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A CARBON-13 AND NITROGEN-15 ISOTOPIC LABELLING STUDY OF INTERMEDIATES AND BY-PRODUCTS IN THE REACTION OF CHALCONE AND PHENYLHYDRAZINE TO GIVE 1,3,5-TRIPHENYL-2-PYRAZOLINE

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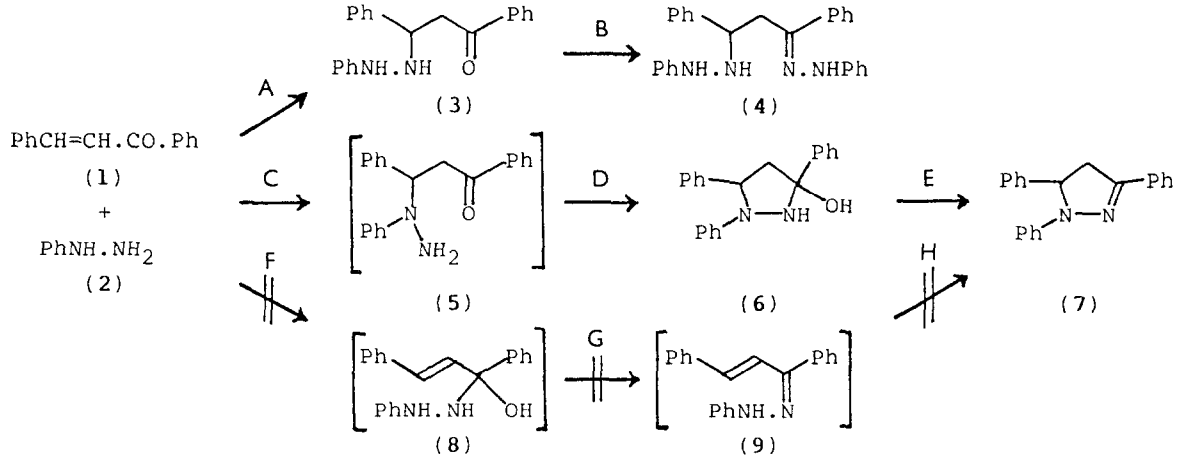
Abstract The formation of 1,3,5-triphenyl-2-pyrazoline **7** from chalcone and phenylhydrazine *via* 1,4-addition followed by an allowed 5-endo-trig cyclisation has been demonstrated by ^{13}C and ^{15}N labelling in time resolved ^{13}C NMR spectroscopy.

The formation of 1,3,5-triphenyl-2-pyrazoline **7** from chalcone (**1**) and phenylhydrazine (**2**) is an early example of the most widely used synthetic route to 2-pyrazolines.[1,2] It has generally been accepted that the reaction proceeds *via* the cyclisation of chalcone phenylhydrazone (**9**: Scheme, reaction H).[2] This Letter presents evidence for a mechanism involving 1,4-addition of phenylhydrazine to chalcone by initial reaction at N-1 to give an intermediate that cyclises to the pyrazoline (**7**) (Scheme, reactions **C**, **D**, **E**) and by initial reaction at N-2 to give by-product **4** (Scheme, reactions **A**,**B**).



Scheme. Reactions between chalcone and phenylhydrazine in methanol-tetrahydrofuran. Species in square brackets were not detected by carbon NMR.

This Letter describes the identification by ^{13}C NMR of the species involved in the reactions between chalcone and phenylhydrazine. The technique is well suited to this type of problem since, under normal operating conditions,

resonances are narrow signals and therefore resonances from different species in a mixture are readily resolved.[3] NMR methods, furthermore, do not perturb the system observed. The use of ^{13}C-substituted compounds dramatically enhances the sensitivity of the technique and also simplifies the spectra since species involved in the reaction are usually observed as single resonances. The improvement in the ratio of signal to noise resulting from isotopic substitution is particularly important in time resolved experiments since the relatively low sensitivity of ^{13}C NMR places practical limits on time resolution. Additional structural information was obtained using selective ^{15}N isotopic substitution in phenylhydrazine (**2**) in order to determine the C-N connectivities in intermediates by the observation of one bond C-N coupling.

Preliminary experiments, using (3-^{13}C)chalcone, gave good qualitative information about the reactions between **1** and **2** in a methanol-tetrahydrofuran mixture[4] (Figure).

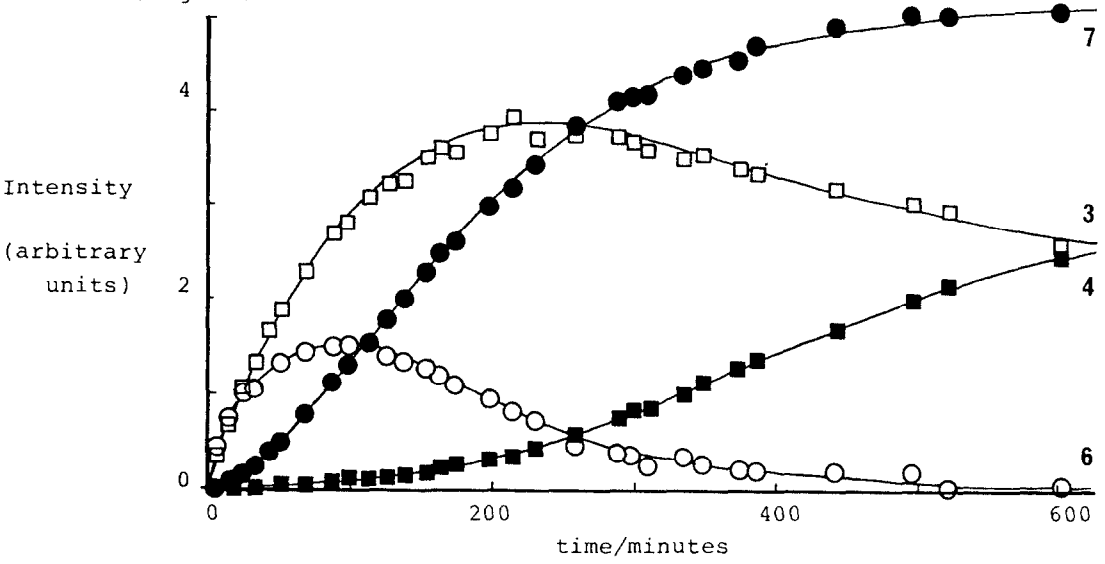


Figure. Intensity against time profiles for four species formed from chalcone and phenylhydrazine.

It was immediately apparent that two species were initially formed competitively. One of these was clearly the precursor of the 2-pyrazoline **7** while the other reacted rather more slowly to give a by-product which could not be isolated but which was stable under the conditions of the experiment for some hours.

Experiments using different (^{13}C)chalcones were performed (Table 1) and it was evident that the precursor of the 2-pyrazoline **7**, the precursor of the by-product, and the by-product were **6**, **3**, and **4** respectively. The data from the reactions of (2-^{13}C) and (3-^{13}C)chalcone clearly demonstrate that the intermediates involve 1,4-addition to chalcone since none of the chemical shifts measured is characteristic of unsaturated carbon.[3] The difference (11.4 ppm)

Table 1. Chemical shifts (ppm downfield from $SiMe_4$) for isotopically substituted species observed in the reactions between (^{13}C)chalcones and phenylhydrazine in methanol-tetrahydrofuran (see note 4).

Species	^{13}C-Isotopically substituted chalcone		
	1-^{13}C	2-^{13}C	3-^{13}C
Chalcone (1)	191.8	123.0	145.4
3	200.4	45.2	61.6
4	143.3	33.8	63.6
6	93.0	54.2	69.1
7	148.2	44.3	63.5

in chemical shifts for **3** and **4** using (2-^{13}C)chalcone allows the stereochemistry of the phenylhydrazone to be assigned as shown in the Scheme.[5] When (1-^{13}C)chalcone was used the intermediate **3** is observed 8.6 ppm downfield from **1**, a value typical of the difference between a related pair of $\alpha\beta$-unsaturated and unconjugated ketones.[3] The 2-pyrazoline precursor is identified as **6** (see below) rather than **5** because the chemical shift observed when (1-^{13}C)chalcone is used is far too low to be consistent with a carbonyl group.[3,6] The chemical shift measured for the precursor of the by-product is consistent with a phenylhydrazone (**4**).[3]

Further experiments using phenyl-(^{15}N)hydrazines and (^{13}C)chalcones confirmed the structures of the various species involved in the reactions. From the $^{1}J_{CN}$ values in Table 2 it is evident that there is competition between two 1,4-additions to chalcone involving the two N atoms of phenylhydrazine. The adduct **5** resulting from the addition of N-1 to chalcone was not detected and presumably cyclises (Scheme, reaction D) rapidly by an allowed 5-exo-trig process[7,8] to give **6**, the observed precursor of **7**.

Table 2. Carbon-13 to nitrogen-15 spin-spin coupling constants measured for species formed in the reaction between (^{13}C)chalcones and phenyl-(^{15}N)hydrazines in methanol-tetrahydrofuran (see note 4).

Species	^{13}C-substituted chalcone and ^{15}N-substituted phenylhydrazine		
	1-^{13}C/1-^{15}N	3-^{13}C/1-^{15}N	3-^{13}C/2-^{15}N
3	0[a]	0[a]	3.6[b]
4	8.5[c]	0[a]	3.5[b]
6	3.5[c]	5.4[b]	0[a]
7	7.4[c]	6.2[b]	0[a]

[a] No resolved splitting: J<1Hz. [b] Digitisation 0.13Hz. [c] Digitisation 0.45Hz

It is not apparent from semi-quantitative experiments such as these why reactions **A** and **C** should be competitive. There is good evidence that phenylhydrazine is protonated at N-2 rather than at N-1, as would be expected. Quantitative kinetic measurements are required to give a basis for explaining the competition between **A** and **C** and these will be reported in a forthcoming paper.[6] The kinetics of the reaction have been studied using polarography but only the concentrations of **1** and **7** were monitored.[9] A kinetically significant intermediate was inferred because the build up of the product **7** lagged behind the decay of the starting material. Because it was not detected by polarography the kinetically significant intermediate was assumed to be **8** rather than the conjugated hydrazone **9**, which was supposed to cyclise rapidly. The cyclisation of **9** to **7**, however, is an example of an unfavourable 5-endo-trig process.[7,8] It is interesting to note that in a closely related reaction chalcone oxime has been shown not to be an intermediate in the formation of 3,5-diphenyl-2-isoxazoline.[10]

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NOTES AND REFERENCES

1. L. Knorr and K. Laubmann, Chem. Ber., 1888, **21**, 1205.

2. L.C. Behr, R. Fusco, and C.H. Jarboe, Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings, Interscience, New York, 1967.

3. G.C. Levy, R.L. Lichter, and G.L. Nelson, Carbon-13 Nuclear Magnetic Resonance, Wiley-Interscience, New York, 1980.

4. (1,1,1-$^{2}H_{3}$)Methanol (85 mol%)/tetrahydrofuran (15 mol%).

5. P.W. Kenny, D.Phil. Thesis, Oxford, 1982.

6. P.W. Kenny and M.J.T. Robinson, in preparation.

7. J.E. Baldwin, J. Chem. Soc. Chem. Commun., 1976, 734.

8. J.E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, R.C. Thomas, J. Chem. Soc. Chem. Commun., 1976, 736.

9. V.F. Lavraushkin, V.D. Bezuglyi, G.C. Belous, and V.G. Tishchenko, Zhur. Obs. Khim., 1964, **34**, 7.

10. R.P. Barnes, G.E. Pinkney, and G.M. Phillips, J. Am. Chem. Soc., 1954, **76**, 276.

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