Heterocycles

2†—Regiospecific Addition of Methylhydrazine to Acetylenic Ketones§

N. R. El-Rayyes,* G. H. Hovakeemian and H. Hammoud
Chemistry Department, Kuwait University, Kuwait

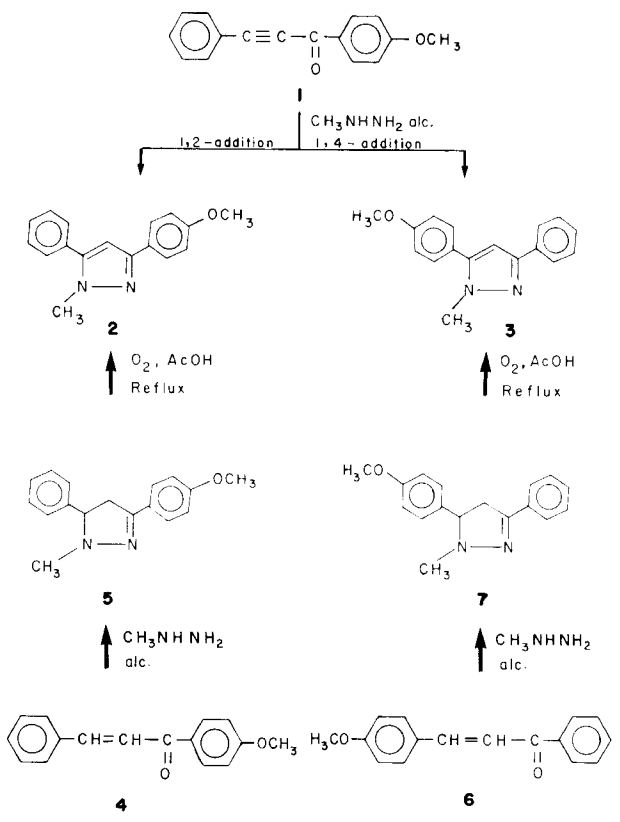
The reaction of 1-*p*-methoxyphenyl-3-phenyl-2-propen-1-one and 3-*p*-methoxyphenyl-1-phenyl-2-propen-1-one with methylhydrazine gave 1-methyl-3-*p*-methoxyphenyl-5-phenylpyrazoline and 1-methyl-3-phenyl-5-*p*-methoxyphenylpyrazoline, respectively. These compounds, on oxidation, gave 1-methyl-3-*p*-methoxyphenyl-5-phenylpyrazole(2) and 1-methyl-3-phenyl-5-*p*-methoxyphenylpyrazole, respectively. When methylhydrazine was made to react with 1-*p*-methoxyphenyl-3-phenyl-2-propyn-1-one, a pyrazole was obtained which proved to be identical with 2. Confirmatory evidence for this identity was obtained from their spectral data.

INTRODUCTION

Numerous studies have been undertaken to establish the mode of addition of hydrazine derivatives to acetylenic ketones. It has been proposed that the initial step of the reaction proceeds either by a 1,2-addition[1,2] or a 1,4-addition,[3–8] followed by cyclization to yield, in each case, the corresponding pyrazole derivative. Each group of investigators claimed the correctness of the structure of their products, and have substantiated it by preparing authentic samples from the corresponding dibromochalcones or from β-bromostyryl phenyl ketone.[1] This discrepancy led to the present investigation, and this paper gives an account of the methods and reasoning in establishing the structure and configuration of the addition products.

RESULTS AND DISCUSSION

The reaction of 1-*p*-methoxyphenyl-3-phenyl-2-propyn-1-one(**1**) with methylhydrazine in ethanol gives either 1-methyl-3-*p*-methoxyphenyl-5-phenylpyrazole(**2**) or 1-methyl-3-phenyl-5-*p*-methoxyphenylpyrazole(**3**), depending on the mode of the initial addition (cf., Scheme 1). When 1-*p*-methoxyphenyl-3-phenyl-2-propen-1-one(**4**) was made to react with methylhydrazine in ethanol, 1-methyl-3-*p*-methoxyphenyl-5-phenylpyrazoline(**5**) was obtained which, upon oxidation,[9] gave the pyrazole **2** as the sole product. Alternatively, the pyrazole **3** was prepared by the action of methylhydrazine on 3-*p*-methoxyphenyl-1-phenyl-2-propen-1-one(**6**) to give 1-methyl-3-phenyl-5-*p*-methoxyphenylpyrazoline(**7**), which was then oxidized. Pyrazoles **2** and **3** had identical ^{1}H NMR spectra, consisting of a singlet at δ 6.50 for one heteroaromatic proton, a typical A_2B_2 pattern for the *p*-substituted phenyl substituent centred at *ca* δ 7.30, a singlet for *N*-CH_3 at δ 3.88 and a multiplet for the unsubstituted phenyl groups at δ 7.40. Pyrazolines **5** and **7** showed a singlet for *N*-CH_3 at δ 2.75, an ABX pattern for the heterocyclic ring hydrogens[10] at δ 2.80, 3.55 and 4.25 and an A_2B_2 pattern for the *p*-substituted phenyl groups centred at *ca* δ 7.30.



Scheme 1

Pyrazoles **2** and **3** contain three donor sites where complexation with the shift reagent can occur, i.e. the methoxy group and the two nitrogens in the heterocyclic ring. There is ample precedent[11] that

* Author to whom correspondence should be addressed.
† For Part 1, see *J. Heterocycl. Chem.* **19,** 415 (1982).
§ Part of the MSc thesis of H. Hammoud.

CCC-0030-4921/83/0021-0243$01.50

ethers are very poor donors towards lanthanide shift reagents, especially when the ether oxygen lone pair can delocalize into an extended π system.[12] The competition between two amino functions for the lanthanide shift reagent is often determined by steric rather than electronic factors.[13] However, molecular models of **2** and **3** show that both nitrogen atoms in the pyrazole ring are equally accessible. It is believed that it is the electronic character of the nitrogens which will determine their donation affinities in these two structures. Claramunt *et al.*[14] have shown that pyridine-like, but not pyrrolic, nitrogens coordinate effectively with LSR. The effect of $Eu(dpm)_3$ on the ^1H NMR spectra of amines was studied by Beauté *et al.*,[12] and the induced shifts in the α-hydrogens of pyridine and pyrrole were found to be 90.0 and 0.4 ppm, respectively. A parallel can be shown between pyridine and pyrrole and the nitrogens in pyrazoles **2** and **3** (imine or pyridine-like and tertiary amine or pyrrole-like); the latter, with a positive nitrogen, has practically no affinity to LSR.

The effects of $Eu(fod)_3$ on the ^1H NMR spectra of **2** and **3** are shown in Fig. 1. All lines have correlation coefficients larger than 0.99. Confirmation that the imine nitrogen is the complexation site comes from the observation that the shifts of H–E moved the fastest (gradients 0.19 and 0.22 ppm for pyrazole **2** and **3**, respectively). The fact that H-B showed slower gradients (0.36 and 0.33 ppm for **2** and **3**, respectively) than H-E, and faster gradients than H-A, H-C and H-D, further confirms the complexation site as the imine nitrogen and excludes the other function. The different gradients for H-E in **2** and **3** show that the europium, complexed at the imine nitrogen, is closer to H-E in **2** than in its regioisomer **3**. In addition, inspection of Fig. 1 shows that the different gradients for H-A (1.30 ppm for **2** and 2.99 ppm for **3**) clearly indicates that the methoxy group in **2** is closer to the complexation site than in **3**. The effect of $Eu(fod)_3$ on the ^1H NMR spectrum of pyrazole **2** prepared indirectly from chalcone **4** (Scheme 1) was also studied, and was found to be identical with that of pyrazole **2** prepared directly from the acetylenic ketone **1**.

Having proved the regioisomeric nature of each of the pyrazoles **2** and **3**, it becomes intuitively obvious that the addition of methylhydrazine to acetylenic ketones is a highly regioselective addition, proceeding via an initial 1,2-addition as opposed to the 1,4-addition mode.

EXPERIMENTAL

Synthesis

The acetylenic ketone **1** and the chalcones **4** and **6** were prepared as described previously.[5,7,8] A mixture of the α,β-unsaturated ketone (**1**, **4**, **6**) (0.01 mol) and methylhydrazine (0.02 mol) in ethanol (50 ml) was refluxed for 3 h. The reaction mixture was concentrated under reduced pressure and left to cool. The precipitated product was filtered off and crystallized from cyclohexane to give pyrazole **2** and pyrazoline **5**

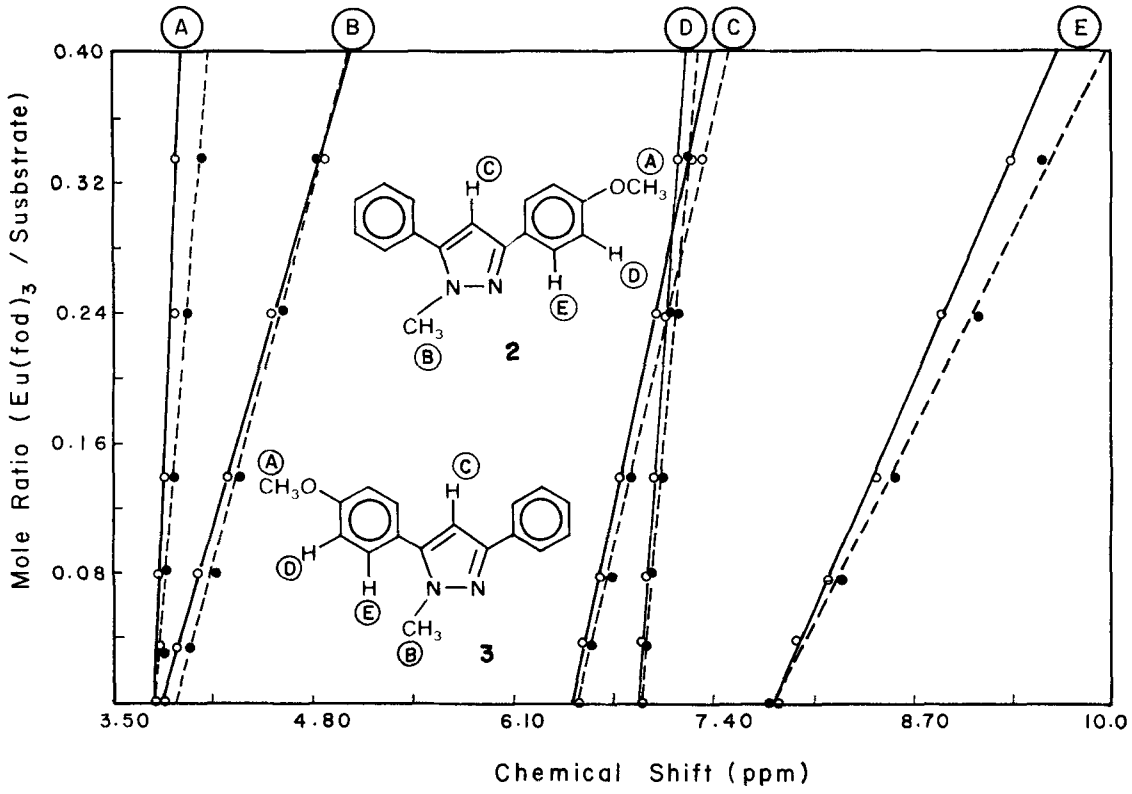


Figure 1. Effects of $Eu(fod)_3$ on the ^1H NMR spectra of **2** (●– – –●) and **3** (○——○).

or **7**, respectively. Pyrazoline **5** had m.p. 94 °C. Elemental analysis: found, C 76.50, H 6.46, N 10.31 %; calculated, C 76.66, H 6.81, N 10.52 %. Pyrazoline **7** is an oil. Elemental analysis: found, C 76.54, H 6.76, N 10.41 %; calculated, C 76.66, H 6.81, N 10.52 %. These analyses were carried out by A. Bernhardt, Microanalytical Laboratory, FRG.

The pyrazolines **5**, **7** were oxidized with molecular oxygen in refluxing glacial acetic acid (6 h); the reaction mixture was left to cool and the precipitated product was crystallized from hexane to give the pyrazoles **2** and **3**, respectively. Pyrazole **2** had m.p. 94 °C. Elemental analysis: found, C 77.31, H 6.24, N 10.49 %; calculated, C 77.25, H 6.10, N 10.59 %. Pyrazole **3** had m.p. 109 °C. Elemental analysis: found, C 77.07, H 6.28, N 10.51 %; calculated, C 77.25, H 6.10, N 10.59 %.

NMR Spectra

The ^{1}H NMR spectra were recorded on a Varian T-60A spectrometer (60 MHz), using TMS as internal standard and approximately 0.4 M solutions in $CDCl_3$, at 25 °C with a sweep width of 500 Hz and a sweep time of 250 s. The NMR shift reagent tris(1,1,1,2,2,3,3-heptafluoro-7,7-C^2H_6-dimethyl-4,6-C^2H_3-octanedionato)europium(III) [Eu(fod)$_3$] was added in *ca* 10 mg increments to solutions of pyrazoles **2** and **3** in the NMR tubes, and the spectrum was recorded after each addition.

Acknowledgement

We thank the Research Council of Kuwait University for supporting this work.

REFERENCES

1. F. G. Baddar, M. N. Basyouni and F. A. Fouli, *J. Indian Chem. Soc.* 589 (1973).
2. R. D. Abell and W. Sidall, *J. Chem. Soc.* 2804 (1953).
3. C. Moureu and M. Brachin, *C.R. Acad. Sci.* **136**, 1264 (1903).
4. J. Sistare and J. Pascaul, *An. R. Soc. Esp. Fis. Quim. Ser. B* 48, 7/8, **6**, 593 (1952).
5. R. P. Barnes and L. B. Dodson, *J. Am. Chem. Soc.* **65**, 1585 (1943).
6. G. Coispeau, J. Elguero and R. Jacquier, *Bull. Soc. Chim. Fr.* 689 (1970); 2717 (1970).
7. N. R. El-Rayyes and F. H. Al-Hajjar, *J. Heterocycl. Chem.* **14**, 367 (1977).
8. F. G. Baddar, F. H. Al-Hajjar and N. R. El-Rayyes, *J. Heterocycl. Chem.* **15**, 385 (1978).
9. N. R. El-Rayyes, G. H. Hovakeemian and H. Hammoud, MSc Thesis of H. Hammoud, University of Kuwait.
10. J. O. Oluwadiya, *J. Heterocycl. Chem.* **18**, 1293 (1981).
11. (a) A. F. Cockerill, G. L. O. Davies, R. C. Harden and D. M. Rackham, *Chem. Rev.* **73**, 553 (1973); (b) J. K. Sanders and D. M. Williams, *J. Am. Chem. Soc.* **93**, 641 (1971).
12. C. Beauté, Z. W. Wolkowski and N. Thoai, *Tetrahedron Lett.* 817 (1971).
13. H. Burzynska, J. Dabrowski and A. Krowezynski, *Bull. Acad. Pol. Sci.* **19**, 587 (1971).
14. R. M. Claramunt, J. Elguero and R. Jacquir, *Org. Magn. reson.* **3**, 595 (1971).

Received 28 June 1982; accepted (revised) 19 October 1982