Synthesis of Long Chain α,β-Alkynoic and α,β-Alkynoic Acids Via β-Keto Esters[1]

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Abstract

A general method for the synthesis of long chain α,β-alkynoic acids from β-keto esters is described. The synthesis involves conversion of the β-keto ester to the corresponding pyrazolone, then halogenation and treatment of the resultant 4,4-dihalo product with dilute aqueous alkali to form the α,β-alkynoic acids. Specifically, 2-octynoic, 2-nonynoic and 2-decadecynoic acids were prepared as representative examples. If the β-keto ester has an alkyl group at the α-position, the final product is a mixture of *cis* and *trans* α-substituted-α,β-unsaturated alkenoic acids, which may be separated by gas-liquid chromatography. Pertinent IR and proton magnetic resonance data are used in characterizing the stereochemistry of products and a possible mechanism for the product forming reactions is presented.

Introduction

During the course of our experiments on biological precursors of fatty acids, it was necessary to develop a general synthetic route to long chain α,β-alkynoic acids. The elegant method developed by Carpino (1) in the preparation of phenylpropiolic and tetrolic acid, which involved reaction of 4,4-dihalopyrazolones with aqueous alkali, was utilized and adapted starting with various β-keto esters. General convenient methods for the preparation of long chain α,β-alkynoic acids have not been readily available. Bromination and debromination of available α,β-alkenoic acids to the corresponding acetylenic acid are incomplete, because of interaction of the carboxyl group with the double bond in the α position as has been shown by Owen (2), Schjanberg (3), and Mercuri (4). Dehydrohalogenation of α,β-dihalo acids or their derivatives is not generally applicable in the aliphatic series and the somewhat inconvenient acetylide-carbonation reaction is widely used.

In view of the ready availability of β-keto esters of all types, it would seem that the method described represents a useful synthetic route to α,β-alkynoic acids difficult to obtain by other methods. By partial catalytic hydrogenation of the triple bond of these acids (5), a general method for preparing disubstituted *cis*-α,β-alkenoic acids from β-keto esters is readily available. Also, this method can be extended to the preparation of *cis,trans*-trisubstituted-α,β-alkenoic acids yielding the least stable *cis* acid which is difficult to obtain by other methods (6).

Experimental Procedures

Analytical Techniques

IR spectra were determined as smears or solids in potassium bromide pellets on a Perkin-Elmer Model 137 Infracord equipped with sodium chloride optics and an air path in the reference beam. Unless otherwise noted, proton resonance spectra were taken in deuteriochloroform solution on a Varian A-60 instrument using tetramethylsilane as internal standard. A Beckman GC-2 equipped with a Thermotrac was used for gas liquid chromatography (GLC). Columns used were 6 ft, o.d. 0.25 in., 15% FFAP (free fatty acid phase) on 80–100 mesh Chromosorb W (Applied Science Laboratories). Analyses are by Weiler and Strauss, Micronanalytical Laboratory, Oxford, England.

Ethyl-3-keto-octanate and Ethyl-3-ketononanate

These β-keto esters, were synthesized utilizing the method of Hauser (7) both in 73% yields.

Ethyl Acetoacetate, Ethyl-2-methylacetoacetate and Ethyl Steroyl Acetate

Readily available materials, were used as received from the Aldrich Chemical Company.

Ethyl-2-ethylacetoacetate

Was prepared by the method of Adkins and Folkers (8) in 70% yield.

Preparation of 3-Alkyl (n-Pentyl, n-Hexyl and n-Heptadecyl)-2-Pyrazolin-5-ones

A solution of the β-keto ester in ethanol was treated slowly with a solution of 64% hydrazine in ethanol at room temperature with vigorous stirring. In the case of *n*-heptadecyl-2-pyrazolin-5-one, the reaction mixture was warmed on a hot plate for a minute before cooling. Equimolar amounts of β-keto ester and 64% hydrazine were used. The solids obtained in each reaction were recrystallized by first adding hot nitromethane and then dissolving the suspension obtained in a minimum amount of hot N,N-dimethylformamide. Average yields for each product were 73% (*n*-pentyl), 74% (*n*-hexyl), and 86% (*n*-heptadecyl) and the melting points for each were 197–199, Lit. (9) 198, 203–205, Literature (9) 201, and 182–184 C, respectively. Analysis for the new compound *n*-heptadecyl-2-pyrazolin-5-one was: C, 74.60; H, 11.90; N, 8.40, Calculated for $C_{20}H_{38}N_2O$: C, 74.53; H, 11.80; N, 8.69.

Preparation of 3,4-Dialkyl (3,4-Dimethyl, 3-Methyl-4-ethyl)-2-Pyrazolin-5-ones

The procedure followed was the same as that of the 3-alkyl derivatives. Average yields for 3,4-dimethyl- and 3-methyl-4-ethyl- were 70% and 91% and the melting points for each were 269–71, Lit. (10) 272, and 231–32, Literature (10) 229 C, respectively.

Preparation of 3-Alkyl (n-Pentyl, n-Hexyl and n-Heptadecyl)-4,4-Dichloro-2-Pyrazolin-5-ones

A suspension of 1 g of the 3-alkyl-2-pyrazolin-5-one in 25 ml of nitromethane was heated to the

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boiling point, removed from the source of heat and chlorine gas was passed into the solution until the solid dissolved (10–15 min). During chlorination, the solution turned a yellow-green.

In the case of the *n*-pentyl- and *n*-hexyl- compounds, the solvent was removed with a rotatory evaporator and yielded an oil. No further attempt was made to purify the product which was immediately used for the subsequent reaction. Average yields for the *n*-pentyl product were 97%, microboiling point 102–104 C, n_D^{25} = 1.4964; *n*-hexyl product, 82%, microboiling point 110–112 C, n_D^{25} = 1.4990.

On cooling the solution containing the *n*-heptadecyl-compound, a white solid separated which was filtered, dried and recrystallized from ligroin or benzene-ligroin solvent pair. The melting point of the product was 43–44 C, average yields 75%. Analysis: Calculated for $C_{20}H_{36}N_2Cl_2O$: C, 61.38; H, 9.20; N, 7.16; Cl, 18.12. Found: C, 61.55; H, 9.55; N, 7.11; Cl, 17.90.

Preparation of 3,4-Dialkyl (3,4-Dimethyl, 3-Methyl-4-ethyl)-4-Chloro-2-Pyrazolin-5-ones

The procedure followed was the same as that of the 3-alkyl derivatives except the nitromethane was not heated to boiling. The products were recrystallized from a benzene-ligroin solvent pair. Average yields for 3,4-dimethyl- and 3-methyl-4-ethyl- compounds were 75% and 89% and the melting points were 57–59, Literature (11) 57–59, and 54–59 C respectively. The analysis for the new 3-methyl-4-ethyl- compound was: C, 44.64; H, 5.73; N, 17.15; and Cl, 22.02, Calculated for $C_6H_9N_2OCl$: C, 44.87; H, 5.65; N, 17.44; Cl, 22.07.

Preparation of 2-Octynoic, 2-Nonynoic and 2-Decadecynoic Acids

A solution containing 0.075 mole of sodium hydroxide in 75 ml of water was cooled with stirring in an ice bath and 0.015 mole of the dichloropyrazolin-5-one was added. The solid dissolved giving the solution a yellow-orange color and evolving nitrogen gas. After 2 hr the ice bath was removed and the stirring continued for 12 additional hours at room temperature. The cold solution was acidified with dilute hydrochloric acid (congo red) and the acids were extracted with one 35 ml portion and eight 15 ml portions of ether. The combined ether extracts were extracted four times with 1.0 M sodium bicarbonate. The sodium bicarbonate extracts were acidified with concentrated hydrochloric acid and the organic acids reextracted with ethyl ether. The ether extracts were dried over magnesium sulfate, filtered and the ether removed with a rotary evaporator. Average yields of 2-octynoic and 2-nonynoic acids were 76% and 72%, respectively, and the boiling points and indices of refraction for each were 114 at 2 mm, n_D^{25} 1.4586. Lit. (12) 114 at 2 mm, n_D^{25} 1.4588, and 118 at 2 mm, n_D^{25} 1.4603, Literature (12) 122 at 2 mm, n_D^{25} = 1.4605.

Because of the relative insolubility of the halopyrazoline, considerable difficulty was encountered when the synthesis of 2-decadecynoic acid was attempted by the previous procedure. The method of Schwartz (14) using a mortar and pestle proved successful and follows.

Two and one half grams (0.06 mole) of sodium hydroxide were ground with 4 ml of water using a mortar and a pestle attached to a stirrer with pressure tubing. This slurry was ice-cooled and 0.75 g (0.002 mole) of 3-heptadecyl-4,4-dichloro-2-pyrazolin-5-one was added. After 30 min of stirring, the resulting solid as washed with two 10 ml portions of ether. The residue was acidified with 10 ml dilute hydrochloric acid and the product extracted with ether three times. The ether was removed and the resulting solid was recrystallized from absolute ethanol and decolorizing carbon. Average yields were 85% and the product melted at 44–46 C. Analysis: Calculated for $C_{20}H_{36}O_2$: C, 77.92; H, 11.69. Found: C, 77.84; H, 11.70.

Preparation of Angelic, Tiglic, 2-Ethylcrotonic, and 2-Ethylisocrotonic Acids

The procedure followed was the same as the preparation of 2-octynoic and 2-nonynoic acids.

The average yield of the mixture of angelic and tiglic acids was 82% and of the mixture of 2-ethylcrotonic and 2-ethylisocrotonic acids, 86%.

The mixtures were readily separated by GLC. No isomerization of the acids occurs under the conditions of gas chromatography as proved by the use of the pure acids. The products were collected in a fraction collector described previously (15).

Average percentages obtained and determined by GLC and proton magnetic resonance (PMR) (16) follows: (a) 53.6% angelic acid and 46.4% tiglic acid; and (b) 62.2% 2-ethylisocrotonic acid and 37.8% ethylcrotonic acid.

The proton magnetic resonance peaks, due to the olefinic proton, appeared in all cases as quartets and the values are reported for the center of each quartet and expressed in parts per million on the δ scale. The olefinic proton value for each acid follows: angelic (6.19), tiglic (6.97), 2-ethylisocrotonic (6.18) and 2-ethylcrotonic (7.00).

TABLE I

Relative Retention Times[a]

	15% Free fatty acid phase column
Angelic acid[b]	1.16
Tiglic acid[b]	1.28
2-Ethylisocrotonic acid[c]	1.55
2-Ethylcrotonic acid[c]	1.73
RS-2-Methylbutanoic acid	1.00

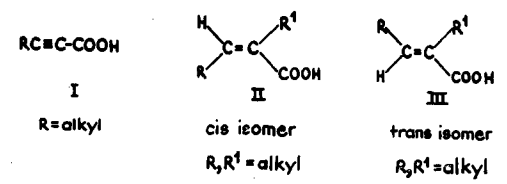
[a] Time corrected for the gas hold-up.

[b] Experimental conditions: inlet temperature 275 C; column temperature program: 68 C at 9.84/min to 186 C, 2/min for 5 min starting at 186 C, 9.84/min to 218 C; pressure 20.0 psi, sample size 20 μl; attenuation 2; detector temperature 238 C; filament current 250 μ A, chart speed 0.5 in./min; flow rate 72.5 ml/min; air peak elution 4.75 mm; RS-2-methylbutanoic acid elution: 130.75 mm.

[c] Experimental conditions: inlet temperature 275 C; column temperature program: 68 C at 15.9/min to 171 C, 0.475/min from 171 to 176 C, 19.5/min to 215 C; pressure 18.0 psi, sample size 9 μl, attenuation 10; detector temperature 238 C; filament current 250 μ A, chart speed 0.5 in./min; flow rate 58.5 ml/min; air peak elution 5.80 mm; RS-2-methylbutanoic acid elution: 119.9 mm.

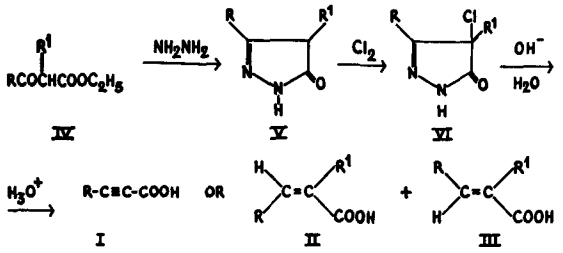
Results and Discussion

The object of this work was an attempt to synthesize long chain α,β-alkynoic acids (I) and trisubstituted α,β-alkenoic acids (II), (III) of the following types from readily available β-keto esters.



These α,β-unsaturated acids are of interest because they could be important intermediates in fatty acid metabolism of biological systems. For purposes of

clarity the overall synthetic scheme will be presented before each reaction is discussed.



	R	R^1
I	$CH_3(CH_2)_4$, $CH_3(CH_2)_5$, $CH_3(CH_2)_{16}$	H
II	CH_3	CH_3, C_2H_5
III	CH_3	CH_3, C_2H_5
IV	CH_3, $CH_3(CH_2)_4$, $CH_3(CH_2)_5$, $CH_3(CH_2)_{16}$	H, CH_3, C_2H_5
V	Same as IV	Same as IV
VI	Same as IV	Cl, CH_3, C_2H_5

The first step in the synthesis involves reaction of the appropriate β-keto ester with hydrazine hydrate to form the corresponding 2-pyrazolin-5-one (V). The 2-pyrazolin-5-one is converted to the halopyrazolin-5-one (VI) by chlorination. If R^1 = H, the 4,4-dichloro product is formed and if R^1 is an alkyl group the 4-monochloro product is obtained. The presence of the dihalosubstituted product at the 4-position is usually detected by the very strong absorption of the carbonyl group between the 5.6–6.2 micron region (12). On the other hand, none of the 4-unsubstituted or 4-monosubstituted pyrazolones showed any absorption in the region 5.6–6.19 μ. Table II summarizes the IR absorptions of the carbonyl groups of pyrazolones synthesized in our study.

The final reaction involves treatment of the resultant 4-chloro- or 4,4-dichloropyrazolin-5-one with dilute aqueous alkali followed by acidification.

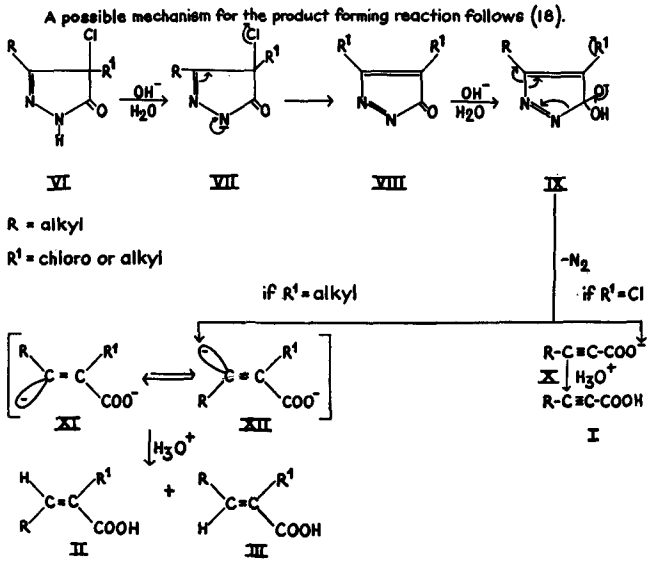
The 4,4-dichloropyrazolones yielded 2-octynoic, 2-nonynoic and 2-decadecynoic acids on the average of 76%, 72% and 85% yields, respectively. The IR spectra showed strong absorptions at 4.50 and 5.90 μ characteristic of a carbon triple bond carbon and carboxylic acid group.

The 4-chloropyrazolones yielded *cis*- and *trans*-2-methylbutenoic acid and 2-ethylbutenoic acid, also commonly called angelic, tiglic, 2-ethylisocrotonic and 2-ethylcrotonic acids, respectively. This method of preparation represents a useful synthetic route to acids difficult to obtain by other methods in that the *cis* labile acids, angelic and 2-ethylisocrotonic acids are formed in predominant amounts, in 53.6% and 62.2% yields, respectively.

GLC (Table I) was used to separate the *cis* and *trans* acids. This method of separation represents an improvement over the fractional extraction method with sodium bicarbonate previously reported (6) in that the latter method is somewhat tedious, adaptable only to water insoluble pairs and, therefore, not applicable to our study.

The quantitative determination of acids was readily accomplished using GLC and PMR. In an analysis of a mixture of *cis* and *trans* isomers utilizing PMR, the olefinic proton peaks are well separated and the relative areas under these peaks are proportional to the ratio of the components. The relative positions of the resonance lines of the olefinic proton are also characteristic of its stereochemistry; the shielding value of the single proton in the *trans* compound is always higher in δ units than that of the corresponding *cis* isomer by about 0.8 ppm. Perhaps the *trans* isomer olefinic proton appears at lower fields than the olefinic proton of the *cis* isomer because of steric inhibition of resonance caused by interactions of the *cis* alkyl and carboxyl groups in the latter case. Also, an insignificant shift occurs in the δ value of the olefinic proton by changing the substituent from methyl to ethyl (16).

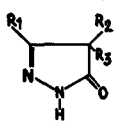
A possible mechanism for the product forming reaction follows (17).



The second step in the mechanism is believed to involve elimination of halide ion from anion VII to give a diazacyclopentadienone intermediate VIII. Ring opening of VIII by hydroxide ion with concomitant loss of nitrogen would yield I, if R^1 is chloro, or the dianions XI and XII if R^1 is an alkyl group. Possibly, due to electronic repulsions which would be greater in XI, the *cis*-dianion XI rapidly isomerizes to the *trans*-dianion XII before protonation occurs. Thus the most stable dianion XII with minimum electronic repulsions would lead to the least stable product II which is formed in predominant amount. This postulation is supported by the fact that as one changes R^1 from methyl to ethyl the amount of *cis* acid obtained increases. One would expect that dianion XII would be more favored than

Table II

CARBONYL INFRARED ABSORPTIONS OF PYRAZOLONES



Cpd.	R_1	R_2	R_3	Position μ
1	$CH_3(CH_2)_4$	H	H	6.19
2	$CH_3(CH_2)_4$	Cl	Cl	5.72
3	$CH_3(CH_2)_5$	H	H	6.20
4	$CH_3(CH_2)_6$	Cl	Cl	5.72
5	$CH_3(CH_2)_{16}$	H	H	6.25
6	$CH_3(CH_2)_{16}$	Cl	Cl	5.70
7	CH_3	CH_3	H	6.20 (first peak of doublet)
8	CH_3	CH_3	Cl	5.77
9	CH_3	C_2H_5	H	6.19 (first peak of doublet)
10	CH_3	C_2H_5	Cl	5.80

XI as one increases the size of R^1 in that XII would minimize the steric interactions of the two alkyl groups.

The postulation that diazacyclopentadienones are intermediates in the decomposition of halopyrazolones is supported by the trapping of these intermediates in previous work with aryl and cycloalkyl halopyrazolones (17–19).

Studies involving the attempted trapping of alkyl diazacyclopentadienones such as VIII are currently in progress and will be reported in a future publication.

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