Russian Journal of Organic Chemistry, Vol. 38, No. 2, 2002, pp. 188–190. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 2, 2002, pp. 207–209.

Synthesis of Unsaturated Carboxylic and Amino Acids of Adamantane Series with the Use of Organophosphorus Reagents

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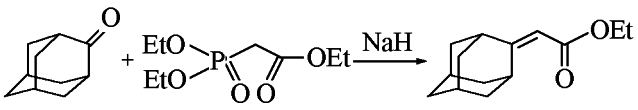
Received October 18, 2000

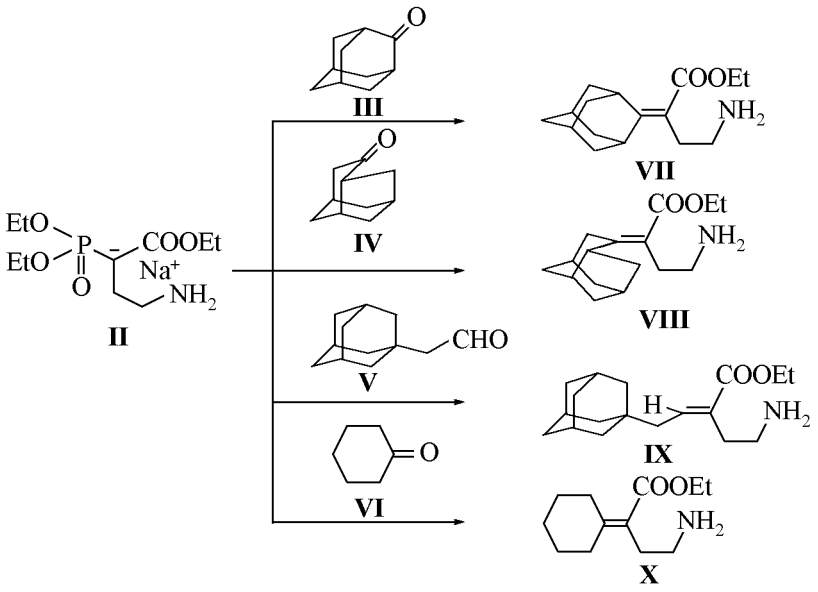
Abstract—Sodium derivative of diethyl(3-amino-1-ethoxycarbonylpropane)phosphonic acid was obtained by reaction of triethyl phosphonoacetate with ethylene imine in the presence of sodium hydride. The compound obtained was brought into Horner–Emmons reaction with carbonyl derivatives of adamantane series to afford the corresponding unsaturated amino acids. From adamantanecarbonyl chlorides and triphenylphosphonium ethoxycarbonylmethylide new phosphorus acylylides that on thermolysis provide ethyl acetylenecarboxylates containing an adamantyl substituent were prepared.

We formerly described [1] a procedure for synthesis of esters of unsaturated carboxylic acids, adamantane derivatives, by reaction of triethyl phosphonoacetate with appropriate carbonyl compounds (Horner–Emmons reaction).



We expected that at the use in the reaction of phosphonoacetates substituted in the methylene group the substituent would be conserved in the reaction product thus providing a possibility of synthesis of unsaturated acids with a substituent in the α-position with respect to the carboxy group. It is known that ylides are capable of reacting with N-substituted aziridines containing electron-withdrawing substituents to provide phosphorus ylides with 2-aminoethyl

Scheme.



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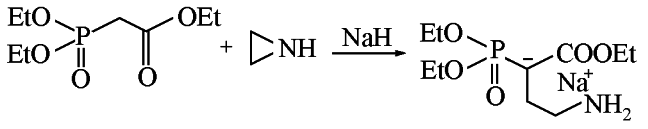
group at the ylide carbon [2]. This reaction is not described in the literature for phosphonoacetates and unsubstituted aziridine.

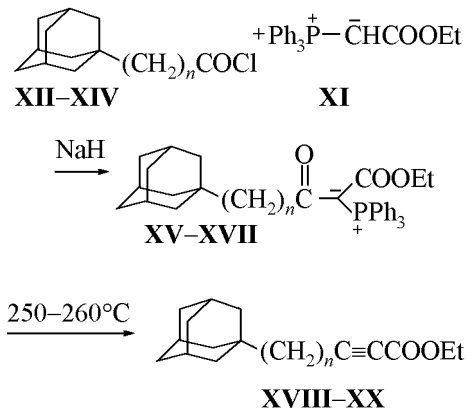
We established that triethyl phosphonoacetate **I** reacted with ethylene imine in the diglyme in the presence of sodium hydride at 100–120°C to afford sodium derivative of phosphonate **II**.



I **II**

The phosphonate can be isolated from the sodium derivative **II** as individual compound at acidification, but compound **II** was used in subsequent reactions without separation from the reaction mixture. Compound **II** reacts with carbonyl compounds in the same way as triethyl phosphonoacetate. As carbonyl compounds we used adamantanone (**III**), protoadamantanone (**IV**), 1-adamantylacetic aldehyde (**V**), and cyclohexanone (**VI**). The reaction proceeds at 100–120°C in diglyme for 25–30 h and affords ethyl γ-aminobutyrates **VII**–**X** in 25–60% yield (see scheme).

According to published data [3, 4, 5] ylides acylated at the ylide carbon atom can be converted into acetylene by various methods: by successive treatment with trifluoromethanesulfonic anhydride and sodium amalgam, or with phosphorus oxychloride and alkali, or by pyrolysis. We synthesized in high yield acylylides containing adamantyl radical by treating with adamantanecarbonyl chlorides triphenylphosphonium ethoxycarbonylmethylide (**XI**).



n = 0 (**XII, XV, XVIII**), 1 (**XIII, XVI, XIX**), 2 (**XIV, XVII, XX**).

Ylides obtained are outstanding in their inertness to hydrolysis, but they relatively readily undergo thermolysis at 250–260°C in a vacuum of 1–2 mm Hg, and in 25–30 min they virtually quantitatively are converted into ethyl acetylenecarboxylates **XVIII**–**XX**.

We failed to synthesize cage-like derivatives of acetylene by thermolysis of acylylides of adamantane series without carboxy group.

The composition and structure of compounds obtained were confirmed by elemental analyses, IR and ^{1}H NMR spectra.

EXPERIMENTAL

^{1}H NMR spectra were recorded on spectrometer Tesla BS-487C (80 MHz) in $CDCl_3$, chemical shifts were given relative to TMS. IR spectra were measured on Specord instrument from solutions in CCl_4. Only characteristic absorption bands of stretching vibrations are listed below. Elemental analyses were carried out on CHN-Analyzer. The melting point were measured on Boetius heating block, and the reported values were corrected.

Ethyl α-adamantylidene-γ-aminobutyrate (VII). To a solution of 1.5 g (6.7 mmol) of triethyl phosphonoacetate (**I**) in 10 ml of anhydrous diglyme was added at stirring in an argon flow 0.168 g (7 mmol) of sodium hydride. The mixture was stirred till the end of hydrogen evolution, then it was charged into an ampule, and 0.344 g (8 mmol) of ethylene imine was added. The ampule was sealed and heated to 100–120°C for 5 h. Then it was opened, and 1 g (6.7 mmol) of adamantanone (**III**) was added, the ampule was sealed again and heated to 100–120°C for 30 h. Afterwards the solvent was distilled off from the reaction mixture in a vacuum, the residue was treated with water, the reaction product was extracted into dichloromethane, the extract was dried with sodium sulfate, the solvent was distilled off, and the residue was subjected to vacuum-distillation. Yield of compound **VII** 0.8 g (45%), bp 160°C (3 mm Hg). IR spectrum (cm^{-1}): 3400–3500 (NH primary), 1700 ($COOC_2H_5$). ^{1}H NMR spectrum (δ, ppm): 3.95 quint (2H, OCH_2), 2.55–2.8 m (6H, $CH_2CH_2NH_2$), 1.45–2.22 m (14H adamantyl), 1.15 t (3H, CH_3). Found, %: C 72.85, 72.90; H 9.35, 9.57; N 5.15, 5.25. $C_{16}H_{25}NO_2$. Calculated, %: C 73.00; H 9.5; N 5.3.

Ethyl α-(4-protoadamantylidene)-γ-aminobutyrate (VIII) was obtained in a similar way from 1.14 g (7.1 mmol) of 4-protoadamantanone. Yield 0.47 g (25%), bp 75–77°C (1–2 mm Hg). IR spectrum (cm^{-1}): 3350–3400 (NH primary), 1700

($COOC_2H_5$) . ^{1}H NMR spectrum (δ, ppm): 4.0 q (2H, OCH_2), 1.1–2.42 m (14H protoadamantyl; 6H, $CH_2CH_2NH_2$; 3H, CH_3). Found, %: C 72.80, 72.95; H 9.32, 9.45; N 5.02, 5.15. $C_{16}H_{25}NO_2$. Calculated, %: C 73.00; H 9.5; N 5.3.

Ethyl α-[2-(1-adamantyl)ethylidene]-γ-aminobutyrate (IX) was obtained in a similar way from 1.18 g (6.6 mmol) of 1-adamantylacetaldehyde (**V**). Yield 1.16 g (60%), bp 132–134°C (2 mm Hg). IR spectrum (cm^{-1}): 3400–3500 (NH primary), 1710 ($COOC_2H_5$). ^{1}H NMR spectrum (δ, ppm): 7.07 m (1H, =CH), 4.0 q.d. (2H, OCH_2), 1.43–2.8 m (15H, adamantyl, 6H, $CH_2CH_2NH_2$), 1.15 t (3H, CH_3). Found, %: C 74.15, 74.32; H 9.85, 9.80; N 4.75, 4.90. $C_{18}H_{29}NO_2$. Calculated, %: C 74.22; H 9.96; N 4.81.

Ethyl α-(cyclohexylidene)-γ-aminobutyrate (X) was obtained in a similar way from 0.65 g (6.6 mmol) of cyclohexanone (**VI**). Yield 0.84 g (60%), bp 65–70°C (3– 4 mm Hg). IR spectrum (cm^{-1}): 3300–3500 (NH primary), 1710 ($COOC_2H_5$). ^{1}H NMR spectrum (δ, ppm): 3.95 q (2H, OCH_2), 1.67–2.25 m (10H, cyclohexyl; 7H, $CH_2CH_2NH_2$), 1.15 m (3H, CH_3). Found, %: C 68.10, 68.36; H 9.70, 9.86; N 6.32, 6.70. $C_{12}H_{21}NO_2$. Calculated, %: C 68.24; H 9.9; N 6.63.

Triphenylphosphonium [α-(1-adamantanecarbonyl)-α-ethoxycarbonyl]methylide (XV). To a solution of 3.9 g (12.2 mmol) of triphenylphosphonium ethoxycarbonylmethylide (**XI**) in anhydrous benzene (30 ml) was added a solution of adamantanecarbonyl chloride (**XII**) (1.1 g, 5.6 mmol) in 10 ml of anhydrous benzene. The reaction mixture was stirred for 10 h at room temperature. The precipitate of ethoxycarbonylmethyltriphenylphosphonium chloride was filtered off, the filtrate was evaporated. We obtained 2.5 g (87%) of compound **XV** that was purified by reprecipitation from a mixture benzene–hexane. ^{1}H NMR spectrum (δ, ppm): 7.17–7.6 m (15H, phenyl), 3.90 q (2H, OCH_2), 1.52–1.92 m (15H, adamantyl), 0.92 t (3H, CH_3). Found, %: P 6.15, 6.25. $C_{33}H_{35}O_3P$. Calculated, %: P 6.07.

Triphenylphosphonium [α-(1-adamantanylacetyl)-α-ethoxycarbonyl]methylide (XVI) was synthesized similarly to compound **XV** from ylide **XI** and 1.4 g (6.6 mmol) of compound **XIII**, yield 2.83 g (82%). ^{1}H NMR spectrum (δ, ppm): 7.10–7.6 m (15H, phenyl), 3.90 q (2H, OCH_2), 1.52–1.92 m (15H, adamantane, 2H, CH_2), 0.92 t (3H, CH_3). Found, %: P 5.80, 5.98. $C_{34}H_{37}O_3P$. Calculated, %: P 5.91.

Triphenylphosphonium {α-[3-(1-adamantanylpropanoyl)]-α-ethoxycarbonyl}methylide (XVII) was synthesized similarly to compound **XV** from ylide **XI** and 1.49 g (6.6 mmol) of compound **XIV**, yield 2.8 g (79%). ^{1}H NMR spectrum (δ, ppm): (15H, phenyl), 3.90 q (2H, OCH_2), 1.52–1.92 m (15H adamantyl, 4H, CH_2CH_2), 0.92 t (3H, CH_3). Found, %: P 5.68, 5.82. $C_{35}H_{39}O_3P$. Calculated, %: P 5.76.

Ethyl 3-(1-adamantyl)propynoate (XVIII). In a round-bottom flask was heated to 250–260°C in a vacuum 1 g (1.96 mmol) of triphenylphosphonium [α-(1-adamantanecarbonyl)-α-ethoxycarbonyl]methylide (**XV**). Thermolysis was accompanied with sublimation of triphenylphosphine oxide. At 180°C and 5 mm Hg was distilled the reaction product that was subsequently twice washed with petroleum ether to purify from triphenylphosphine oxide. Yield of oily compound **XVIII** 0.4 g (88%). IR spectrum (cm^{-1}): 2230 (C≡C), 1700 ($COOC_2H_5$). ^{1}H NMR spectrum (δ, ppm): 3.97 q (2H, OCH_2), 1.3–1.87 m (15H, adamantyl), 1.15 t (3H, CH_3). Found, %: C 77.34, 77.48; H 8.45, 8.60. $C_{15}H_{20}O_2$. Calculated, %: C 77.58; H 8.62.

Ethyl 4-(1-adamantyl)butynoate (XIX) was obtained in a similar way from 3.45 g (6.6 mmol) of compound XVI. Yield 1.07 g (66%), bp 165–170°C (7 mm Hg). IR spectrum (cm^{-1}): 2200 (C≡C), 1700 ($COOC_2H_5$). ^{1}H NMR spectrum (α, ppm): 3.7 q (2H, OCH_2), 1.3–2.0 m (15H, adamantyl, 2H, CH_2), 1.15 t (3H, CH_3). Found, %: C 77.90, 78.10; H 8.75, 8.85. $C_{16}H_{22}O_2$. Calculated, %: C 78.04; H 8.94.

Ethyl 5-(1-adamantyl)pentynoate (XX) was obtained in a similar way from 3.55 g (6.6 mmol) of compound **XVII**. Yield 0.41 g (82%), bp 140°C (3–6 mm Hg). IR spectrum (cm^{-1}): 2230 (C≡C), 1700 ($COOC_2H_5$). ^{1}H NMR spectrum (α, ppm): 3.97 q (2H, OCH_2), 1.3–2.0 m (15H, adamantyl, 4H, CH_2CH_2), 1.15 t (3H, CH_3). Found, %: C 78.35, 78.52; H 9.05, 9.15. $C_{17}H_{24}O_2$. Calculated, %: C 78.46; H 9.23.

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