Exceptionally Easy Isomerization of Acetylenic Alcohols with Potassium 3-Aminopropylamide. A New, High Yield Synthesis of Functionally Differentiated αω-Difunctional Structures

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Summary Potassium 3-aminopropylamide, readily prepared *in situ* from KH and 3-aminopropylamine, effects rapid, multipositional isomerization of the triple bond in prop-2-ynylic and other acetylenic alcohols to the chain terminus remote from the hydroxy function, within minutes at 0—20 °C.

RECENTLY, we reported that potassium 3-aminopropylamide (KAPA)[1] causes rapid, quantitative, multipositional isomerization of the triple bond in dialkylacetylenes to the chain terminus.[2,3]

Multipositional isomerization of the triple bond in functionalized acetylenes such as alcohols (Ia) presents an attractively simple route to long chain structures with chemically differentiated remote functionality; these are potent synthons for lipid structures such as *Lepidoptera* sex pheromones.[4]

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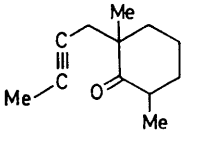
Isomerizations of functionalized alkynes with conventional metal amide systems[5,6a] appear extremely rare and limited to methyl acetylenes. Isomerization of (III) ($NaNH_2$, PhMe, reflux, 12 h)[7] and (IV) (KNH_2, liquid NH_3, 2·5 h)[6b] were successful, but (V) proved inert.[6c]



(III)

$Me-C\equiv C-CH_2-NEt_2$

(IV)

$Me-C\equiv C-C(OH)R^1R^2$

(V) R^1 = H or alkyl
R^2 = H or alkyl

Migration of the triple bond towards the functionality can produce side reactions (*e.g.*, conjugation, elimination, and enolate formation). In the case of acetylenic alcohols, quantitative conversion of C–OH into C–O^- (Ib) would presumably suppress elimination. Moreover, because isomerization involves an anionic intermediate [–C–C=C–] (VI),[8] migration of the triple bond towards alkoxide would be retarded when *n* becomes small [reaction (1)].

TABLE [*Cf.* reaction (2)]

R^1	R^2	*m*	*n*	Time/ min	Temp./ °C	Yield/ %
H	H	2	1	30	20	96,83[b,c]
H	H	5	0	30	20	83[b,c]
H	H	4	1	30	20	95[b,c]
H	H	8	6	60	20	90[d,e]
Et	H	4	1	30	0	92[b,c]
Pr^n	H	4	0	30	0	98[b,c]
Me	Me	4	0	90	0	88[b,c,e]

[a] *ca.* 3 mmol KAPA, 1·25 M in 3-aminopropylamine/mmol substrate: [b]10·0 mmol of substrate. [c] Semi-isolated yield. Reaction mixture was treated as in isolation (see text) but without concentration of solution of product in ether; then g.l.c. analysis was performed with an added internal standard. Analytical samples were collected by preparative g.l.c. [d] 20·0 mmol of substrate. [e] Total isolation of reaction product (see text). [f] The substantially longer reaction times needed compared to isomerization of dialkylacetylenes (ref. 2) appear to be the result of the low solubility in 3-aminopropylamine of the alkoxide formed by initial deprotonation of the hydroxy-group by KAPA.

We have realized successful migration of the triple bond of internal acetylenic alcohols to the terminus remote from the hydroxy-group in high yield under mild conditions, using KAPA. For example, hexadec-7-yn-1-ol,‡ 20·0 mmol,

$$X\text{–}[CH_2]_n\text{–}C{\equiv}C\text{–}[CH_2]_m\text{–}H \xrightarrow[ii.\ H_2O]{i.\ KAPA} X\text{–}[CH_2]_{m+n}\text{–}C{\equiv}C\text{–}H \quad (1)$$

(I) a; X = OH
b; X = O^- (II); X = OH

$$R^1R^2C(OH)\text{–}[CH_2]_n\text{–}C{\equiv}C\text{–}[CH_2]_m\text{–}H \xrightarrow[ii.\ H_2O]{i.\ KAPA} R^1R^2C(OH)\text{–}[CH_2]_{m+n}\text{–}C{\equiv}C\text{–}H \quad (2)$$

was added at 20 °C under argon to 60 mmol of KAPA prepared in 45 ml of the amine.§ After stirring (substantial precipitate) for 60 min, the reaction was quenched by addition of 10 ml of water with ice cooling. Further dilution, extraction, concentration, and purification by sublimation gave a 90% yield of hexadec-15-yn-1-ol, m.p. 49—52 °C, as a waxy white solid; <1% total of internal isomers remained (g.l.c.). Similarly a variety of primary, secondary, and tertiary acetylenic alcohols with even closer proximity of C–C and OH were isomerized. Representative examples [equation (2)] are shown in the Table.

This easy multipositional isomerization of acetylenic alcohols provides a novel synthetic tool, particularly for lipid synthesis, and allows generation from readily available precursors of structures which are otherwise difficult to obtain.[9,10]

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‡ Prepared from a sample of hexadec-7-yn-1-yl acetate generously provided by Dr. K. W. Greenlee.

§ For details of the preparation of KAPA, see ref. 2.

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[9] The method described herein has been successfully applied in the synthesis of (*E,Z*)-dodeca-7,9-dien-1-yl acetate, the sex pheromone of the European grape vine moth (*Lobesia botrana*): E. Negishi and A. Abramovitch, personal communication.
[10] *Added in proof.* An initial report of KAPA isomerization of octyn-1-ols to oct-7-yn-1-ol was presented by C. A. Brown, Paper ORGN 142, 166th National Meeting of the American Chemical Society, Chicago, Illinois, August 26—31st 1973; subsequently multiposition isomerization of triple bonds has been confirmed under similar conditions: J. C. Lindhoudt, G. L. van Mourik, and H. J. J. Pabon, *Tetrahedron Letters*, 1976, 2565; K. Utimoto, personal communication, H. Nozaki, personal communication.