Tetrahedron Letters No. 6, pp 487 - 489, 1972. Pergamon Press. Printed in Great Britain.

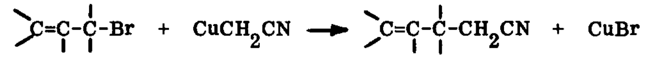
ONE-STEP SYNTHESIS OF γ,δ-UNSATURATED NITRILES FROM ALLYLIC HALIDES USING CYANOMETHYLCOPPER

E. J. Corey and Isao Kuwajima

Department of Chemistry, Harvard University, Cambridge, Massachusetts, U. S. A. 02138

(Received in USA 9 December 1971; received in UK for publication 5 January 1972)

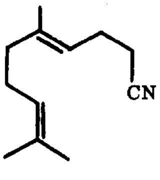
We have found that the reagent generated from cyanomethyllithium (1) and cuprous iodide in equimolar ratio, designated herein as cyanomethylcopper, is outstandingly useful for the conversion of allylic halides to γ,δ-unsaturated nitriles according to the equation:



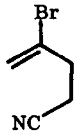
$$>C=\underset{|}{C}-\overset{|}{\underset{|}{C}}-Br \quad + \quad CuCH_2CN \longrightarrow >C=\underset{|}{C}-\overset{|}{\underset{|}{C}}-CH_2CN \quad + \quad CuBr$$

Advantages over the conventional process involving the conjugate base of cyanoacetic ester include brevity, operational simplicity, and avoidance of dialkylation and the concomitant difficulties in purification of reaction product.

The formation of cyanomethylcopper was effected by reaction in tetrahydrofuran (THF) of cyanomethyllithium (from acetonitrile and n-butyllithium (1 equiv.) at -78° (1)) and cuprous iodide (1 equiv.) at -25° for 10 min. (2). Reaction of the copper reagent so obtained with trans-geranyl bromide at -25° for 1 hr. gave trans-homogeranyl cyanide (I) (3) in 92% yield (4). Reaction of I with methyllithium produced trans-geranyl acetone which was identified (3) by comparison with an authentic sample. Under the same conditions the unsaturated nitrile II (3) was produced in 92% yield from 2-bromoallyl bromide, and III (3) was formed in 89% yield from 1-bromo-3-iodo-trans-2-decene (5). Reaction of ethyl α-bromomethylacrylate with cyanomethylcopper proceeded similarly even at -78° (1 hr.) to give IV (3) in 89% yield.



I



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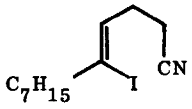

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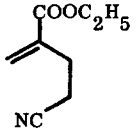
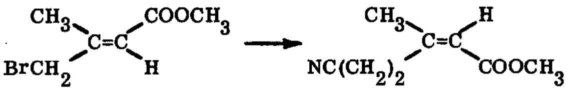
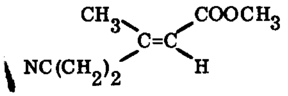
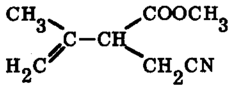


IV

In contrast to these facile and efficient reactions with allylic bromides, cyanomethylcopper did not affect benzyl bromide (24 hr. at 0°) or unactivated alkyl bromides. This selectivity for allylic halides is an interesting and obviously useful feature of the cyanomethylcopper reagent. On the other hand, reaction of cyanomethylcopper with the unsaturated bromo ester V appeared too complex to be useful, since a mixture of products was formed from which 46% of VI (3), 21% of VII (3), and smaller amounts of VIII were obtained by thin layer chromatography. The configurations of VI and VII were assigned on the basis of n.m.r. data including the chemical shifts of the β-methyl substituent at 1.94 and 2.07 p.p.m., respectively.


V VI


VII


VIII

The synthesis of γ,δ-unsaturated aldehydes by an analogous process involving the copper reagent derived from the Schiff base of acetaldehyde and cyclohexylamine (via the lithio derivative (6, 7)) has also been investigated briefly. Although alkylated acetaldehyde derivatives could be obtained from geranyl bromide, 2-bromoallyl bromide and 1-bromo-3-iodo-*trans*-2-decene, the yields obtained were only approximately 50%, and no advantage of the copper reagent over the lithium reagent is evident. The extension of these studies to an effective synthesis of esters using ethoxycarbonylmethylcopper will be described by one of us (I. K.) in a separate note.

The following experimental procedure illustrates the reaction of cyanomethylcopper with allylic halides for the specific case of geranyl bromide: A cooled solution of *n*-butyllithium in pentane (2.0 ml., 1.3 *M*) was added to a solution of 137 mg. (3.34 mmoles) of acetonitrile in 5 ml. of THF at -78° under argon. After 40 min. at -78° the mixture was warmed to -25° and 640 mg. (3.37 mmoles) of cuprous iodide was added. After stirring for 15 min. at -25° the brick-colored solution (negative Gilman test) of cyanomethylcopper was treated with 215 mg. (0.98 mmole) of *trans*-geranyl bromide in 3 ml. of THF. After 1 hr. at -25°, aqueous ammonium chloride was added and the product was extracted with ether. Evaporation of the extract after drying gave 180 mg. of crude product from which 165 mg. (95%) of *trans*-homogeranyl cyanide (I) was obtained by chromatographic separation using silica gel. Isolation of I can be accomplished more conveniently on a larger scale by distillation under reduced pressure. The purity of I so obtained was found to be ca. 97% by v.p.c. analysis (10 ft. x 0.125 in. 3% OV 17 on Gaschrome Q column at 140°). The molecular ion found for the sample purified by v.p.c. was 177.1520 (calcd. 177.1517) using an AEI MS-9 spectrometer. The infrared spectrum of I (in CCl_4) manifested peaks due to cyano at 4.44 μ and C=C at 6.00 μ; the p.m.r. spectrum (CCl_4) showed peaks at 1.50–1.83 δ (multiplet 9 H, 3 CH_3), 2.02 δ (doublet, 4 H, $C{=}CCH_2CH_2C{=}C$), 2.23 δ (multiplet, 4 H, $C{=}CCH_2CH_2CN$), 4.90–5.34 δ (broad, 2 H, olefinic) (8).

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2. All use of organometallic reagents was carried out under an atmosphere of nitrogen or argon.
3. This assignment of structure was indicated by (a) infrared spectral, (b) mass spectral and (c) proton magnetic resonance spectral data obtained on a purified specimen which was homogeneous by thin layer chromatographic and vapor phase chromatographic analysis.
4. For some previous papers on the application of copper reagents to cross coupling reactions with halides, see (a) E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **90**, 5615 (1968); (b) E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967); (c) E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *ibid.*, 89, 4245 (1967); (d) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *ibid.*, **90**, 5618 (1968); and (e) G. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Baske, and H. O. House, *ibid.*, **91**, 4871 (1969).
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8. This research was assisted financially by a grant from the National Science Foundation.