with aqueous acetic acid.[5b] Pure bradykinin (610 mg., 51% of the material liberated from the solid support) was obtained from the major Sakaguchi positive peak.

The product was homogeneous and indistinguishable from authentic bradykinin[7] by paper electrophoresis and paper chromatography (detected by ninhydrin and Sakaguchi reagents): R_{arg} 0.62 (0.1 M pyridine acetate, pH 5.0); R_{glu} 1.38 (formic acid–acetic acid–H$_2$O, 1.5:1:100, pH 2.1); R_f 0.50 (propanol–H$_2$O, 2:1); R_f 0.49 (sec-butyl alcohol–formic acid–H$_2$O, 100:16:16); R_f 0.26 (isoamyl alcohol–pyridine–H$_2$O, 35:35:30); $[\alpha]^{25}$D $-76.5°$ (c 1.37, 1 N acetic acid). Amino acid ratios were: arg, 1.90; pro, 2.71; phe, 2.04; gly, 1.00; ser, 1.01.

Anal. Calcd. for C$_{50}$H$_{73}$O$_{11}$N$_{15}$·3CH$_3$CO$_2$H: C, 54.2; H, 6.9; N, 16.9. Found: C, 54.3; H, 6.9; N, 17.2.

The synthetic bradykinin possessed the full biological activity of the natural hormone. It was compared quantitatively with an authentic standard in the isolated rat uterus assay and in the rat duodenum assay. Over the range of 10^{-10} to 10^{-9} g./ml., the two preparations were equally active in both tests.

The over-all yield of biologically active bradykinin was 32%. The total time required for the synthesis starting with t-BOC amino acids and ending with chromatographically pure bradykinin was 8 days.

Acknowledgment.—Supported in part by Grant A-1260 from the U. S. Public Health Service. The author wishes to express his appreciation to Dr. D. W. Woolley for his interest and advice, and to Miss Angela Corigliano for her expert technical assistance throughout this work.

(7) Obtained through the courtesy of Dr. E. D. Nicolaides, Parke, Davis & Company, Ann Arbor, Michigan.
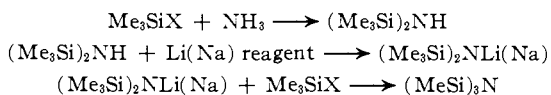
THE ROCKEFELLER INSTITUTE　　　　　R. B. MERRIFIELD
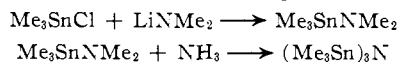NEW YORK 21, NEW YORK

Preparation of Tris(trimethylsilyl)- and Tris(trimethylstannyl)amines

Sir:

It is reported in the literature[1-3] that attempts to prepare tris(trimethylsilyl)amine directly by reaction of trimethylchlorosilane with ammonia failed, even at 500° with pyridine as solvent. Successful preparations of this material[2,3] and of the analogous tin compound, tris(trimethylstannyl)amine,[4] have required at least two steps, one of which involved the preparation of an N-lithio or N-sodio intermediate.

$$Me_3SiX + NH_3 \longrightarrow (Me_3Si)_2NH$$
$$(Me_3Si)_2NH + Li(Na) \text{ reagent} \longrightarrow (Me_3Si)_2NLi(Na)$$
$$(Me_3Si)_2NLi(Na) + Me_3SiX \longrightarrow (MeSi)_3N$$

The tin compound has been prepared as follows.

$$Me_3SnCl + LiNMe_2 \longrightarrow Me_3SnNMe_2$$
$$Me_3SnNMe_2 + NH_3 \longrightarrow (Me_3Sn)_3N$$

The purpose of this paper is to describe a simple, convenient, one-step synthesis of these materials by the use of the novel new reagent, lithium nitride (I).[5] It has been found that a slurry of lithium nitride in tetrahydrofuran (THF) will react with trimethylchlorosilane (IIa) and trimethylchlorostannane (IIb) to give the corresponding tris(trimethylmetallo)amine (IIIa,b)

(1) R. O. Sauer and R. H. Hasek, *J. Am. Chem. Soc.*, **68**, 241 (1946).

(2) U. Wannagat and H. Niederprum, *Angew. Chem.*, **71**, 574 (1959).

(3) J. Goubeau and J. Jimenez-Barbera, *Z. anorg. allgem. Chem.*, **303**, 217 (1960).

(4) K. Jones and M. F. Lappert, *Proc. Chem. Soc.*, 358 (1962).

(5) Commercially available from Foote Mineral Company, Philadelphia 44, Pennsylvania.

in good yield. Koenig and co-workers[6] reported that lithium nitride reacts "with organotin halides, which presumably reacted metathetically, since the lithium halide separated" but did not indicate the nature of the other product.

$$Li_3N + 3Me_3MCl \longrightarrow (Me_3M)_3N + LiCl$$
$$I \qquad\qquad II \qquad\qquad\qquad III$$
$$a, M = Si; \ b, M = Sn$$
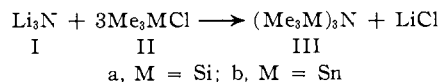
The general procedure used was as follows. To a slurry of 0.05 mole of I in 50 ml. of dry THF, maintained under an atmosphere of dry nitrogen, was added dropwise, with stirring, a solution of II, 0.15 mole in 50 ml. of THF, over a period of 1 hr. Care was exercised during the addition due to the extremely exothermic nature of the reaction. After the addition was completed the reaction mixture was heated at reflux for 2 hr. The major portion of the THF was removed by distillation, 150 ml. of petroleum ether (b.p. 30–60°) was added to the concentrate, and the mixture filtered to remove insoluble LiCl. The filtrate was concentrated and the residue distilled to give the desired product. The silyl compound (IIIa) was obtained in 72% yield and was identified by comparison of its infrared[3] and n.m.r.[7] spectra with values published in the literature and its elemental analysis and molecular weight. The stannyl compound (IIIb) was obtained in 59% yield and was identified by a comparison of its boiling point, 84° (.40 mm.), with the value published in the literature and by the determination of its molecular weight. *Anal.* Calcd: 505. Found: 515, 519. The n.m.r. of IIIb exhibited only a single peak, 11.0 c.p.s. downfield from tetramethylsilane (CCl$_4$ solution) consistent with its structure. No attempts were made to optimize the yields of these reactions.

It is expected that the reaction of lithium nitride with haloorganometallo compounds will be a general reaction and will be applicable to the preparation of a wide variety of other tris(organometallo)amines of the group III, IV, V, and VI elements. Work is proceeding along these lines.

(6) P. E. Koenig, et al., *J. Org. Chem.*, **26**, 4777 (1961).

(7) H. Schmidbaur, *J. Am. Chem. Soc.*, **85**, 2336 (1963).

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Large Salt Effects and Mechanism in Acetone and Ether[1,2]

Sir:

Salt effects on rate of ionization of organic substrates can become enormous in poorly ionizing solvents.[3] In this communication we call attention to the magnitude and specific pattern of such salt effects on ionization of p-methoxyneophyl p-toluenesulfonate[3] (ROTs) and the spirodienyl p-nitrobenzoate[4] (I-OPNB). Some mechanistic features of salt-promoted ionization are also discussed.

Salt effects on rate of ionization of ROTs in acetone,[3] measured by acid production, are moderately large. Addition of 0.05 M LiClO$_4$ increases the rate by a factor of 3.4. With I-OPNB first-order rate constants for production of HOPNB and tetralin show much greater

(1) Research supported by the National Science Foundation.

(2) Research sponsored by the U. S. Army Research Office (Durham).

(3) S. Winstein, S. Smith, and D. Darwish, *J. Am. Chem. Soc.*, **81**, 5511 (1959).

(4) E. C. Friedrich and S. Winstein, *Tetrahedron Letters*, **No. 11**, 475 (1962).

sensitivity to salts. Thus, the rate of acid production from I-OPNB in acetone is accelerated by a factor of 10^3 by 0.05 M LiClO$_4$. The relative effects of different salts in promoting reaction of both substrates are summarized in Table I by means of b values from eq. 1.[5]

$$k_t = k_t^0[1 + b(\text{salt})] \qquad (1)$$

$$k_t = k_t^0[1 + b(\text{salt}) + c(\text{salt})^n] \qquad (2)$$

III-OPNB
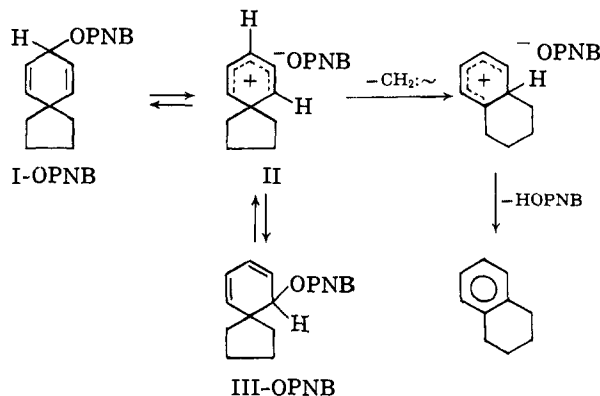
In ether as solvent, the LiClO$_4$ salt effects are much larger than in acetone,[3] and the rate of I-OPNB is again more sensitive to salt than is ROTs. Addition of 0.1 M LiClO$_4$ accelerates the rate by a factor of 10^5 for ROTs and 10^6 for I-OPNB. A good fit of the rate data in ether may be made to eq. 2, and this is summarized in Table II. As far as products from I-OPNB are concerned, tetralin is obtained in 99–100% yields in both ether and acetone solvents, with or without added 0.025 M LiClO$_4$.

TABLE I

SUMMARY OF b VALUES FOR SALT EFFECTS IN ACETONE (EQ. 1)

Anion	Li	Na	Bu$_4$N
ROTs^a			
ClO$_4$	47^b	16.5^b	3.4^b
Br	31^b		4.8^c
Cl	20^c		6^c
I-OPNB^d			
ClO$_4$	20,000^{e,g}	2100^{e,g}	12^f
OPNB			7^f

^{a} 75.1°, $k_t^0 = 8.57 \times 10^{-6}$ sec.$^{-1}$. ^{b} 0–0.05 M salt. ^{c} 0.02 and 0.04 M Bu$_4$NBr, 0.006 and 0.01 M LiCl, and 0.025 M Bu$_4$NCl. ^{d} 0–0.10 M salts. ^{e} 25.0°, $k_t^0 = 5.85 \times 10^{-8}$ sec.$^{-1}$ extrapolated from data at higher temperatures. ^{f} 75.0°, $k_t^0 = 2.37 \times 10^{-5}$ sec.$^{-1}$. ^{g} Some curvature in plot of k_t vs. (salt), approximate fit by eq. 1.

As regards the relative accelerating effects of different salts, both substrates, ROTs and I-OPNB, show a cation order, Li > Na > Bu$_4$N, identical with the order of increasing ionic radius. Considerable anion specificity is also evident. With perchlorates, the cation order, Li > Bu$_4$N is commonly observed in other solvents as well.

The magnitude of the salt effects and the observed cation order suggest that the chief role of the salt in causing the very large accelerations is to provide specific electrophilic assistance to ionization. For example, assistance to ionization by a salt ion pair,[5] M$^+$Y$^-$, may be depicted as in eq. 3. Whereas salt-unassisted ionization leads to an ion pair, R$^+$X$^-$, salt ion pair-assisted ionization leads to an ion quadruplet.[5b] In fact, estimated interaction energies between two ion pairs are consistent with very large assistance to ionization provided by a salt ion pair in media of low dielectric constant. However, the very large specific accelerative effects of salts on ionization rates cannot

(5) (a) A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, **78**, 2763, 2780 (1956); (b) S. Winstein and G. C. Robinson, *ibid.*, **80**, 169 (1958), and other papers in this series.

TABLE II

LiClO$_4$ SALT EFFECTS IN ETHER (EQ. 2)

Compound	$10^5 k_t^0$, sec.$^{-1}$	10^{-5} b	10^{-7} c	Av. fit, % of k
ROTs (50.0°)	6	0.298	0.265^a	1.3^b
I-OPNB (25.0°)	1^c	2.1	14.5^d	2^e

^{a} $n = 1.5$. ^{b} 0.01–0.10 M LiClO$_4$. ^{c} Rough value extrapolated from data at higher temperatures. ^{d} $n = 2$. ^{e} 0.01–0.075 M LiClO$_4$.

be ascribed exclusively to salt ion pairs over the whole concentration and solvent range where they have been observed. Judging from the kinetic pattern of the salt effects, often quite linear, and the varying states of aggregation of the salts as their concentration and the solvent change, salt-promoted ionizations can involve assistance, not only from ion pairs, but also from single ions and ion aggregates larger than pairs.

$$RX + M^+Y^- \longrightarrow R^+X^-M^+Y^- \qquad (3)$$
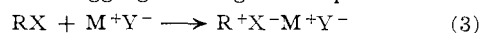
$$k_t = F_0 k_1 + F_{\text{salt}} k_{\text{salt}} (\text{salt}) \qquad (4)$$

Once we distinguish between salt-unassisted and salt-promoted ionization processes, we can express the first-order titrimetric rate constant, k_t, as in eq. 4 for a case with a linear pattern of salt effects on ionization.[5] In this equation, k_1 and k_{salt} are first-order salt-unassisted and second-order salt-promoted ionization rate constants, respectively, and F_0 and F_{salt} are the corresponding fractions of ionization leading to product instead of "covalent return."[6] In salt-unassisted ionization, F_0 is often markedly increased by "special salt effects" of added noncommon ion salts.[5]

An interesting question which has been formulated earlier[5] has to do with F_{salt} from salt-promoted ionization and its comparison with F_0. In acetone and ether, salt effects of LiClO$_4$ are so large that we can observe the behavior of I-OPNB where its reactions are nearly exclusively salt-promoted and we can thus make direct determinations of F_{salt} to compare with F_0.

In the reaction of I-OPNB in 90% acetone,[4] ion pair return (allylic isomerization to III-OPNB) competes with methylene shift.[4] Thus, F_0 is considerably less than unity. In acetone at 50 or 75° and ether at 100° the same thing is true, since extensive allylic isomerization accompanies tetralin formation. The allylic isomerization was inferred from the kinetics and directly observed by reisolation of unreacted ester at various stages of reaction. In acetone containing 0.025–0.10 M LiClO$_4$, allylic isomerization is still important. Thus, F_{salt} is well below unity, covalent return by the $^-$OPNB from its affiliation with the added salt species being competitive with methylene shift. However, in ether containing 0.025 M LiClO$_4$, where reaction of I-OPNB is salt-accelerated by a factor of 10^5, allylic isomerization is now completely absent. Recovery of unreacted I-OPNB after substantial reaction shows it to be undetectably isomerized. Thus, covalent return leading to allylic rearrangement does not occur. Probably, covalent return to the original carbon atom is absent as well, and F_{salt} is equal to unity. The affiliation of the $^-$OPNB with salt species in the salt-promoted ionization of I-OPNB in ether now makes covalent return unable to compete with methylene shift.

The present results and discussion illustrate the important distinctions which may arise between salt-unassisted and salt-promoted reactions of ionizing organic substrates. They point up an interesting area of ionic organic reaction mechanisms and suggest that carrying out such reactions under "salt-promoted"

(6) Covalent return is a more general term than ion-pair return.[5] The latter is not suitable when the regeneration of covalent RX is from an ion quadruplet or a still undefined ionic aggregate.

conditions may be useful practically and interesting theoretically.

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RECEIVED DECEMBER 5, 1963

The Reaction of Vinyllithium with Tetraphenylphosphonium Bromide and the Formation of Phosphinemethylenes by RLi Addition to Vinylphosphonium Halides[1]
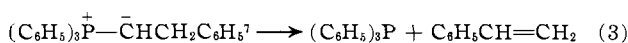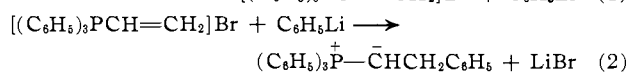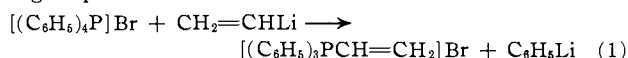
Sir:

The action of phenyllithium on tetraphenylphosphonium bromide results in formation of pentaphenylphosphorus,[2] but on the other hand, the reaction of methyl- or ethyllithium with tetraphenylphosphonium bromide produces benzene and the respective triphenylphosphinealkylidene as the major product.[3] Therefore it was of interest to us to determine which (if either) type of behavior would be observed in the reaction of vinyllithium with tetraphenylphosphonium bromide. In particular, we were interested in the possible stability of the unknown $(C_6H_5)_4PCH=CH_2$. Our study has shown that still a third type of behavior is possible in the $[(C_6H_5)_4P]Br-RLi$ system.

When ethereal vinyllithium (25.4 mmoles, obtained *via* the procedure involving solid vinyllithium[4]) was added to a slurry of tetraphenylphosphonium bromide (25.7 mmoles) in 50 ml. of ether, a reddish brown solution was formed during rapid consumption of the organolithium reagent. Gas chromatographic analysis of the volatile products obtained in a high-vacuum bulb-to-bulb distillation and work-up of the residue showed that styrene[5] (65%) and triphenylphosphine[6] (82%) were the major products of the reaction. The main reaction, therefore, proceeded according to the following equation.

$$[(C_6H_5)_4P]Br + CH_2=CHLi \longrightarrow$$
$$(C_6H_5)_3P + C_6H_5CH=CH_2 + LiBr$$
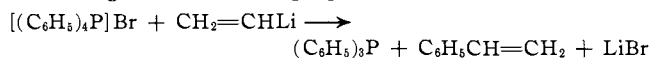
Two possible mechanisms have been considered for this reaction. First, the reaction possibly could involve initial formation of $(C_6H_5)_4PCH=CH_2$, followed by its subsequent decomposition to the observed products. Alternatively, an exchange mechanism was considered which could lead to the products by the following steps.

$$[(C_6H_5)_4P]Br + CH_2=CHLi \longrightarrow$$
$$[(C_6H_5)_3PCH=CH_2]Br + C_6H_5Li \quad (1)$$
$$[(C_6H_5)_3PCH=CH_2]Br + C_6H_5Li \longrightarrow$$
$$(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCH_2C_6H_5 + LiBr \quad (2)$$
$$(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCH_2C_6H_5{}^7 \longrightarrow (C_6H_5)_3P + C_6H_5CH=CH_2 \quad (3)$$

Precedence exists for step 2; addition of nucleophiles to vinylphosphonium salts has been reported to occur readily.[8,9] However, decomposition (or rearrangement,

(1) Part VIII of the series "Studies in Phosphinemethylene Chemistry", Part VII: D. Seyferth and J. M. Burlitch, *J. Org. Chem.*, **28**, 2463 (1963).

(2) G. Wittig and M. Rieber, *Ann.*, **562**, 187 (1949).

(3) D. Seyferth, J. K. Heeren, and W. B. Hughes, *J. Am. Chem. Soc.*, **84**, 1764 (1962).

(4) D. Seyferth and M. A. Weiner, *ibid.*, **83**, 3583 (1961).

(5) Identified by its infrared spectrum and retention time and by conversion of a g.l.c. sample to $C_6H_5CHBrCH_2Br$, m.p. 71.5–73°.

(6) Identified by melting point and mixture melting point and by conversion of all the $(C_6H_5)_3P$ to known $[(C_6H_5)_3PCH_3]I$.

(7) Or a rearrangement product, such as $(C_6H_5)_3\overset{+}{P}-CH_2\overset{-}{C}HC_6H_5$.

(8) G. Wittig, H. Eggers, and P. Duffner, *Ann.*, **619**, 10 (1958).

(9) M. Grayson and P. T. Keough, Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 64Q.

followed by decomposition) of a phosphinemethylene such as $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCH_2C_6H_5$ is not very likely. Nevertheless, this point was investigated by examining independently step 2 of the above sequence. In a typical experiment, a suspension of 16.0 mmoles of vinyltriphenylphosphonium bromide[10] in 95 ml. of ether was treated with 15.5 mmoles of phenyllithium in ether. The mixture became deep red and most of the solid disappeared. After several hours, acetone was added and the reaction mixture was heated at reflux for *ca.* 8–10 hr. All volatiles were distilled off under high vacuum. Gas chromatographic analysis showed the distillate to contain benzene[11] (44%), styrene (0.4%, but in other experiments yields of up to 5% were obtained), and 2-methyl-4-phenyl-2-butene[12] (in 33% yield, the product expected from the reaction of $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCH_2C_6H_5$ with acetone). Small amounts of triphenylphosphine also were found. In an experiment in which the vinylphosphonium salt was added slowly in small portions to an excess of phenyllithium, very similar (59% benzene, 5% styrene, 32% 2-methyl-4-phenyl-2-butene) results were obtained. These experiments are of interest in several respects. They show that the sequence 1–3 does not occur in the vinyllithium–tetraphenylphosphonium bromide reaction, leaving a route *via* transient $(C_6H_5)_4PCH=CH_2$ as the best possibility. They indicate that phenyllithium attacks vinyltriphenylphosphonium bromide *at three different sites:* (a) to a minor extent at phosphorus, giving styrene and triphenylphosphine, presumably by way of $(C_6H_5)_4PCH=CH_2$; (b) to a major extent in a Michael-type addition to the activated double bond, leading to $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCH_2C_6H_5$; and (c) at the vinyl group's α-C–H bond, which is rendered more acidic by the adjacent electron-withdrawing phosphonium function, to give benzene and $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}=CH_2$.[13] The latter should in principle react with acetone, producing 1,1-dimethylallene, but none could be found. Other attempts to isolate allenes when other carbonyl substrates were used also were unsuccessful.[14]

This procedure based on $[(C_6H_5)_3PCH=CH_2]Br$ may be of value in some cases where a particular phosphonium halide of structure $[(C_6H_5)_3PCH_2CH_2R]X$ is for some reason unavailable.[15] A more practical procedure goes directly from $[(C_6H_5)_3PCH_2CH_2Br]Br$[16] to $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCH_2C_6H_5$ (again in *ca.* 35% yield) by reaction of the former with two molar equivalents of phenyllithium, the first equivalent being used to dehydrobrominate the β-bromoethylphosphonium salt *in situ.*

(10) M.p. 185–187°. Prepared by dehydrobromination of $[(C_6H_5)_3-PCH_2CH_2Br]Br$ with moist silver oxide.

(11) Identified by means of its infrared spectrum and retention time.

(12) N.m.r. and infrared spectra were consistent with this structure and identical with spectra of an authentic sample prepared by the reaction of triphenylphosphineisopropylidene and phenylacetaldehyde.

(13) It is to be noted that H. Gilman and R. A. Tomasi [*J. Org. Chem.*, **27**, 3647 (1962)] have reported the reaction of phenyllithium with $[(C_6H_5)_3-PCH=C(C_6H_5)_2]Br$ to give $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}=C(C_6H_5)_2$.

(14) In a recent paper it has been reported that the Wittig reaction apparently is not applicable to the synthesis of allenes of types $R_2C=C=CHR$ and $R_2C=C=CH_2$ [G. Wittig and A. Haag, *Chem. Ber.*, **96**, 1535 (1963)]. Therefore our failure to isolate the expected terminal allenes is not surprising.

(15) The example given above is a case in point. We have found that pure $[(C_6H_5)_3PCH_2CH_2C_6H_5]Br$, required for the generation of $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCH_2C_6H_5$ by standard methods, cannot be prepared readily by the reaction of β-bromoethylbenzene with triphenylphosphine because of complicating side reactions.

(16) M.p. 190.5–192.5° N m r spectrum is consistent with this structure; prepared *via* $[(C_6H_5)_3PCH_2CH_2OH]Br + HBr$ (concd.).