On the Synthesis of α-Azidovinyl Ketones. Mechanism and Stereochemistry of Vinyl Bromide Substitution[1]

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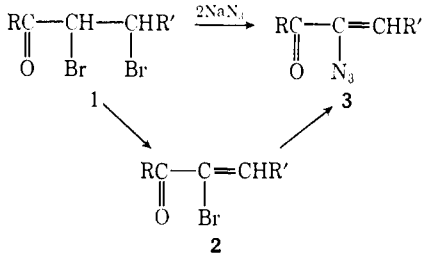
Abstract: A general method for the synthesis of α-azidovinyl ketones (**3**) involves the reaction of the dibromides of α,β-unsaturated ketones with 2 equiv of sodium azide in DMF at room temperature. Although in most cases the reaction proceeds *via* an α-bromovinyl ketone intermediate **2**, the conversion of **2** to the vinyl azide **3** does not involve an SN2-type displacement. A detailed mechanistic study of the reaction, using nmr techniques, reveals that *erythro*-ethylideneacetophenone dibromide (**1a**) reacts mainly through pathway **1** → **2** → **7** → **8** → **3**, whereas *erythro*-benzylideneacetophenone dibromide (**1b**) and *erythro*-benzylideneacetone dibromide (**1c**) react by both pathways: **1** → **2** → **3** and **1** → **2** → **7** → **8** → **3**. Under the same reaction conditions *meso*-1,2-dibenzoylethylene dibromide (**13**) gives the isoxazole (**15**) exclusively. Finally, a trans configuration is assigned to the α-azidovinyl ketones on the basis of stereochemical arguments.

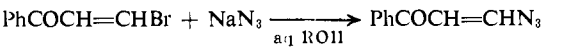
More than 3 decades ago, Kusmin, Friedmann, and Semliansky[2] reported the conversion of dibromo ketone **1** to an azidovinyl ketone and concluded, on the basis of saponification, hydrolysis, and oxidation experiments, that the azido group occupies the α position (*i.e.*, **3**). Since its description in 1935 the reaction **1** → **3** has apparently not been investigated further, although it could constitute an excellent method for the synthesis of α-azidovinyl ketones (**3**).

Our interest in the chemistry of azides, in particular of vinyl azides,[3] led us to an investigation of this synthetic sequence. We were able to show that the conversion **1** → **3** is general and to confirm the α-azidovinyl structure **3** (R = Ph, R′ = Me) by means of nmr (see Discussion).

There are several possible pathways for the transformation **1** → **3**. A likely mechanism involves SN2 displacement of bromide by azide ion, since the α-carbon in **1** is activated by the carbonyl group, followed by elimination of HBr. Alternately HBr elimination from **1** should lead to α-bromovinyl ketone **2**, which may undergo conversion to **3** by various pathways.[4]



Recently, Nesmeyanov and Rybinskaya[5] developed a method for the synthesis of β-azidovinyl ketones (**5**) by treating β-chloro- (or bromo-) vinyl ketones (**4**) with

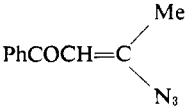


4 **5**

sodium azide. Their studies led them to conclude that this nucleophilic substitution proceeds predominantly with retention of configuration about the C=C bond. This reaction undoubtedly involves conjugate addition of azide ion to the Br-carrying carbon of the α,β-unsaturated ketone. If a similar process were operating on the regioisomeric[6] α-bromovinyl ketone **2**, then addition of N_3^- rather than substitution of Br^- may be expected. These considerations led us to a detailed mechanistic and stereochemical study by nmr of the conversion **1** → **3** and **2** → **3**.

Results and Discussion

By chosing ethylideneacetophenone dibromide **1** (R = Ph, R′ = Me) as a substrate we were able to confirm by nmr that the reaction of sodium azide with the dibromide **1** leads to the formation of an α-azidovinyl ketone **3**. The product **3** (R = Ph, R′ = Me) obtained in *ca.* 90% yield (for an improved general procedure, see Experimental Section) shows a coupling constant J_{MeH} of 7 Hz in its nmr spectrum. The magnitude of this coupling constant is consistent with a structure having both H and Me groups in a geminal position. The regioisomeric azidovinyl ketone **6** should exhibit a coupling constant J_{MeH} between 0 and 2 Hz.



6

We also discovered that the α-azidovinyl ketones (**3**) are readily prepared by treating α-bromovinyl ketones (**2**) with a mixture of 2 equiv of sodium azide and 1 equiv of hydrobromic acid in DMF at room temperature. Furthermore, **2** are intermediates in the conver-

(1) (a) Stereochemistry. LVII. For the previous paper, see A. Hassner and V. R. Fletcher, *Tetrahedron Lett.*, in press; (b) National Science Foundation Undergraduate Research Participant, 1968.

(2) W. A. Kusmin and S. G. Friedmann, *Mem. Inst. Chem. Ukrain. Akad. Sci.*, 2, 55 (1935); *Chem. Abstr.*, 31, 46605 (1937); W. A. Kusmin and N. J. Semliansky, *Mem. Inst. Chem. Ukrain. Akad. Sci.*, 2, 183, 191 (1935); *Chem. Abstr.*, 31, 34671 (1937); *Mem. Inst. Chem. Ukrain. Akad. Sci.*, 3, 61 (1936); *Chem. Abstr.*, 31, 49789 (1937); S. G. Friedmann, *Mem. Inst. Chem. Ukrain. Akad. Sci.*, 3, 587 (1936); *Chem. Abstr.*, 31, 78614 (1937).

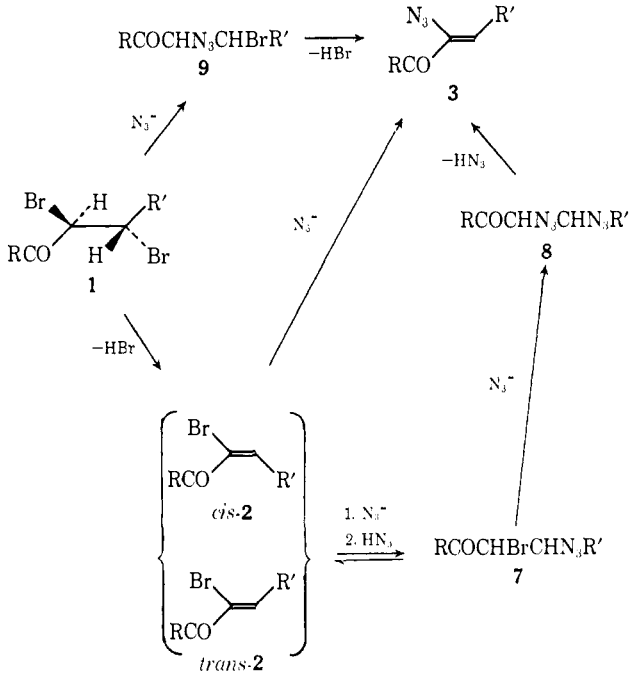
(3) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, 89, 2077 (1967); A. Hassner and F. W. Fowler, *J. Org. Chem.*, 33, 2686 (1968).

(4) For the behavior of amines with α,β-dibromo ketones and with α-bromo-α,β-unsaturated ketones, see N. H. Cromwell, *Chem. Rev.*, 38, 83 (1946).

(5) Review: M. I. Rybinskaya, A. N. Nesmeyanov, and N. K. Kochetkov, *Russ. Chem. Rev.*, 38, 961 (1969).

(6) Regio is used to describe directional preference in bond making or breaking: A. Hassner, *J. Org. Chem.*, 33, 2684 (1968).

Scheme I



a, R = Ph; R' = Me
b, R = Ph; R' = Ph
c. R = Me; R' = Ph

sion of vinyl ketone dibromides **1** into α-azidovinyl ketones **3**. The results obtained with several *erythro*-dibromides **1a–c** point to the general mechanism presented in Scheme I (nmr data are given in Table I), which involves the following three pathways: **1 → 2 → 3**, **1 → 2 → 7 → 8 → 3**, and **1 → 9 → 3**. In order to elucidate the mechanistic and stereochemical aspects, the reaction of **1** with sodium azide was stopped at different stages and the nmr spectra were recorded and analyzed. These studies were carried out with the bromine adducts of *trans*-ethylideneacetophenone (**1a**), *trans*-benzylideneacetophenone (**1b**), and *trans*-benzylideneacetone (**1c**); each system will be considered separately.

***erythro*-Ethylideneacetophenone Dibromide (1a).** This compound was allowed to react with 2 equiv of sodium azide in DMF at room temperature, to furnish α-azidoethylideneacetophenone (**3a**) in 91% yield after a reaction time of 30 min. When the reaction was worked up at different stages of the overall conversion, the nmr spectra showed four intermediates, which are consistent with the structures of the *cis*- and *trans*-vinyl bromides *cis*-**2a** and *trans*-**2a**, the bromoazide **7a**, and the bisazide **8a** (the τ values are listed in Table I). The intensities of the nmr peaks increased at first and then decreased as the reaction progressed. The last intermediate to appear, after *ca.* 4 min when all the other intermediates were still present, was bisazide **8a**.

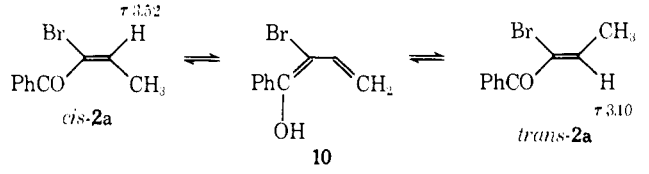
Since the first step in the observed reaction sequence involves elimination of HBr from **1a** by sodium azide, it was important to test the possibility of dehydrobromination with another reagent of similar basicity. Therefore **1a** was treated with sodium acetate under the same reaction conditions and **2a** was isolated in 90% yield. The nmr spectrum, recorded immediately after work-up, showed both isomers in a cis/trans ratio of about 80/20. A trans structure is assigned to the minor product because its vinylic proton is shifted downfield

Table I. Nmr Data (τ Values)[a]

Compd	
1a	1.8–2.1 (m, 2 H), 2.3–2.6 (m, 3 H), 4.55 (d, 1 H, J = 10.5 Hz), 4.95–5.5 (octet, 1 H), 7.95 (d, 3 H, J = 7 Hz)
cis-**2a**	1.9–2.15 (m, 2 H), 2.2–2.7 (m, 3 H), 3.52 (q, 1 H, J = 7.5 Hz), 8.35 (d, 3 H, J = 7.5 Hz)
trans-**2a**	2.2–2.7 (m, 5 H), 3.10 (q, 1 H, J = 6.5 Hz), 7.97 (d, 3 H, J = 6.5 Hz)
7a	1.8–2.1 (m, 2 H), 2.3–2.7 (m, 3 H), 4.88 (d, 1 H, J = 8.0 Hz), 5.5–6.1 (octet, 1 H), 8.65 (d, 3 H, J = 6.5 Hz)
8a	*Ca.* 5.0 (d, 1 H), 5.2–5.5 (m, 1 H), 8.60 (d, 3 H, J = 7 Hz); since this compound has not been isolated in the pure state, the exact position of the phenyl absorption is unknown
9a	1.8–2.1 (m, 2 H), 2.3–2.7 (m, 3 H), 5.02 (d, 1 H, J = 9.0 Hz), 5.5–6.1 (m, 1 H), 8.43 (d, 3 H, J = 6.5 Hz)
3a	2.15–2.7 (m, 5 H), 4.15 (q, 1 H, 7 Hz), 8.12 (d, 3 H, J = 7 Hz)
1b	1.8–2.0 (m, 2 H), 2.3–2.7 (m, 8 H), 4.13 (d, 1 H, J = 11.5 Hz), 4.38 (d, 1 H, J = 11.5 Hz)
cis-**2b**	1.9–2.4 (m, 4 H), 2.45–2.8 (m, 6 H), 2.87 (s, 1 H)
trans-**2b**	2.00–2.25 (m, 2 H), 2.30 (s, 1 H), 2.35–2.7 (m, 3H)
7b	1.8–2.05 (m, 2 H), 2.3–2.7 (m, 3 H), 2.56 (s, 5 H), 4.75 (broad s, 2 H)
3b	2.1–2.3 (m, 4 H), 2.4–2.75 (m, 6 H), 3.53 (s, 1 H)
1c	2.60 (s, 5 H), 4.65 (d, 1 H, J = 11.5 Hz), 5.10 (d, 1 H, J = 11.5 Hz), 7.53 (s, 3 H)
cis-**2c**	2.00 < τ < 2.8 (1 H), 2.70 (s, 5 H), 7.75 (s, 3 H)
trans-**2c**	1.98 (s, 1 H), 2.0–2.3 (m, 2 H), 2.5–2.7 (m, 3 H), 7.42 (s, 3 H)
3c	2.0–2.35 (m, 2 H), 2.5–2.75 (m, 3 H), 3.35 (s, 1 H), 7.58 (s, 3 H)

[a] The nmr spectra were recorded with a Varian A-60-A spectrometer using TMS as an internal standard. The multiplicity is indicated as follows: s = singlet, d = doublet, q = quartet, m = multiplet.

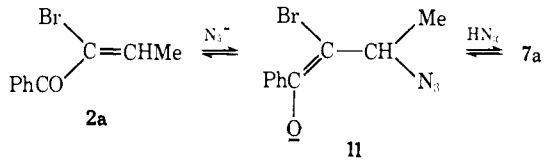
by 0.4 ppm relative to the major product; the deshielding effect of a carbonyl group on the vinylic proton in cis position is well known.[7] In addition, we observed that the *cis*-bromovinyl ketone isomerized quantitatively into the trans form at room temperature within 1 day. This can best be rationalized in terms of a facile formation of an enol **10** in which rotation about the C–C single bond may occur in order to produce the thermodynamically most stable *trans*-**2a**.



When a mixture of *cis*- and *trans*-**2a** or pure *trans*-**2a** was treated with sodium azide in DMF at room temperature, the ir and nmr of the product implied the presence of only a small amount of the α-azidovinyl ketone **3a** together with tar product. This result clearly indicates that a direct substitution of the α-bromovinyl ketone **2a** by sodium azide (pathway **2a → 3a**) occurs only to a very small extent in the overall conversion of **1a** to **3a**. The sequence **1a → 2a → 7a → 8a → 3a** thus constitutes the major pathway followed. From the

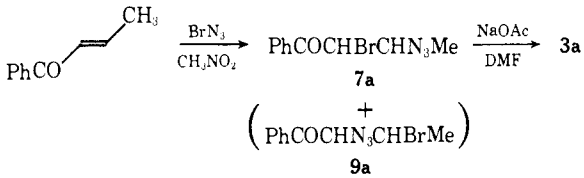
(7) L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2886 (1960); R. R. Fraser, *Can. J. Chem.*, **38**, 549 (1960); R. R. Fraser and D. E. McGreer, *ibid.*, **39**, 505 (1961); J. E. Baldwin, *J. Org. Chem.*, **30**, 2423 (1965); see also D. D. Faulk and A. Fry, *ibid.*, **35**, 364 (1970).

mechanistic point of view, it is interesting to note that the conversion of **2a** into **7a** is not a simple HN_3 addition, since **2a** fails to react with HN_3 in DMF at room temperature. However, when the reaction of the *cis*,*trans*-**2a** mixture or of the pure *trans*-**2a** was carried out with an equimolecular amount of hydrazoic acid and sodium azide, **3a** was isolated in 70–72% yield and the expected intermediates **7a** and **8a** were observed in the nmr spectra, taken as the reaction progressed. These results are logical if one considers the step **2a** → **7a** as a conjugate addition of the azide ion to the β-carbon atom of the vinyl ketone **2a** to give the enolate **11**. The latter can be converted into bromoazide **7a** (presumably as a mixture of erythro and threo isomers) only when a proton source (HN_3) is present. It was further noticed that the *cis*-α-bromovinyl ketone **2a**, because of its higher ground-state energy, reacted faster with NaN_3–HN_3 than its trans isomer.



2a **11**

Since it was not possible to isolate intermediate **7a** from the reaction **2** → **7** → **8** → **3**, an independent synthesis was sought. Addition of bromine azide to *trans*-ethylideneacetophenone is expected to lead chiefly to **7a**, by analogy with XN_3 additions to chalcone.[3,8] The reaction was carried out in nitromethane in the presence of sulfuric acid and led among other minor products (such as **2a**), mainly to two BrN_3 adducts, which could not be separated but were analyzed as a mixture. These are either an erythro–threo mixture of **7a** or a mixture of **7a** and **9a**. The nmr spectrum of the isomer mixture



shows the proton α to the carbonyl as doublets at τ 4.88 and 5.02, respectively, and the methyl absorption as doublets at τ 8.65 and 8.43.[9] Interestingly, the mixture of bromoazides was converted into **3a** on treatment with an excess of sodium acetate in DMF at room temperature. Elimination of HBr from **9a** could produce **3a** directly. The conversion of β-azido ketone **7a** to the α-azidovinyl ketone **3a** is noteworthy and apparently proceeds *via* **8a** by the action of small amounts of N_3^-. Elimination of HN_3 from **7a** and from **8a** under the basic conditions provides the source of the necessary azide ions.

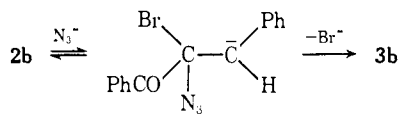
Compound **8a** cannot be prepared independently, but its nmr τ values (see Table I), especially the CH_3 chemical shift at τ 8.60, correlate well with the other structures: **1a** (τ 7.95), **7a** (τ 8.65), and **9a** (τ 8.43) (the N_3 group causes less deshielding of the methyl protons than the Br group).

Since step **7a** → **8a**, displacement of an α-halo ketone with azide ions, is essentially the same as **1a** → **9a**, the possible occurrence of pathway **1a** → **9a** → **3a** was checked. We found some evidence that this reaction may account for somewhat less than 10% of **3a**. For instance, we observed that **3a** appeared faster in the reaction of **1a** with sodium azide (after 40 sec) than in the reaction of **2a** with NaN_3–HN_3 (after 1 min). Hence, the formation of **3a** in the very early stage of the reaction with the dibromide **1a** can be attributed to pathway **1a** → **9a** → **3a**. The dehydrobromination reaction, **9a** → **3a**, is considered to be faster than the N_3^- displacement, **1a** → **9a**, because **9a** was never observed in the nmr spectra during reaction.

erythro-**Benzylideneacetophenone Dibromide (1b).** When **1b** was treated with 2 equiv of sodium azide in DMF at room temperature for 5 hr, α-azidochalcone **3b** was obtained in 87–91% yield. The nmr spectra, recorded at different reaction times, implied the presence of at least two intermediates: *cis*-**2b** and **7b**.

cis-α-Bromochalcone (*cis*-**2b**) resulted from antidehydrobromination of **1b** by sodium azide, and its maximum concentration (*ca.* 70%) was observed after a reaction time of 20 min. Likewise, the reaction of **1b** with sodium acetate in DMF at room temperature led stereospecifically to pure *cis*-**2b** in 90–92% yield.[10] This *cis*-vinyl bromide was partly isomerized into the trans form by heating (under nitrogen) at 160° or by warming a chloroform solution in the presence of iodine. As expected, *trans*-**2b** exhibited a vinylic proton absorption at lower field than *cis*-**2b**.

Unlike **2a**, treatment of **2b** with sodium azide in DMF at room temperature for 5 hr led to **3b** in nearly quantitative yield. This result strongly supports a substitution mechanism on **2b** by azide ion proceeding *via* intermediate **12** in which the negative charge is stabilized by the phenyl group. Since β-bromostyrene did



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not react at all with sodium azide under the same reaction conditions, we concluded that the presence of both an activating group in the α position and a carbanion-stabilizing group in the β position is required for the direct conversion of vinyl bromides to vinyl azides.

Although hydrazoic acid did not react with **2b**, it catalyzed the reaction of **2b** with sodium azide. Under these acid-catalyzed conditions, the appearance and disappearance of the absorption at τ 4.75 (reported for **7b**)[8] were observed. The data indicate that two pathways, **1b** → **2b** → **12** → **3b** and **1b** → **2b** → **7b** → **8b** → **3b**, are operating at the same time.

erythro-**Benzylideneacetone Dibromide (1c).** This bromide reacted with 2 equiv of sodium azide according to pathways **1c** → **2c** → **3c** and **1c** → **2c** → **7c** + **8c** → **3c**.

(8) A. Hassner and F. Boerwinkle, *J. Amer. Chem. Soc.*, 90, 216 (1968).

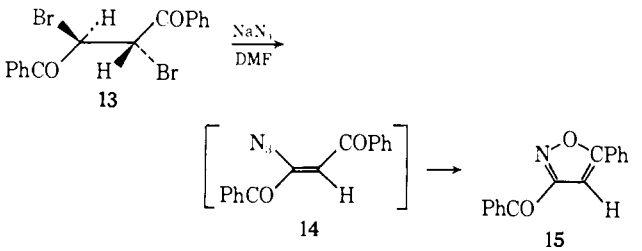
(9) Our preference for assigning the regioisomeric structures **7a** and **9a** to the BrN_3 adducts of this reaction (as well as to the analogous IN_3 adducts) is based on a comparison of the nmr spectra of the adducts with those of the *erythro*- and *threo*-dibromides of the same unsaturated ketone. A detailed description of this phenomenon, as well as a mechanistic rationalization, is being published elsewhere (A. Hassner and G. L'abbé, *J. Org. Chem.*, **36**, 258 (1971)).

(10) Previously, the dehydrobromination of **1b** with potassium acetate was carried out in refluxing ethanol and led to **2b** in a cis/trans ratio of 34/66: R. E. Lutz, D. F. Hinkley, and R. H. Jordan, *J. Amer. Chem. Soc.*, 73, 4647 (1951).

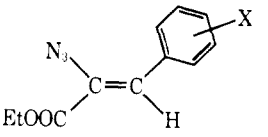
cis-**2c** was formed in the early stage of the reaction (within 5 min) but isomerized completely into *trans*-**2c** before any further reaction occurred. Thus, after 15 min, the nmr showed a clean spectrum of pure *trans*-**2c**. Within 24 hr *trans*-**2c** was then converted into **3c** (isolated in 86% yield). α-Bromobenzylideneacetone (**2c**) was prepared independently in a cis/trans ratio of 60/40 by the reaction of **1c** with sodium acetate in DMF. In order to differentiate between the nmr absorptions of both geometrical isomers the mixture was isomerized into the most stable *trans*-**2c** under the influence of iodine at 60°, in which case the *cis*-$COCH_3$ absorption disappeared from the nmr spectrum.

The vinyl bromide **2c** was only partly (60%) transformed into **3c** when treated with sodium azide in DMF for 1 day, whereas complete conversion occurred when additional hydrazoic acid was present (and no conversion at all when **2c** was treated with hydrazoic acid alone in DMF). These results substantiate both pathways given above. Furthermore, the isolation of *trans*-**2c** in the pure state after 15 min eliminates the possibility of occurrence of pathway **1c** → **9c** → **3c**.

Stereochemistry of the Vinyl Azides 3a–c. A last, but important point to be stressed is the geometrical configuration of the vinyl azide products **3**. Since both *cis*- and *trans*-α-bromovinyl ketones (**2**) were converted into the same α-azidovinyl ketone (**3**), the latter is assumed to exist in its thermodynamically most stable trans configuration. In addition, all attempts to isomerize **3** under conditions where *cis*-**2** was easily isomerized into *trans*-**2**, failed. For instance, *cis*-**2b** isomerized readily in chloroform solution in the presence of iodine at 60°, whereas **3b** remained unaffected. Last but not least, we observed that *meso*-1,2-dibenzoylethylene dibromide (**13**), when allowed to react with 2 equiv of sodium azide, afforded 3-benzoyl-5-phenylisoxazole (**15**) in high yield. The formation of this product is regarded as the result of decomposition of vinyl azide **14**, which has both the α-azido- and β-carbonyl groups in a cis configuration. This conclusion is in agreement with the findings of Nesmeyanov and Rybinskaya[5] that *trans*-**5** can be isolated in pure state whereas *cis*-**5** is unstable and gives the corresponding isoxazole.



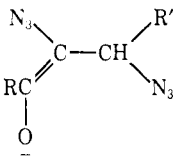
Recently, Hemetsberger, Knittel, and Weidmann[11] claimed that a vinylic azido group deshields the ortho protons of a phenyl substituent in the cis position (*e.g.* **16**), whereas a carbonyl group has no effect. On the basis of this argument they attributed a trans structure to the α-azidovinyl esters **16**, obtained by condensation of azidoacetic ester with substituted benzaldehydes in the presence of base. Although our α-azidovinyl ketones **3b** and **3c** showed the predicted deshielding effect in their nmr spectra, we challenge the value of this



16

criterion because the deshielding phenomenon was also observed for *cis*-**2b**, *trans*-**2b**, and *trans*-**2c** (see Table I).

In our discussion we assumed that both *erythro*- and *threo*-**8** are formed in the reaction. We must now establish how both stereoisomers are converted into only one vinyl azide. Since N_3^- is a poorer leaving group than Br^-, it is very likely that an elimination *via* **17** is favored



17

over a concerted anti elimination in step **8** → **3**. The formation of the enolate **17** is accompanied by the disappearance of distinctive epimeric configurations and hence, elimination of N_3^- from this intermediate would give the most stable *trans*-vinyl azide **3**. The same applies for the formation of **3b** from **2b** *via* **12**, as already discussed above.

Experimental Section

The starting materials **1a–c** were prepared by treating the respective *trans*-α,β-unsaturated ketones with bromine in carbon tetrachloride.[12]

Procedures for the Synthesis of α-Azidovinyl Ketones 3a–c. A. From Dibromides 1a–c. The dibromide (0.1 mol) and 0.22 mol of sodium azide were stirred in 200 ml of DMF (dried over molecular sieves, Type 4A) at room temperature for the appropriate reaction time (1 hr for **1a**, 5 hr for **1b**, and 24 hr for **1c**). The solution was then poured into a mixture of water–ether, and the ether layer washed several times with water and dried ($MgSO_4$). After removing the ether under vacuum, the α-azidovinyl ketones **3a–c** (ir 2120 cm^{-1}) were obtained in a pure state (checked by nmr).

α-Azidoethylideneacetophenone (3a) was obtained as a yellow liquid in 91% yield and was further purified by column chromatography on aluminum oxide with petroleum ether (bp 40–60°) as the eluent. It solidified on cooling, mp 28–30°.

Anal. Calcd for $C_{10}H_9N_3O$ (187): C, 64.16; H, 4.85. Found: C, 64.25; H, 4.91.

α-Azidochalcone (3b) was obtained in 87–91% yield and was recrystallized from petroleum ether, mp 63.5–64°.

Anal. Calcd $C_{10}H_{11}N_3O$ (249): C, 72.29; H 4.42. Found: C, 72.32; H, 4.41.

α-Azidobenzylideneacetone (3c) was obtained in 86% yield and was recrystallized from petroleum ether, mp 79.5–80.0.

Anal. Calcd for $C_{10}H_9N_3O$ (187): C, 64.16; H, 4.85. Found: C, 64.20; H, 4.96.

B. From Vinyl Bromides 2a–c. Sodium azide (0.044 mol) was allowed to react with 0.02 mol of hydrobromic acid (48%) in 50 ml of DMF at room temperature for 10 min. Then 0.02 mol of **2a–c** was added and the reaction was stirred for the appropriate time (0.5 hr for **2a**, 5 hr for **2b**, and 24 hr for **2c**). The solutions were worked up in the manner described under A to give 72% **3a**, 80% **3b**, and 88% **3c**.

In order to achieve complete conversion, a 10% excess of sodium azide was used in the preparative procedures. This 10% excess was omitted in the mechanistic studies which were carried out with 0.2 *M* solutions of **1** and **2**. At several time intervals, a 10-ml

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sample was worked up in the usual manner and the nmr spectra were recorded in $CDCl_3$.

Attempted Reactions of 2a–c with Hydrazoic Acid. Sodium azide (0.02 mol) was allowed to react with a slight excess of hydrobromic acid in 50 ml of DMF at room temperature for 10 min. Then 0.02 mol of **2a–c** was added and the mixture was stirred for the same time as given in procedure B. The nmr spectra, after work-up, indicated no reaction. The α-bromovinyl ketones **2a–c** were recovered in 76–86% yield.

Dehydrobromination of 1a–c. Dibromides **1a–c** (0.1 mmol) and 0.2 mol of sodium acetate were stirred in 200 ml of dry DMF at room temperature for the appropriate reaction time (0.5 hr for **1a**, 5 hr for **1b**, and 1 hr for **1c**). After work-up the following yields were obtained: 90% **2a** in a cis/trans ratio of 80/20, 90–92% *cis*-**2b**, and 89% **2c** in a cis/trans ratio of 60/40.

Cis–trans Isomerization of Vinyl Bromides 2. *cis*-α-Bromoethylideneacetophenone (**2a**) isomerized spontaneously and quantitatively into *trans*-**2a** (mp 66.5–67.0°, petroleum ether) within 1 day upon standing at room temperature. When *cis*-α-bromochalcone (**2b**) was heated under nitrogen at *ca.* 160° for 1 hr, the nmr spectrum showed a large decrease of the τ 2.87 absorption relative to the aromatic multiplet indicating a cis/trans ratio of about 30/70. This reaction mixture was allowed to crystallize from *n*-hexane at low temperature, and yielded *trans*-**2b** as a pale yellow crystalline product, mp 38–39° (lit.[10] mp 42°).

Anal. Calcd for $C_{15}H_{11}OBr$ (387): C, 62.74; H, 3.86. Found: C, 62.95; H, 3.92.

Isomerization also occurred to an extent of 40% cis/60% trans when a chloroform solution of *cis*-**2b**, containing some iodine, was warmed at 60° for 1 day.

Similarly, a chloroform solution of α-bromobenzylideneacetone (**2c**) (cis/trans = 60/40), with trace amounts of iodine, isomerized completely to *trans*-**2c** at 60° within 4 hr.

Reaction of *trans*-Ethylideneacetophenone with Bromine Azide. Bromine azide (0.1 mol) in 200 ml of methylene chloride[8] was added to 200 ml of nitromethane containing 6 g of 30% fuming sulfuric acid at 0°. This solution was poured into 300 ml of nitromethane containing 0.04 mol of *trans*-ethylideneacetophenone and the mixture was allowed to stand for 2 hr at room temperature. Usual work-up gave 10.4 g of a brown oil which was chromatographed on silica gel with petroleum ether–benzene as the eluent. One of the fractions (2.0 g) was a pure mixture of the regioisomers **7a** and **9a**.

Anal. Calcd for $C_{10}H_{10}BrN_3O$ (268): C, 44.77; H, 3.73; Br, 29.85; N, 15.67. Found: C, 44.71; H, 3.89; Br, 30.06; N, 15.49.

3-Benzoyl-5-phenylisoxazole (15). A mixture of 39.6 g of *meso*-1,2-dibenzoylethylene dibromide (**13**) and 0.22 mol of sodium azide (14.3 g) was stirred in 500 ml of dry DMF at room temperature. The reaction was exothermic and nitrogen evolved. After 3 hr, the mixture was worked up with water–ether and the isoxazole was obtained in *ca.* 90% yield. It was recrystallized from 500 ml of ethanol (yield 61%): mp 86–87° (lit.[13] mp 89–90°); nmr ($CDCl_3$) τ 1.5–2.8 (m, 10 H), 2.98 (s, 1 H).

Anal. Calcd for $C_{16}H_{11}NO_2$ (249): C, 77.09; H, 4.45. Found: C, 77.21; H, 4.35.

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Base-Catalyzed β-Elimination Reactions in Aqueous Solution. V. Elimination from 4-(*p*-Substituted-phenoxy)-2-butanones[1]

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Abstract: Reactions of 4-(*p*-X-phenoxy)-2-butanones (X = CH_3O, CH_3, H, Cl, and CN) in aqueous solution to give 3-buten-2-one and para-substituted phenols are general base catalyzed by tertiary amines. Saturation kinetics observed at high amine buffer concentrations provide kinetic evidence for the E1cB mechanism wherein partitioning of the enolate anion is kinetically important. Relative to $\rho' = 1$ for the ionizations of para-substituted phenols, $\rho' = 0.066 \pm 0.002$ for formations of enolates, and $\rho' = 0.67 \pm 0.08$ for the decompositions of the enolates to products in 2-dimethylaminoethanol buffers.

The β eliminations of para-substituted benzoates from 4-(*p*-substituted-benzoyloxy)-2-butanones are general base catalyzed and are virtually insensitive to the nature of the para substituent;[2] β elimination of methanol from 4-methoxy-2-butanone is specific base catalyzed and the rate of general base catalyzed α-methylene proton exchange in D_2O is faster than the rate of elimination.[3] Although a case can be made for alternative mechanisms, the E1cB mechanism of eq 1

$$SH \underset{k_2(BH^+)}{\overset{k_1(B)}{\rightleftharpoons}} S^- \xrightarrow{k_3} \text{products} \qquad (1)$$

unifies these results. Thus for SH possessing good leaving groups, $k_3 > k_2(BH^+)$ and k_1 is rate determining; for SH possessing poor leaving groups, $k_2(BH^+) > k_3$ and k_3 is rate determining. If the above reactions do indeed proceed *via* the E1cB mechanism, then for SH possessing leaving groups with pK values intermediate between carboxylic acids (pK = 4) and methanol (pK = 16) partitioning of the intermediate S^- could be kinetically significant and experimentally detectable.[4] For this condition the mechanism of eq 1 predicts that the rate of elimination be first order with respect to B ($B \neq OH^-$) at low base concentrations and zero order with respect to B at high base concentrations. The base-catalyzed

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