

SIMPLE, STEREOSPECIFIC PREPARATION OF Z-3-IODOACRYLIC ACID FROM PROPIOLIC ACID
 AND METHYLMAGNESIUM IODIDE

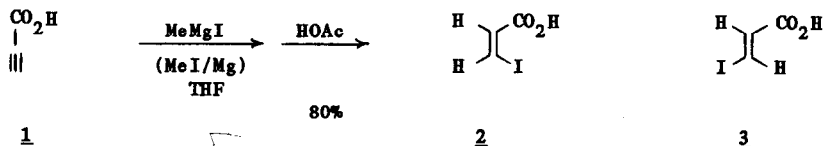
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Abstract: Addition of propiolic acid to 2.2 equiv of methylmagnesium iodide in THF followed by workup with acetic acid produces only the Z-isomer of 3-iodoacrylic acid, 2, in high yield.

Recently Tishler reported the formation of the Grignard dianion of propiolic acid and its condensation with aldehydes at the acetylenic carbon to give 4-hydroxy-2-alkynoic acids which were then converted into butenolides.^{3a} We now report that under slightly different conditions this reaction does not occur but rather a different but very interesting process takes place.

In order to have an authentic sample of tetrahydrocerulenin and its synthetic intermediates on hand for comparison with material from a new synthetic approach, we attempted to follow the published synthesis of Tishler.^{3a} We wished to prepare 4-hydroxy-1-dodecynoic acid from the condensation of the dianion of propiolic acid with nonanal. Since this work was done before the full experimental details of the reaction were published,^{3b} we therefore used slightly different conditions for the reaction and obtained completely different results as follows. To a solution of methyl Grignard reagent prepared from methyl iodide and magnesium turnings, in tetrahydrofuran (THF) at 25°C was added a solution of propiolic acid 1 in THF at a rate which caused the solution to reflux. Addition of nonanal followed by stirring at room temperature and a normal aqueous workup did not provide any of the desired compound. Instead a new crystalline material 2 [mp 63-65°C; ¹H NMR (CDCl₃) δ 10.3 (1H, s); 7.7 (1H, d, J = 9 Hz); 7.04 (1H, d, J = 9 Hz)] was isolated in excellent yield. This compound was shown to be Z-3-iodoacrylic acid 2 by comparison of its melting point and NMR spectra to those reported in the literature.⁴ Repetition of the experiment omitting the addition of the aldehyde provided the same acid product, indicating that the aldehyde was extraneous to the reaction, as expected. Under all conditions tried thus far, we have isolated none of the isomeric E-3-iodoacrylic acid, 3, and therefore believe the reaction to be stereospecific. The yield of the acid 2 varied from very low (10-20%, in ether solution at room



temperature or in THF solution at low temperatures, both with an aqueous acid workup) to a high of 80% (refluxing THF, workup with glacial acetic acid). The reason for the lowering of the yield during the aqueous workup is not known at present but is not due to the water solubility of 2

(partition coefficient between diethyl ether and water ≈ 5). Thus the difference of using methylmagnesium iodide at 25°C instead of ethylmagnesium bromide at 0°C caused a totally different reaction course to be followed.

All of the previous syntheses of 2 have involved the addition of aqueous hydriodic acid to propiolic acid.⁴ In aqueous solution, the mechanism has been shown^{4b} to involve nearly complete trans addition of HI across the carbon-carbon triple bond leading to the Z-isomer as the predominant (> 98%) product. We believe that a similar process is occurring in the present case, namely the stereospecific trans addition of an iodide anion and a magnesium cation across the triple bond. However the product 2 is not formed when either propiolic acid 1 or its sodium salt is reacted with magnesium iodide, thus making less likely the simple addition of magnesium iodide⁵ across the triple bond of the iodomagnesium propiolate. It has been shown that a C-2 organometallic species is involved since quenching the reaction with DCI/DOAc (from D₂O and acetyl chloride) affords the acid 2 with a deuterium atom at C2 (collapse of the doublet at δ 7.7 to a broad singlet and disappearance of the doublet at δ 7.04). The exact nature of the adding group has not been determined and therefore all present mechanistic reasoning is speculation.⁶

An attempt was made to extend this reaction to other acetylenic acids with substituents in the 3-position. However, treatment of tetrolic acid (2-butyric acid) and 3-phenylpropiolic acid with methylmagnesium iodide in THF under analogous conditions did not produce any of the β -iodoacrylic acids analogous to 2. Thus the method of choice for the preparation of these acids is still that of Bowden and Price.^{4b}

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References and Notes

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5. Magnesium iodide is likely to be present along with dimethylmagnesium in the Schlenk equilibrium of methylmagnesium iodide.
6. One possible mechanism involves nucleophilic attack of iodide ion at the β -carbon of the initially-formed iodomagnesium propiolate to give the β -iodo acid dianion salt. Protonation on carbon would occur trans to the large iodide atom to give the Z-iodoacrylate which would then be protonated on oxygen to give the observed product 2. This is but one of several possibilities that could be put forth on the mechanism of this process. We cannot yet rule out the possibility that the reaction may occur upon addition of the acid in the workup, generating iodide ion in a mildly acidic medium which would then add to the propiolate to give 2.

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