acetic acid followed by treatment of cinnamaldehyde gave alnustone **1** at a yield of 73% (Scheme). All physical, NMR and EI-MS data of alnustone **1** are in agreement with data given in the literature[7,8].



2 **3** **4** **1**

Reagents and Conditions:

(i) Acetone, 10% NaOH, r.t. then HCl **(ii)** H_2, Pd-C, EtOH **(iii)** Pyrrolidine, AcOH, cinnamaldehyde, 60 h

Scheme

In conclusion, a new, cheaper and efficient procedure for the synthesis of alnustone **1** was described starting from benzaldehyde with an overall yield of 57%. Although alnustone **1** has been obtained in small amounts from nature (e.g. 3.34 g/6.59 kg flowers of *A. pendula*[5]), our synthesis procedure supplies gram-scale preparation for further biological and chemical studies.

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