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# DIHYDRO AZOLES AND FREE RADICALS. Part I. 1-ARYL-4-METHYLENE-5-MORPHOLINO-v-TRIAZOLINES AND HALOMETHYL RADICALS: FRAGMENTATION OF TRIAZOLINIC RADICAL SIGMA COMPLEXES.

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Abstract - 1-Aryl-4-methylene-5-morpholino-v-triazolines 1 were reacted with halomethyl radicals generated by reaction of halomethanes 2 with benzoyl peroxide or copper(I)chloride. In the former case the corresponding 1-aryl-4-trihaloethyl—v-triazoles 3 and 1-aryl-4-halomethyl-v-triazoles 4 were formed. In the second case the corresponding 1-aryl-4-trihaloethyl-5-morpholino v-triazoles 5 accompanied by triazoles 4 were obtained. Reaction mechanisms are discussed.

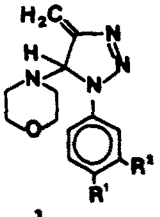
The readily accessible 1-aryl-4-methylene-4,5-dihydro-5-morpholino-v-triazoles 1[1] have been shown to react with nucleophiles through addition or addition-elimination processes producing v-triazolines or v-triazole derivatives, respectively.[2,3] Much work has been done also on their reactivity in cycloaddition reactions.[4]

Recently we reported an $^1$H-NMR study evidencing the electronic features of the exocyclic double bond of substrates 1.[5]

As a part of our research program on v-triazolines and owing to our interest in radical chemistry we have now studied the reaction of substrates 1 with halomethyl radicals.

## RESULTS

The reaction of 1a-e with halomethanes 2a-d was performed by heating the v-triazolines in excess halomethane,acting both as reactant and solvent, in presence of an equimolar amount of purified benzoyl peroxide.



**1**

| | $R^1$ | $R^2$ |
|---|---|---|
| 1a | H | $CF_3$ |
| b | $NO_2$ | H |
| c | COOEt | H |
| d | Me | H |
| e | Cl | H |
| f | H | $NO_2$ |

$Y-CX_3$

**2**

| | Y | X |
|---|---|---|
| 2a | Cl | Cl |
| b | H | Br |
| c | H | Cl |
| d | Br | Cl |
| e | Br | Br |

The reaction mixture was refluxed for 2.5-5 h. When carbon tetrachloride 2a and bromotrichloromethane 2d were used a mixture of products 3 and 4 (3a,4a; 3a,4b; 3c, 4c; 3e,4d respectively) was obtained. Starting with chloroform 2c and bromoform 2b a single product, i.e. 3a,b,d,f-h, was formed. In all cases the reaction products were separated and /or purified by column chromatography. Both compounds 3 and 4 were readily identified by their analytical data and by their $^1$H-NMR spectra, showing a typical singlet in the δ 4.0-5.0 region which is associated with the $CH_2$ group.

Table 1 - Reactional data for products 3 and 4

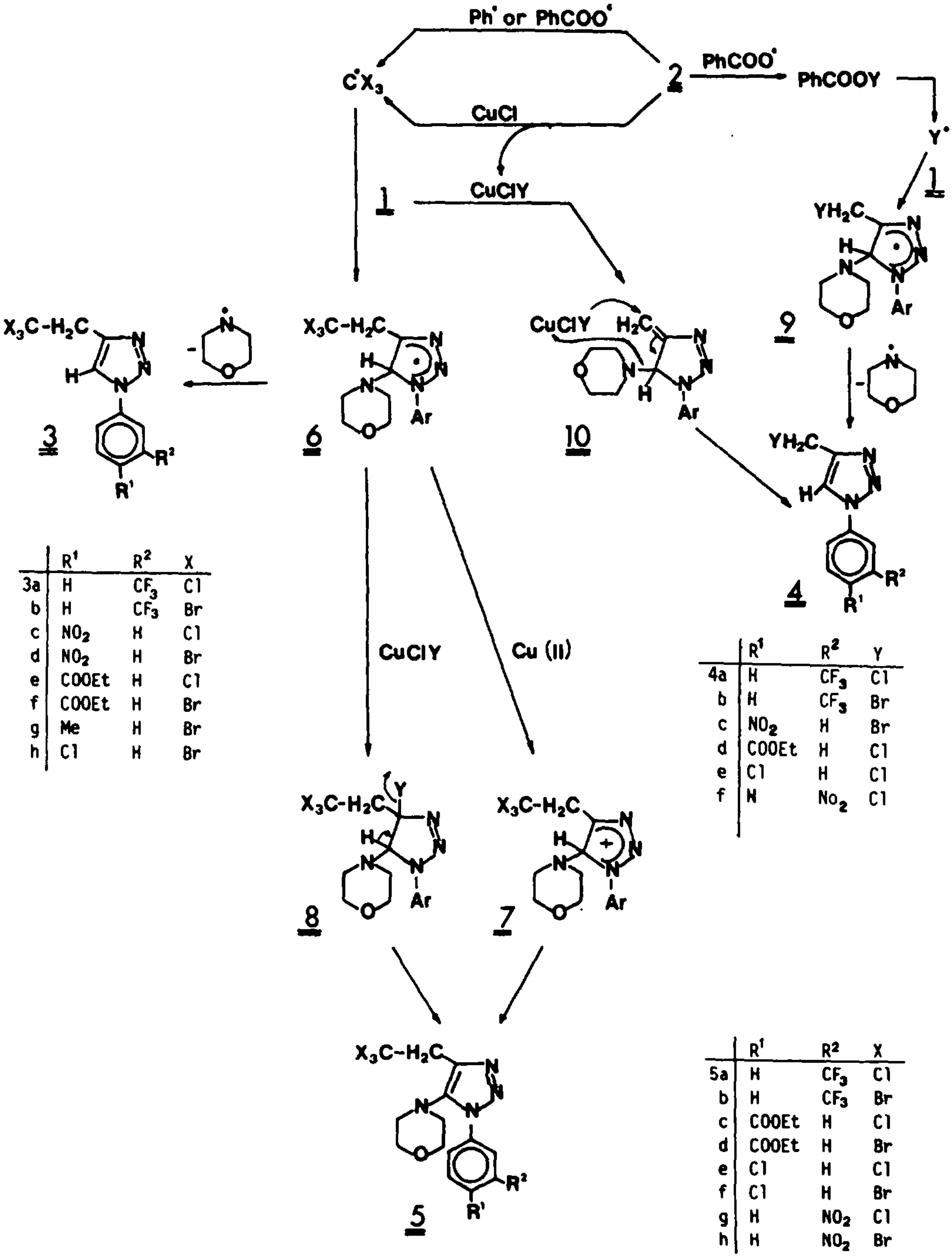
| Starting compound | Reactant | Products | | | |
|---|---|---|---|---|---|
| | | 3 | Yield % | 4 | Yield % |
| 1a | 2a | 3a | 31 | 4a | 4 |
| 1a | 2b | 3b | 62 | — | — |
| 1a | 2c | 3a | 33 | - | - |
| 1a | 2d | 3a | 26 | 4b | 4 |
| 1b | 2d | 3c | 27 | 4c | 5 |
| 1b | 2b | 3d | 61 | — | — |
| 1c | 2a | 3e | 35 | 4d | 5 |
| 1c | 2b | 3f | 58 | — | — |
| 1d | 2b | 3g | 51 | — | — |
| 1e | 2b | 3h | 55 | — | — |

Table 2 - Reactional data for products 4 and 5

| Starting compound | Reactant | Products | | | |
|---|---|---|---|---|---|
| | | 4 | Yield % | 5 | Yield % |
| 1a | 2a | 4a | 13 | 5a | 37 |
| 1a | 2e | 4b | 15 | 5b | 22 |
| 1c | 2a | 4d | 37 | 5c | 30 |
| 1c | 2e | 4d | 21 | 5d | 15 |
| 1e | 2a | 4e | 30 | 5e | 25 |
| 1e | 2e | 4e | 20 | 5f | 18 |
| 1f | 2a | 4f | 43 | 5g | 18 |
| 1f | 2e | 4f | 34 | 5h | 20 |

H-5 gives rise to a singlet in the expected range of δ 8-8.5.[6] Moderate to fair yields of products 3 were obtained. Instead, when present, by products 4 were formed in 3-5% yield only. In all cases the starting triazoline 1 reacted completely and some tarry material was found. No other definite products were present.
The yields of products 3 and 4 are listed in Table 1. Physical, analytical and spectroscopical data of 3 and 4 are collected in Table 3.

The course of the radical reaction of substrates 1 was also studied with CuCl as radical generator. Carbon tetrachloride 2a and carbon tetrabromide 2e were reacted with 1a,c,e,f, in presence of CuCl. In the former case the reaction was performed at the refluxing temperature by using a large excess of 2a as reactant and solvent. In the second case both reactants 1 and 2e in a 1:2 ratio were dissolved in carbon tetrachloride and the reaction mixture was heated to reflux.The CuCl radical generator was used in a 2.5:1 ratio with respect to 1. A mixture of triazoles 4 and 5 was formed in any case. The yields of the products,which were separated and purified by column chromatography,are listed in Table 2. Compounds 5 were easily identified by their analytical and $^1$H-NMR spectra showing a singlet in the $\delta$ 4.0-5.0 region which is associated with the $CH_2$ group and is in good agreement with the corresponding signals in products 3 and the multiplets centered at about $\delta$ 3.1-3.2 and $\delta$ 3.6-3.7



| | R$^1$ | R$^2$ | X |
|---|---|---|---|
| 3a | H | $CF_3$ | Cl |
| b | H | $CF_3$ | Br |
| c | $NO_2$ | H | Cl |
| d | $NO_2$ | H | Br |
| e | COOEt | H | Cl |
| f | COOEt | H | Br |
| g | Me | H | Br |
| h | Cl | H | Br |

| | R$^1$ | R$^2$ | Y |
|---|---|---|---|
| 4a | H | $CF_3$ | Cl |
| b | H | $CF_3$ | Br |
| c | $NO_2$ | H | Br |
| d | COOEt | H | Cl |
| e | Cl | H | Cl |
| f | N | $No_2$ | Cl |

| | R$^1$ | R$^2$ | X |
|---|---|---|---|
| 5a | H | $CF_3$ | Cl |
| b | H | $CF_3$ | Br |
| c | COOEt | H | Cl |
| d | COOEt | H | Br |
| e | Cl | H | Cl |
| f | Cl | H | Br |
| g | H | $NO_2$ | Cl |
| h | H | $NO_2$ | Br |

typical of the morpholino substituent. In Table 3 physical, analytical and spectroscopical data for compounds 5 are listed.

## DISCUSSION

According to the foregoing results it is established that the exocyclic double bond of compounds 1 shows a good reactivity with halomethyl radicals, the reaction being normally completed within about four hours. No starting compound was recovered even when relatively low yields of products were obtained. This is to be ascribed to the thermal unstability of substrates 1 and, perhaps to a greater extent, to the presence of competing side reactions which, however, do not produce definite compounds.

By considering that three kinds of products can be formed and that products 5 are obtained only when copper(II) ions are present, the following mechanistic picture arises. As shown in the Scheme the $^{\cdot}CX_3$ radical produced from 2 and benzoyl peroxide attacks compounds 1 producing the radical intermediate 6 which has the feature of a radical σ complex. According to this, it looses a morpholinyl radical to give the aromatic triazole product 3. Similarly and concurrently, a $Y^{\cdot}$ radical, produced by interaction of $PhCOO^{\cdot}$ and 2, adds to 1 yielding the σ complex 9 which in turn eliminates a morpholinyl radical forming 9. It is known[7] that radical σ complexes show a trend to eliminate a radical species and form aromatic products.

In the present case the σ complex is not formed, as usually, through radical addition to an aromatic compound but by addition to an alkene structure. On the whole the reaction corresponds to a radical addition followed by fragmentation of a β-aminoalkyl radical. Under this point of view this fragmentation should not be expected as the more favourable process, being known that alkene substrates prefer to give, with halomethanes, addition reactions.[8] In fact such processes, when the leaving group is an amino one, are not precedented to our knowledge. Cases of substitution of amino groups on aromatic systems through σ intermediates, formed by radical attack, are equally unknown. However, in the case of substrates 1, the formation of σ complex is made possible by the fact that the starting material has not aromatic character and hence is readily attacked by radicals. While it is expected that the trend to eliminate an amino radical is not great, here the observed trend should be explained by the energy gain of the system through the aromatization. Unfortunately, all attempts to trap the morpholinyl radical failed till now.

When copper(I)chloride is used the attacking radical is produced by abstraction of the Y atom from 2 and Cu(II) is formed. Two mechanisms, both acquainting for the formation of 5, are possible. According to the former, the intermediate 6 undergoes a ligand-transfer oxidation producing triazoline 8 from which hydrogen chloride is eliminated, with the intramolecular assistance of the basic substituent at C-5. Another possibility is the electron-transfer oxidation of 6 which affords the cationic σ complex 7 which is deprotonated to 5.[9]

While both mechanisms could be acceptable, the latter is preferred both because compound 8 was not isolated and is not expected to be exceedingly labile and because, in this case, the electron-transfer oxidation produces a stabilized cationic species.

The formation of 4 in presence of copper ions occurs in relatively high amount but is not accompanied by the formation of the corresponding 4-halomethyl-5-morpholino-v-triazole which should be formed by reaction of 9 with a cupric species. This points out that its formation mechanism should be different. As shown in the Scheme, a possibility is offered by ionic halogen-transfer to the $CH_2$ group from $CuX_2$ which is assisted by binding of the morpholino leaving group to the copper atom and aromatization of the triazole ring.[10] This hypothesis is strongly supported by the very quick reaction of 1 with $CuCl_2$ in acetonitrile affording high yields of 4. This process represents an unavoidable side reaction which lowers the yield of products 5.

Table 3 - Physical, analytical and spectroscopical data for products 3, 4 and 5

| | | $^1$H-NMR [b] | | | Analysis [c] | | |
|---|---|---|---|---|---|---|---|
| Products | m.p. [°C] [a] | $\delta$ $CH_2$ | $\delta$ $H_5$ | $\delta$ morpholino | C | H | N |
| 3a | 105-107 | 4.25 | 8.25 | - | 38.45<br>(38.35) | 2.0<br>(2.05) | 12.15<br>(12.2 ) |
| 3b | 112-113 | 4.65 | 8.30 | - | 27.85<br>(27.65) | 1.6<br>(1.5 ) | 8.75<br>( 8.8 ) |
| 3c | 170-172 | 4.30 | 8.25 | - | 37.65<br>(37.35) | 2.15<br>(2.2 ) | 17.65<br>(17.4 ) |
| 3d | 200-205 dec | 4.70 | 9.25 | - | 26.55<br>(26.4 ) | 1.6<br>(1.55) | 12.3<br>(12.3 ) |
| 3e | 117-118 | 4.30 | 8.29 | - | 45.05<br>(44.8 ) | 3.45<br>(3.45) | 11.9<br>(12.05) |
| 3f | 133-134 | 4.75 | 8.15 | - | 32.45<br>(32.4 ) | 2.6<br>(2.5 ) | 8.5<br>( 8.5 ) |
| 3g | 163-165 | 4.60 | 8.20 | - | 31.45<br>(31.15) | 2.4<br>(2.4 ) | 10.0<br>( 9.9 ) |
| 3h | 156-158 | 4.65 | 8.25 | - | 26.85<br>(27.0 ) | 1.7<br>(1.6 ) | 9.25<br>( 9.45) |
| 4a | 74-76 | 4.80 | 8.25 | - | 45.5<br>(45.9 ) | 2.65<br>(2.7 ) | 16.05<br>(16.05) |
| 4b | 77-78 | 4.65 | 8.15 | - | 39.65<br>(39.2 ) | 2.45<br>(2.3 ) | 13.9<br>(13.7 ) |
| 4c | 152-154 | 4.65 | 9.30 | - | 38.15<br>(38.2 ) | 2.6<br>(2.5 ) | 19.8<br>(19.6 ) |
| 4d | 113-114 | 4.80 | 8.15 | - | 53.95<br>(54.25) | 4.4<br>(4.55) | 15.65<br>(15.8 ) |
| 4e | 134-135 | 4.80 | 8.15 | - | 47.3<br>(47.4 ) | 3.1<br>(3.1 ) | 18.2<br>(18.4 ) |
| 4f | 100-102 | 4.80 | 8.25 | - | 45.25<br>(45.3 ) | 2.90<br>(2.95) | 23.5<br>(23.5 ) |
| 5a | 116-117 | 4.25 | - | 3.15-3.70 | 41.85<br>(41.9 ) | 3.1<br>(3.2 ) | 13.0<br>(13.0 ) |
| 5b | 130-131 | 4.60 | - | 3.20-3.75 | 32.2<br>(31.9 ) | 2.65<br>(2.5 ) | 10.15<br>( 9.95) |
| 5c | 149-150 | 4.25 | - | 3.15-3.70 | 47.0<br>(47.05) | 4.3<br>(4.4 ) | 13.0<br>(13.0 ) |
| 5d | 158-160 | 4.60 | - | 3.15-3.70 | 36.25<br>(36.0 ) | 3.55<br>(3.4 ) | 9.8<br>( 9.9 ) |
| 5e | 153-155 | 4.25 | - | 3.15-3.70 | 42.35<br>(42.4 ) | 3.5<br>(3.55) | 14.10<br>(14.15) |
| 5f | 172-174 | 4.60 | - | 3.15-3.75 | 31.6<br>(31.75) | 2.6<br>(2.65) | 10.7<br>(10.6 ) |
| 5g | 187-188 | 4.25 | - | 3.10-3.70 | 41.15<br>(41.35) | 3.50<br>(3.45) | 17.05<br>(17.2 ) |
| 5h | 183-184 | 4.60 | - | 3.20-3.75 | 31.45<br>(31.15) | 3.0<br>(2.6 ) | 13.25<br>(13.0 ) |

[a] All compounds crystallized from $CH_2Cl_2$/n-pentane.

[b] All spectra in $CDCl_3$ except 3d (DMSO). Other signals were found in expected ranges.

[c] Required values in brackets.

## EXPERIMENTAL

Melting points are uncorrected and were taken on a Tottoli instrument. $^1$H-NMR spectra were recorded on a Varian EM 390 spectrometer, chemical shifts being given in ppm from $Me_4Si$. Ready-touse silica gel plates were employed for TLC.

*Materials* - Benzoyl peroxide was purchased and purified by dissolving in chloroform and reprecipitating with methanol. Copper(I)chloride was freshly prepared before each reaction. 5-Morpholino-4-methylene-v-triazolines **1a,b,c,d,e** have been described previously (**1a**[4], **1b**[1], **1c-e**[5]). Compound **1f** was prepared by analogous procedure (m.p. 118-120°C dec.).

*Reactions of **1a-e** with $CX_3Y$ and benzoyl peroxide* - The triazoline reactant **1** (3.3 mmol) was dissolved or suspended in the solvent reactant **2** (10 ml) and the solution was brought to reflux. Then, benzoyl peroxide (3.3 mmol) was added in one portion and refluxing was continued until disappearance of benzoyl peroxide (TLC benzene/ethyl acetate 4:1) (about 3-5 h). The reaction mixture was cooled and basified by adding an aqueous solution of sodium hydrogen carbonate. The organic layer was separated, washed twice with water and dried over sodium sulphate. After evaporation the residue was chromatographed on a silica gel column with cyclohexane/ethyl acetate (4:1). Yields and physical data for the isolated products are listed in Tables 1 and 3.

*Reactions of **1a,c,e,f** with copper(I)chloride and $CCl_4$* - The triazoline reactant **1** (3.3 mmol) was dissolved or suspended in carbon tetrachloride (10 ml) and the mixture was heated at 70°C. Freshly prepared copper(I)chloride (8.25 mmol) was added and the reaction mixture was stirred at the same temperature for four hours. Silica gel for chromatography (1.5 g) was added and the mixture was evaporated at reduced pressure. The residue was charged on a silica gel column and chromatographed with ethyl acetate/cyclohexane (1:9). Yields and physical data for the products are listed in Tables 2 and 3.

*Reactions of **1a,c,e,f** with copper(I)chloride and $CBr_4$* - The triazoline reactant **1** (3.3 mmol) was dissolved or suspended in a solution of $CBr_4$ (6.6 mmol) in $CCl_4$ (10 ml). After heating at 70°C freshly prepared copper(I)chloride (8.25 mmol) was added. The reaction was performed and elaborated as described above for $CCl_4$ alone. Yields and physical data for the products are listed in Tables 2 and 3.

*Reaction of **1a** with copper(II)chloride* - The triazoline **1a** (1 mmol) was dissolved in acetonitrile (5 ml) and solid copper(II)chloride (1 mmol) was added. After stirring for 5 min the reaction mixture was charged on a silica gel column and chromatographed with cyclohexane/ethyl acetate (4:1) yielding pure **4a**.

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[10] Bromo derivatives were formed in lower yield with respect to chloro compounds preventing their isolation in many cases.