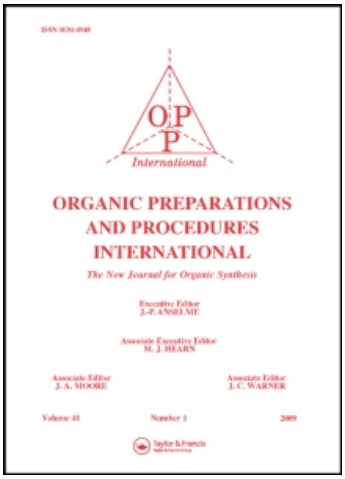

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3-(5)ALKYL PYRAZOLES

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3-(5)ALKYL PYRAZOLES

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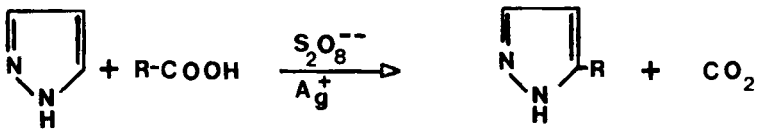
The electrophilic alkylation of the pyrazole ring is of limited application and the alkyl group can only be introduced in the 4-position.[1] In our continuing studies[2] of the reaction of nucleophilic free radicals with heteroaromatic compounds, we have considered the possibility of alkylating the pyrazole ring. We now report the highly selective homolytic alkylation of pyrazole in the 3-position.



This result was achieved by alkylation of the protonated base using as radical source, the silver ion catalyzed decarboxylation of carboxylic acid. The silver(II) ion was generated by peroxydisulfate according to the following redox chain reactions.

$$S_2O_8^{--} + Ag^+ \longrightarrow SO_4^{-\cdot} + SO_4^{--} + Ag^{++}$$

$$SO_4^{-\cdot} + Ag^+ \longrightarrow SO_4^{--} + Ag^{++}$$

$$R\text{-}COOH + Ag^{++} \longrightarrow R\cdot + CO_2 + Ag^+ + H^+$$

Although we obtained good results with isopropyl and t-butyl

radicals, yields were lower with primary alkyl radicals. This behavior, as well as the high selectivity of attack at the 3-position, can be ascribed to the stronger nucleophilic character of the secondary and tertiary alkyl radicals. This is the first example of homolytic alkylation of the pyrazole ring.

EXPERIMENTAL

Melting points are uncorrected. The nmr spectra were obtained on a Varian A-60 spectrometer; chemical shifts are in ppm(δ) from TMS as an internal standard. The gas chromatographic analyses were carried out with a C. Erba Fractovap G. V. instrument with a flame ionization detector on a 2 m. x 3 mm. i. d. pyrex column, packed with 10% DEGS on Chromosorb W-A. W. 80-100 mesh, at a column temperature of 160°. The alkylpyrazoles were isolated by chromatography on a silica gel column, using a 9:1 hexane-ethyl acetate mixture as eluent.

3-(5)t-Butylpyrazole.- A mixture of 2.25 g.(0.033 mole) of pyrazole, 1.8 ml.(0.033 mole) of conc. sulfuric acid, 10.2 g. (0.10 mole) of pivalic acid and 0.85 g.(0.005 mole) of silver nitrate in 10 ml. of water was heated to 60°. Then a solution of 12 g.(0.05 mole) of ammonium peroxydisulfate in 2o ml. of water was added in one portion. Heating at 60° was continued for an additional 30 min. After basification with 6N sodium hydroxide, the solution was extracted with chloroform. Removal of the solvent left a residue(2.7 g.) which on analysis by glc showed the presence of pyrazole(30.5%) and of 3-(5)t-butylpyrazole(69.5%). Chromatography of the residue gave 1.8 g.(44%) of pure 3-(5)t-butylpyrazole as a white solid, mp. 54-55°, lit.[3] mp. 53-55°. The structure was further confirmed by the

nmr spectrum[4] in trifluoroacetic acid which exhibited peaks at δ 1.33(s, 9H), 6.65-6.70(d, 1H), 8.0-8.1(d, 1H).

3-(5)Isopropylpyrazole.- The reaction was performed as described above except that isobutyric acid was used in this case. Glc analysis of the crude product(1.5 g.) indicated the presence of pyrazole(16.5%) and of 3-(5)isopropylpyrazole(80%). The pure product was isolated as a colorless liquid in 30% yield by chromatography, n_D^{20} 1.4849, lit. n_D^{20} 1.4850. Its nmr spectrum($CDCl_3$) was consistent with the assigned structure exhibiting peaks at δ 1.20(s, 3H), 1.31(s, 3H), 2.76-3.31 (septet, 1H), 5.9-6.5(d, 1H), 7.24-7.7(d, 1H).

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