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I. SELECTIVE ALKYLATION OF 2-BUTYNOIC ACID

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Recent studies of the γ-alkylation of α, β-unsaturated systems[1a] have furnished practical synthetic routes to trisubstituted olefins[2] that are important biological compounds. Pitzele et al[3] have alkylated 2-butynoic acid (tetrolic acid) and obtained a mixture of α and γ-isomers. The latter were converted to nerol[3] and various isomers of farnesol[1b]. We have found conditions that specifically give the α or γ-alkylation product of 2-butynoic acid. The dianion of 2-butynoic acid formed from n-butyllithium (BuLi) and tetramethylethylenediamine (TMEDA) in tetrahydrofuran (THF) is regiospecifically alkylated in the γ-position, in contrast to specific α-alkylation when it is formed from lithium diisopropylamide (LDA) and CuI. The results of using different alkylating agents and chlorotrimethylsilane (CTMS) are found in Table I.

$$RCH_2\text{-}C{\equiv}C\text{-}CO_2H \longleftarrow [\bar{C}H_2\text{-}C{\equiv}C\text{-}CO_2^-] \longrightarrow CH_2{=}C{=}C(R)(CO_2H)$$

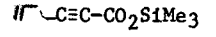
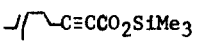
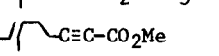
γ-alkylation α-alkylation

Treatment of 2-butynoic acid with 2 equiv of BuLi-TMEDA[4,5] followed by silylation with excess CTMS rather specifically gave the γ-product 1[6] (Table I): H^1NMR($CDCl_3$) δ0.16(S,9H), 0.3(S,9H), 1.6(S,2H); IR(neat) 2250 (C≡C), 1730(C=O), 1410, 1250(Si-CH_3), 1130, 1050 cm^{-1}(C-O, Si-O); mass spectrum m/e (rel intensity) 228(M^+, 0.2), 213(6), 169(15), 147(70), 73(100), 66(9). White insoluble BuLi-TMEDA complex was formed in a dry atmosphere by stirring 18 ml of 1.6M (28mmol) n-BuLi in hexane and 0.8g (7mmol) of freshly distilled TMEDA in 5 ml of pentane for 1 hour. At -78°, 1.1g (13mmol) of tetrolic acid dissolved in 15 ml of THF and 25 ml of pentane was added dropwise to give a bright yellow suspension (presumably the dianion). After 2 hours 7 ml of CTMS was added and after another hour the mixture was allowed to warm to 15°, filtered (glove box) and concentrated under reduced pressure at low temperature. The product was subjected to GLC analysis. Similarly 2-butynoic acid alkylated with 1 equiv of allyl bromide (-78°, 2 hours) and then CTMS gave 2: H^1NMR($CDCl_3$) δ0.3(S,9H), 4.7-6.3(M,3H), 2.4(M,4H); IR(neat) 2270(C≡C), 1730 cm^{-1}(C=O). Alkylation with 1 equiv of 1-bromo-3-methyl-2-butene and then CTMS gave 3 regiospecifically. Compound 4 was obtained similarly when methyl iodide replaced CTMS. It was isolated in 60% yield without the problem of isomer separation encountered by Pitzele in the synthesis of nerol.[3]

Reaction of 2-butynoic acid and 3 equiv[7] of LDA[8b] followed by CTMS gave a 2:1 mixture of 1 and the α-silyl compound 5: H^1NMR δ0.16(S,9H), 0.3(S,9H), 3.3(S,2H); IR(neat) 1970(C=C=C), 1730(C=O), 1410, 1260(Si-CH_3), 1050 cm^{-1}(Si-O, C-O); mass spectrum m/e (rel intensity) 228(M^+, 0.2), 213(0.2), 169(4.2), 113(24.1), 112(27.3), 97(88.7), 73(100), 66(9.4).

Compound 5 was obtained regiospecifically from 2-butynoic acid using LDA as the base, followed by treatment with CuI[9] (equal mole LDA, -78°, 1 hr) and then silylation with CTMS in the presence of triethylamine[10]. Compound 6 was obtained similarly when 1 equiv of allyl bromide was employed followed by silylation. 6: H^1NMR($CDCl_3$) δ0.3(S,9H), 4.5-6.3(M,5H), 3.0(M,2H); IR(neat) 1970(C=C=C), 1730 cm^{-1}(C=O).

Table I. Reaction Products of 2-Alkynoic Acid with Strong Bases Followed by Alkylation/Silylation

Base	Alkylating Reagents	Products		Yield, %[a]
BuLi-TMEDA	CTMS	Me_3Si-C≡C-CO_2SiMe_3	(1)	90
	 /CTMS		(2)	70
	 /CTMS		(3)	80
	 /CH_3I		(4)	60[b]
LDA	CTMS	1 + H_2C=C=C(CO_2SiMe_3)($SiMe_3$) (2:1)[c]	(5)	60
LDA/CuI	CTMS-Et_3N	5		60
	 /CTMS-Et_3N	H_2C=C=C(CO_2SiMe_3)- 	(6)	60

a. All silyl esters were isolated by preparative GLC using a 0.25 inch x 6 foot column of 10% UC-W98 on 60-80 WAW DMCS700. Distillation resulted in polymerization. The yield was determined by GLC using internal standards and/or by assuming it is the same as that of the readily isolated alkylated acid.

b. Isolated yield, identified by comparison with authentic sample - see Acknowledgment.

c. Consistent with the data of Pitzele - ref. 3.

Solvolysis of all alkylated silyl esters with methanol (room temp, 1 hr) gave the corresponding alkylated carboxylic acids. Treatment with aqueous NaOH not only hydrolyzed the silyl esters but also cleaved the C-Si bonds[13] of silylated silyl esters. Both the γ-trimethyl-silyl ester 1 and the corresponding α-isomer 5 gave allenic acid[14].

$$\underline{1} \text{ or } \underline{5} \xrightarrow[2.\ H_3O^+]{1.\ NaOH} CH_2{=}C{=}CHCO_2H$$

Extensions of this study are described in communications that follow this one.

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References:

1. (a) For leading references see 1(b).

   (b) B. S. Pitzele, J. S. Baran and D. H. Steinman, Tetrahedron, 32, 1347 (1976).

2. A. Marfat, P. R. McGuirk, R. Kramer and P. Helquist, J. Am. Chem. Soc., 99, 253 (1977) record leading references to this topic.

3. B. S. Pitzele, J. S. Baran and D. H. Steinman, J. Org. Chem., 40, 269 (1975).

4. A. W. Langer Jr., ed. "Polyamine-Chelated Alkali Metal Compounds" Advances in Chemistry Series 130, American Chemical Society 1974.

5. T. L. Chwang and R. West, J. Am. Chem. Soc., 95, 3324 (1973).

6. The γ-alkylation compound 1 is the kinetically controlled product. When the crude reaction mixture was heated at 30-50°, 1 disappeared and the isomeric α-alkylation product 5 together with some polymer was formed. Pure compound 1 did not thermally rearrange to 5 at 100° for 4 hours, indicating a base catalyzed rearrangement in the crude mixture.

7. Use of 2 equiv of LDA gave significant amount of monosilylation product, which was avoided by using 3 equiv of LDA.

8. (a) C. Ainsworth and Y.-N. Kuo, J. Organomet. Chem., 46, 73 (1972).

(b) Formed by adding BuLi dropwise to a stirred solution of diisopropylamine in THF at -78° or 0°. THF was freshly distilled from lithium aluminum hydride and the amine was distilled from CaH_2, ref. 8a.

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10. The use of CTMS-Et_3N as a silylating agent[11] was developed from our study of the reaction of methyl tetrolate and lithium dimethylcopper. Like the report of Siddall[12] we were unable to silylate this cuperate using CTMS alone. However, the reaction was accomplished in the presence of the tertiary amine.

$$CH_3C{\equiv}CCO_2CH_3 \xrightarrow{Me_2CuLi} \xrightarrow{CTMS\text{-}Et_3N} (CH_3)_2C{=}C(SiMe_3)CO_2CH_3 \quad (7)$$

7: $H^1NMR(CDCl_3)$ δ0.18(S,9H), 1.78(S,3H), 1.83(S,3H), 3.7(S,3H); IR(neat) 1730(C=O), 1610 cm^{-1}(C=C).

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