SILVER CARBONATE PROMOTED REACTION OF HYDRAZONYL CHLORIDES WITH ALLYLIC ALCOHOLS

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Abstract - The title reaction affords two main kinds of products: (i) pyrazole derivatives due to cycloaddition of a nitrile imine intermediate to the ethylenic bond; (ii) open-chain carbonyl compounds due to the electrophilic attack of a nitrilium-like carbocation to the ethylenic bond. Mechanistic possibilities are discussed.

Nitrile imines[1] are familiar to a large number of chemists interested in heterocyclic synthesis. The intermediacy of these labile species was first envisaged by Fusco and Romani[2] and later established by Huisgen's monumental work.[3-5] Direct evidence of the existence of nitrile imines has been achieved by uv and ir spectroscopies at low temperature[6-9] and by photoelectron spectroscopy in gas phase.[10] Among the various procedures for the *in situ* generation of nitrile imines, the most common method is the base treatment of hydrazonyl halides, which involves deprotonation of the NH group and subsequent loss of the halide anion.[1] A few papers[11,12] have described that silver carbonate behaves as an efficient enhancer of the reactivity of hydrazonyl chlorides.

Although such a fact is far from being strange, doubts arise about the formation mechanism of nitrile imines under the latter conditions and even about the real intervention of nitrile imine species in silver carbonate promoted reactions of hydrazonyl chlorides. To gain information on these points, we have undertaken the present investigation, dealing with the reactions between chlorohydrazone (**1**) and a series of allylic alcohols (**2**) in the presence of silver carbonate.

RESULTS

The reactions under study were carried out in acetonitrile at room temperature by using two mole equivalents of silver carbonate. Times, products, and yields are summarised in Table 1.

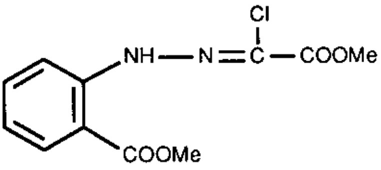
Table 1. Silver Carbonate Promoted Reaction of Chlorohydrazone 1 with Alkenols **2**.

Compd	Time (h)	Products and Yields[a]							Eluent
		3	4	5	6	7	8	9	
2a	17	10	--	--	12	--	3	3	Chloroform 4 Ethyl Acetate 1
2b	14	15 (R*, S*) 13 (R*, R*)	--	5	--	--	3	6	Ether
2c	2.5	11 (R*, S*) 4 (R*, R*)	--	6	--	4	3	4	Ether
2d	20	14	14	--	--	--	5	5	Dichloromethane 8 Ethyl Acetate 1
2e	16	26	26	--	--	--	3	3	Ether

[a] Some amount of uncharacterisable material was usually formed.

The product structures were assigned on the basis of analytical and spectral data (see Tables 2 and 3). In addition, the unexpected compound (7) was independently prepared by reacting **1** with benzoylethylene. The coupling constants of the pyrazolinic protons in compounds (**3d,e**) and (**4d,e**) fit well to the literature for a *trans* configuration,[13] which is consistent with the usual retention of stereochemistry of concerted cycloadditions.[14] Both compounds (**3b**) and (**3c**) were obtained in two diastereoisomeric forms, which exhibited some differences in the spectral properties (particulary as concerns the coupling constants of the pyrazolinic proton in 5-position). Nevertheless, this evidence did not permit secure stereochemical assignments. However, the X-ray diffractometric analysis of the major cycloadduct deriving from **2c** revealed a R*, S* configuration.[15] Owing to the similarity of the nmr spectra, we were confident to assign the same configuration to the diastereoisomeric form of **3b** having mp 125°C.

For the sake of comparison, the reaction between **1** and **2c** was repeated in the presence of a more classical base such as triethylamine. Neither **5c** nor **7** were detected in the product mixture, which however contained the two diastereoisomeric cycloadducts (**3c**).



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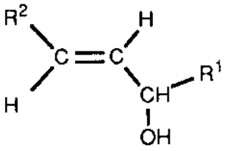
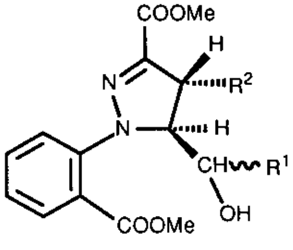
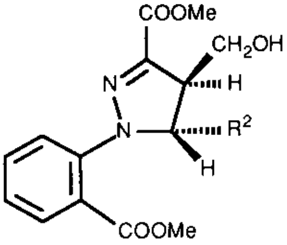


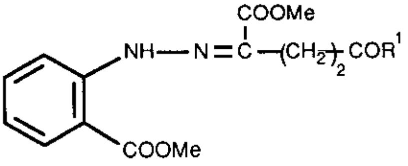
2a - e



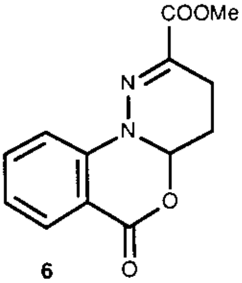
3a - e



4d, e



5b, c



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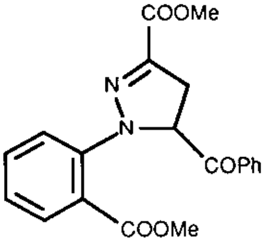

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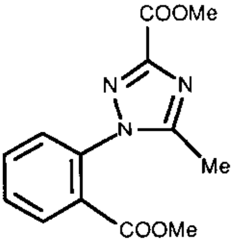

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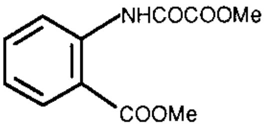


9

Entry	R^1	R^2
a	H	H
b	Me	H
c	Ph	H
d	H	Me
e	H	Ph

Table 2. Characterisation of new compounds (**3**-**9**).[a]

Compd		mp (°C)	ms m/z (M^+)	Ir (nujol) ν (cm^{-1})	Microanalyses (%)		
					C calcd found	H calcd found	N calcd found
3a		120	292	3450, 1730, 1710	57.5 57.6	5.5 5.4	9.6 9.6
3b	(R^*, S^*)	125	306	3530, 1740, 1720	58.8 58.8	5.9 5.8	9.1 9.0
	(R^*, R^*)	139	306	3430, 1730, 1690	58.8 58.6	5.9 5.8	9.1 9.0
3c	(R^*, S^*)	118	368	3390, 1720, 1705	65.2 65.0	5.5 5.6	7.6 7.5
	(R^*, R^*)	176	368	3470, 1720, 1705	65.2 65.3	5.5 5.4	7.6 7.6
3d		151	306	3500, 1740, 1720	58.8 58.6	5.9 5.8	9.1 9.0
3e		126	368	3430, 1730, 1720	65.2 65.3	5.5 5.4	7.6 7.5
4d		136	306	3500, 1740, 1720	58.8 58.6	5.9 5.8	9.1 9.0
4e		106	368	3500, 1730, 1710	65.2 65.0	5.5 5.4	7.6 7.6
5b		123	306	1710, 1690	58.8 58.6	5.9 5.9	9.1 9.0
5c		122	368	1720, 1700	65.2 65.0	5.5 5.4	7.6 7.7
6		138	260	1740, 1720	60.0 60.1	4.6 4.5	10.8 10.7
7		165	366	1720, 1700	65.6 65.5	5.0 4.8	7.6 7.5
8		88	275	1740, 1720	56.7 56.9	4.8 4.8	15.3 15.4
9		149	237	3250. 1750, 1730, 1700	55.7 55.8	4.7 4.8	5.9 5.8

[a]Nmr data are collected in Table 3.

Table 3. ^{1}H - Nmr data of new compounds (**3** - **9**).

Compd	^{1}H - Nmr ($CDCl_3$)[a] δ, J (Hz)
3a	3.23 - 3.30 (2H, m), 3.40 (1H, br s), 3.42 (1H, dd, J=12.3, 3.9), 3.75 (3H, s), 3.78 (1H, dd, J=12.3, 3.9), 3.92 (3H, s), 4.69 (1H, m), 7.04 - 7.08 (2H, m), 7.35 (1H, t, J=7.0), 7,50 (1H, d, J=7.0)
3b R^*, S^*	1.08 (3H, d, J=8.0), 3.11 (1H, dd, J=17.7, 13.1), 3.38 (1H, dd, J=17.7, 7.9), 3.70 (1H, br s), 3.79 (3H, s), 3.87 (3H, s), 4.12 (1H, dq, J=8.0, 1.3), 4.57 (1H, ddd, J= 13.1, 7.9, 1.3), 7.03 - 7.12 (2H, m), 7.40 (1H, t, J=8.4), 7.57 (1H, d, J=8.4)
3b R^*, R^*	1.07 (3H, d, J=8.0), 3.16 (1H, br s), 3.19 (1H, dd, J=18.0, 6.6), 3.29 (1H, dd, J=18.0, 12.5), 3.78 (3H, s), 3.85 - 3.92 (4H, m), 4.68 (1H, ddd, J=12.5, 6.6, 3.9), 7.07 - 7.12 (2H, m), 7.40 (1H, t, J=8.5), 7.57 (1H, d, J=8.5)
3c R^*, S^*	3.04 (1H, dd, J=18.0, 13.1), 3.19 (1H, dd, J=18.0, 7.1), 3.79 (3H, s), 3.93 (3H, s), 4.36 (1H, br s), 4.89 (1H, ddd, J=13.1, 7.1, 2.4), 5.12 (1H, d, J=2.4), 7.18 (1H, t, J=7.5), 7.25 - 7.38 (6H, m), 7.53 (1H, t, J=7.5), 7.69 (1H, d, J=7.5)
3c R^*, R^*	3.27 (1H, dd, J=17.9, 7.0), 3.39 (1H, dd, J=17.9, 12.0), 3.79 (3H, s), 3.93 (3H, s), 4.30 (1H, br s), 4.82 (1H, d, J=3.3), 5.05 (1H, ddd, J=12.0, 7.0, 3.3), 6.62 (1H, d, J=8.3), 6.88 - 7.14 (7H, m), 7.49 (1H, d, J=8.3)
3d[a]	1.41 (3H, d, J=7.0), 3.45 - 3.50 (1H, m), 3.65 (1H, m)[b], 3.81 (3H, s), 3.83 - 3.90 (1H, m), 3.91 (3H, s), 4.18 - 4.23 (1H, m), 7.10 - 7.18 (2H, m), 7.41 (1H, t, J=8.0), 7.60 (1H, d, J=8.0)
3e[a]	3.56 (1H, dd, J=13.0, 2.1), 3.69 (3H, s), 3.92 (3H, s), 3.95 (1H, dd, J=13.0, 2.2), 4.54 (1H, ddd, J=5.7, 2.2, 2.1), 4.67 (1H, d, J=5.7), 7.09 (1H, d, J=8.5), 7.17 (1H, t, J=8.5), 7.23 - 7.45 (6H, m), 7.61 (1H, d, J=8.5)
4d[a]	1.22 (3H, d, J=8.0), 3.19 (1H, m), 3.70 - 3.80 (2H, m), 3.84 (3H, s), 3.87 (3H, s), 4.45 (1H, dq, J=8.0, 7.5), 7.11 (1H, t, J=8.0), 7.19 (1H, t, J=8.0), 7.42 (1H, t, J=8.0), 7.63 (1H, d, J=8.5)
4e	3.08 (1H, t, J=7.5)[c], 3.47 (1H, m), 3.84 (3H, s), 3.92 (2H, m), 3.92 (3H, s), 5.30 (1H, d, J=7.7), 6.78 (1H, d, J=8.0), 7.00 (1H, t, J=8.0), 7.21 (1H, t, J=8.3), 7.26 - 7.35 (5H, m), 7.50 (1H, d, J=8.3)
5b	2.20 (3H, s), 2.80 - 2.95 (4H, m), 3.87 (3H, s), 3.92 (3H, s), 6.93 (1H, t, J=8.3), 7.50 (1H, t, J=8.3), 7.82 (1H, d, J=8.9), 7.93 (1H, d, J=8.9), 11.60 (1H, br s)
5c	3.08 (2H, t, J=8.3), 3.23 (2H, t, J=8.3), 3.87 (6H, s), 6.90 (1H, t, J=7.6), 7.42 - 7.57 (4H, m), 7.86 (1H, d, J=7.6), 7.92 - 8.00 (3H, m), 11.68 (1H, br s)
6	2.23 - 2.64 (3H, m), 2.87 (1H, ddd, J=18.7, 6.2, 4.4), 3.90 (3H, s), 5.52 (1H, dd, J=8.4, 4.7), 7.15 (1H, t, J=6.2), 7.58 - 7.67 (2H, m), 8.02 (1H, d, J=8.3)
7	3.25 (1H, dd, J=17.8, 13.4), 3.70 (1H, dd, J=17.8, 8.0), 3.84 (6H, s), 6.08 (1H, dd, J=13.4, 8.0), 7.05 (1H, t, J=8.3), 7.13 (1H, d, J=8.3), 7.32 - 7.65 (5H, m), 7.90 - 7.95 (2H, m)
8	2.31 (3H, s), 3.66 (3H, s), 3.93 (3H, s), 7.36 (1H, d, J=9.0), 7.54 - 7.70 (2H, m), 8.07 (1H, d, J=9.0)
9	3.92 (3H, s), 3.98 (3H, s), 7.17 (1H, t, J=7.2), 7.59 (1H, t, J=7.2), 8.07 (1H, d, J=9.0), 8.74 (1H, d, J=9.0), 12.50 (1H, br s)

[a] $CDCl_3 + D_2O$

[b] Doublet (J=5.5) after irradiation of the signal at δ 1.41.

[c] Exchangeable with D_2O

DISCUSSION

The above results present some peculiar features, the most striking of which is the formation of compounds (5) that has no precedent in base-promoted reactions of hydrazonyl halides with alkenols.[1,17,18] As a possible rationalisation of the whole experimental evidence, we suggest the mechanistic picture illustrated in the Scheme.

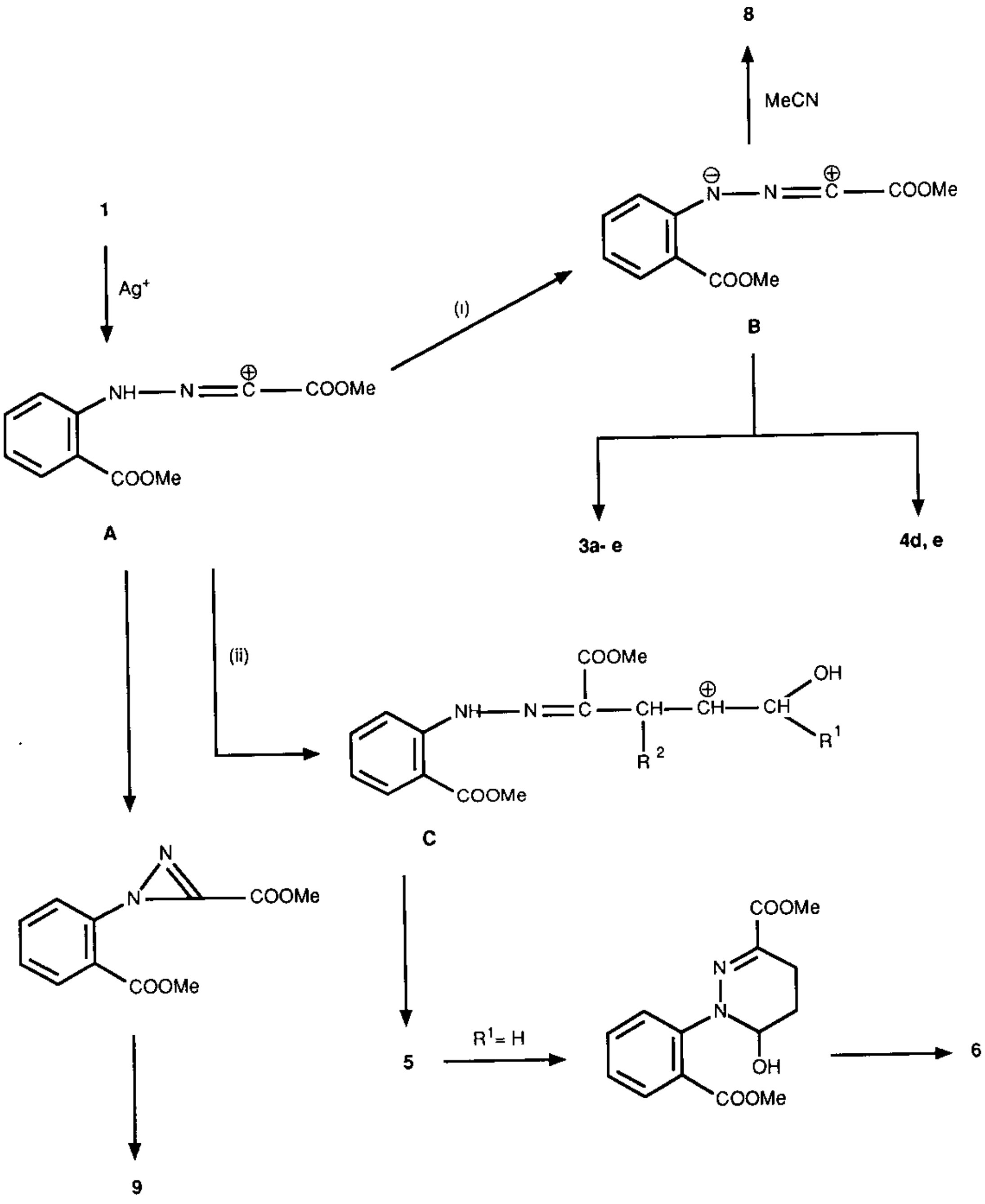
In the light of the well-known ability of the silver ion to facilitate the heterolysis of the carbon-halogen bond,[19] it is reasonable to posit the initial formation of the nitrilium-like carbocation A.[20] This intermediate would then evolve following two alternative pathways: (i) proton elimination to generate the nitrile imine species **B**; (ii) electrophilic attack to the π bond of the alkenol (**2**) to form the new carbocation **C**. The pinacol-type rearrangement of the latter[22] would just produce the carbonyl derivatives (**5**). In the case of **5a**, the further transformation illustrated in the Scheme accounts for the obtainment of **6**. The observed distribution between the pathways (i) and (ii) can be explained on considering that the latter pathway is more sensitive to the steric hindrance of the R^2 substituent. At this point, one may think that the carbocation intermediate **C** might be the common precursor of all reaction products, namely in other words that the pyrazole derivatives (**3**) and (**4**) might be formed through an ionic pathway without intervention of the nitrile imine species **B**. However, such mechanistic hypothesis seems unlikely since the retention of stereochemistry in the case of **2d,e** and the observed regiochemical preferences reflect usual features of nitrile imine cycloadditions to ethylenic dipolarophiles.[1,14,17] It remains to be noted that, in the case of the chiral alkenols (**2b,c**), the cycloaddition process implies a diastereoselectivity phenomenum. The obtained results indicate a modest degree of diastereoselectivity, which is not surprising in the light of the literature data dealing with 1,3-dipolar cycloadditions on similar alkene derivatives.[23,24]

Little can be said about the unexpected formation of **7**, for which a convincing explanation is still lacking. The oxidising power of the silver ion is not responsible for this result since both **2c** and **3c** did not change upon treatment with silver carbonate in acetonitrile at room temperature. Plausible pathways leading to the side-products **8** and **9** are outlined in the Scheme[12].

EXPERIMENTAL

Melting points were taken on a Büchi apparatus and are not corrected. Ir spectra were recorded on a FT IR Perkin Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H Nmr spectra were obtained on a Bruker 300 MHz apparatus; chemical shifts are given as ppm from Me_4Si.

Scheme


8
MeCN
1
Ag+
(i)
NH—N=C⊕—COOMe
COOMe
A
⊖N—N=C⊕—COOMe
COOMe
B
3a- e
4d, e
(ii)
COOMe
OH
NH—N=C—CH—CH⊕—CH
R2
R1
COOMe
C
N
N
COOMe
COOMe
5
R1= H
COOMe
N
N
OH
COOMe
6
9

Compounds (**2a-e**) are commercially available products. Formulae **2b,c** refer to racemic compounds.

Preparation of the Hydrazonyl Chloride 1. A solution of methyl antranilate (1.51 g, 15 mmol) in water (25 ml) was treated with 10N hydrochloric acid (5 ml) and then cooled to 0°C. Sodium nitrite (1.04 g, 15 mmol) in water (15 ml) was added dropwise to the reaction mixture whilst it was cooled and stirred. After 30 min, the cold mixture was adjusted to pH=5 with sodium acetate and then methyl 2-chloroacetoacetate (1.51 g, 10 mmol) in methanol (15 ml) was added whilst it was cooled and stirred. The mixture was stirred at room temperature for 15 h and then extracted with ether. The organic solution was washed with aqueous 5% $NaHCO_3$, dried over Na_2SO_4 and evaporated. Recrystallisation from diisopropyl ether gave pure **1** (1.48 g, 55%); mp 113°C; ms (m/z) 270 (M^+); ir (nujol): 3180, 1740, 1700 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 3.92 (6H, s), 6.97 (1H, td, J=7.5, 1.5), 7.52 (1H, td, J=7.5, 1.5), 7.79 (1H, dd, J=8.2, 2.2), 7.99 (1H, dd, J=8.2, 2.2), 11.80 (1H, br s); *Anal.* Calcd for $C_{11}H_{11}N_2O_4Cl$: C, 48.8; H, 4.1; N, 10.3; Cl, 13.1. Found: C, 48.9; H, 4.1; N, 10.3; Cl, 13.3.

Reaction between 1 and Alkenols 2 in the Presence of Silver Carbonate. A solution of **1** (2.0 g, 7.4 mmol) and the proper alkenol (14.8 mmol) in acetonitrile (70 ml) was treated with silver carbonate (4.07 g, 14.8 mmol) and stirred at room temperature in the dark for the time indicated in Table 1. The undissolved material was filtered off, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column to give the products reported in Table 1. Characteristic data of the products are collected in Tables 2 and 3. The reaction of **1** with benzoylethylene[25] in the same conditions gave **7** in 55% yield.

Reaction between 1 and 2c in the Presence of Triethylamine. A solution of **1** (2.0 g, 7.4 mmol) and **2c** (0.99 g, 7.4 mmol) in acetonitrile (100 ml) was treated with triethylamine (3.71 g, 37 mmol) and stirred at room temperature for 8 days. The solvent was removed under reduced pressure, the residue was dissolved in chloroform (50 ml), washed with 0.1N hydrochloric acid and then with water (100 ml). The organic solution was separated, dried (Na_2SO_4), and the solvent was evaporated. The residue was chromatographed on a silica gel column with ether to give the two diastereoisomeric cycloadducts (**3c**) in 12 and 6% yields.

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REFERENCES AND NOTES

1. P. Caramella and P. Grünanger, "1,3-Dipolar Cycloaddition Chemistry", ed. by A. Padwa, Wiley-Interscience, New York, 1984, Vol. 1, Ch. 3.
2. R. Fusco and R. Romani, *Gazz. Chim. Ital.*, 1946, **76**, 439.
3. R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, 1962, **17**, 3.
4. R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565 and 633.
5. R. Huisgen, W. Fliegl, and W. Kolbeck, *Chem. Ber.*, 1983, **116**, 3027.
6. H. Meyer, W. Heinzelmann, and H. Heimgartner, *Chimia*, 1980, **34**, 504 and 506.
7. N. H. Toubro and A. Holm, *J. Amer. Chem. Soc.*, 1980, **102**, 2093.
8. C. Wentrup, S. Fisher, A. Maquestian, and R. Flammang, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 56.
9. G. Sicard, A. Bacereido, and G. Bertrand, *J. Amer. Chem. Soc.*, 1988, **110**, 2663.
10. H. Bock, R. Dammel, S. Fisher, and C. Wentrup, *Tetrahedron Lett.*, 1987, **28**, 617.
11. A. Padwa and S. Nahm, *J. Org. Chem.*, 1981, **46**, 1402.
12. G. Broggini, L. Garanti, G. Molteni, and G. Zecchi, *Heterocycles*, 1994, in press.
13. T. J. Batterham, "NMR Spectra of Simple Heterocycles", Wiley-Interscience, New York, 1973, p. 206.
14. R. Huisgen, "1,3-Dipolar Cycloaddition Chemistry", ed. by A. Padwa, Wiley-Interscience, New York, 1984, Vol. 1, Ch. 1.
15. Details of the crystallographic study have been published elsewhere (ref. 16).
16. T. Pilati and G. Casalone, *Acta Cryst. Section C*, 1994, **50**, 88.
17. G. Bianchi, C. De Micheli, and R. Gandolfi, "The Chemistry of Double Bonded Functional Groups", ed. by S. Patai, Wiley & Sons, London, 1977, Part 1, Ch. 5, p. 421.
18. A. S. Shawali and C. Párkányi, *J. Heterocycl. Chem.*, 1980, **17**, 833.
19. P. B. D. De la Mare and B. E. Swedlund, "The Chemistry of the Carbon-Halogen Bond", ed. by S. Patai, Wiley & Sons, London, 1973, Part 1, Ch. 7, p. 454.
20. The intervention of such kind of carbocation in the solvolysis of *N,N*-disubstituted *C*-halohydrazones is a documented matter (ref. 21).
21. A. F. Hegarty, M. P. Cashman, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 1972, 44.
22. C. J. Collins, *Quart. Rev.*, 1960, **14**, 357.
23. K. N. Houk, S. R. Moses, Y. D. Wu, N. G. Rondan, V. Jäger, R. Schohe, and F. R. Fronczeck, *J. Amer. Chem. Soc.*, 1984, **106**, 3880.

24. A. P. Kozikowsky and A. K. Ghosh, *J. Org. Chem.*, 1984, **49**, 2762.

25. A. I. Vogel, "Textbook of Practical Organic Chemistry", IV th edition, Longman, London, 1978, p. 816.

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