Synthesis of α-Azidovinyl Ketones from the Iodine Azide Adducts of α,β-Unsaturated Ketones[1a]

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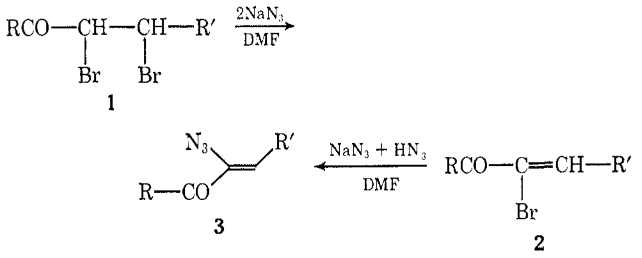
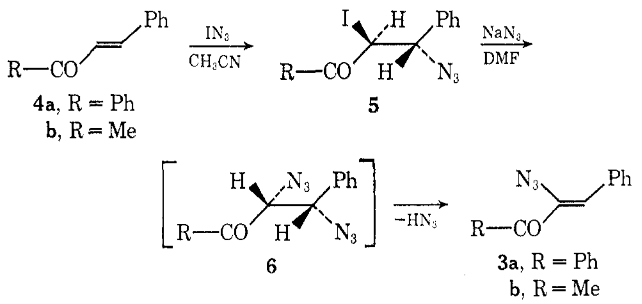
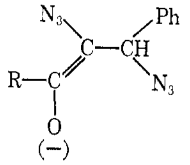
A synthetic approach to α-azidovinyl ketones is provided by the reaction of the iodine azide adducts of α,β-unsaturated ketones with sodium azide in DMF at room temperature. α-Azidochalcone (**3a**), α-azidobenzylideneacetone (**3b**), and α-azidoethylideneacetophenone (**3c**) were prepared in good yields and subsequently converted to the corresponding iminophosphoranes on treatment with triphenylphosphine. The mechanism of the synthetic method, which involves in part transposition of an azide function, is discussed, as is the regiochemistry of IN_3 additions to unsaturated carbonyl compounds.

α-Azidovinyl ketones (**3**), which are regioisomeric[1b] with the readily available β-azidovinyl ketones,[2] were obtained recently by two synthetic methods developed in this laboratory.[3] The first method consists of reacting the dibromides of α,β-unsaturated ketones (**1**) with 2 equiv of sodium azide in DMF at room temperature. The second method involves treatment of the α-bromovinyl ketones (**2**) with an equimolar mixture of sodium azide and hydrazoic acid in DMF.



We now wish to report a third facile approach to this rare class of vinyl azides.[4] Treatment of the *trans*-α,β-unsaturated ketones, **4a** and **4b**, with iodine azide in acetonitrile solution yields the *erythro*-iodo azides, **5a** and **5b**, in high yields. The latter are smoothly converted by sodium azide in DMF to the azidovinyl ketones, **3a** and **3b**. The reaction can be rationalized by an S_N2 attack of the azide ion on the iodine bearing carbon of **5** to give the bisazide **6** which on elimination of hydrazoic acid yields the *trans*-vinyl azide (**3**). Step **6** → **3** can either be considered an anti elimination of hydrazoic acid, or it can involve the loss of a proton from **6** under the basic reaction conditions (NaN_3 in DMF) to give intermediate **7** which is subsequently transformed to the thermodynamically most stable *trans*-vinyl azide (**3**). Bisazides of type **6** are unstable and have never been isolated in the pure state, but their presence can be inferred from the nmr spectra, as described elsewhere.[3]





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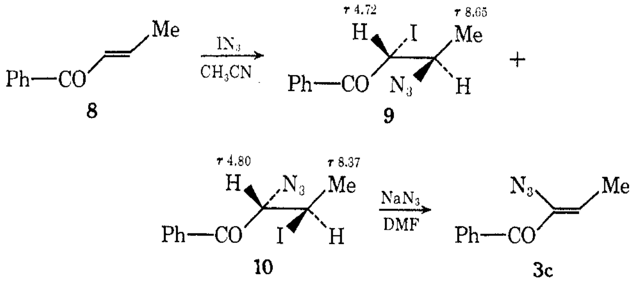
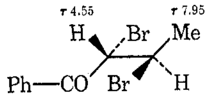
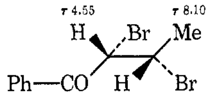
When *trans*-ethylideneacetophenone (**8**) was treated with iodine azide in acetonitrile, a mixture of two products in a ratio of 40:60 was obtained which analyzed correctly for the IN_3 adducts. We assign the regioisomeric structures **9** and **10** to these components on the basis of the nmr data. One other possibility, namely an erythro–threo mixture, is most unlikely in view of the chemical shift values and coupling constants observed. For comparison, we prepared the *erythro*- and *threo*-dibromides of ethylideneacetophenone (**11** and **12**) by the method of Lutz[5] and observed that the α-hydrogen atoms exhibit the same chemical shifts (τ 4.55) but sharply different coupling constants (J = 10.5 Hz for **11** and J = 7 Hz for **12**) as expected for different dihedral angles. On the contrary, the α-hydrogen atoms of the





11 (erythro)



12 (threo)

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* To whom correspondence should be addressed.

[1] (a) Steveochemistry. LIX. For paper LVIII, see G. L'abbé, M. J. Miller, and A. Hassner, *Chem. Ind.* (*London*), 1321 (1970). (b) Regio is used to describe directional preference in bond making or breaking: A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

[2] Review: M. I. Rybinskaya, A. N. Nesmeyanov, and N. K. Kochetkov, *Russ. Chem. Rev.*, **38**, 961 (in Engl. 433) (1969).

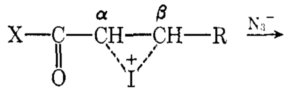
[3] A. Hassner, G. L'abbé, and M. J. Miller, *J. Amer. Chem. Soc.*, in press.

[4] After our research had been completed, Knittel, Hemetsberger, and Weidmann [*Monatsh. Chem.*, **101**, 157 (1970)], reported a fourth synthetic method for α-azidovinyl ketones by the condensation of azidoacetophenone with substituted benzaldehydes.

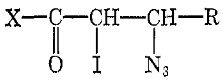
[5] R. E. Lutz, D. F. Hinkley, and R. H. Jordan, *J. Amer. Chem. Soc.*, **73**, 4647 (1951).

iodine azide adducts **9** and **10** show the same coupling constants ($J = 9$ Hz) but different chemical shifts (τ 4.72 for **9** and 4.80 for **10**) in accordance with expectations. In addition, the widely separated methyl absorptions at τ 8.65 and 8.37 are consistent with the regioisomeric structures **9** and **10** rather than with diastereomers. Ionic addition of BrN_3 to **8** also afforded two regioisomers (the Br analogs of **9** and **10**) in which the α protons absorb at τ 4.88 and 5.02, respectively, and the methyl absorption occurs at τ 8.65 and 8.43.[3]

The formation of **9** and **10** deserve comment. The regiochemistry of IN_3 additions to olefins has been shown to be dependent on electronic and steric factors operating during the opening of the iodonium ion intermediate (*e.g.*, **13**).[6] Since a carbonyl group is known to destabilize an adjacent incipient positive charge, opening of **13** would be expected to occur at the β-carbon atom leading to regioisomer **14**. However, opening of **13** can also be viewed as an S_N2 displacement which is known to occur with ease in α-halo ketones and esters. A β-phenyl group in vinyl ketones and a β-methyl group in vinyl esters (see **13**, R = Ph or Me, respectively) are sufficient to counteract the latter effect, so that **13** is opened exclusively at the β carbon. If, on the contrary, the β substituent cannot substantially contribute to the stabilization of a positive charge on the β-carbon atom, displacement occurs at the α and the β position and both regioisomers, **14** and **15**, are obtained. Thus methyl acrylate on IN_3 addition gave a mixture of **14** and **15** (X = OMe, R = H) in a ratio of 12:88,[6b] and vinyl ketone **8** is likewise converted into both isomers **9** and **10**.



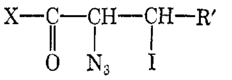
13



$$\mathrm{X{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{I}{|}}{CH}{-}\underset{\underset{N_3}{|}}{CH}{-}R}$$

14

and/or

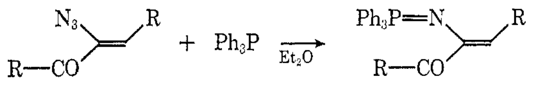


$$\mathrm{X{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{N_3}{|}}{CH}{-}\underset{\underset{I}{|}}{CH}{-}R'}$$

15

For the synthesis of the vinyl azide **3c**, no further separation of **9** and **10** is necessary since both isomerr are cleanly converted into **3c** upon treatment with sodium azide in DMF. Interestingly, the vinyl azide **3c** is also obtained when the mixture of **9** and **10** is treated with sodium acetate, a base of similar basicity as sodium azide. While the conversion of **10** into **3c** by a base is unexceptional, the transformation of **9** into **3c** by sodium acetate requires explication. Elimination of hydrazoic acid from adduct **9** by sodium acetate occurs to some extent and provides the necessary azide ions for the conversion of the remaining **9** into **3c** *via* **6**. Evidence for this interpretation is provided by the nmr spectrum of the crude reaction product which shows, in addition to the vinyl azide **3c**, the α-iodovinyl ketone (vinyl H at τ 3.28) derived from **9** in *ca.* 5–10% yield.[7]

The three α-azidovinyl ketones prepared in this work react readily with triphenylphosphine with nitrogen evolution to give the vinyliminophosphoranes **16** in high yield. The mechanism of this general reaction for azides has been recently reviewed.[8]



3

16a, R = Ph; R′ = Ph
b, R = Me; R′ = Ph
c, R = Ph; R′ = Me

Experimental Section

All-melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 457 spectrophotometer. Nmr spectra were recorded with a Varian A-60-A spectrometer using tetramethylsilane as an internal standard. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Addition of Iodine Azide to the α,β-Unsaturated Ketones.—The IN_3 adducts were prepared by treating the respective α,β-unsaturated ketones with iodine azide (reaction time, 1 day) according to the general procedure described elsewhere.[6a]

1-Phenyl-1-azido-2-iodo-3-phenyl-3-propanone (5a) was obtained from chalcone in nearly quantitative yield: mp 104–104.5° (reported[6a] 100–102°); nmr ($CDCl_3$) τ 1.75–2.10 (m, 2 H), 2.3–2.8 (m, 3 H), 2.57 (s, 5 H), 4.48 (d, 1 H, $J = 11$ Hz), 4.70 (d, 1 H, $J = 11$ Hz).

1-Phenyl-1-azido-2-iodo-3-methyl-3-propanone (5b) was obtained from benzylideneacetone in 85% yield and recrystallized from ethanol: mp 86–87°; nmr ($CDCl_3$) τ 2.60 (s, 5 H), 4.97 (d, 1 H, $J = 11$ Hz), 5.38 (d, 1 H, $J = 11$ Hz), 7.50 (s, 3 H). *Anal.* Calcd for $C_{10}H_{10}IN_3O$ (315): C, 38.10; H, 3.17; N, 13.33. Found: C, 37.92; H, 3.02; N, 13.42.

Adducts 9 and 10.—When **8** was treated with iodine azide and worked up in the usual manner, a brown oil was obtained whose nmr spectrum showed, among other impurities, the two regioisomeric adducts **9** and **10** in a ratio of about 40:60. The oil was chromatographed on silica gel with petroleum ether–benzene as the eluent, and gave a pure mixture of **9** and **10** in 23% yield: nmr ($CDCl_3$) τ 1.8–2.8 (two multiplets), 4.72 (d, $J = 9$ Hz), 4.80 (d, $J = 9$ Hz), 5.5–6.1 (octet), 8.37 (d, $J = 6.5$ Hz), 8.65 (d, $J = 6.5$ Hz). *Anal.* Calcd for $C_{10}H_{10}N_3IO$: C, 38.10; H, 3.17; N, 13.33. Found: C, 38.41; H, 3.24; N, 13.03.

Reaction of the Iodine Azide Adducts with Sodium Azide.—The IN_3 adduct (0.02 mol) was allowed to react with sodium azide (0.02 mol) in 100 ml of DMF (dried over molecular sieves, type 4A) at room temperature for the appropriate reaction time (1 hr for **5a**, 2 hr for **5b**, and 0.5 hr for **9–10**). The solution was then poured into a mixture of water–ether, and the ether layer was washed several times with water and dried ($MgSO_4$). After removing the ether under vacuum the α-azidovinyl ketones were obtained as follows.

α-Azidochalcone (3a) was isolated as a red oil and was purified by passing through a small column of neutral aluminum oxide using petroleum ether–50% benzene as the eluent. The yellow fraction was collected and gave, after removal of the solvent, the pure azide in 60–72% yield, mp 63.5–64° (from petroleum ether, bp 20–40°). When the reaction was carried out with 2 equiv of sodium azide, the α-azidochalcone was obtained pure in 68% yield.

α-Azidobenzylideneacetone (3b) was obtained as a crude yellow solid and recrystallized from petroleum ether (bp 20–40°) in 67% yield, mp 79.5–80.0°.

α-Azidoethylideneacetophenone (3c) was obtained as a pure yellow liquid in 83% yield and did not need further purification. When the reaction was carried out with 1 equiv of sodium acetate instead of sodium azide, the vinyl azide **3c** was obtained crude in 85% yield. The nmr spectrum indicated the presence of a small amount of the α-iodoethylideneacetophenone (τ 3.28, q, $J = 6.5$ Hz; τ 7.92, d, $J = 6.5$ Hz). The latter compound was also obtained in *ca.* 10% yield (in addition to starting material) when the reaction was carried out with 2 equiv of silver acetate for 2 hr. Chromatography on silica gel failed to lead to the isolation of this labile vinyl iodide.

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[6] (a) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **89**, 2077 (1967); (b) A. Hassner and F. W. Fowler, *J. Org. Chem.*, **33**, 2686 (1968).

[7] A referee suggested that another possible reaction course could be the displacement of iodine ion from **9** by acetate, followed by loss of hydrazoic acid. This should result in the formation of α-acetoxyethylideneacetophenone which has not been observed.

[8] Review: G. L'abbé, *Ind. Chim. Belge*, **34**, 519 (1969).

All three α-azidovinyl ketones were identified by comparison with authentic samples prepared by the two other methods.[3]

Reaction of the α-Azidovinyl Ketones with Triphenylphosphine.—The azidovinyl ketone (0.01 mol) was allowed to react with 0.01 mol of triphenylphosphine in 50 ml of ether at room temperature. Nitrogen evolution was observed and the iminophosphorane precipitated partly from the mixture. After 1 day the solution was cooled, and the precipitate was filtered, washed with petroleum ether, and dried.

α-**(Triphenylphosphinimino)chalcone (16a)** was obtained as a *yellow crystalline product in 87–93% yield and was recrystallized* from carbon tetrachloride–petroleum ether: mp 163–163.5°; nmr ($CDCl_3$) τ 1.6–2.9 (three multiplets), 3.75 (d, 1 H, J = 7 Hz). *Anal.* Calcd for $C_{33}H_{26}NOP$ (483): C, 77.50; H, 5.09. Found: C, 77.65; H, 5.29.

α-**(Triphenylphosphinimino)benzylideneacetone (16b)** was obtained in 88% yield and recrystallized from carbon tetrachloride–petroleum ether: mp 166–166.5°; nmr ($CDCl_3$) τ 1.5–3.0 (three multiplets), 3.38 (d, 1 H, J = 8 Hz), 7.72 (s, 3 H). *Anal.* Calcd for $C_{28}H_{24}NOP$ (421): C, 79.81; H, 5.70. Found C, 80.08; H, 5.92.

α-**(Triphenylphosphinimino)ethylideneacetophenone (16c)** was obtained in 86% yield and recrystallized from carbon tetrachloride: mp 146–147°; nmr ($CDCl_3$) τ 1.9–2.9 (two multiplets), 4.2–4.7 (dq, 1 H), 7.92 (dd, 3 H, J = 7 and 1 Hz). *Anal.* Calcd for $C_{28}H_{24}NOP$ (421): C, 79.81; H, 5.70. Found: C, 79.76; H, 5.78.

The ir spectra (KBr) of the iminophosphoranes showed the expected C=O bands at 1630–1600 and C—P bands at 1410–1430, 1120, and 990–1000 cm^{-1}.

Registry No.—**3a,** 26309-08-0; **3b,** 26309-09-1; **3c,** 26309-10-4; **5b,** 26309-13-7; **9,** 26309-11-5; **10,** 26309-12-6; **16a,** 26309-14-8; **16b,** 26309-15-9; **16c,** 26309-16-0.

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The Nature of the Ortho Effect. VI. Polarographic Half-Wave Potentials

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Twenty-seven sets of polarographic half-wave potentials and related data for ortho-substituted benzene derivatives have been correlated with the equations $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \varphi r_V + h$ and $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h$. Significant correlations were obtained with 18 of the sets correlated with the former, and 22 of the sets correlated with the latter equation. The results obtained for correlations with the former equation show that, in general, ψ is not significant. As successful correlations were obtained with the latter equation in most cases, there is no steric effect exerted by ortho substituents in the majority of the sets studied. Their effect is generally purely electrical in nature. The magnitude and composition of the electrical effect seems to be independent of the medium but strongly dependent on the group being reduced.

In continuation of our interest in the nature of the ortho effect, it seemed worthwhile to extend our investigations to polarographic half-wave potentials. The problem seems to have first been studied by Bennett and Elving,[1] who reported a correlation of $E_{0.5}$ values for 2-substituted nitrobenzenes with the Taft $\sigma_o{}^*$ constants by means of the simple Hammett equation

$$Q_X = \rho\sigma_X + h \qquad (1)$$

Zuman[2] has studied the correlation of $E_{0.5}$ values for ortho-substituted benzene derivatives with the equation

$$\Delta E_{0.5,X} = \rho\sigma_{o,X}{}^* + \delta E^\circ{}_{S,X} \qquad (2)$$

in an attempt to determine the presence or absence of steric effects. Hussey and Diefenderfer[3] have correlated $E_{0.5}$ values for 2-substituted phenyl bromides and iodides with the simple Hammett equation using σ_o constants defined by the expression

$$\sigma_o = 2.4\sigma_I + (1 - \text{S.F.})\sigma_R \qquad (3)$$

where S.F. is a steric hindrance factor defined as the fraction of overlap between the reaction site radius and the substituent radius. The radii were obtained from data on the resolution of diphenyls. As we have recently shown[4] that the $E_S{}^\circ$ values proposed by Taft[5] as a measure of the steric effect of ortho substituents are in fact electrical effect parameters, it seemed useful to investigate the correlation of $E_{0.5}$ values with the aim of determining whether or not a steric effect is present.

It is convenient at this point to review our method for ascertaining the presence or absence of steric effects. There are several possible cases to consider,[6] of which four are of major interest to us. They are (1) the steric effect obeys a linear free-energy relationship.[5] Then, if a suitable steric effect parameter is available, we may write a linear free-energy relationship including electrical and steric terms. For a steric effect parameter we have chosen the van der Waals radius of that atom or group of atoms of the substituent which is bonded to the benzene ring. Then, in this case, we write the linear free-energy relationship[4,7,8]

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi r_{V,X} + h \qquad (4)$$

(2) The steric effect does not obey a linear free-energy relationship. In this case, we may write for any particular datum in the set

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + S_X + h \qquad (5)$$

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[1] C. E. Bennett and P. J. Elving, *Collect. Czech. Chem. Commun.*, **25**, 3213 (1960).

[2] P. Zuman, *ibid.*, **27**, 648 (1962); "Substituent Effects in Organic Polarography," Plenum Publishing Co., New York, N. Y., 1967, p 75.

[3] W. W. Hussey and A. J. Diefenderfer, *J. Amer. Chem. Soc.*, **89**, 5359 (1967).

[4] M. Charton, *ibid.*, **91**, 615 (1969).

[5] R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 565.

[6] M. Charton, *J. Org. Chem.*, **34**, 278 (1969).

[7] M. Charton, *J. Amer. Chem. Soc.*, **91**, 619 (1969).

[8] M. Charton, *ibid.*, **91**, 624 (1969).