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SYNTHESIS OF ALLYLACETYLENES FROM TERMINAL ACETYLENES AND

ALLYL HALIDES

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The 1-en-4-yne fragment is frequently encountered in naturally occurring compounds [1]. The most general method of preparing allylacetylenes utilizes the reaction of metal acetylides with allyl halides. Li, Na, and Mg acetylides react with allyl halides under rather severe conditions (HMPA, 100°C, 5 h) [2-4]. The use of these reagents is restricted to those not containing many functional groups which are sensitive to reactive organometallic compounds. For this reason, it was of interest to employ Cu acetylides for this purpose. However, the reaction of allyl halides with Cu acetylides requires quite severe conditions (boiling in DMF [5], 40 h at 100°C in HMPA [6], 20 h at 85°C in benzonitrile [7]). It has previously been shown that in the presence of the nucleophilic additives MX (M = Li, Na, Mg; X = C1, Br, CN [4, 7]) or BuLi [8] these reactions proceed under milder conditions (80-85°C. 1-20 h; 25°C, 15-20 h), evidently as a result of the formation of highly reactive at-complexes [RC=CCuX]⁻M⁺. Corresponding at-complexes can be obtained from Cu [7] as well as Li, Na [4], and Mg [2] acetylides, the reaction rates being highly dependent on the anion used as the nucleophilic catalyst [7]. On the other hand, we have shown [9] that the addition of alkali metal or tetraalkylammonium halides, particularly iodides, permits the reaction of PhC=CCu (I) with aryl iodides catalyzed by Pd complexes to give virtually quantitative yields of unsymmetrical tolanes to be obtained at $\sim 20^{\circ}$ C:

 $\begin{array}{l} \text{RC} \equiv \text{CCu} + \text{MX} \rightleftharpoons [\text{RC} \equiv \text{CCuX}]^-\text{M}^+ \rightleftharpoons \text{RC} \equiv \text{CM} + \text{CuX} \\ & \downarrow^{\text{CH}_2 = \text{CHCH}_2\text{X}} \\ \text{RC} \equiv \text{CCH}_2\text{CH} = \text{CH}_2 + \text{MX} + \text{CuX} \end{array}$

We have found that the use of I⁻ as the nucleophilic catalyst enables the reaction of Cu acetylides with allyl halides to be carried out under extremely mild conditions. For example, (I) reacts with allyl bromide (II) in the presence of two equivalents of NaI at $\sim 20^{\circ}$ C within 15 min to give 94% of allyl(phenyl)-acetylene (III):

$$\begin{array}{c|c} PhC \equiv CCu + CH_2 = CHCH_2Br \xrightarrow{DMF} \\ (I) & (II) \end{array} \xrightarrow{DMF} \xrightarrow{1 h} PhC \equiv CCH_2CH = CH_2 \\ \hline NaI (2 eq.) \\ \hline 15 min \end{array} (III) 94\%$$

The coupling of allyl halides with Cu acetylides can also be carried out in the absence of added I⁻, if the starting acetylide is obtained from a terminal acetylene and CuI. In this case, the at-complex is formed *in situ*:

 $\begin{array}{l} \mathrm{RC} \cong \mathrm{CH} + \mathrm{B} + \mathrm{CuI} \rightleftharpoons [\mathrm{RC} \cong \mathrm{CCuI}]^{-}\mathrm{BH^{+}} \rightleftharpoons \mathrm{RC} \cong \mathrm{CCu} \downarrow + \mathrm{BH^{+}l^{-}} \\ \downarrow^{\mathrm{CH}_{2} = \mathrm{CHCH}_{2} \mathrm{X}} \\ \mathrm{RC} \equiv \mathrm{CCH}_{2}\mathrm{CH} = \mathrm{CH}_{2} + \mathrm{CuI} + \mathrm{BH^{+}X^{-}} \end{array}$

Triethylamine, potassium carbonate, and sodium carbonate have been used as the base B (Table 1), but triethylamine reacts with allyl halides to form unreactive quaternary ammonium salts, so that in reactions in which this base is used the allyl halide must be added following the formation of the Cu acetylide. It should be pointed out that even with phenylacetylene (IV), in the presence of 1.5 equiv. of triethylamine in DMF the acetylide is

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TABLE 1. Reaction of Phenylacetylene with Allyl Bromide (CuI (1 equiv.), Base, DMF, 20° C, C₀ = 0.25 M)

No.in		Base/ PhC \equiv CH	Time,	Yield, ^a percent			
order	Base	ratio	min	(III)	(IV)		
1 2 3 4	Et ₃ N K ₂ CO ₃ Na ₂ CO ₃ Na ₂ CO ₃ b	1,5 2 2 2 2	$15 \\ 40 \\ 60 \\ 60 \\ 60$	85 98 23 -	15 Not measured 53 c		

^aYield measured by GC.

^bIn acetone.

^CThe remaining phenylacetylene gave PhC=CCu.

TABLE 2. Reactions of Terminal Acetylenes RC=CH with Allyl Halides R'X (K_2CO_3 (2 equiv.), CuI, RC=CH/R'X = 1/1.2, $C_0 = 0.25 \mu$)

No.in	В	B'X	CuI,	Solvent	T °C	Time, h	Yield ^a , percent	
		11 24	%	1.	1., U		RC≡CR′	RC=CH
1	Ph	CH ₂ =CHCH ₂ Br	100 b	DMF	20	0,5	100	0
2	»	»	10	» ·	20	4	83	12
3	»	· »	10	»	40	2	100 -	0
4	»	»	100	Acetone	20	3	Trace	
5	»	»	100	»	20 C	2	100 .	0
6	»	»	10	»	45	3	59	40
7	»	»	100	»	20 c ,d	4	40	58
						20	89	11
8	»	$CH_2 = CHCH_2CI$	100	DMF .	20_	2	11	0e
9	»	»	100	*	201	2	62	-
10	»	»	100	»	45	2	97	0
11	»	»	100	Acetone	45 ^r	4	- 99	
12	»	$Me_2C = CHCH_2CI$	100	DMF	40	1,3	99	-
13	»	$MeC(Cl) = CHCH_2Cl$	100	»	45 f	1,7	100	0
14	CH ₂ OH	$CH_2 = CHCH_2Br$	100	»	20	0,7	92	0
15	»	»	100	Acetone	20f	2,5	100	0
16	»	»	10	»	45f	7	99	0
17	C_5H_{11}	»	100	DMF	20	1,5	100	0
18	»	»	10	»	50	4	97 B	3
				J				

^aYield found by GC. ^{b5} equiv. of K_2CO_3 . ^CIn the presence of one equiv. of NaI. ^dBase Na₂CO₂ (2 equiv.). ^eResidual RhC≅CH as PHC≡CCu. ^fIn the presence of 2 equiv. of NaI. $8C_0 = 0.66$ M.

not formed in quantitative yield. Under these conditions, the yield of (III) is no greater than 85% (Table 1). When potassium carbonate was used, which does not react with allyl halides, irrespective of the order of mixing the reactants the yield of product was quantitative. Increasing the excess of base from two to five equivalents had virtually no effect on the reaction rate. The time required for the coupling of (II) with (IV) is considerably increased when potassium carbonate is replaced by sodium carbonate (Table 1):

$$\frac{PhC = CH + (II)}{(IV)} \frac{K_{2}CO_{3} (2 eq), Cul(1 eq)}{DMF 20^{\circ}, 40 min} (III) \\ 98\%$$

The polarity of the solvent has a considerable effect. For instance, the reaction of (II) with (IV) in the presence of potassium carbonate and CuI (one equiv.) in acetone gives only traces of allylation product, whereas in DMF the yield of (II) was virtually quantitative after only 40 min (Table 1, No. 2 and Table 2, No. 4). The reaction rate in acetone is increased considerably by the addition of one equiv. of NaI:

 $(IV) + (II) \frac{K_2CO_3, \text{ CuI (1 eq.), Nal (1 eq.)}}{\text{acetone } 20^\circ, 2 \text{ h}} (III)$

In this case, the reaction requires two equivalents of I⁻, one of which is consumed in the formation of the at-complex [PhC=CCuI]⁻M⁺, and the other in the formation of allyl iodide:

$$(II) + NaI \stackrel{acetone}{\longleftrightarrow} CH_2 = CHCH_2I + NaBr \downarrow$$

This equilibrium is shifted almost completely to the right, since NaBr, unlike NaI, is sparingly soluble in acetone. Under these conditions, replacement of potassium carbonate by sodium carbonate gives a yield of 89% of (III) after 20 h (Table 2, No. 7).

Allyl chlorides react much more slowly than the bromides. For instance, the reaction of (IV) with allyl chloride in the presence of two equivalents of potassium carbonate and one equivalent of CuI in DMF at 45°C is complete in 2 h (Table 1, No. 2). The reaction of allyl chlorides in acetone requires the presence of I⁻ (Table 2, No. 11).

Under these conditions, the reactions of terminal acetylenes with allyl halides are not accompanied by allyl rearrangement. Thus, in the reaction of (IV) with prenyl chloride $Me_2C=CHCH_2C1$ (V) in DMF in the presence of one equivalent of CuI at 40°C, a quantitative yield of the coupling product (VI) is obtained after 1.3 h.



In the reaction of (IV) with 1,3-dichloro-2-butene, again only one regioisomer (VII) is formed:

$$CH_{3}^{a}C(Cl) = CH_{2}^{b}CH_{2}^{c}C \equiv CPh$$
(VII)

Also studied were the reactions of (II) with propargyl alcohol (VIII) and 1-heptyne (IX). Quantitative yields of 3-allylpropargyl alcohol (X) and dec-1-en-4-yne (XI) were obtained under mild conditions (Table 2, Nos. 14, 15, 17).

It has been shown previously [10, 11] that terminal propargyl alcohols react with allyl chlorides in aqueous alkali or primary amine at 70-80°C in the presence of catalytic amounts of Cu_2Cl_2 . However, other terminal acetylenes do not undergo this reaction, and furthermore it is necessary to maintain careful control of the pH of the solution during the reaction. A more general method for the preparation of 1-en-4-ynes is the reaction of terminal acetylenes with allyl bromides in the presence of potassium carbonate and catalytic amounts of Cu_2Cl_2 [7]. A deficiency of these reactions is the rather severe conditions required, and increasing the amount of Cu_2Cl_2 to one equivalent results in a decrease in the reaction rate and the yield of allylation product:

$$(IX) + (II) \xrightarrow{\text{K}_2\text{CO}_3, \text{ Cu}_2\text{CI}_2 (0.5 \text{ mol. }\%)}_{\text{HMPA}, 104^\circ, 8 \text{ h}} n-C_5H_{11}\text{C} \equiv \text{CCH}_2\text{CH} = \text{CH}_2$$

We have shown that it is preferable to use CuI in this reaction, rather than Cu_2Cl_2 :

$$(IX) + (II) \xrightarrow{K_2CO_3 (2 \text{ eq }), \text{ CuI } (0,1 \text{ eq.})}{\text{DMF}, 50^\circ, 4 \text{ h}} \xrightarrow{(XI)} 97\%$$

It is noteworthy that the rate of the CuI catalyzed reaction of RC=CH with $CH_2=CHCH_2X$ is substantially less than stoichiometric, but heating to 40-50°C is frequently sufficient for the reaction to proceed to completion (Table 2, Nos. 2, 13, 16, 18).

EXPERIMENTAL

GC analyses were carried out on an LKhM-8MD chromatograph, flame ionization detector, $3 \text{ m} \times 3 \text{ mm}$ column with 3% SP-2100 on Chromatone N-Super, carrier gas nitrogen, using an internal standard. PMR spectra were obtained on a Varian T-60 instrument, in CDCl₃ from TMS.

<u>Reactions of Phenylacetylene with Allyl Bromide</u>. In a two-necked flask fitted with a magnetic stirrer were placed 2 ml of DMF, 138 mg (1 mmole) of K_2CO_3 , 73 mg (0.6 mmole) of (II), 51 mg (0.5 mmole) of (IV), and 9.5 mg (0.05 mmole) of CuI, under argon $\sim 20^{\circ}$ C. After 4 h, 71.1 mg (0.5 mmole) of decame was added. According to GLC, the yield of (III) was 83%. A similar reaction using tenfold amounts of the reactants gave, after the usual workup, 0.50 g (70%) of (III), bp 69°C (2 mm), n_D^{25} 1.5574 (cf. [5]).

The reaction of (IV) with CH_2 =CHCH₂Cl was carried out similarly (Table 2).

<u>Reactions of Propargyl Alcohol with Allyl Bromide</u>. In a two-necked flask fitted with a magnetic stirrers were placed 2 ml of acetone, 28 mg (0.5 mmole) of (VIII), 73 mg (0.6 mmole) of (II), 138 mg (1 mmole) of K_2CO_3 , 150 mg (1 mmole) of NaI, 95 mg (0.5 mmole) of CuI and 71.1 mg (0.5 mmole) of decane under argon at 20°C. According to GC, after 2.5 h the yield of (X) was 100%. When the reaction was carried out with ten times the amounts of the reactants, 0.44 g (92%) of (X) was obtained, bp 73-75°C (15 mm) (cf. [6]).

The reaction of (IX) with (II) was carried out similarly, to give 0.61 g (89%) of (XI), bp 72°C (22 mm) (cf. [6]).

<u>1-Phenyl-5-methylhex-4-en-1-yne (VI)</u>. To a solution of 0.626 g (6 mmole) of (V) and 0.51 g (5 mmole) of (IV) in 20 ml of DMF was added 1.38 g (10 mmole) of K_2CO_3 and 0.95 g (5 mmole) of CuI under argon at 40°C. After 1.3 h, the mixture was poured into 20 ml of 1 N HC1, 80 ml of water added, and the mixture extracted with ether (4 × 15 ml). The extract was washed with water (3 × 25 ml), and dried over MgSO₄. After removal of the ether, the residue was distilled in vacuo to give 0.80 g (94%) of (VI). According to GC (internal standard dodecane 190°C), the yield of (VI) was 99%, bp 129-132°C (20 mm). Found: C 92.08; H 8.01%. $C_{13}H_{14}$. Calculated C 91.70; H 8.30%. PMR spectrum (60 MHz, CDCl₃): 1.52 br.s (3H^b), 1.58 br.s(3H^a), 2.97 br.d.s(2H^a, J_{cd} = 7 Hz), 5.15, t.m (1H^c, J_{cd} = 7, J_{ac} = 1.5 Hz), 6.97-7.42 m (5H, Ph).

<u>1-Pheny1-5-chlorohex-4-en-1-yne (VII)</u>. In a two-necked flask, fitted with a magnetic stirrer, were placed 40 ml of DMF, 5.5 g (40 mmole) of K_2CO_3 , 2.47 g (20 mmole) of 1,3-dichlorobut-2-ene, 0.38 g (2 mmole) of CuI, 6.0 g (40 mmole) of NaI, and 2.02 g (20 mmole) of (IV), and the mixture stirred under argon for 1.7 h at 45°C. It was then poured into 40 ml of 1 N HCl, 150 ml of water added, and extracted with ether (5 × 20 ml). The ether was evaporated, and the residue vacuum distilled to give 3.5 g (92%) of (VII). According to GC (internal standard dodecane, 210°C), the yield of (VII) was 100%, bp 99.5°C (0.3 mm). PMR spectrum (60 MHz, CDCl₃): 2.07 d.m (3H^a, J_{ab} = 1.3 Hz), 3.23 d.q (2H^c. J_{bc} = 7 Hz), 5.55 t.q (1H^b, J_{ab} = 1.3, J_{bc} = 7 Hz), 7.07-7.48 m (5H, Ph) (Table 2, Nos. 12, 13).

CONCLUSIONS

1. Terminal acetylenes have been reacted with allyl halides under mild conditions to give quantitative yields of the coupling products.

2. The best base for these reactions is K_2CO_3 , and the most active catalyst is CuI.

3. Under these conditions, the reaction is not accompanied by allyl rearrangement of 1,1-disubstituted prop-1-ene 3-halides.

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