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COMPETITION BETWEEN FISCHER INDOLIZATION AND [5,5] SIGMATROPIC REARRANGEMENT OF ARYLHYDRAZONES

R. Fusco and F. Sannicolo'
Istituto di Chimica Industriale dell'Universita'
CNR, Centro di studio sulla sintesi e stereochimica di speciali sistemi organici
Via Golgi, 19 - 20133 Milano

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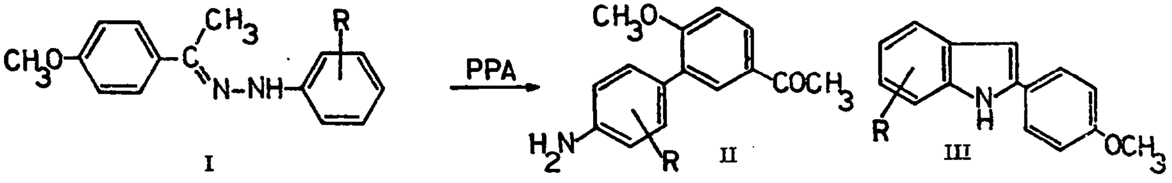
We have recently shown[1] that a few arylhydrazones of aromatic aldehydes and ketones incapable of Fischer indole rearrangement undergo a novel [5,5] sigmatropic rearrangement promoted by polyphosphoric acid (PPA) and heat leading to biphenyl derivatives. We have illustrated this behaviour only in a few instances (2,6-dimethyl-phenylhydrazones of anisaldehyde, 4,4'-dimethoxy-benzophenone and fluorenone), but it seems now to be of a much wider validity. In fact, we shall show in this paper that, even arylhydrazones capable of indolization, under particular circumstances, can undergo the same [5,5] sigmatropic rearrangement exclusively or in competition with the Fischer reaction.

When the 2,6-dimethyl-phenylhydrazone of 4-methoxy-acetophenone (Ia) (m.p. 52-4°C, from ethanol) was heated at 100-110°C with ten parts of PPA for 30 minutes, the mixture poured in water and the pH adjusted to 6 with ammonium hydroxide, a product separated from which a basic solid fraction could be extracted. The 3-acetyl-4'-amino-6-methoxy-3',5'-dimethylbiphenyl (IIa) was obtained in about 50% yield by crystallization from methanol (m.p. 110°C). PMR[2]: 2.1 (2H, m, aromatic in position 2 and 4); 2.87 (2H, s, aromatic in position 2' and 6'); 3.05 (1H, d, aromatic in position 5); 6.15 (3H, s, OCH_3); 6.45 (2H, broad s exchangeable with D_2O, NH_2); 7.44 (3H, s, $COCH_3$); 7.78 (6H, s, 2 CH_3). Only traces of the expected 4,7-dimethyl-2-(4-methoxyphenyl)indole (IIIa)[3] could be detected.



I II III

a R = 2,6-diMe	a R = 3',5'-diMe	a R = 4,7-diMe
b R = H	b R = H	b R = H
c R = 3,5-diMe	c R = 2',6'-diMe	c R = 4,6-diMe

The formation of (IIa) can be explained on the basis of a [5, 5] sigmatropic rearrangement of the protonated substrate, according to a scheme we have already reported in a previous paper[1].

The phenylhydrazone of 4-methoxyacetophenone (Ib)[4], when submitted to the same treatment, gave, beside a larger quantity of the known indole derivative (IIIb)[4], a basic product in about 10% yield (m.p. 131°C from isopropanol), to which the structure of 3-acetyl-4'-amino-6-methoxybiphenyl (IIb) was assigned. PMR: 2.10 (2H, m, aromatic in position 2 and 4); 2.70 and 3.32 (each 2H, ddC_6H_4-NH_2); 3.05 (1H, d, aromatic in position 5); 6.16 (3H, s, OCH_3); 6.35 (2H, broad s exchangeable with D_2O, NH_2); 7.45 (3H, s, $COCH_3$).

In order to investigate the influence of steric and electronic factors on the two competing reaction paths, we examined the behaviour of the 3, 5-dimethyl-phenylhydrazone of 4-methoxyacetophenone (Ic) (m.p. 94°C from methanol), which was treated as previously described for (Ia) and (Ib). The 2-(4-methoxyphenyl)-4, 6-dimethylindole (IIIc) (m.p. 129-130° C from ethanol) was recovered from the neutral fraction in a 40% yield.

The basic fraction afforded the 3-acetyl-4'-amino-6-methoxy-2', 6'-dimethylbiphenyl (IIc) in a 50% yield (m.p. 139°C from ethanol); PMR: 2.1 (2H, m, aromatic in position 2 and 4); 3.0 (1H, d, aromatic in position 5); 3.52 (2H, s, aromatic in position 3' and 5'); 6.20 (3H, s, OCH_3); 6.36 (2H, broad s exchangeable with D_2O, NH_2); 7.45 (3H, s, $COCH_3$); 8.08 (6H, s, 2 CH_3).

These new experimental results show that favourable structural features allow in arylhydrazones the [5, 5] sigmatropic rearrangement, which can successfully compete with the Fischer indolization. Of paramount importance in this context seems to be the presence of an electron donating group in the position "para" to the carbonyl group of the acetophenone, but a significant role is played also by the presence of methyl groups in the arylhydrazine moiety of the substrate.

References and notes

1) R. Fusco and F. Sannicolo', Tetrah. Letters, 36, 3163 (1977)

2) Chemical shifts are given in τ (TMS as internal standard and $CDCl_3$ as solvent) and refer to the centre of the signal. s=singlet, m=multiplet, dd=doublet of doublets.

3) The 1, 2-shift of an alkyl group is a general feature of indolization of 2, 6-alkyldisubstituted phenylhydrazones: B. Robinson, Chem. Rev., 63, 378 (1963); 69, 230 (1969).

4) K. Kaji and H. Nagashima, J. Pharm. Soc. Japan, 72, 1589 (1952).