

LETTERS

(E)- or (Z)-β-Iodoacrolein. A Novel Versatile Synthron

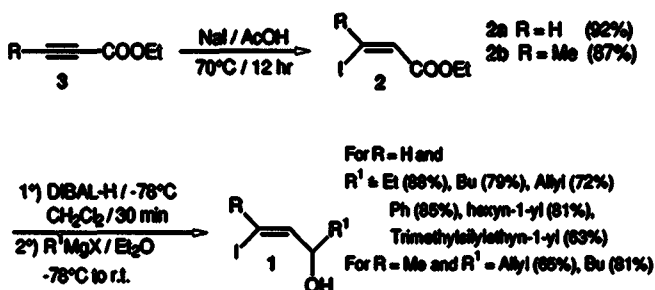
Christophe Meyer, Ilane Marek,* Jean-F. Normant*

Laboratoire de Chimie des Organo-Éléments, CNRS UA 473, Université P. et M. Curie, 4 Place Jussieu, F-75252 Paris Cedex 05, France

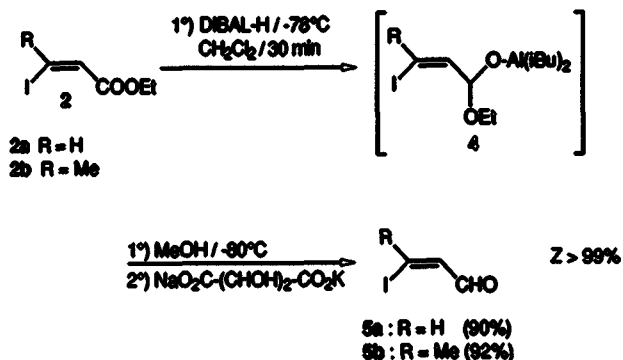
Received 2 March 1993

Abstract: Starting from the (Z)-β-iodo acrylate, the (E)- or (Z)-γ-iodo allylic alcohols, (Z)-γ-iodo allylic amines, as well as the (E)- or (Z)-β-iodo acroleins are very easily obtained.

In a previous letter¹, we have reported a very easy preparation of (Z)-γ-iodo allylic alcohols **1**, by a regio and stereospecific hydroiodination of propiolates derivatives^{2,3} **3** leading to (Z)-β-iodo acrylate **2**, followed in a second step by a "reduction-C-alkylation" of the ester group:



We wish to report now that the low-temperature DIBAL-H reduction of carboxylic esters **2** is of great synthetic value because it allows a one step conversion of such esters to the very sensitive aldehydes **5**⁴:



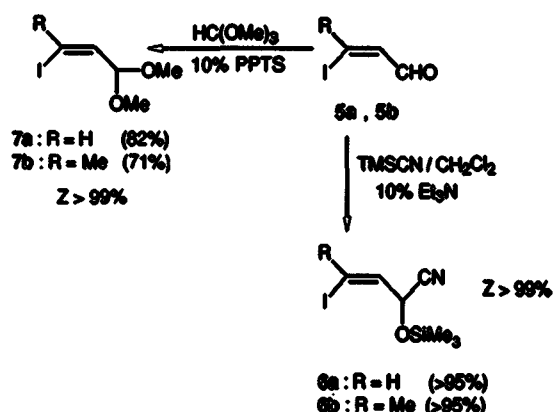
Scheme 1

The (Z)-β-iodo acrolein **5a** and (Z)-β-iodo crotonaldehyde **5b** can be isolated from the reaction mixture by simple dropwise addition of an excess of methanol to the reaction mixture immediately followed by an alkaline hydrolysis (aqueous solution of sodium and potassium tartrate). The corresponding aldehydes **5a** and **5b** are obtained in 90 and 92% yield, respectively with a stereoisomeric purity of the Z double bond > 99%. One reason for the fact that overreduction is not a problem may be that the strength of the Al-O bond inhibits expulsion of alkoxide ion from the intermediate **4** at very low temperatures.

The (Z)-β-iodoacrolein⁵ **5a** and crotonaldehyde **5b** are thus obtained as yellow liquids⁶, easily handled as ether or dichloromethane solutions

and can be stored in the refrigerator within a few weeks without decomposition or isomerisation.

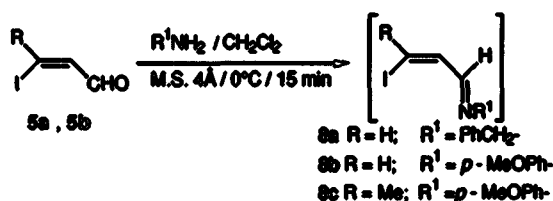
The treatment of these aldehydes with TMSCN generates the corresponding O-silylated cyanohydrins⁷ **6a** and **6b** in virtually quantitative yield with a pure Z stereochemistry:



In a similar way, the reaction of **5a** and **5b** with trimethylorthoformate furnishes the dimethyl acetals **7a** and **7b** without isomerisation of the double bond.

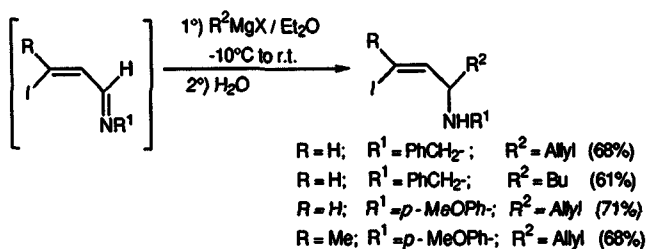
These interesting synthons led us to investigate the synthesis of (Z)-γ-iodo allylic amines, for which, to the best of our knowledge, no general methods exist in the literature. In addition, the substituted allylic amines are not only useful synthetic intermediates⁸, but also potentially useful for the synthesis of peptide isosteres⁹.

Thus, treatment of **5a** or **5b** with an amine in dichloromethane at 0°C, in the presence of molecular sieves quantitatively leads to the unisolated corresponding imines **8**:

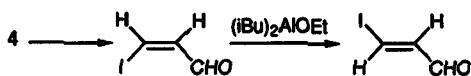


Attempts to carry out this transformation at higher temperatures from **5a** into **8a** or **8b** leads to extensive decomposition since the corresponding imines are unstable at room temperature. In contrast, **8c** shows a remarkable stability.

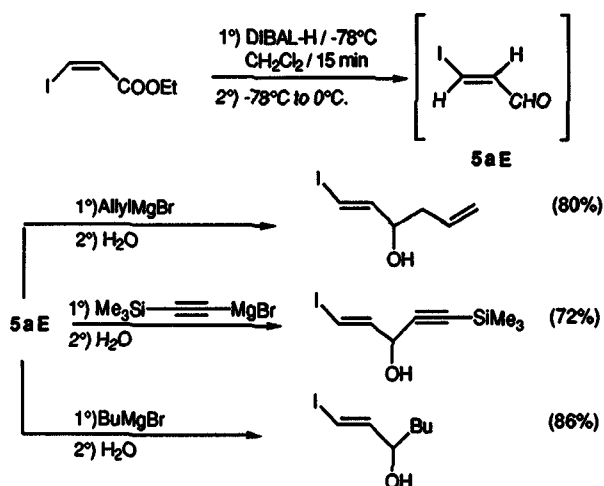
Addition of various organometallic reagents provides an efficient route to (Z)-γ-iodo allylic amines¹⁰:



During our experiments, we have observed that the stereoisomeric purity of the (Z)-β-iodo acrolein depends on the quenching temperature (see Scheme 1). Instead of quenching the reaction mixture at -78°C, but between 0°C and 10°C, we obtained, after similar work-up, the crystalline (E)-β-iodo acrolein (E/Z = 96/4)¹¹. However, at these temperatures variable amounts of overreduction are detected in the crude product (< 35%). The thermally labile aluminoyacetal, generated by delivery of one hydride to the ester group, collapses at an intermediate temperature to furnish, the (Z)-β-iodo acrolein in the presence of EtOAl(iBu)₂. This weak Lewis acid must be responsible for the Z to E isomerisation of this derivative¹². This hypothesis has been checked by mixing the pure (Z)-β-iodo acrolein with 1 equivalent of EtOAl(iBu)₂ in dichloromethane at room temperature¹³. Under these conditions, we effectively observe a clean isomerisation of the double bond.



Taking advantage of this isomerisation, by warming the reaction mixture, we have synthesised different (E)-γ-iodo allylic alcohols with a E/Z ratio = 96/4. Reaction of (Z)-β-iodo ethyl acrylate 2a with diisobutylaluminium hydride at low temperature (-78°C, 15 min) followed by warming to 0°C and subsequent reaction with a Grignard reagent (-20°C to r.t.) now leads to the (E)-γ-iodo allylic alcohols :



The stereoisomeric ratio can be improved to 99/1 when 1 equivalent of BF₃·Et₂O is added at -70°C to the reaction mixture before the introduction of the Grignard reagent.

All attempts to isomerize the (Z)-β-iodo crotonaldehyde into its E isomer by warming the reaction mixture to room temperature were unsuccessful¹⁴.

In conclusion, we have shown that, starting from (Z)-β-iodo ethylacrylate, (E) and (Z) iodo allylic alcohols are easily obtained in a highly stereoselective manner by reduction followed by introduction of a Grignard reagent at the required temperature. Noteworthy is the fact that (Z)-β-iodo acrolein can be easily isolated in good yields from the reaction mixture and gives rise to various derivatives (cyanohydrin, acetals and imines) of special interest as organic synthons.

Acknowledgments . We thank Mrs M. Baudry for the preparation of the Grignard reagents.

References and Notes

- Marek, I. ; Alexakis, A. ; Normant, J.F., *Tetrahedron Lett.*, **1991**, *32*, 5329.
- a). Ma, S. ; Lu, X. ; Li, Z., *J. Org. Chem.*, **1992**, *57*, 709; b). Ma, S. ; Lu, X., *J. Chem. Soc., Chem. Commun.*, **1990**, 733 and 1643.
- The NaI, AcOH methodology has been applied to the synthesis of enantiomerically pure (Z)-2-haloalkenyl sulfoxides with a great success : Pradilla, R.F. ; Morente, M. ; Paley, R., *Tetrahedron Lett.*, **1992**, *33*, 6101.
- a). Winterfeldt, E., *Synthesis* **1975**, 617; b). Maruoka, K. ; Yamamoto, H., *Tetrahedron*, **1988**, *44*, 5001.
- The (Z)-β-iodo acrolein seems to be much more stable than the related β-bromo or β-chloro acrolein: Meyers, A.I.; Babiak, K.A.; Campbell, A.L.; Comins, D.L.; Fleming, M.P.; Henning, R.; Heuschmann, M.; Hudspeth, J.P.; Kane, J.M.; Reider, P.J.; Roland, D.M.; Shimizu, K.; Kyoshi, T.; Walkup, R.D. *J. Am. Chem. Soc.*, **1983**, *105*, 5015.
- Typical procedure : To a solution of 2a (2.26 g, 10 mmol) in dry dichloromethane (20 ml) were added dropwise at -78°C, 10 mL of DIBAL-H (1M solution in hexanes). After stirring for 20 min (reaction followed by TLC, eluent cyclohexane/ethyl acetate 4/1), the reaction mixture was treated with 5 mL of methanol at -70°C followed immediately by alkaline hydrolysis (aqueous solution of sodium and potassium tartrate). After stirring at room temperature for 20 min, the mixture was filtered through a pad of celite, extracted with ether and dried (K₂CO₃). Evaporation of the solvents *in vacuo*, yields 90% (1,654 g) of 5a as a yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ 9.67 (d, 1H, J = 6.6 Hz), 7.79 (d, 1H, J = 8.25 Hz), 6.77 (dd, 1H, J = 8.25 ; 6.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 195.4, 136.4, 103.0. I.R.(film, cm⁻¹) 3050, 2820, 2730, 1675, 1610, 690.
- Kobayashi, S. ; Tsuchiya, Y. ; Mukaiyama, T., *Chem. Lett.*, **1991**, 537.
- a). Deleris, G. ; Dunogues, J. ; Gadras, A., *Tetrahedron*, **1988**, *44*, 4243; b). Whitesell, J. ; Yaser, H., *J. Am. Chem. Soc.*, **1991**, *113*, 3526; c). Hung, R. ; Straub, J. ; Whitesides, G., *J. Org. Chem.*, **1991**, *56*, 3849.
- a). Beaulieu, P. ; Duceppe, J.S. ; Johnson, C., *J. Org. Chem.*, **1991**, *56*, 4196; b). Ibuka, T. ; Habashita, H. ; Funakoshi, S. ; Fuji, N. ; Oquchi, T. ; Uyehara, T. ; Yamamoto, Y., *Angew. Chem. Int. Ed. Engl.*, **1990**, *29*, 801.

10. Particularly interesting are the imines derived from *para*-anisidine since the *p*-methoxy phenyl group is easily removed by oxidative cleavage : Kronenthal, D.R. ; Han, C.Y. ; Taylor, M.K., *J. Org. Chem.*, **1982**, *47*, 2765.
Typical procedure : To a solution of **5a** or **5b** (10 mmol) in dry dichloromethane (20 mL) in the presence of molecular sieves, was added dropwise at -10°C , 1 equivalent of amine. After stirring for 15 min at 0°C , the reaction mixture was cooled to -10°C and the Grignard reagent RMgX was introduced. The temperature is allowed to rise slowly and then, the reaction mixture was hydrolyzed at -10°C with 20 mL of saturated aqueous sodium bicarbonate, dried (K_2CO_3) and concentrated under vacuum. The residue was chromatographed on SiO_2 (Ether / Ethyl Acetate : 80/20).
11. The Z isomer treated by an aqueous solution of hydrochloric acid (1N) does not show any isomerisation.
12. The E isomer can be obtained as a pur compound by crystallization in ether. ^1H NMR (400 MHz, CDCl_3) δ 9.52 (d, 1H, $J = 7.15$ Hz), 7.79 (d, 1H, $J = 15.4$ Hz), 7.16 (dd, 1H, $J = 15.4 ; 7.15$ Hz). ^{13}C NMR (100 MHz, CDCl_3) δ 190.4, 147.0, 107.8. I.R. (film, cm^{-1}) 3020, 2805, 2710, 1680, 1610, 1565, 945, 695.
13. $\text{EtOAl}(\text{iBu})_2$ has been generated by reaction between EtOH and DIBAL-H.
14. The assignment of the stereochemistry of (Z)- β -iodo crotonaldehyde was deduced from the coupling constant between the two vicinal protons ($J = 15.23\text{Hz}$) of the (E)-oct-2-en-4-ol obtained by metal-halogen exchange of the corresponding iodo derivatives, generated by treatment of **5b** with BuMgX. The (E)- β -iodo crotonate has been described by addition of hydrogen iodide to tetrolic acid, followed by an isomerization (sealed tube, 100°C , 12hr) to the E-iodo crotonic acid and esterification: Le Noble, W.J., *J. Am. Chem. Soc.*, **1961**, *83*, 3897.