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A CONVENIENT SYNTHESIS FOR α,β-ACETYLENIC KETOXIMES

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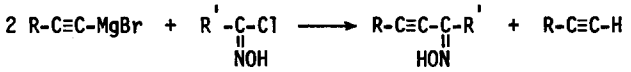
Recent interest in α,β-acetylenic ketoximes[2] prompts us to report a method that we have used with success for the synthesis of this new class of oximes which we needed in another connection. This method is fairly simple, gives better yields of the oximes and seems to be of general applicability. A dry ethereal solution of the hydroximoyl chloride (II)(prepared from



I II III IV

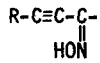
the corresponding aldoxime) is allowed to react with the acetylenic Grignard reagent (I) at 0° following which the reaction mixture is worked up by treating with 10% sulfuric acid and the solvent is removed under reduced pressure at room temperature. The acetylenic ketoximes (III) obtained in this manner are uncontaminated with the isoxazoles. The only contaminant, the acetylene (IV), being a gas or low boiling liquid in most cases, is easily removed under pressure at room temperature. The results are summarized in the Table.

The reaction between acetylenic Grignard reagents and hydroximoyl chlorides has been used for the synthesis of 3,5-disubstituted isoxazoles, earlier by Palazzo[3] and more recently, in a slightly modified form, by Feurer and Markofsky[4]. However, in these reports no attempts have been directed towards the isolation of the intermediate oximes. Hydroximoyl chlorides are also known to react with sodium derivatives of acetylenes to yield 3,5-disubstituted isoxazoles[5].

The oximes cyclize easily to the expected, isomerically pure, isoxazole (V) as determined by NMR spectroscopy. The ring closure is facilitated by heat and by traces of base. With sodium or potassium hydroxide in aqueous alcoholic solutions the cyclization is highly exothermic. Ring closure to the isoxazoles proceeds slowly even at room temperature. However,

TABLE

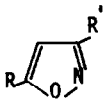
α,β- Acetylenic Ketoximes*



No.	R	R'	Yield (%)	Melting Point °C	NMR(DMSO) δ_{OH}(TMS)	IR($CHCl_3$)cm^{-1} $\nu_{C\equiv C}$	IR($CHCl_3$)cm^{-1} ν_{OH}
1.	C_6H_5	CH_3	35	liquid	11.71	2230	3600; 3295
2.	C_6H_5	CH_3CH_2	36	liquid	11.55	2220	3580; 3280
3.	C_6H_5	$CH_3CH_2CH_2$	45	liquid	11.70	2220	3580; 3280
4.	C_6H_5	$(CH_3)_2CH$	61	89-90	11.60	2220	3580; 3275
5.	C_6H_5	$CH_3CH(C_6H_5)$	39	81-82	11.64	2210	3590; 3300
6.	C_6H_5	$CH_3CH_2CH(CH_3)$	51	82-83	11.58	2220	3595; 3290
7.	C_6H_5	$C(CH_3)_3$	69	102-103	11.62	2220	3600; 3300
8.	C_6H_5	C_6H_5	70	100-101	12.28	2220	3580; 3300
9.	$C(CH_3)_3$	$(CH_3)_2CH$	65	liquid	11.33	2210	3580; 3290
10.	$C(CH_3)_3$	$CH_3CH_2CH(CH_3)$	69	liquid	11.65	2230	3590; 3300
11.	$C(CH_3)_3$	$C(CH_3)_3$	67	liquid	11.70	2230	3585; 3310
12.	$CH_2=C(CH_3)$	CH_3	42	liquid	11.33	2210	3585; 3300
13.	$CH_2=C(CH_3)$	$C(CH_3)_3$	57	47-48	11.20	2210	3600; 3300
14.	CH_3	$C(CH_3)_3$	68	81-82	11.23	2235	3600; 3300
15.	CH_3	$(CH_3)_2CH$	47	liquid	11.23	2220	3600; 3300

* All oximes reported in the Table, except 1,2 and 8, are hitherto unknown; oximes 1,2 and 8 were reported in the earlier communication[2], with undetermined yields and physical characteristics.

several of these oximes have been stored in the refrigerator for periods of over a year without any appreciable isoxazole formation. Attempts at sublimation, distillation or chromatography over alumina converted the oximes to the isoxazoles, but chromatography over silica gel was found satisfactory. The oximes give solid carbamate derivatives with phenylisocyanate.



V

All the oximes had the expected IR and NMR spectral characteristics and the solid oximes and all carbamate derivatives gave satisfactory elemental analyses. The oximes obtained by this method seem to be a single isomer in each case, as evidenced by the melting points and the NMR spectra (single, sharp signals for hydroxyl protons in DMSO solution). They appear to have a configuration in which the hydroxyl group is syn with respect to the acetylenic function for the same reasons as advanced in the earlier report[2]. Our results of the Beckmann rearrangement studies of these oximes will be published shortly.

General Procedure. Ethylmagnesium bromide (0.2 mol) is prepared in anhydrous ether (300 ml) in the usual manner in a 1-l. three-necked flask equipped with a mechanical stirrer, a Dry Ice condenser, and an addition funnel. To this, 0.2 mol of the appropriate acetylene is added and the mixture is stirred at gentle reflux until a lower layer separates (2-3 hr). (In the case of tert-butyl acctylene a gelatinous white precipitate is obtained in 4-5 hr. Methylacetylene is allowed to bubble through at room temperature at the rate of 150-200 ml/min, and usually in ca. 3 hr the lower layer separates.) Meanwhile, the appropriate hydroximoyl chloride (0.1 mol) is prepared[6] from the corresponding aldoxime and is extracted into ether (250 ml) and dried for 5 min over anhydrous $CaCl_2$ and then for another 5 min over molecular sieve pellets (Linde Type 4A). (Benzaldoxime and trimethyl acetaldoxime used are pure syn isomers; other oximes are syn and anti mixtures as determined by nmr spectroscopy.) The dry etheral solution of the hydroximoyl chloride is added dropwise, with stirring, during 1 hr, to the acetylenic Grignard maintained at 0°. After stirring for 10 min more the mixture is slowly acidified with 200 ml of 10% sulfuric acid. The ether layer is separated and the aqueous layer is extracted with ether and the combined ether layers are washed with saturated NaCl solution and then dried

(Na_2SO_4). The ether is removed at room temperature at reduced pressure by using a Rotavapor to yield an oily residue. Removal of last traces of ether and low-boiling acetylenes is accomplished at room temperature by using a vacuum pump at 1-2 mm. (In cases where phenylacetylene is one of the products, it can be recovered from the cold trap used in conjunction with the pump.) The solid acetylenic ketoximes separate at his stage and can be recrystallized from petroleum ether (66°-75°).

ACKNOWLEDGEMENT

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