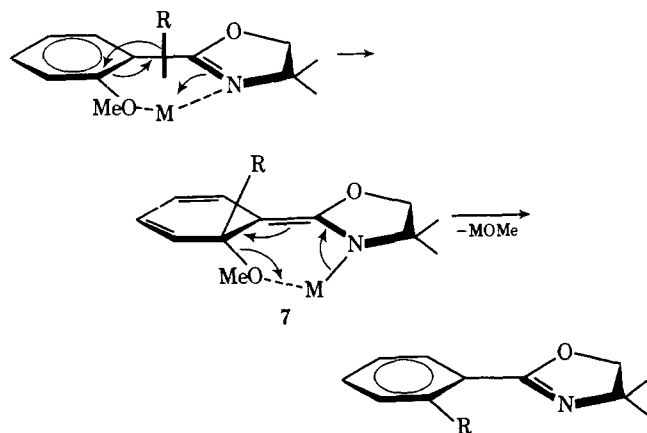


tert-butyl. In all cases, addition to the nitrile function was a troublesome side reaction. Furthermore, the reaction proceeded only when the vicinal methoxy groups were present. Fuson⁵ has extensively studied nucleophilic substitution on highly hindered *o*-methoxybenzophenones utilizing Grignard and organolithium reagents and the yields rarely exceeded 50%, whereas Risaliti⁶ reported nucleophilic displacement of aryl methoxyl groups in azobenzenes using aryl Grignard reagents. In all previous observations involving methoxyl group displacement by organometallics, a mechanism has been invoked which involved complexation of the metal to both the methoxyl group and the "activating" group followed by 1,4-addition. The oxazoline moiety provides an excellent activating group and it is undoubtedly a more effective ligand than the cyano or the azo function (the latter requires a specific conformation in order to be effective) due to the ready chelation which leads to the enamine-like intermediate **7**.



The present method was also shown to provide excellent latitude with respect to the synthesis of biphenyls and benzoic acids possessing labile substituents. The oxazoline moiety may be removed under alkaline conditions when substituents are acid-sensitive (entries 5 and 13). In both of these examples acid cleavage of **5** resulted in loss of the *t*-Boc group and *tert*-butyl group, respectively. However, if **5** is converted to its methiodide salt (MeI, 5–7 equiv. 25°, 15 hr) and then treated with 1:1 methanol–20% NaOH (reflux, 15 hr), the *t*-Boc-substituted biphenyl and *o*-(*tert*-butyl)benzoic acid are isolated without event.

Studies are continuing to determine the scope of this novel nucleophilic substitution which promises to provide a versatile approach to various biphenyl and monoaryl derivatives.^{7,8}

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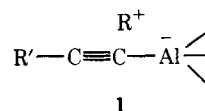
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A Convenient Method for the Tertiary Alkyl-Alkynyl Coupling via Organoalanes

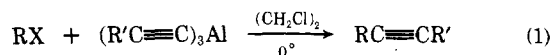
Sir:

We wish to provide a solution to a long-pending problem of developing a direct and satisfactory procedure for the tertiary alkyl-alkynyl coupling. In our study directed toward the synthesis of terpenoids and related compounds, it became desirable to be able to introduce a quaternary carbon in a position adjacent to an alkyne group. No general and satisfactory method permitting direct tertiary alkyl-alkynyl coupling appeared available,¹ the reaction of alkynylmetals containing lithium, magnesium, or certain transition metals with tertiary alkyl halides being dominated by elimination and other side reactions.

The following facts and reasoning led us to investigate the feasibility of using alkynylalanes as intermediates. (1) Tertiary carbocations are reasonably stable with respect to elimination under nonbasic or weakly basic conditions.² (2) Certain trisubstituted aluminum compounds not only promote the formation of carbocations from the corresponding halides and sulfonates but transform the anion residues into much weaker bases. (3) Alkynylaluminum derivatives might be particularly suited for effecting the tertiary alkyl-alkynyl coupling via an electrostatically directed substitution at the α alkynyl carbon involving the ion pair **1**.



We have indeed found that trialkynylalanes, readily obtainable from the corresponding alkynyllithiums and anhydrous aluminum chloride, undergo a remarkably clean reaction with tertiary alkyl halides to produce cross-coupled products in high yields (eq 1, X = Cl, Br, or sulfonate).



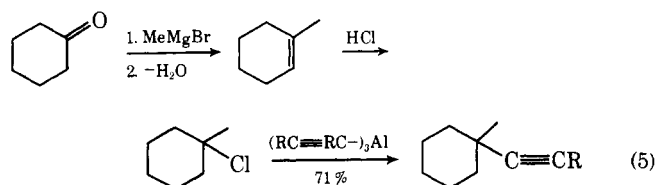
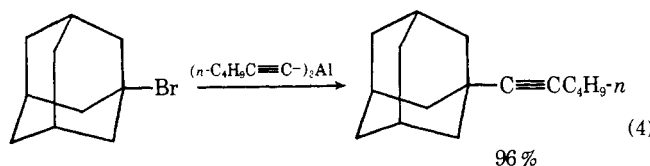
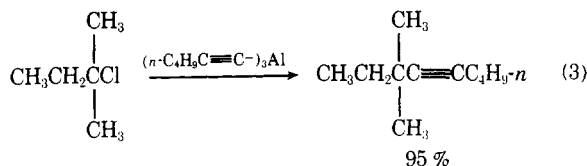
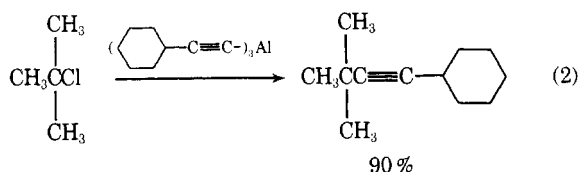
As indicated by the following examples, the reaction appears general with respect to the structural types of tertiary alkyl halides. The yields reported here are based on alkyl halides or sulfonates. Two of the three acetylene molecules that are not utilized can be recovered nearly quantitatively, if the reaction mixture is worked up soon after the completion of the desired coupling. These results sharply contrast with those observed in the reactions of tertiary alkyl halides with alkynes and certain alkyne derivatives in the presence of Friedel-Crafts catalysts,^{1c} where the yields of the coupling products are, in general, disappointingly low. It is worth pointing out that the reaction permits a novel geminal alkyl-alkynylation of ketones which should find a number of applications in the natural product synthesis.

The development of the successful procedure is critically dependent on proper selection of alkynylalanes and solvents. Alkynyldialkylalanes, such as those derived from diethyl-

Table 1. Reaction of Trialkynylalanes with Tertiary Alkyl Halides and Secondary Alkyl Mesylates^a

$RX + (R'C\equiv C)_3Al \xrightarrow{0^\circ} RC\equiv CR'$					Product ^b	
R	X	R'	Solvent	Yield, ^c %	Bp, °(mm) [lit. bp]	<i>n</i> ^d _D [lit. <i>n</i> ^d _D]
<i>tert</i> -Butyl	Cl	<i>n</i> -Butyl	CH ₂ Cl ₂	98		<i>n</i> ²⁰ _D 1.4273 [<i>n</i> ²⁰ _D 1.4270] ^d
<i>tert</i> -Butyl	Cl	Cyclohexyl	(CH ₂ Cl) ₂	90 ^e		<i>n</i> ²⁰ _D 1.4581
<i>tert</i> -Butyl	Cl	3-Chloropropyl	(CH ₂ Cl) ₂	86	49–50 (35)	<i>n</i> ²⁴ _D 1.4446
<i>tert</i> -Amyl	Cl	<i>n</i> -Butyl	(CH ₂ Cl) ₂	95 (85) ^f	82–83 (40) [82 (40)] ^d	<i>n</i> ²⁰ _D 1.4314 [<i>n</i> ²⁰ _D 1.4312] ^d
1-Adamantyl	Br	<i>n</i> -Butyl	CH ₂ Cl ₂	96		<i>n</i> ²¹ _D 1.5091
1-Methylcyclohexyl	Cl	<i>n</i> -Butyl	(CH ₂ Cl) ₂	71	69–70 (2.5)	<i>n</i> ²³ _D 1.4637
Isopropyl	OSO ₂ CH ₃	<i>n</i> -Butyl	CH ₂ Cl ₂	99 (80)	142–143 [140] ^g	<i>n</i> ²⁵ _D 1.4221 [<i>n</i> ²⁰ _D 1.4226] ^g
Cyclopentyl	OSO ₂ CH ₃	<i>n</i> -Butyl	CH ₂ Cl ₂	60	123–124 (12)	
3-Methyl-2-butyl	OSO ₂ CH ₃	<i>n</i> -Butyl	CH ₂ Cl ₂	60 ^h		

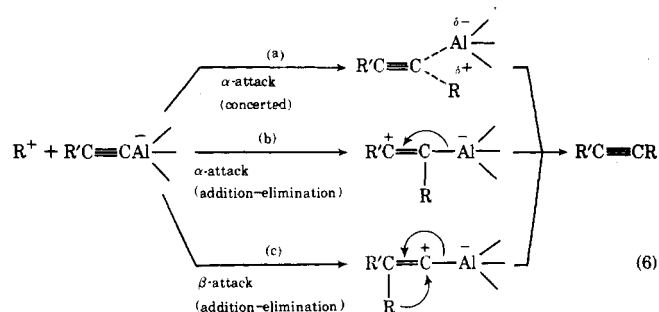
^a Unless otherwise mentioned the reaction time is 1 hr. ^b All new products yielded satisfactory analytical and spectral data. ^c By GLC. The numbers in parentheses are isolated yields. ^d Reference 8. ^e The reaction time was 3 hr. ^f When dichloromethane was used as solvent, the yield was 55%. ^g H. H. Schlubach and K. Repenning, *Justus Liebigs Ann. Chem.*, 614, 37 (1958). ^h 3,3-Dimethyl-4-nonyne was the only cross-coupled product detected.



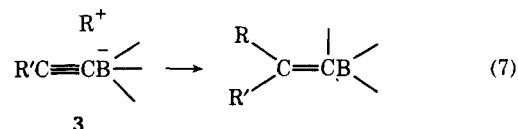
aluminum chloride and diisobutylaluminum chloride, are not dependable alkynylating agents. Whereas their reaction with *tert*-butyl chloride or bromide produces the desired alkyne in high yield (~70%), their reaction with other tertiary alkyl halides, such as *tert*-amyl bromide and 1-bromo-1-methylcyclohexane, results in predominant elimination of the halides, producing the desired alkynes in low yields. An interesting observation is the formation of 1-ethyladamantane (43%) along with a 10% yield of the desired alkyne in the reaction of 1-bromoadamantane with 1-hexynyldiethylalane. Alkynylalanes derived from alkynyllithiums and aluminum chloride in the 1:1 or 2:1 ratio are unsatisfactory with respect to the product yield. Of various solvents tested³ 1,2-dichloroethane appears the best with respect to the product yield. Dichloromethane is less satisfactory but acceptable.

Although we have been preoccupied with the development of the new synthetic procedure, a few reasonable speculations on the mechanism of the reaction can be made

based on the experimental results obtained to date. First, our assumption that the reaction involves carbocationic species has been supported by the following observations. (1) Tertiary alkyl chlorides and bromides as well as secondary alkyl sulfonates, e.g., mesylates, react readily, whereas secondary alkyl chlorides and bromides as well as primary alkyl halides and sulfonates do not. (2) The reaction of 3-methyl-2-butyl mesylate with trihexynylalane produced an isomerization product, 3,3-dimethyl-4-nonyne, as the only cross-coupled product. Second, the carbocation derived from the corresponding halide or sulfonate can, in principle, interact with alkynylaluminum derivatives in various manners, of which the following three seem to deserve serious considerations. The reaction of *trans*-1-hexenyldiisobutyla-



lane (2) with isopropyl mesylate yielded a 30:70 mixture of *cis*- and *trans*-2-methyl-2-octenes. Under the reaction conditions the alkene products do not undergo isomerization. These results seem to render the path (a) implausible. On the other hand, both the paths (b) and (c) appear plausible, and the presently available data do not permit us to favor one over the other. It is instructive to note that the reaction of alkynylborate anions with alkyl halides which presumably proceeds in some cases via **3**, the boron analogue of **1**, involves predominant β attack⁶ (eq 7).



Irrespective of the precise mechanism, for the first time, the synthetic chemists have at their disposal procedures for the direct coupling of alkynyl groups with alkyl groups of small,^{1a,b} medium⁷ and large steric requirements. The following preparation of 3,3-dimethyl-4-nonyne is representa-

tive. To 4.92 g (7.0 ml, 60 mmol) of 1-hexyne dissolved in 50 ml of *n*-hexane were added 25 ml (60 mmol) of 2.40 *M* *n*-butyllithium (0°, 30 min) and 2.70 g (20 mmol) of aluminum chloride (0°, 30 min). *n*-Hexane was removed under reduced pressure (~1 mm). To the residue thus obtained were added 100 ml of 1,2-dichloroethane and 2.13 g (20 mmol) of 2-chloro-2-methylbutane at 0°. After stirring for 1 hr at this temperature, the reaction mixture was poured into ice-cold aqueous hydrochloric acid (3 *N*). The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water, dried (MgSO₄), and distilled to yield 2.58 g (85%) of 3,3-dimethyl-4-nonyne: bp 82–83° (40 mm) [lit.⁸ bp 82° (40 mm)]; *n*_D²⁰ 1.4314 [lit.⁸ *n*_D²⁰ 1.4312]; ¹H NMR (CCl₄, Me₄Si) δ 0.9–0.93 (t, *J* = 6 Hz, 6 H), 1.1 (s, 6 H), 1.23–1.66 (m, 6 H), and 2.1 (t, 6 Hz, 2 H) ppm.

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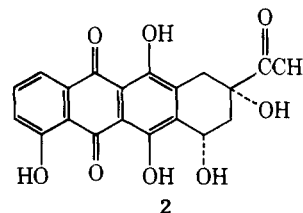
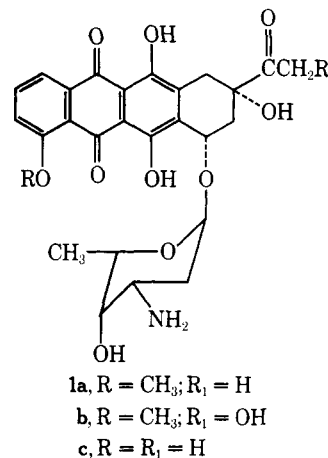
Received June 2, 1975

The Structure of Carminomycin I¹

Sir:

The useful antineoplastic properties of certain anthracycline antibiotics are now widely recognized. Both daunomycin² (**1a**) and adriamycin³ (**1b**), produced respectively by *Streptomyces peucetius* (Streptomycetaceae family) and a mutant strain, have displayed pronounced anticancer activity in various experimental tumor systems and in certain types of human cancer.⁴ However, the utility of anthracyclines **1a** and **1b** in human treatment is restricted by a dose-limiting cardiotoxicity (congestive heart failure).^{4a,5} The need for related substances with superior antineoplastic activity but devoid (or with less) such toxic properties is presently of great concern.

In 1973 the very promising anthracycline, carminomycin I (**1c**), was isolated from *Actinomadura carminata* sp. nov. (Actinomycetaceae family)⁶ and assigned a desmethyl daunomycin structure.⁷ The stereochemistry in ring D appeared to differ somewhat from that of daunomycin but was



not definitely established. Subsequently carminomycin was found to be more effective than the related antibiotics **1a** and **1b** in inhibiting DNA synthesis⁸ and growth of murine lymphoid leukemia L1210 (some cures).⁷ Also anthracycline **1c** was found to suppress the growth (by 95%) of a murine bronchogenic lung carcinoma,⁷ to give evidence of less severe cardiotoxicity (rabbit evaluation) and to be better absorbed from the gastrointestinal tract than daunomycin.⁹ In view of the promising antineoplastic activity of carminomycin I this anthracycline is now in clinical trial in the Soviet Union, and we have undertaken an x-ray crystal structure determination to confirm the overall structure and to define the stereochemistry of ring D substituents.

Carminomycin I hydrochloride was purified by chromatography on a Merck prepacked silica gel column (elution with 32:9.5:1.6 chloroform:methanol:water) and recrystallization from ethanol-benzene to afford brick red crystals decomposing at 210–212°; ORD in methanol [α]_D²⁵₅₈₉ +290°, [α]_D²⁵₃₇₀ +465°, and [α]_D²⁵₃₀₅ –4180°. The corresponding free base (**1c**) was prepared (5.3 mg → 4.8 mg) by ion exchange chromatography (DEAE Sephadex A-50, treated with 0.5 *N* sodium hydroxide, elution with 10% acetic acid) and isolated as a red powder; ORD in methanol [α]_D²⁵₅₈₉ +330°, [α]_D²⁵₃₆₆ +666°, and [α]_D²⁵₃₀₂ –3830°; CD in methanol [θ] nm +5370 (345), +3530 (318), and –7370 (286). The specimen of carminomycin I (**1c**) was found to be identical¹⁰ with a specimen of carminomycin I isolated by Wall and colleagues from a different microorganism.¹¹ In addition the specimens of carminomycin I from both sources were individually hydrolyzed (5 mg of **1c** in 6.1 ml of 0.1 *N* HCl, 60–80° for 25 min, chromatographed on a silica gel column and eluted with 9:1 chloroform-methanol) to yield 1.2 mg of the aglycone (**2**) decomposing at 205–212°; ORD in chloroform [α]_D²⁵₅₈₉ +330°, [α]_D²⁵₃₆₆ +1700°, [α]_D²⁵₃₃₄ +400°, and [α]_D²⁵₃₁₆ +1030°; mass spectrum *m/e* 384 (*M*⁺), 366 (*M* – H₂O), 348 (*M* – 2H₂O), 341 (*M* – CH₃CO), 333 (348 – CH₃), 323 (341 – H₂O), 305 (348 – CH₃, and from 333 – CO), 295 (323 – CO), 277 (305 – CO), 249 (277 – CO), and 221 (249 – CO) with metastable ions observed for 348 → 333, 333 → 305, 323 → 295, 305 → 277, and 277 → 249. The specimens of carminomycin aglycone obtained in this manner were found to be identical.¹⁰

Single crystals of carminomycin I HCl·H₂O of sufficient