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Supplementary Material Available: ^1H NMR spectra ($CDCl_3$, 200 MHz) of the CoTPP-catalyzed rearrangement of *cis*-3,6-dimethyl-1,2-dioxene after 45 min and 12 h at room temperature; the figure clearly displays the isomeric hemiketals and the clean quantitative formation of 2,5-dimethylfuran (1 page). Ordering information is given on any current masthead page.

A Facile Procedure for Synthesis of Capsaicin[1]

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Capsaicin (**1a**), a pungent principle of capsicums, has been known to exhibit a variety of biological activities,[2] including recent findings concerning its mutagenicity.[3-6] The family of natural capsaicinoids consists of more than 15 vanillylamides including nordihydrocapsaicins, capsaicin, dihydrocapsaicin, homocapsaicins, homodihydrocapsaicins, bishomocapsaicin, and trishomocapsaicin.[7] Recently Gannett et al. suggested adding two capsaicinoids (nornorcapsaicin and norcapsaicin) as new members to this group.[3] Several groups have reported interesting synthetic routes characterized by their own key reactions,[3,8-12] which were developed to introduce an *E* double bond at the C_6 position of the side chain of capsaicin.

It has been reported that *E*-olefins of fatty acids[13,14] or sex pheromones[15] are produced by the nitrous acid induced $Z \rightarrow E$ isomerization reaction of the carbon–carbon double bond.[14] We were interested in testing this technique of introducing the C_6-*E* double bond into the 8-methylnonenoic acid molecule. The results of our study show that by using this technique capsaicin is readily obtained in a concise route amenable to other capsaicinoids.

Phosphonium salt **2**, prepared from commercially available 6-bromohexanoic acid in 88% yield, was treated with ^{t}BuOK and isobutylaldehyde in DMF.[16-18] The product, (*Z*)-8-methyl-6-nonenoic acid (**3b**) (74%), was found to be contaminated with the *E* isomer in a 1:11 *E*/*Z* ratio by GLC analysis through esterification with diazomethane. Subsequent treatment of **3b** with HNO_2 in HNO_3 at 70 °C for 30 min[15] afforded the *E* isomer **3a** (77%, *E*/*Z* = 8:1). No other isomer due to double bond migration was detected.[14]

$(CH_3)_2CHCH{=}CH(CH_2)_4COR$ (**a** = *E*, **b** = *Z* double bond)

$Br^-Ph_3P^+(CH_2)_5COOH$ (**2**)

1: R = $NHCH_2C_6H_3$-3-OCH_3, 4-OH
3: R = OH
4: R = Cl

The other end of the capsaicin molecule is a vanillylamine moiety, which had been prepared by reduction of vanillin oxime.[3,10,19] The Leuckart reaction of vanillin using ammonium formate[20] could also produce pure vanillylamine hydrochloride (47.5%). The (*E*)-acid chloride **4a** was treated with free vanillylamine to yield the crude amide (91%, *E*/*Z* = 8:1), whose fractional crystallizations from hexane–ether furnished capsaicin (**1a**) (53%) in a pure state. Similar treatment of the (*Z*)-acid chloride **4b** led to *cis*-capsaicin (**1b**) (66%), which does not occur naturally.[2a,21,22]

Experimental Section

Melting points were determined on a MEL-TEMP apparatus (Laboratory Devices) and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a FTS-65 (BIO-RAD) spectrophotometer. ^1H NMR spectra were run in $CDCl_3$ solution with Me_4Si as an internal standard (δ = 0 ppm) and resistered on a JEOL GX-270 (270 MHz) or JEOL PS-100 (100 MHz) spectrometer. Mass spectra were obtained on a INCOS 50 (Finnigan MAT Instruments, Inc.) at 70 eV under electron impact conditions, or a JEOL JMS-D300 instrument under field ionization condition. Gas chromatography was carried out on a YANACO G180 instrument [Yanagimoto, a 30-m glass capillary column (0.28 mm in diameter) coated with Silicone OV-101; column temperature 140 °C; injector temperature 200 °C; detector temperature 200 °C; carrier gas N_2; flow rate 0.51 mL/min].

(6-Carboxyhexyl)triphenylphosphonium Bromide (2). A mixture of 6-bromohexanoic acid (25.8 g, 0.13 mol) and triphenylphosphine (34.7 g, 0.13 mol) was heated to 145 °C for 4 h. The cooled glassy reaction mixture was triturated with dry $CHCl_3$ and diluted with ether. The precipitate (58.3 g, 96%), mp 200–203 °C, was recrystallized from $CHCl_3$ to give an analytically pure white powder **2** (53.4 g, 88%): mp 202–203 °C; IR (KBr) 3200–2600 (COOH), 1705 (C=O) cm^{-1}; ^1H NMR (270 MHz) δ 1.62–1.72 (6 H, m, $C_{3,4,5}$-H), 2.39 (2 H, t, J = 7.0 Hz, C_2-H), 3.58–3.70 (2 H, m, C_6-H), 7.70–7.84 (15 H, m, Ar-H); (100 MHz) δ 10.75 (1 H, br s, COOH). Anal. Calcd for $C_{24}H_{26}O_2PBr$: C, 63.03; H, 5.73; Br, 17.47. Found: C, 62.90; H, 5.75; Br, 17.32.

(*Z*)-8-Methyl-6-nonenoic Acid (3b). A mixture of the salt **2** (22.8 g, 50 mmol) and isobutylaldehyde (3.6 g, 59 mmol) in dry DMF (100 mL) was added to a suspension of KO^{t}Bu (11.55 g, 102.5 mmol) in dry DMF (125 mL) under an atmosphere of N_2 at 0 °C during the course of 15 min. After vigorous stirring for 15 h at room temperature, the resulting slurry was poured into ice–water (150 mL). Precipitated triphenylphosphine oxide was removed by suction filtration. The filtrate was washed with benzene (30 mL × 2) and acidified with 2 M HCl. The product was extracted with ether (20 mL × 4), washed with saturated brine (15 mL × 4), dried over anhydrous Na_2SO_4, and subjected to short pass distillation to give the acid **3b** (6.25 g, 74%): bp 109–110 °C (3 Torr) [lit.[23] bp 150–150 °C (13 Torr)]; IR (neat) 3000–2500

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(COOH), 740 (C=C) cm^{-1}; ^1H NMR (270 MHz) δ 0.94 (6 H, d, J = 6.6 Hz, CH_3 × 2), 1.41, 1.66 (each 2 H, quint, J = 7.5 Hz, $C_{3,4}$-H), 2.06 (2 H, dt, J = 7.3, 7.3, 5.9 Hz, C_5-H), 2.36 (2 H, t, J = 7.5 Hz, C_2-H), 2.58 (1 H, m, C_8-H), 5.16–5.23 (2 H, m, CH=CH); (100 MHz) δ 11.50 (1 H, br s, COOH); EI-MS m/z (relative intensity) 170 (M^+, 14), 152 (M^+ - 18, 13), 137 (19), 109 (13), 95 (28), 81 (22), 69 (100), 55 (77), 41 (85). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.44; H, 10.66. This acid was esterified with CH_2N_2, and the E/Z ratio was found to be 1:11 [E isomer (t_R 10.6 min); Z-isomer (t_R 10.3 min)] by GLC analysis.

Isomerization of the (*Z*)-Acid 3b. 2 M $NaNO_2$ (3.2 mL) and 6 M HNO_3 (2.15 mL) were added to the (*Z*)-acid **3b** (7.7 g, 45.3 mmol) warmed at 70–75 °C under an atmosphere of N_2.[15] The mixture was then stirred vigorously for 0.5 h. The cooled reaction mixture was diluted with ether (50 mL), washed with water (50 mL) and saturated brine (30 mL × 3), dried over anhydrous Na_2SO_4, and evaporated. The oily residue was distilled under reduced pressure to give the (*E*)-acid **3a** (5.94 g, 77%): bp 117–120 °C (2.8 Torr) [lit.[9] bp 100–103 °C (3 Torr), lit.[10] bp 130–132 °C (12 Torr), lit.[12] bp 120–122 °C (5–6 Torr)]. GLC analysis revealed that E/Z ratio of **3a** was 8:1: IR (neat) 3300–2500 (COOH), 1710 (C=O), 970 (C=C) cm^{-1}; ^1H NMR (270 MHz) δ 0.96 (6 H, d, J = 6.6 Hz, CH_3 × 2), 1.41, 1.64 (each 2 H, quint, J = 6.6 Hz, $C_{3,4}$-H), 2.00 (2 H, q, J = 6.6 Hz, C_5-H), 2.35 (2 H, t, J = 6.8 Hz, C_2-H), 2.17–2.30 (1 H, m, C_8-H), 5.32–5.38 (2 H, m, CH=CH); (100 MHz) δ 11.50 (1 H, br s, COOH); FI-MS m/z (relative intensity) 171 (MH^+, 19.9), 170 (M^+, 100); EI-MS m/z (relative intensity) 170 (M^+, 20), 152 (16), 137 (24), 109 (20), 95 (33), 81 (24), 69 (100), 55 (79), 41 (95). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.69; H, 10.88.

Vanillylamine. A mixture of vanillin (15.2 g, 0.1 mol) and ammonium formate (20 g, 0.32 mol) was heated at 180 °C for 3 h[20] and, after cooling, evaporated until the odor of ammonia disappeared. To the residue was added concentrated HCl (12 mL). The mixture was refluxed for 1 h and then evaporated until the odor of HCl disappeared. The HCl salt was crystallized by adding EtOH (70 mL). Two recrystallizations from 95% EtOH yielded pure vanillylamine hydrochloride (8.99 g, 47.5%), mp 216–218 °C dec (lit.[3] mp 219–222 °C dec, lit.[10] mp 214 °C). IR and ^1H NMR data were identical with those reported in the literature.[3] Anal. Calcd for $C_8H_{12}NClO_2$: C, 50.67; H, 6.38; N, 7.39; Cl, 18.70. Found: C, 50.44; H, 6.40; N, 7.47; Cl, 18.90.

To a vigorously stirred solution of vanillylamine hydrochloride (3.66 g, 19.31 mmol) in water (50 mL) was added 2 M NaOH solution (9.38 mL, 18.76 mmol). The resulting white solid of free vanillylamine was collected by suction filtration, washed with water, dried over P_2O_5 in a vacuum desiccator, and amounted to 2.54 g (89%), mp 135–136 °C (lit.[9] mp 132 °C, lit.[19] mp 131–133 °C), which was used in the following steps without further purification.

(*E*)-*N*-(4-Hydroxy-3-methoxybenzyl)-8-methylnon-6-enamide (Capsaicin) (1a). The (*E*)-acid **3a** (334 mg, 1.96 mmol) and thionyl chloride (720 mg, 5.88 mmol) were stirred at room temperature for 8 h and then heated at 100 °C for 0.5 h. The excess thionyl chloride was removed under reduced pressure. The resulting acid chloride **4a** [bp 100–102 °C (12 Torr)][24] was dissolved in dry ether (10 mL) and added to a stirred suspension of dry vanillylamine (600 mg, 3.92 mmol) in dry ether (25 mL) under an atmosphere of N_2. The mixture was kept at room temperature for 2 h and then gently refluxed for 2 h. After cooling, the precipitate was removed by suction filtration, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel (Fuji-gel BW-200, 15 g, elution with 2:1 hexane–ethyl acetate). The oily product (542 mg, E/Z = 8:1,[25] 91%) was treated with 2:1 hexane–ether to give a crystalline solid (473 mg, E/Z = 12:1,[25] 79%), mp 60–63 °C. Two recrystallizations from the same solvents gave capsaicin (318 mg, 53%), mp 64–65 °C (lit.[3,8,12] mp 64–65 °C, lit.[9] mp 63.8 °C, lit.[10] mp 65 °C) as a white solid. IR, ^1H NMR, and mass spectral data were essentially identical with those reported in the literatures.[3,9] Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.69; H, 9.02, N, 4.49.

(*Z*)-*N*-(4-Hydroxy-3-methoxybenzyl)-8-methylnon-6-enamide (*cis*-Capsaicin) (1b). The (*Z*)-acid **3b** (464 mg, 2.72 mmol) was treated with thionyl chloride (1.0 g, 8.17 mmol) in the same manner as noted above. The obtained acid chloride **4b** [bp 99–102 °C (13 Torr)][24] in dry ether (10 mL) was added to a suspension of dry vanillylamine (835 mg, 5.45 mmol) in dry ether (30 mL) under an atmosphere of N_2. The workup in the same manner as noted above gave the crude oily amide **1b** (745 mg, E/Z = 1:11,[25] 90%), which on crystallization from 2:1 hexane–ether afforded a crystalline solid (674 mg, 81%, E/Z = 1:13).[25] Two recrystallizations from the same solvents afforded *cis*-capsaicin (**1b**) (548 mg, 66%), mp 68.5–69.5 °C (lit.[23] mp 70 °C), as a white solid. IR, ^1H NMR, and mass spectral data were essentially identical with those reported by Gannett et al.[3] Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.78; H, 9.08; N, 4.61.

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Nitrobenzophenone Oxime Based Resins for the Solid-Phase Synthesis of Protected Peptide Segments[1]

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This laboratory has reported the development of an oxime resin that allows the rapid synthesis and isolation of protected peptides.[3,4] This oxime support has been used successfully in the synthesis of an apolipoprotein model peptide[5] and a synthetic hemeprotein[6] and is now being applied in the syntheses of several small proteins.[7,8] During our efforts to synthesize peptides corresponding to partial and full sequences of our target proteins we have encountered difficulties in the use of our polystyrene-based oxime resin both in the synthesis of specific sequences of certain short peptides (<10 residues) and in the recoupling of smaller protected peptide segments on the oxime resin to assemble large peptides. Difficulties in the latter instance have necessitated the use of solution-phase couplings to couple larger protected peptides of about >15 residues. Nevertheless, we would still like to have a solid support as an effective option for use in the coupling of protected peptide segments. This paper describes our initial effort to explore alternative oxime solid-phase supports for the synthesis and assembly of protected peptides through the synthesis of a nitrobenzophenone oxime derivative and its attachment to a polyamide resin. We also report an improved procedure for the synthesis of our previously reported polystyrene-based oxime resin **1**.[3,4]

Results and Discussion

Because the 4-nitrobenzophenone oxime (NBO) moiety has proved reliable in previous synthetic work, we decided to synthesize a molecule that would contain the NBO functionality and, in addition, a linker arm through which the oxime could be attached to a solid support. While the standard oxime resin is obtained by direct modification of polystyrene beads (Scheme I), this new approach offers

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