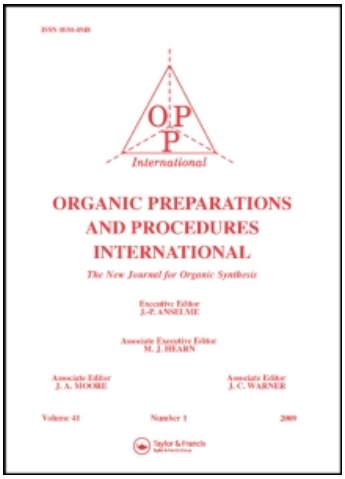

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A CONVENIENT SYNTHESIS OF NEW HALOTHIENYL β-AMINOACIDS AS VERSATILE BUILDING BLOCKS

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A CONVENIENT SYNTHESIS OF NEW HALOTHIENYL β-AMINOACIDS AS VERSATILE BUILDING BLOCKS

Submitted by (10/21/96)

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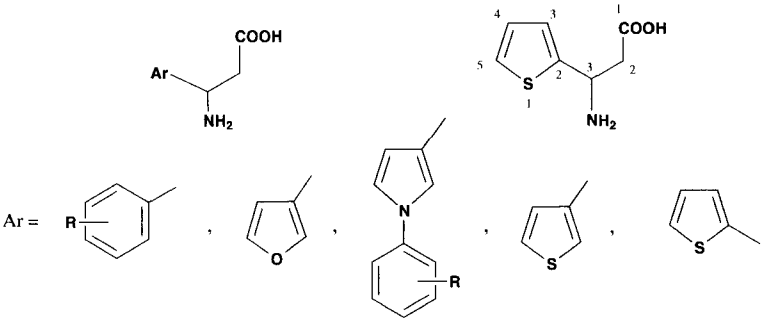
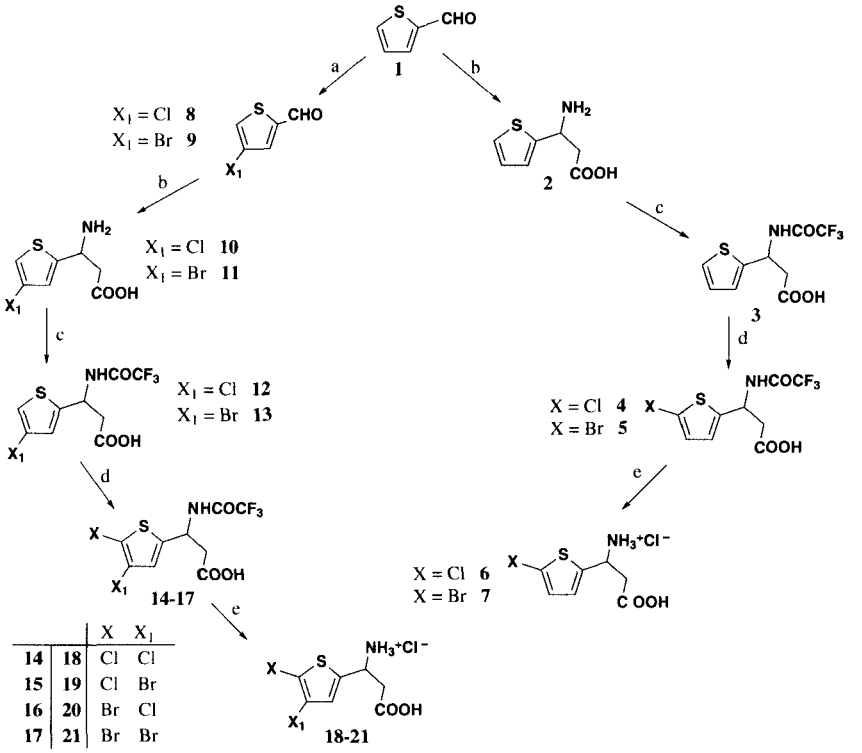
During the course of our work on the synthesis of new thiophene derivatives with therapeutic interest,[1,2] we needed reasonable quantities of new β-aminoacids which are versatile building-blocks in heterocyclic chemistry and in the synthesis of peptidomimetics.[3-5] We previously reported the preparation and the chemical reactivity of several β-amino-β-arylpropionic acid derivatives (Scheme 1).[6-10] The present work describes the multigram scale preparation of new 3-amino-3-(thien-2-yl)propionic acids bearing one or two bromine or chlorine atoms at the 4 and/or 5 position of the thiophene ring.



Scheme 1

Starting from thiophene-2-carboxaldehyde (**1**), several approaches such as the formation of β-aminoacids followed by a first and a second halogenation may be used. We present here the best synthetic pathway for each of the eight new title halothienyl β-aminoacids (Scheme 2). Thus, chlorination of trifluoroacetamide **3**[10] with excess chlorine in ether at 0° gave selectively the 5-chloro derivative **4**. In a similar manner, treatment of **3** with two equivalents of bromine in ether at 0° gave selectively the 5-bromo derivative **5**. Hydrolysis of the trifluoroacetamide group, in refluxing aqueous hydrochloric acid solution, furnished the amino acids as their ammonium chlorides **6** and **7** with an overall yield of 43-46% from **1**. These sequences are preferred to the pathway which could use 5-halothiophene-2-carboxaldehydes as intermediates.



		X	X_1
14	18	Cl	Cl
15	19	Cl	Br
16	20	Br	Cl
17	21	Br	Br

a) $AlCl_3$ (2.5 eq.), Cl_2 (excess) / $CHCl_3$ or Br_2 (1.1 eq.) / CH_2Cl_2 b) $CH_2(COOH)_2$ (1eq.), NH_4OAc (2.5 eq.), EtOH
c) TFAA (1.1 eq.), Et_2O, 0° d) Cl_2 (excess) or Br_2 (2 eq.), Et_2O 0° e) HCl (6N), reflux 3.

Scheme 2

On the other hand, the strategy was different to obtain the 4-halo derivatives. First, the selective halogenation of thiophene-2-carboxaldehyde (**1**) at the 4 position was realized according to Raggon's method [12] using either excess chlorine gas in chloroform or 1.1 equivalent of bromine in methylene chloride in the presence of $AlCl_3$. Then, application of Rodionov's method[11] to the 4-chlorothiophene-2-carboxaldehyde (**8**) and to the 4-bromothiophene-2-carboxaldehyde (**9**) gave the desired 4-substituted amino acids **10** and **11**, respectively. Furthermore, the introduction of the second

halogen atom can be achieved only from the 4-substituted amino acids **10** and **11**, which led selectively to the 4- and 5-dihalogenated amino acids without traces of halogenation in the 3 position. It is important to note that halogenation of 5-subtituted *N*-protected amino acids **4** and **5** did not occur at the 3- and 4-positions and that Rodionov's reaction of 4,5-dihalothiophene-2-carboxaldehyde was unsuccessful. The second halogenation required protection of the amino acids **10** and **11** with trifluoroacetic anhydride to afford trifluoroacetamides **12** and **13**. Treatment of the latter compounds, in a similar manner as for **3**, gave the corresponding 4,5-dihalothien-2-yl trifluoroacetamides **14-17**. Final hydrolysis of the trifluoroacetamides **14-17** gave the amino acids as their ammonium chlorides **18-21** with overall yields of 32-46% from **1** (Scheme 2).

All the title compounds were prepared on a multigram scale (10g). Further investigations of their chemical reactivity are in progress.

EXPERIMENTAL SECTION

Mps were taken on a Köfler bank and are uncorrected. Infrared spectra were recorded as KBr pellets. NMR spectra were obtained on a JEOL Lambda 400 spectrometer in DMSO-d_6 solution using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS.

3-(5-Chlorothien-2-yl)propion-3-ylammonium Chloride (6).- Chlorine was bubbled at 0° into an ethereal solution (100mL) of **3** (12.6g, 0.0471 mol) for 3-5 min. After stirring for 30 min., the excess chlorine was reduced by adding a saturated solution of sodium thiosulfate. The organic layer was separated and the solvent was removed under reduced pressure to give **4** as a white solid (12.1g, 85%). A suspension of **4** (12.1g, 0.040 mol) in 50mL of a 6N aqueous hydrochloric acid solution was refluxed for 3 h. The solvent was removed under reduced pressure to give **6** as a white solid (9.2g, 43% from **3**), mp. > 260°.

Anal. Calcd for $C_7H_9Cl_2NO_2$: C, 40.03; H, 4.32; N, 6.67. Found: C, 39.98; H, 4.34; N, 6.68

IR: 3450-2900 (OH, NH_3^+), 1735 (CO), 1492, 1214, 812 cm^{-1}. ^1H NMR 9.09 (s, 3H, NH_3), 7.22 (d, 1H, H'_4, $J_{H'_4H'_3}$ = 3.8 Hz), 7.04 (d, 1H, H'_3, $J_{H'_3H'_4}$ = 3.8 Hz), 4.71 (dd, 1H, H_3, $J_{H_3H_{2a}}$ = 4.9 Hz, $J_{H_3H_{2b}}$ = 9.4 Hz), 3.21 (dd, 1H, H_{2a}, $J_{H_{2a}H_{2b}}$ = 16.6 Hz, $J_{H_{2a}H_3}$ = 4.9 Hz), 2.99 (dd, 1H, H_{2b}, $J_{H_{2b}H_{2a}}$ = 16.6 Hz, $J_{H_{2b}H_3}$ = 9.4 Hz). ^{13}C NMR 170.3 (C1), 46.1 (C2), 55.7 (C3), 139.2 (C'2), 125.2 (C'3), 124.1 (C'4), 127.1 (C'5).

3-(5-Bromothien-2-yl)propion-3-ylammonium Chloride (7).- To an ethereal solution (100mL) of **3** (12.6g, 0.0471 mol), was added bromine (4.8mL, 0.094 mol) at room temperature. After stirring for 1 h, the excess bromine was reduced by adding a saturated solution of sodium thiosulfate. The organic layer was separated and the solvent was removed under reduced pressure to give **5** as a white solid (14.7g, 90%). A suspension of **5** (14.7g, 0.0425 mol) in 50mL of a 6N aqueous hydrochloric acid solution was refluxed for 3 h. The solvent was removed under reduced pressure to give **7** as a white solid (11.6g, 46% from **3**), mp. > 260°.

Anal. Calcd for $C_7H_9BrClNO_2$: C, 33.03; H, 5.56; N, 5.50. Found: C, 32.98; H, 3.58; N, 5.54

IR: 3450-2900 (OH, NH_3^+), 1725 (CO), 1492, 1217, 810 cm^{-1}. ^1H NMR 8.96 (s, 3H, NH_3), 7.15 (d, 1H, H'_4, $J_{H'_4H'_3}$ = 3.1 Hz), 7.12 (d, 1H, H'_3, $J_{H'_3H'_4}$ = 3.1 Hz), 4.73 (dd, 1H, H_3, $J_{H_3H_{2a}}$ = 4 Hz, $J_{H_3H_{2b}}$ = 9.3 Hz), 3.16 (dd, 1H, H_{2a}, $J_{H_{2a}H_{2b}}$ = 16.6 Hz, $J_{H_{2a}H_3}$ = 4 Hz), 2.96 (dd, 1H, H_{2b}, $J_{H_{2b}H_{2a}}$ = 16.6 Hz, $JH_{2b}H_3$ = 9.3 Hz). ^{13}C NMR 170.0 (C1), 46.4 (C2), 55.4 (C3), 141.1 (C'2), 127.5 (C'3), 130.7 (C'4), 110.8 (C'5).

3-Amino-3-(4-chlorothien-2-yl)propionic Acid (10).- Chlorine was bubbled into 200mL of chloroform at 10°. Thiophene-2-carboxaldehyde (**1**) (10g, 0.090 mol) was charged with 100mL of chloroform and then the reaction mixture was cooled to 0°. To this solution, $AlCl_3$ (26.8g, 0.200 mol) was added in portions, maintaining the reaction mixture at 0°. The chlorine solution was then added, and the mixture was stirred for 14 h. The solution was poured into 300mL of ice with 50mL of a 6N aqueous hydrochloric acid solution, and stirred for 30 min. The organic layer was separated and the solvent was removed under reduced pressure to give **8** (11.2g, 85%). To a solution of **8** (10g, 0.0682 mol) in ethanol (20mL), were added ammonium acetate (21g, 0.273 mol) and malonic acid (7.10g, 0.068 mol). The reaction mixture was refluxed for 15 h. The resulting precipitate was collected and washed with boiling ethanol to give **10** as a white solid (4.60g, 32% from **1**), mp. > 237°.

Anal. Calcd for $C_7H_9Cl_2NO_2$: C, 40.03; H, 4.32; N, 6.67. Found: C, 40.01; H, 4.35; N, 6.69

IR: 3450-2900 (OH, NH_3^+), 1725 (CO), 1492, 1217, 810 cm^{-1}. ^1H NMR 8.9 (s, 3H, NH_3), 7.58 (s, 1H, H'_5), 7.38 (s, 1H, H'_3), 4.73 (dd, 1H, H_3, $J_{H_3H_{2a}}$ = 4.76 Hz, $J_{H_3H_{2b}}$ = 9.15 Hz), 3.19 (dd, 1H, H_{2a}, $J_{H_{2a}H_{2b}}$ = 16.6 Hz, $J_{H_{2a}H_3}$ = 4.76 Hz), 2.99 (dd, 1H, H_{2b}, $J_{H_{2b}H_{2a}}$ = 16,6 Hz, $J_{H_{2b}H_3}$ = 9.15 Hz). ^{13}C NMR 170.2 (C1), 46.1 (C2), 55.7 (C3), 140.2 (C'2), 127.1 (C'3), 124.2 (C'4), 122.1 (C'5).

3-Amino-3-(4-bromothien-2-yl)propionic Acid (11).- Thiophene-2-carboxaldehyde (**1**) (10g, 0.090 mol) was charged with 100mL of dichloromethane and the reaction mixture was then cooled to 0°. To this solution was added in portions $AlCl_3$ (26.8g, 0.200 mol) while the temperature of the reaction mixture was maintained at 0°. Bromine (5.00mL, 0.1 mol) was added and the mixture was refluxed for 3 h. This solution was poured into 300mL of ice with 50mL of a 6N aqueous hydrochloric acid solution, and stirred for 30 min. The organic layer was separated and the solvent was removed under reduced pressure to give **9** (16.2g, 95%). To a solution of **9** (10g, 0.0523 mol) in ethanol (15mL) were added ammonium acetate (16.2g, 0.0210 mol) and malonic acid (5.45g, 0.0523 mol). The reaction mixture was refluxed for 15 h. The resulting precipitate was filtered and washed with boiling ethanol to give **11** as a white solid (6.13g, 46% from **1**), mp. > 242°.

Anal. Calcd for $C_7H_9BrClNO_2$: C, 33.03; H, 5.56; N, 5.50. Found: C, 33.01; H, 3.57; N, 5.55

IR: 3450-2900 (OH, NH_3^+), 1728 (CO), 1491, 1214, 808 cm^{-1}. ^1H NMR 9.02 (s, 3H, NH_3), 7.67 (s, 1H, H'_5), 7.37 (s, 1H, H'_3), 4.78 (dd, 1H, H_3, $J_{H_3H_{2a}}$ = 4.6 Hz, $J_{H_3H_{2b}}$ = 9.15 Hz), 3.18 (dd, 1H, H_{2a}, $J_{H_{2a}H_{2b}}$ = 16.8 Hz, $J_{H_{2a}H_3}$ = 4.6 Hz), 2.99 (dd, 1H, H_{2b}, $J_{H_{2b}H_{2a}}$ = 16.8 Hz, $J_{H_{2b}H_3}$ = 9.15 Hz). ^{13}C NMR 170.2 (C1), 46.2 (C2), 55.5 (C3), 140.8 (C'2), 129.9 (C'3), 108.3 (C'4), 124.5 (C'5).

3-(4,5-Dichlorothien-2-yl)-propion-3-ylammonium Chloride (18).- To a suspension of **10** (4.75g, 0.0231 mol) in ether (50mL), was added at 0° trifluoroacetic anhydride (3.2mL, 0.023 mol). After stirring for 15 min., the solvent was evaporated under reduced pressure and the solution was poured

into water (100mL) to give **12** as a white solid (6.82g, 98%). Chlorine was bubbled at 0° into an ethereal solution (70mL) of **12** (6.82g, 0.0226 mol) for 3-5 min. After stirring for 30 min., the excess chlorine was reduced by adding a saturated solution of sodium thiosulfate. The organic layer was separated and solvent was removed under reduced pressure to give **14** as a white solid (6.45g, 85%). A suspension of **14** (6.45g, 0.0192 mol) in 50mL of a 6N aqueous hydrochloric acid solution was refluxed for 3 h. The solvent was removed under reduced pressure to give **18** as a white solid (4.50g, 27% from **10**), mp. > 260°.

Anal. Calcd for $C_7H_8Cl_3NO_2$: C, 34.39; H, 3.30; N, 5.73. Found: C, 34.01; H, 3.32; N, 5.77

IR: 3450-2900 (OH, NH_3^+), 1738 (CO), 1491, 1214 cm^{-1}. ^1H NMR 8.98 (s, 3H, NH_3), 7.43 (s, 1H, H'_3), 4.73 (dd, 1H, H_3, $J_{H_3H_{2a}}$ = 4.6 Hz, $J_{H_3H_{2b}}$ = 9.2 Hz), 3.19 (dd, 1H, H_{2a}, $J_{H_{2a}H_{2b}}$ = 16.7 Hz, $J_{H_{2a}H_3}$ = 4.6 Hz), 3.02 (dd, 1H, H_{2b}, $J_{H_{2b}H_{2a}}$ = 16.7 Hz, $J_{H_{2b}H_3}$ = 9.2 Hz). ^{13}C NMR 170.4 (C1), 46.1 (C2), 55.2 (C3), 142.3 (C'2), 124.5 (C'3), 120.7 (C'4), 122.2 (C'5).

3-(5-Chloro-4-bromothien-2-yl)propion-3-ylammonium Chloride (19).- To a suspension of **11** (5.80g, 0.0232 mol) in ether (50mL), was added at 0° trifluoroacetic anhydride (3.2 mL, 0.023 mol). After stirring for 15 min., the solvent was evaporated under reduced pressure and the solution was poured into water (100mL) to give **13** as a white solid (7.90 g, 98 %). Chlorine was bubbled into a cooled (0°) ethereal solution (80mL) of **13** (7.90g, 0.0228 mol) for 3-5 min. After stirring for 30 min., the excess chlorine was reduced by adding a saturated solution of sodium thiosulfate. The organic layer was separated and the solvent was removed under reduced pressure to give **15** as a white solid (7.36g, 85%). A suspension of **15** (7.36g, 0.0193 mole) in 50mL of a 6N aqueous hydrochloric acid solution was refluxed for 3 h. The solvent was removed under reduced pressure to give **19** as a white solid (5.90g, 39% from **11**), mp. > 260°.

Anal. Calcd for $C_7H_8BrCl_2NO_2$: C, 29.10; H, 2.79; N, 4.85. Found: C, 28.95; H, 2.81; N, 4.85

IR: 3450-2900 (OH, NH_3^+), 1734 (CO), 1492, 1210 cm^{-1}. ^1H NMR 8.97 (s, 3H, NH_3), 7.40 (s, 1H, H'_3), 4.74 (dd, 1H, H_3, $J_{H_3H_{2a}}$ = 5.32 Hz, $J_{H_3H_{2b}}$ = 9.0 Hz), 3.19 (dd, 1H, H_{2a}, $J_{H_{2a}H_{2b}}$ = 16.7 Hz, $JH_{2a}H_3$ = 5.32 Hz), 3.02 (dd, 1H, H_{2b}, $J_{H_{2b}H_{2a}}$ = 16.7 Hz, $J_{H_{2b}H_3}$ = 9.0 Hz). ^{13}C NMR 170.3 (C1), 46.1 (C2), 55.2 (C3), 142.2 (C'2), 126.2 (C'3), 105.0 (C'4), 124.7 (C'5).

3-(4-Chloro-5-bromothien-2-yl)propion-3-ylammonium Chloride (20).- To a suspension of **10** (4.4g, 0.0214 mol) in ether (50mL), was added at 0° trifluoroacetic anhydride (3mL, 0.021 mol). After stirring for 15 min., the solvent was evaporated under reduced pressure and the solution was poured into water (100mL) to give **12** as a white solid (6.3g, 98%). To an ethereal solution (70mL) of **12** (6.3g, 0.0209 mol), was added bromine (2.1mL, 0.042 mol) at room temperature. After stirring for 1 h, the excess bromine was reduced by adding a saturated solution of sodium thiosulfate. The organic layer was separated and the solvent was removed under reduced pressure to give **16** as a white solid (7.1g, 90%). A suspension of **16** (7.1g, 0.0187 mol) in 50mL of a 6N aqueous hydrochloric acid solution was refluxed for 3 h. The solvent was removed under reduced pressure to give **20** as a white solid (5.72g, 29% from **10**), mp. > 260°.

Anal. Calcd for $C_7H_8BrCl_2NO_2$: C, 29.10; H, 2.79; N, 4.85. Found: C, 28.97; H, 2.80; N, 4.90

IR: 3450-2900 (OH, NH_3^+), 1732 (CO), 1494, 1220 cm^{-1}. ^1H NMR 9.02 (s, 3H, NH_3), 7.40 (s, 1H, H'_3), 4.74 (dd, 1H, H_3, $J_{H_3H_{2a}}$ = 3.84 Hz, $J_{H_3H_{2b}}$ = 8.95 Hz), 3.21 (dd, 1H, H_{2a}, $J_{H_{2a}H_{2b}}$ = 16.75 Hz, $J_{H_{2a}H_3}$ = 3,84 Hz) ; 3.03 (dd, 1H, H_{2b}, $J_{H_{2b}H_{2a}}$ = 16.75 Hz, $J_{H_{2b}H_3}$ = 8.95 Hz). ^{13}C NMR 170.0 (C1), 46.4 (C2), 55.0 (C3), 143.2 (C'2), 126.1 (C'3), 127.9 (C'4), 106.1 (C'5).

3-(4,5-Dibromothien-2-yl)propion-3-ylammonium Chloride (21).- To a suspension of **11** (5.92g, 0.0237 mol) in ether (50mL), was added at 0° trifluoroacetic anhydride (3.3mL, 0.024 mol). After stirring for 15 min., the solvent was evaporated under reduced pressure and the solution was poured into water to give **13** as a white solid (8.03g, 98%). To an ethereal solution of **13** (8.03g, 0.0232 mol), was added bromine (2.4mL, 0.044 mol) at room temperature. After stirring for 1 h, the excess bromine was reduced by adding a saturated solution of sodium thiosulfate. The organic layer was separated and the solvent was removed under reduced pressure to give **17** as a white solid (8.87g, 90%). A suspension of **17** (8.87g, 0.0209 mol) in 50mL of a 6N aqueous hydrochloric acid solution was refluxed for 3 h. The solvent was removed under reduced pressure to give **21** as a white solid (7.25g, 41.5% from **11**), mp. > 260°.

Anal. Calcd for $C_7H_8Br_2ClNO_2$: C, 25.22; H, 2.42; N, 4.20. Found: C, 25.18; H, 2.44; N, 4.21

IR: 3450-2900 (OH, NH_3^+), 1738 (CO), 1492, 1214 cm^{-1}. ^1H NMR 8.96 (s, 3H, NH_3), 7.25 (s, 1H, H'_3), 4.62 (dd, 1H, H_3, $J_{H_3H_{2a}}$ = 6 Hz, $J_{H_3H_{2b}}$ = 6.9 Hz), 2.86 (dd, 1H, H_{2a}, $J_{H_{2a}H_{2b}}$ = 16.4 Hz, $J_{H_{2a}H_3}$ = 6 Hz), 2.79 (dd, 1H, H_{2b}, $J_{H_{2b}H_{2a}}$ = 16.4 Hz, $J_{H_{2b}H_3}$ = 6.9 Hz). ^{13}C NMR 170.4 (C1), 46.6 (C2), 54.8 (C3), 143.1 (C'2), 130.7 (C'3), 112.2 (C'4), 108.6 (C'5).

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NEW SIMPLE SYNTHESIS OF THE HOUSEFLY SEX ATTRACTANT

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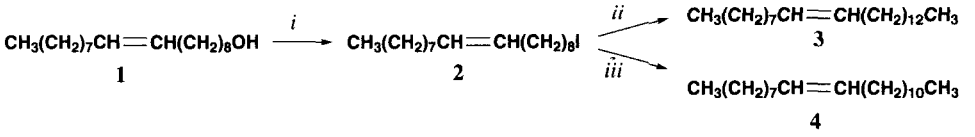
Muscalure [(Z)-9-tricosene, **3**], a sex attractant of the housefly (Musca domestica L.), has been prepared in a number of different ways, such as the transformations of acetylene,[1] oleic acid,[2] and olefin disproportionation.[3] Most of the chemical syntheses involve multistep processes.[4] We now describe a simple, convenient, and more efficient synthesis of muscalure proceeding *via* a cuprate-catalyzed Grignard coupling reaction as the key step.

As shown in Scheme 1, commercially available oleyl alcohol (**1**) was efficiently converted to oleyl iodide (**2**) by treament with triphenylphosphine, diethyl azodicarboxylate and lithium iodide.[5] The oleyl iodide was then coupled with pentylmagnesium bromide in the presence of dilithium trichlorocuprate (Li_2CuCl_3).[6,7] The reaction was complete in 4 h at room temperature to yield (Z)-9-tricosene. The product was purified by column chromatography to obtain pure (Z)-9-tricosene in 86% yield.



i) PPH_3, DEAD, LiI (91%) *ii*) $C_5H_{11}MgBr$, Li_2CuCl_3 (86%) *iii*) C_3H_7MgBr, Li_2CuCl_3 (87%)