Tetrahedron. Vol. 29, pp. 101 to 105. Pergamon Press 1973. Printed in Great Britain

REACTIONS OF DIMETHYL ACETYLENEDICARBOXYLATE – VI

REACTION WITH ALDEHYDE AND KETONE PHENYLHYDRAZONES[1]

M. K. SAXENA, M. N. GUDI and M. V. GEORGE*
Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur-16, India

(*Received in the UK* 2 *May* 1972; *Accepted for publication* 25 *August* 1972)

Abstract – Benzaldehyde phenylhydrazone with dimethyl acetylenedicarboxylate gives dimethyl 1,3-diphenylpyrazoline-4,5-dicarboxylate, dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate and trimethyl 1-phenylpyrazole-3,4,5-tricarboxylate; *p*-chlorobenzaldehyde phenylhydrazone gives trimethyl 1-phenyl-3,4,5-tricarboxylate and 1,2-(bis-phenylazo)-1,2-di-*p*-chlorophenylethane. Under similar conditions, *p*-tolualdehyde phenylhydrazone gives only trimethyl 1-phenylpyrazole-3,4,5-tricarboxylate. Acetophenone phenylhydrazone with dimethyl acetylenedicarboxylate gives dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate. Benzophenone phenylhydrazone, on the other hand, gives a mixture of dimethyl 1,3-diphenylpyrazoline-4,5-dicarboxylate and dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate. Benzyl methyl ketone and dimethyl acetylenedicarboxylate gives an enamine maleate, which is the Michael addition product.

The reactions of a few Schiff's bases with acetylenic esters have been reported.[2] Benzalaniline, for example, reacts with dimethyl acetylenedicarboxylate to give dimethyl α-benzal-α′-phenyliminosuccinate. It has been suggested that this product is formed through the reaction of the aniline addition product with benzaldehyde. Both banzaldehyde and aniline have been assumed to be formed through the hydrolysis of benzalaniline, under the reaction conditions. The reactions of benzalmethylamine, cinnamalaniline and cinnamalmethylamine, with dimethyl acetylenedicarboxylate, on the other hand give rise to the corresponding dihydropyridine derivatives.[3,4]

There are only a few reported examples of the reactions of aldehyde and ketone phenylhydrazones with acetylenic esters. Benzaldehyde phenylhydrazone, has been reported to undergo an addition reaction with ethyl phenylpropiolate to give rise to ethyl 1,3,5-triphenylpyrazole-4-carboxylate.[5] Similarly, *p*-nitrobenzaldehyde phenylhydrazone reacts with ethyl phenylpropiolate giving rise to the corresponding pyrazole derivative.[5] The reaction of an aldehyde phenylhydrazone such as propionaldehyde phenylhydrazone with dimethyl acetylenedicarboxylate has been reported to give an unidentified product.[5] Recently, Nelson has reported the reaction of acetone dimethylhydrazone with dimethyl acetylenedicarboxylate[6] and has shown that products such as dimethyl N-isopropylidine-N-dimethylamino-2-aminomaleate and a dihydropyridine derivative are formed. It has been suggested that the formation of both these products is through a zwitterionic intermediate, arising through nucleophilic attack of the imino nitrogen.

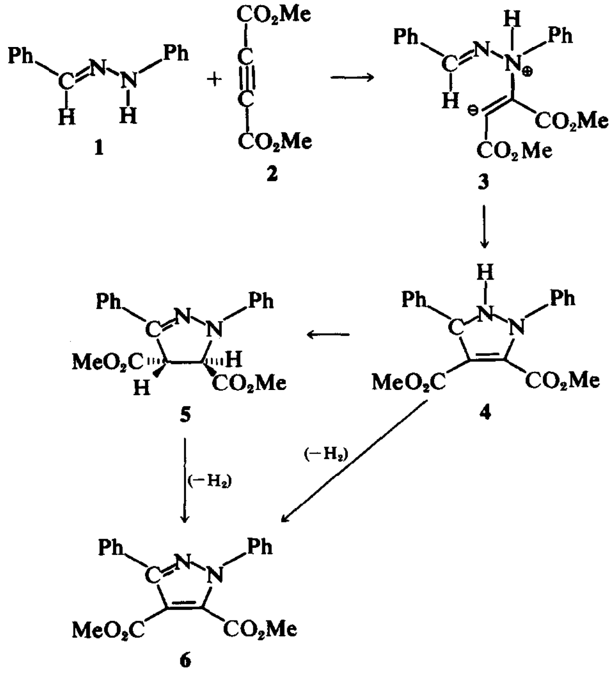
The object of the present investigation was to examine the reactions of a few aldehyde and ketone phenylhydrazones with dimethyl acetylenedicarboxylate, and to study the products formed.

Treatment of benzaldehyde phenylhydrazone (1) with dimethyl acetylenedicarboxylate (2) around 150° resulted in the formation of a 3% yield of dimethyl 1,3-diphenylpyrazoline-4,5-dicarboxylate (5), a 16% yield of dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate (6) (Scheme 1) and a 5% yield of trimethyl 1-phenylpyrazole-3,4,5-tricarboxylate (9) (Scheme 2). The structures of 5 and 6 were established on the basis of analytical data, spectral evidences and independent syntheses.[7] It was also observed that 5 undergoes dehydrogenation in presence of chloranil to give 6. A probable route to the formation of 5 and 6 is shown in Scheme 1. In this scheme we assume that benzaldehyde phenylhydrazone initiates the nucleophilic addition to dimethyl acetylenedicarboxylate, leading to zwitterionic intermediate 3 which then cyclizes to give the pyrazoline 4. Isomerization of 4 would result in the formation of the pyrazoline 5, which on dehydrogenation would give the pyrazole 6. It is quite possible that dimethyl acetylenedicarboxylate itself is bringing about this dehydrogenation and most probably through a free-radical process.

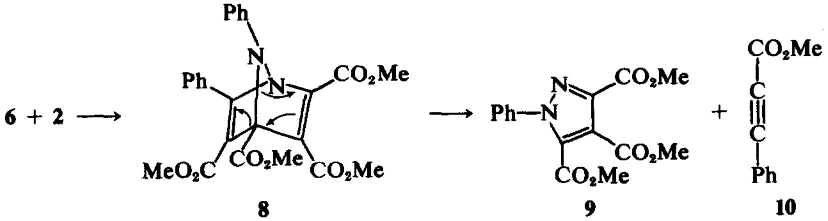
The structure of trimethyl 1-phenylpyrazole-3,4,5-tricarboxylate (9) has been established on the basis of analytical and spectral data. The IR spec-

---

*To whom enquiries should be addressed.



SCHEME 1



SCHEME 2

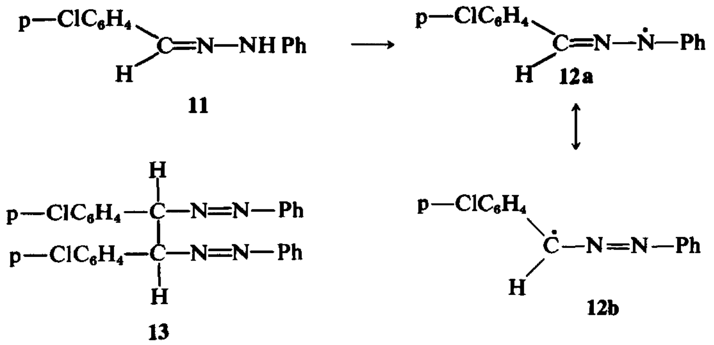
trum of **9** showed a characteristic ester carbonyl band at 1730 cm^{-1}. The UV spectrum of **9** in MeOH showed an absorption maximum at 250 nm (ϵ 6,800), as present in a number of pyrazoles.[8] The NMR spectrum of **9** showed a multiplet centred around δ 7·46 (5H) due to the aromatic protons. In addition, the spectrum showed two singlets at δ 3·95 (6H) and δ 3·80 (3H) due to the ester methyl protons. The mass spectrum of **9** showed a molecular ion peak at *m/e* 318.

A probable route to the formation of **9** is through a Diels-Alder type addition of pyrazole **6** with dimethyl acetylenedicarboxylate leading to intermediate **8** which can undergo a retro Diels-Alder type reaction, as shown in Scheme 2.

The reaction of *p*-chlorobenzaldehyde phenylhydrazone with dimethyl acetylenedicarboxylate in refluxing MeOH gave a 19% yield of **9** and a 30% yield of 1,2-(bis-phenylazo)-1,2-di-*p*-chlorophenylethane (**13**). The UV spectrum of **13** in $CHCl_3$ showed absorption maxima at 222 nm (ϵ, 47,000), 276 (24,000) and 402 (500), characteristic of bisazoalkanes.[8] The NMR spectrum of **13** showed a multiplet centred around δ 7·2 (18H) due to the aromatic protons. The methine protons appeared as a sharp singlet at δ 5·46 (2H). The mass spectrum of **13** showed a molecular ion peak at *m/e* 458.

A probable route to the formation of **13** is shown in Scheme 3. In this scheme we assume that *p*-chlorobenzaldehyde phenylhydrazone (**11**) undergoes oxidation to a free-radical intermediate **12a**, probably brought about through the action of dimethyl acetylenedicarboxylate at high temperatures. The pseudo allylic radical **12b** can then undergo a C—C coupling to give the bisazoalkane **13**. In this connection, it might be mentioned that the oxidation of aromatic aldehyde phenylhydrazones to bisazoalkanes are reported to proceed through such free-radical intermediates.[9]

From the reaction of *p*-tolualdehyde phenylhydrazone with dimethyl acetylenedicarboxylate, the only product that could be isolated was **9** (11%

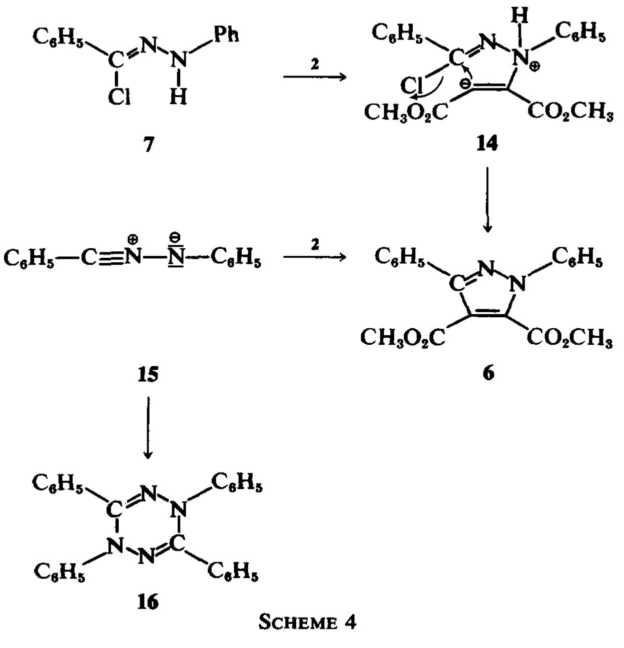


SCHEME 3

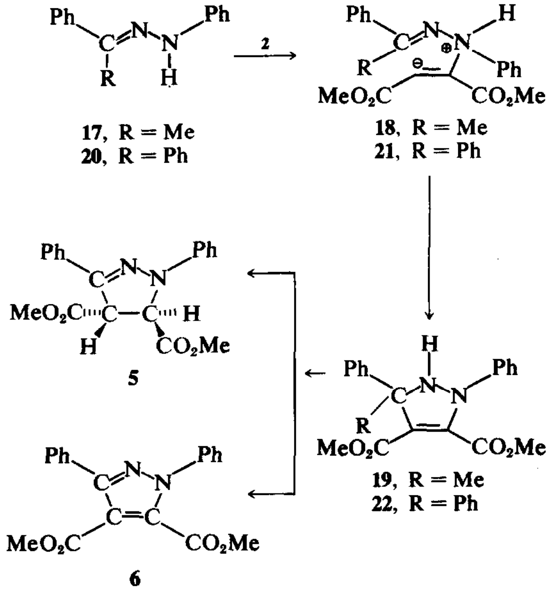
yield); none of the pyrazoline and pyrazole, corresponding to **5** and **6** could be isolated.

If the formation of pyrazoline and pyrazole derivatives from the reaction of benzaldehyde phenylhydrazone with dimethyl acetylenedicarboxylate is proceeding through intermediate **3** (Scheme 1), then it would be reasonable to assume that the cyclization step is favoured if the nucleophile contains a good leaving group, which will be displaced intramolecularly as in the case of α-chlorobenzaldehyde phenylhydrazone (**7**). Treatment of **7** with **2** around 180–190° in a sealed tube and in the absence of any base gave a 64% yield of **6**. It is known that **7** undergoes dehydrohalogenation in presence of organic bases to give N,C-diphenylnitrileimine (**15**) and therefore, we felt it necessary to check whether **15** is formed under the thermal conditions. Heating **7** alone for 1 h around 100–190° resulted in 10% yield of 2,3,5,6-tetraphenyl-2,5-dihydrotetrazine (**16**)[10] showing thereby, that only a small amount of **7** is being converted to **16** under our reaction conditions. It would, therefore, be reasonable to assume that reaction of **7** with dimethyl acetylenedicarboxylate is probably proceeding through intermediate **14** (Scheme 4).

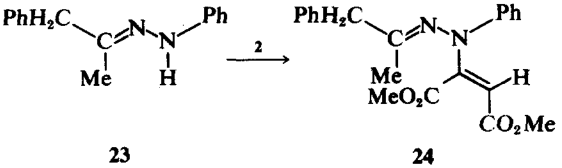
In continuation of our studies we have examined the reactions of some ketone phenylhydrazones with dimethyl acetylenedicarboxylate. Heating a mixture of acetophenone phenylhydrazone (**17**) with **2** at 190° in a sealed tube for 30 min. gave 57% yield of **6**. A probable route to the formation of **6** is through the zwitterionic intermediate **18** (Scheme 5). Intermediate **18** can undergo cyclization to give pyrazoline **19** which loses elements of methane under the reaction conditions, resulting in the formation of pyrazole **6**. The loss of methane may probably be taking place through a free-radical process, brought about by dimethyl acetylenedicarboxylate. Similarly, from the reaction of benzophenone phenylhydrazone (**20**) with dimethyl



SCHEME 4



SCHEME 5



SCHEME 6

acetylenedicarboxylate a 38% yield of **6** was isolated. In addition, a small amount (10%) of **5** was also isolated. The formation of pyrazole **6** may be rationalized through the zwitterionic intermediate **21**, which gives rise to pyrazoline derivative **22** and this ultimately loses benzene resulting in the formation of **6** (Scheme 5). In this connection it might be mentioned that such an elimination reaction involving the loss of benzene has been reported in the reaction of N-phenyl-C-methylsydnone with 1,1-diphenylethylene.[11] The exact mode of formation of **5**, however, is not clear. It might arise through a free-radical type of hydrogen transfer to the pyrazole or any other intermediate.

To discover whether a pyrazole derivative is formed in the reaction of benzyl methyl ketone phenylhydrazone (**23**) with dimethyl acetylenedicarboxylate, we treated **23** with **2** and obtained a product identified as **24** (Scheme 6) in 35% yield.

EXPERIMENTAL

Benzaldehyde phenylhydrazone, m.p. 156°, *p*-chlorobenzaldehyde phenylhydrazone, m.p. 132°, *p*-tolualdehyde phenylhydrazone, m.p. 112–113°, α-chlorobenzaldehyde phenylhydrazone, m.p. 131°, acetophenone phenylhydrazone, m.p. 105°, benzophenone phenylhydrazone, m.p. 137° and benzyl methyl ketone phenylhydrazone, m.p. 85° were prepared by literature methods.

Reaction of benzaldehyde phenylhydrazone with dimethyl acetylenedicarboxylate. **1** (15 g, 0·076 mol) and **2** (11 g, 0·077 mol) were heated at 145° for 10 min. The mixture which became a brown homogenous mass was left at room temp for 20 h. The red-brown mass was triturated with MeOH to give 4·5 g (16%) of dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate (**6**), m.p. 154–155°, after recrystallization from MeOH. (Found: C, 67·9; H, 4·8; N, 8·4. $C_{19}H_{16}N_2O_4$ requires, C, 67·8; H, 4·8; N, 8·3%.) IR (KBr): 1739 cm^{-1} (C=O); UV (MeOH): 232 nm (ϵ, 18,000); NMR ($CDCl_3$): δ 7·50 (10H, aromatic), 3·82 (3H, carbomethoxy), 3·80 (3H, carbomethoxy).

Further confirmation of **6** was derived by comparison of its m.p. and IR spectrum with that of an authentic sample.

Removal of solvent from the mother liquor gave a residue which was chromatographed over alumina. Elution with a mixture (1 : 1) of benzene and petroleum ether (b.p. 60–80°) gave 0·7 g (3%) of dimethyl 1,3-diphenylpyrazoline-4,5-dicarboxylate (**5**), m.p. 154°, after recrystallization from MeOH. (Found: C, 67·7; H, 5·1; N, 8·3; Mol. Wt. (MS), 338. $C_{19}H_{18}N_2O_8$ requires: C, 67·5; H, 5·3; N, 8·3%; Mol. Wt., 338). IR (KBr): 1724 cm^{-1} (C=O); UV (MeOH): 244 nm (ϵ, 15,000), 302 (6,000), 356 (18,000); NMR ($CDCl_3$): δ 7·50 (10H, aromatic), 5·30 (1H, methine), 4·70 (1H, methine), 3·85 (3H, carbomethoxy) and 3·8 (3H, carbomethoxy).

Further confirmation of the structure of **3** was derived by its conversion to **6**, on treatment with chloranil. Refluxing a mixture of **5** (0·5 g, 1·4 mmol) and chloranil (0·37 g, 1·4 mmol) in xylene for 42 h and work-up in the usual manner gave a 98% (0·33 g) of **6**, m.p. 154–155° (m.m.p.).

Subsequent elution of the alumina column with benzene gave 1·2 g (5%) of trimethyl 1-phenylpyrazole-3,4,5-tricarboxylate (**9**), m.p. 89°, on recrystallization from MeOH. (Found: C, 56·8; H, 4·7; N, 9·0; Mol. Wt. (MS), 318. $C_{15}H_{14}N_2O_6$ requires: C, 56·6; H, 4·4; N, 8·8%; Mol. Wt., 318). IR (KBr): 1730 cm^{-1} (C=O), UV (MeOH): 250 nm (ϵ, 6,800); NMR ($CDCl_3$): 7·46 (5H, aromatic), 3·95 (6H, carbomethoxy), 3·80 (3H, carbomethoxy).

Reaction of p*-chlorobenzaldehyde phenylhydrazone with dimethyl acetylenedicarboxylate.* **11** (2·30 g, 0·01 mol) **2** (1·42 g, 0·01 mol) in 25 ml MeOH were refluxed for 24 h. Solvent removal gave a red viscous liquid which was chromatographed on alumina. Elution of the column with petroleum ether (b.p. 60–80°) and benzene mixture (3 : 1) gave 0·37 g (30%) of 1,2-bisphenylazo-1,2-di-*p*-chlorophenylethane (**13**), m.p. 174°, after recrystallization from EtOH. (Found: C, 67·8; H, 4·3; N, 11·9; Mol. Wt. (MS), 458. $C_{28}H_{20}N_4Cl_2$ requires: C, 68·0; H, 4·4; N, 12·2%; Mol. Wt., 458. UV ($CHCl_3$): 222 nm (ϵ, 47,000), 276 (24,000), 402 (500); NMR (CCl_4): δ7·20 (18H, aromatic), 5·46 (2H, methine).

Further elution with benzene gave 0·62 g (19%) of **9**, m.p. 89° (m.m.p.).

Reaction of p*-tolualdehyde with dimethyl acetylenedicarboxylate.* A mixture of *p*-tolualdehyde phenylhydrazone (2·1 g, 0·01 mol) and dimethyl acetylenedicarboxylate (1·42 g, 0·01 mol) was heated in a sealed tube at 150° for 1 h. The reddish brown liquid was chromatographed over alumina. Elution with benzene gave 0·35 g (11%) of **9**, m.p. 89° (m.m.p.).

Reaction of α-chlorobenzaldehyde phenylhydrazone with dimethyl acetylenedicarboxylate. **7** (1·4 g, 0·006 mol) and **2** (2·6 g, 0·018) were heated in a sealed tube at 185° for 1 h. The dark brown viscous mass was triturated with MeOH to give 1·3 g (64%) of **6**, m.p. 154°; no depression in m.p. of **6**, when mixed with an authentic sample.

Pyrolysis of α-chlorobenzaldehyde phenylhydrazone. α-Chlorobenzaldehyde phenylhydrazone was heated in a sealed tube at 190° for 1 h. The dark brown mixture was chromatographed on alumina. Elution with a mixture (1 : 1) of petroleum ether (b.p. 60–80°) and benzene gave 0·14 g (10%) 2,3,5,6-tetraphenyl-2,5-dihydrotetrazine (**16**), m.p. 210° after recrystallization from MeOH. (Found: C, 80·8; H, 5·1; N, 14·2. $C_{26}H_{20}N_4$ requires: C, 80·4; H, 5·2; N, 14·4%.) UV (MeOH): 270 nm (ε, 10,000), 330 (16,000).

Reaction of acetophenone phenylhydrazone with dimethyl acetylenedicarboxylate. Acetophenone phenylhydrazone (2·1 g, 0·01 mol) and **2** (1·42 g, 0·01 mol) were heated at 190° in a sealed tube for 30 min. The dark brown mixture was chromatographed over alumina using benzene to give 1·7 g (59%) of **6**, m.p. 154° (m.m.p.).

Reaction of benzophenone phenylhydrazone with dimethyl acetylenedicarboxylate. A mixture of benzophenone phenylhydrazone (2·72 g, 0·01 mol) and **2** (1·42 g, 0·01 mol) was heated in a sealed tube at 190°. Work-up of the mixture in the usual manner gave 1·42 g (38%) of **6**, m.p. 154° (m.m.p.), after recrystallization from MeOH.

Further elution of the column with a mixture (1:1) of petroleum ether (b.p. 60–80°) and benzene yielded 0·3 g (10%) of **5**, m.p. 154° (m.m.p.).

Reaction of benzyl methyl ketone phenylhydrazone with dimethyl acetylenedicarboxylate. Benzyl methyl ketone phenylhydrazone (2·24 g, 0·01 mol) and **2** (1·42 g, 0·01 mol) were heated at 150° in a sealed tube for 2 h. The reddish brown viscous liquid on trituration with MeOH gave a product identified as **24** (1·28 g, 33%), m.p. 148°, after recrystallization from MeOH. (Found: C, 68·8; H, 6·5; N, 7·3; Mol. Wt. (MS), 366. $C_{21}H_{24}N_2O_4$ requires: C, 68·9; H, 6·0; N, 7·7%, Mol. Wt., 366). IR (KBr): 1724 cm^{-1} (C=O); 1587 cm^{-1} (C=C); UV (MeOH): 286 nm (ε, 1,000).

Acknowledgement—The authors wish to thank Mr. A. H. Siddiqui for his help in microanalysis. The award of a Research Fellowship from the Indian Institute of Technology, Kanpur (MNG) and a Senior Research Fellowship from the Council of Scientific and Industrial Research, New Delhi (MKS) are gratefully acknowledged.

REFERENCES

[1] M. N. Gudi, J. G. Hiriyakkanavar and M. V. George, *Ind. J. Chem.*, **9**, 743 (1971).

[2] H. R. Snyder, H. Cohen and W. J. Tapp, *J. Am. Chem. Soc.* **61**, 3560 (1939).

[3] J. M. F. Gagan, *J. Chem. Soc.* (C), 1121 (1966).

[4] R. Huisgen and K. Herbig, *Ann.* **688**, 98 (1965).

[5] C. Musante, *Gazz. Chim. Ital.* **67**, 682 (1967); *Chem. Abs.* **32**.

[6] S. F. Nelson, *J. Org. Chem.* **34**, 2248 (1969).

[7] R. Huisgen, *Angew. Chem.* **75**, 604 (1963); *Angew. Chem. Inter. Ed.* **2**, 565 (1963).

[8] N. H. Cromwell and G. D. Mercer, *J. Am. Chem. Soc.* **79**, 3815 (1957).

[9] I. Bhatnagar and M. V. George, *J. Org. Chem.* **32**, 2252 (1967).

[10] R. Huisgen, J. Sauer and M. Seidel, *Chem. Ber.* **94**, 2503 (1961).

[11] R. Huisgen, R. Grashey and J. Sauer, *The Chemistry of Alkenes*, p. 858. Ed. S. Patai, Interscience Publishers, London (1964).