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The Stereochemistry of Base-catalyzed Additions of *p*-Toluenethiol to Several Negatively-substituted Acetylenes. An Exception to the Rule of *trans*-Nucleophilic Addition[1,2]

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The Rule of *trans*-Nucleophilic Addition to Acetylenes has been further tested with several negatively-substituted acetylenes. An exception to this rule has been noted in the base-catalyzed addition of *p*-toluenethiol to sodium propiolate to give *trans*-β-*p*-tolylmercaptoacrylic acid. Similar additions to ethyl propiolate and phenyl ethynyl ketone proceed in the more usual *trans* fashion.

Previous papers in this series have established the *trans* nature of the base-catalyzed additions of methanethiol to phenylacetylene and of *p*-toluenethiol to phenylacetylene, chloroacetylene, *p*-tolylmercaptoacetylene, 1-hexyne and 2-butyne, *e.g.*

$$C_6H_5C{\equiv}CH + p\text{-}C_7H_7SNa(EtOH) \longrightarrow cis\text{-}C_6H_5CH{=}CHSC_7H_7$$

These results and the resulting theory[1] suggested that nucleophilic additions to acetylenes in general will occur in a stereospecific *trans* manner. In fact, prior to this series of papers, there had been indications in the literature of only one stereoisomer being obtained in nucleophilic additions, *e.g.*, to the four acetylenic systems, phenylacetylene or a ring-substituted derivative,[3] ethyl propiolate or a β-substituted ethyl propiolate,[4] diethyl acetylenedicarboxylate[4b,c] and acetylenic ketones.[5]

This work concerns the further testing of this Rule of *trans*-Nucleophilic Addition in the nucleophilic addition of *p*-toluenethiol to monosubstituted acetylenes carrying the electronegative groups $-CO_2^-$, $-CO_2Et$ and $-COC_6H_5$.

Addition of an ethanolic solution of *p*-toluenethiol containing a catalytic amount of sodium ethoxide to an aqueous ethanolic solution of sodium propiolate either at room temperature or with external cooling gave a quantitative yield of two acids, m.p. 144.5–145.5° (I) and m.p. 136–137° (II). Both were characterized as β-*p*-tolylmercaptoacrylic acids on the basis of their neutral equivalents, analyses and infrared spectra. Compound I made up 85–90% of the total product with the remainder being II.

Infrared spectra suggested that compound I was *trans*-β-*p*-tolylmercaptoacrylic acid and II was the corresponding *cis* acid. Compound I exhibited a band at 8.42 μ (m), characteristic of the in-plane bending of *trans*-ethylenic hydrogens[6]; however, the band usually present at from 10.20 to 11.25 μ,[6,7] indicative of the out-of-plane bending for *trans*-ethylenic hydrogens, was weak and broad, 10.25–10.60 μ. Isomer II exhibited strong bands at 7.79 and 14.82 μ suggestive of in-plane and out-of-plane bending vibrations of *cis*-ethylenic hydrogens.[6] A rather strong band for II at 10.30 μ was unaccounted for. There were no bands in either spectrum which would indicate the presence of a $>C{=}CH_2$ group.

This assignment of configuration was at odds with a literature report on a different synthesis of *cis*- and *trans*-β-*p*-tolylmercaptoacrylic acids, where melting points of 104–107° and 136–138°, respectively, were obtained.[8] Accordingly, we repeated this work and found, after a single recrystallization, two fractions melting over the reported ranges. However, the infrared spectrum of the low-melting material was a composite of the spectra for the two acids (I and II) we had obtained by addition of the thiol to sodium propiolate. In fact, by careful recrystallization we separated the "acid" having m.p. 104–107° into I and II.

Further evidence for the configurations of I and II was obtained by subjecting each to treatment with phosphorus pentachloride and then aluminum chloride for short periods of time at room temperature.[4b] While practically all of I was recovered unchanged, II gave an almost quantitative yield of the cyclization product, 6-methylthiochromone. Under more vigorous conditions compound I also cyclized, due to preliminary isomerization under these Friedel–Crafts conditions.

The exothermic reaction of ethyl propiolate with thiolate reagent gave two products, ethyl β,β-diethoxypropionate and ethyl β-*p*-tolylmercaptoacrylate. Saponification of the latter compound gave only the *cis*-acid II (an almost negligible amount of the *trans*-acid I was detected). It should be mentioned that refluxing solutions of both I and II in alcoholic base for 24 hr. resulted in no isomerization, thus precluding the possibility of an isomerization occurring during some stage of the experimental work.

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[1] This constitutes Paper VI in the series,' 'Stereospecific Reactions of Nucleophilic Agents with Acetylenes and Vinyl-type Halides"; for preceding paper see THIS JOURNAL, **79**, 1770 (1957). Taken from the Ph.D. thesis of R.F.H.

[2] NOTE ADDED IN PROOF: This rule will be applicable only to negatively-charged nucleophilic agents. With uncharged nucleophilic agents, *e.g.*, amines, the attacking grouping would be developing a positive charge in the transition state to addition, and hence would tend to bring the displaced electron pair into a *cis*-arrangement relative to itself. Some evidence supporting this prediction of *cis* addition with amines exists [E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.*, 1423 (1949)] and is being currently developed in this laboratory with less complicated acetylenic systems.

[3] (a) S. J. Cristol, *et al.*, THIS JOURNAL, **76**, 4558 (1954); (b) C. Dufraisse and R. Chaux, *Bull. soc. chim.*, [4], **39**, 905 (1926); (c) T. L. Jacobs and W. R. Scott, THIS JOURNAL, **75**, 5502 (1953).

[4] (a) E. R. H. Jones, *et al.*, *J. Chem. Soc.*, 237 (1950); (b) S. Ruhemann and F. Beddow, *ibid.*, **77**, 984 (1900); (c) S. Ruhemann and H. E. Stapleton, *ibid.*, **77**, 1179, 1119 (1900).

[5] (a) C. Cavallito, THIS JOURNAL, **77**, 4159 (1955); (b) K. Bowden, E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 945 (1946); (c) E. R. H. Jones, *et al.*, *ibid.*, 45 (1946).

[6] W. E. Truce and M. M. Boudakian, THIS JOURNAL, **78**, 2748 (1956).

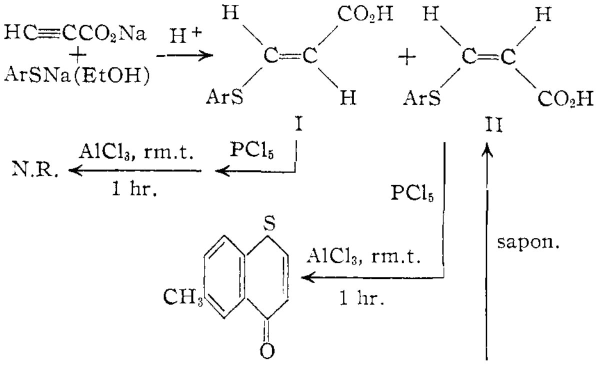
[7] F. Miller in H. Gilman, "Organic Chemistry," Vol. III, Chapter 2, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 149.

[8] W. J. Croxall and L. R. Freimiller, U. S. Patent 2,532,292 to Rohm and Haas Co., Philadelphia, Pa. (1950); *C. A.*, **45**, 3420 (1951).

TABLE I

Reactants	Catalyst	Solvent	Product
$HC\equiv CCOC_6H_5 + C_7H_7SH$	EtONa	EtOH	$(EtO)_2CHCH_2COC_6H_5 +$ $C_7H_7SCH{=}CHCOC_6H_5$
$HC\equiv CCOC_6H_5 + C_7H_7SH$	$C_5H_{11}N$	Et_2O	$C_7H_7SCH{=}CHCOC_6H_5$
$HC\equiv CCOC_6H_5 + C_7H_7SH$	$C_5H_{11}N$	EtOH	$C_7H_7SCH{=}CHCOC_6H_5$
$HC\equiv CCOC_6H_5 + C_7H_7SH$	....	Benzene–toluene	$C_7H_7SCH{=}CHCOC_6H_5$
$HC\equiv CCOC_6H_5 + C_7H_7SH$	Equimolar amt. EtONa	EtOH	$C_7H_7SCH{=}CHCOC_6H_5$

The base-catalyzed addition of *p*-toluenethiol to phenyl ethynyl ketone was carried out under several different conditions (Table I). In every case but one, only one compound was isolated in quantitative yield. This product was identified as *cis*-*p*-$CH_3C_6H_4SCH{=}CHCOC_6H_5$ on the basis of its facile oxidation to the previously-identified *cis*-sulfone.[5b] Here again the infrared spectrum did not clearly define the geometry of this initial product. A strong band at 13.55 μ (13.76 μ for the corresponding sulfone) was suggestive of a *cis* configuration; however, only a weak band was present at 7.55 μ (7.62 μ (m) for its sulfone). A strong band at 11.25 μ in the sulfide (absent in the sulfone) was not accounted for. Incidentally, the spectrum of the adduct obtained from thiophenol[5b] was identical with that of the product obtained using *p*-toluenethiol, with the exception, of course, of differences due to the aromatic residue.

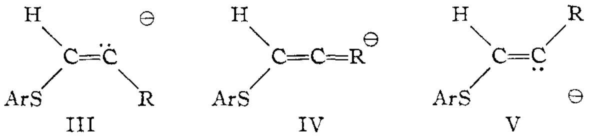


$$HC\equiv CCO_2Et + ArSNa(EtOH) \longrightarrow (EtO)_2CHCH_2CO_2Et + ArSCH{=}CHCO_2Et$$

(Ar = *p*-$CH_3C_6H_4$-)

The violation of the Rule of *trans*-Nucleophilic Addition by sodium propiolate is apparently associated with the presence of a *negatively charged* group (ethyl propiolate, phenyl ethynyl ketone and the other acetylenes which we have studied[3] obey the Rule and bear uncharged substituents). A satisfactory explanation for the usual *trans* nucleophilic additions is based on coulombic repulsion between the attacking negatively-charged thiolate ion and the pair of electrons being displaced from the triple bond, thereby forcing the displaced electron pair to the *trans* position where it abstracts a proton from the solvent.[1] With propiolate ion, however, a competing coulombic repulsion between the negatively-charged carboxylate substituent and the thiolate group would tend to force these groups into a *trans* relationship and the over-all addition to proceed *cis*.[9] Such repulsions would certainly be much less pronounced with carbethoxy or carbonyl substituents, thereby explaining the normal behavior of ethyl propiolate and phenyl ethynyl ketone.

An alternative explanation for the abnormal behavior of sodium propiolate toward thiolate reagent, based on a resonance-stabilized carbanion, should it be an intermediate in the reaction,[10] was rejected. Such a resonance hybrid, made up of forms III, IV and V, does not adequately explain the normal behavior of ethyl propiolate and phenyl ethynyl ketone. Furthermore, in view of their different geometries, these forms would violate one of the rules of resonance.[11]



R = CO_2H, CO_2Et or COC_6H_5

One interesting point is that of activation of the acetylenic bond toward nucleophilic attack. The substituent group has a powerful effect on the reactivity of an acetylene toward nucleophilic attack. The three acetylenes used in the present study were found to undergo extremely fast, exothermic reactions with the thiolate reagent. This would be expected, of course, because of the strong electron-accepting effects of carboxyl and carbonyl groups. 1-Hexyne and 2-butyne, on the other hand, required drastic conditions for such reactions to proceed.[3] A general order of reactivity of monosubstituted acetylenes of the type HC≡CR (based on our qualitative observations), where the R's are arranged in the order of increasing reactivity of the acetylene, is alkyl < ArS ≤ Cl ≤ $C_6H_5 < CO_2^{\ominus} < CO_2R <$ COAr. Presumably, a similar order of reactivity for various nucleophilic agents would apply to these additions as apply to aromatic nucleophilic displacements.[12]

Experimental[13]

Starting Materials.—*p*-Toluenethiol (Eastman Kodak Co., white label) was used without further purification. Samples of this material tested in connection with other work showed no trace of disulfide impurity. Propiolic acid was obtained by decarboxylation of the monopotassium salt of acetylenedicarboxylic acid[14]; b.p. 65–68° (25 mm.),

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[9] There is a report of the addition of ammonium sulfite to salts of propiolic acid which reportedly gives rise to a *trans*-β-sulfoacrylic acid. This would constitute another exception to the rule and would lend support to our interpretation of the results; H. J. Backer and A. E. Beute, *Rec. trav. chim.*, **54**, 523 (1935).

[10] W. E. Truce and R. F. Heine, forthcoming publication.

[11] G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 414 ff.

[12] J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 273 (1951).

[13] All microanalytical analyses, with a noted exception, were carried out by Mrs. C. S. Yeh and Mrs. S. L. Margerum of the Purdue Chemistry Microanalytical Laboratory. All infrared spectra were run by Mrs. B. Polister of the Purdue Chemistry Infrared Laboratory using a Perkin-Elmer infrared spectrophotometer, model 21. All boiling and melting points are uncorrected.

[14] T. W. Abbott, R. T. Arnold and R. B. Thompson in A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 10.

58–61° (14–16 mm.). Ethyl propiolate obtained by esterification of propiolic acid[15] had b.p. 117°. Phenyl ethynyl ketone, m.p. 50–51°, was prepared by the method of Jones, *et al.*[4b]

Reaction of Propiolic Acid with *p*-Toluenethiol.—A solution prepared from 2.76 g. (0.12 mole) of sodium, 14.9 g. (0.12 mole) of *p*-toluenethiol and 70 ml. of absolute ethanol was added dropwise, with stirring and under nitrogen, to a solution prepared from 3.29 g. (0.143 mole) of sodium, 150 ml. of absolute ethanol and 10.0 g. (0.143 mole) of propiolic acid. Water added to redissolve solid formed upon mixing the two solutions improved the yield of products but did not change the isomer distribution. After stirring the aqueous alcoholic solution for 5 hr., it was made slightly acidic with dilute hydrochloric acid and filtered to yield 12.4 g. of crystals, m.p. 142–144°, m.p. 144.5–145.5° upon recrystallization from ethanol. A second crop of crystals from the chilled mother liquor weighed 10.3 g. and melted at 90–100°. Recrystallization from ethanol and benzene, separately, gave 6.3 g., m.p. 143–144°, and 3.5 g., m.p. 136–137°. The small amount remaining, m.p. 104–107°, could be laboriously separated further into the above two fractions; total yield, 91.5%.

Anal. Calcd. for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.18; neut. equiv., 194.2. Found for m.p. 144.5–145.5°: C, 61.83, 62.15; H, 5.25, 5.31; neut. equiv., 193.8, 194.3. Found for m.p. 136–137°: C, 62.07; H, 5.22; neut. equiv., 194.1, 192.9.

Reaction of Ethyl Propiolate with *p*-Toluenethiol.—To a stirred solution of approximately 10.0 g. (1.1 moles) of ethyl propiolate in 30 ml. of absolute ethanol slowly was added an alcoholic solution prepared from 100 ml. of ethanol, 0.5 g. (0.02 mole) of sodium and 12.4 g. (0.10 mole) of *p*-toluenethiol. A nitrogen atmosphere was maintained throughout, and external cooling was applied to keep the temperature at or below room temperature. The color of the solution turned red, presumably due to the anion $(EtO)_2CH\ddot{C}HCO_2Et$. The addition took 1 hr. and the mixture was stirred an additional 2 hr. After standing overnight the mixture was acidified with concd. hydrochloric acid to a *p*H of approximately 6. The solvent was distilled off until the residue became cloudy. The resulting two layers were separated and the heavier one was distilled under vacuum to yield two fractions: (1) b.p. 50–54° (1.75 mm.), 3.2 g.; (2) 134–138° (1.3–1.5 mm.), $n^{20}D$ 1.5748, 12.4 g. of ethyl *β-p*-tolylmercaptoacrylate (lit.[8] b.p. 134–138° (1–2 mm.), $n^{20}D$ 1.5752). An infrared spectrum of fraction 1 was identical with that of an authentic sample of ethyl *β,β*-diethoxypropionate.[8]

Treatment of fraction 2 with 30% peroxide in glacial acetic acid gave a crystalline sulfone, m.p. 80–81°, plus a very small amount of a higher melting product.

Anal. Calcd. for $C_{12}H_{14}O_4S$: C, 56.7; H, 5.52. Found: C, 56.74; H, 5.59.

A portion (3.0 g., 0.13 mole) of fraction 2, ethyl *β-p*-tolylmercaptoacrylate, was added to 120 ml. of aqueous ethanol (90%) containing sodium ethoxide (0.13 mole). The mixture was refluxed for 2 hr., neutralized, concentrated and extracted twice with ether. The extracts, dried over anhyd. magnesium sulfate and chilled, yielded 2.3 g. of an acid, m.p. 136–137°; undepressed by, and having an infrared spectrum identical with that of, an authentic sample of *cis-β-p*-tolylmercaptoacrylic acid, obtained as indicated earlier.

A sample of ethyl *β-p*-tolylmercaptoacrylate, obtained by another procedure,[8] was oxidized to the sulfone, m.p. 80–81° (by-product had m.p. 89–95°). There was no depression in melting point of the admixture of this sulfone and the sulfone of ethyl *β-p*-tolylmercaptoacrylate obtained from ethyl propiolate and *p*-toluenethiol.

Saponification of this ester gave two acids, m.p. 134–138° and m.p. 104–108°. Recrystallizations from absolute ethanol raised the m.p. of the first acid to 136–137° and gave two fractions from the second material having m.p. 136–137° and 144–145°. Melting points were undepressed when mixed with the corresponding *β-p*-tolylmercaptoacrylic acids obtained by addition of *p*-toluenethiolate reagent to sodium propiolate.

Attempted Isomerization of *β-p*-Tolylmercaptoacrylic Acids.—*cis-β-p*-Tolylmercaptoacrylic acid (1.94 g., 0.01 mole), m.p. 136–137°, was dissolved in 100 ml. of a solution of 0.015 mole of sodium ethoxide in absolute ethanol. After 24 hr. of refluxing, dilute hydrochloric acid, sufficient to neutralize the base, was added and the solution was filtered. The air-dried residue weighed 1.92 g., had a m.p. 136–137° and showed no depression in melting point when mixed with starting material. After like treatment of the *trans* isomer, m.p. 144.5–145.5°, only unchanged starting material was obtained.

A solution of 1.0 g. of *cis-β-p*-tolylmercaptoacrylic acid, m.p. 136–136.5°, in 50 ml. of sulfur-free benzene in a quartz flask was irradiated for 24 hr. by a 100-watt, G.E. mercury-vapor ultraviolet lamp placed two inches from the flask. On chilling the reaction solution, 0.95 g. of a product, m.p. 104–107°, was obtained. An infrared spectrum of this material was different from that of the starting material, mainly in the intensity of the bands and in the addition of weak bands corresponding to those of the *trans* isomer, m.p. 144.5–145.5°. The isomerization effected probably amounted to only about 10% and no attempt was made to separate the isomers by fractional crystallization.

Preparation of 6-Methylthiochromone.[4c]—To a solution of 2.13 g. (0.011 mole) of *cis-β-p*-tolylmercaptoacrylic acid, m.p. 136–137°, in 60 ml. of benzene was added, with stirring over a 20-minute period, 2.92 g. (0.014 mole) of phosphorus pentachloride. On adding 2.80 g. (0.021 mole) of aluminum slowly to the stirred solution, it rapidly assumed a deep red-gold color. After stirring for 1 hr. at room temperature, the reaction mixture was poured onto cracked ice. The mixture was extracted with ether, the extracts dried over anhyd. magnesium sulfate and then concentrated. The residue was distilled under vacuum to yield 1.5 g. of 6-methylthiochromone, b.p. 138.0° (1.0 mm.), m.p. 64–65°, 69–70° after recrystallization from petroleum ether (lit.[16] b.p. 194° (12 mm.), m.p. 69–70°).

Anal. Calcd. for $C_{10}H_8OS$: C, 67.9; H, 5.12. Found: C, 68.09; H, 4.90.

Treatment of *trans-β-p*-tolylmercaptoacrylic acid, m.p. 144.5–145.5°, under similar conditions returned practically all of the starting material. However, refluxing the reaction mixture for 3 hr. and stirring overnight at room temperature gave almost a quantitative yield of 6-methylthiochromone.

Reaction of Phenyl Ethynyl Ketone with *p*-Toluenethiol.—A solution of 2.5 g. (0.020 mole) of *p*-toluenethiol and three drops of piperidine in 25 ml. of anhydrous ether was added, with stirring and over a 15-minute period, to a solution of 3.0 g. (0.023 mole) of phenyl ethynyl ketone in 25 ml. of anhydrous ether. A solid which began forming before half the thiol was added was filtered at the end of the reaction and air-dried; the light yellow needles (94.6% yield) had m.p. 136–137.5°.

Anal. Calcd. for $C_{16}H_{14}OS$: C, 75.6; H, 5.52; S, 12.60. Found: C, 75.91, 76.01; H, 5.96, 5.91; S, 12.57.[17]

Oxidation of the product by hydrogen peroxide in glacial acetic acid at 50° for 2 hr. gave *cis*-1-benzoyl-2-*p*-tolylsulfonylethene, m.p. 129–130° (lit.[5b] m.p. 129–130°).

Anal. Calcd. for $C_{16}H_{14}O_3S$: C, 67.40; H, 4.89. Found: C, 67.21; H, 5.30.

The other reactions, listed in the Discussion, were run much as this one, with yields ranging from 87.4 to 99.0%. In several of the reactions in ethanol a very small amount of product, m.p. 88–90°, was obtained, which did not give a good infrared spectrum in a Nujol mull. It appeared to be a mixture of the major product together with, perhaps, some *trans* isomer.

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[15] E. H. Ingold, *J. Chem. Soc.*, **127**, 1199 (1925).

[16] F. Krollpfeiffer, *et al.*, *Ber.*, **58B**, 1654 (1925).

[17] Analysis for sulfur done by Galbraith Microanalytical Laboratories. Knoxville, Tenn.