Chemistry of Heterocyclic Compounds, Vol. 33, No. 11, 1997

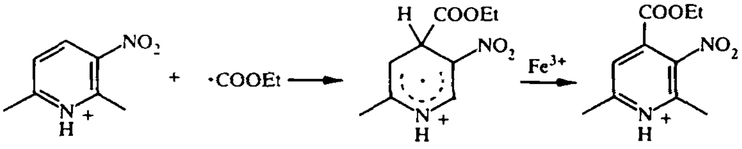
HOMOLYTIC ETHOXYCARBONYLATION OF 3-NITROPYRIDINES

M. A. Yurovskaya and O. D. Mit'kin

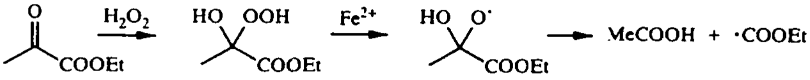
The homolytic ethoxycarbonylation of alkyl-3-nitropyridines has been accomplished for the first time by the action of ethyl pyruvate and hydrogen peroxide in the presence of ferrous sulfate.

Homolytic substitution in pyridines is virtually the only method for the direct introduction of functional groups such as acyl, alkoxycarbonyl, and carbamoyl groups into the electron-poor azine ring. Cyano- and acetylpyridines served as substrates in these reactions [1, 2]. There have been no reports of the use of nitropyridines in these reactions.

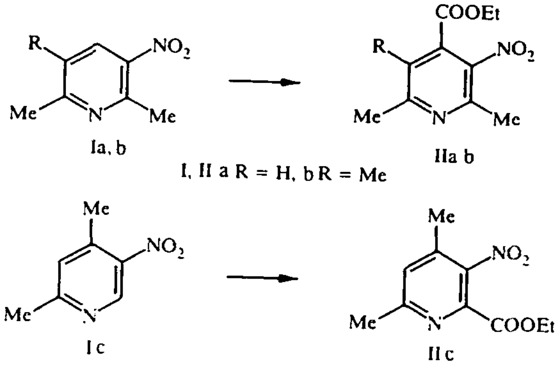
Homolytic substitution proceeds through the addition of a nucleophilic radical to a protonated azine with subsequent oxidation of the radical–cation formed by ferric ion:



The ethoxycarbonyl radical was generated by reduction of the adduct of hydrogen peroxide with ethyl pyruvate using ferrous sulfate:



The presence of a nitro group should strongly enhance the electrophilicity of the azine ring and facilitate the reaction without regard to the presence of alkyl substituents. However, yields did not exceed 35% in the homolytic carboethoxylation of nitropyridines Ia and Ib. Significant amounts of the starting compounds could not be isolated upon work-up of the reaction mixture.



Ia, b

IIa b

I, II a R = H, b R = Me

Ic

IIc

The participation of the nitro group in oxidation–reduction reactions may account for the low yields.

M. V. Lomonosov Moscow State University, 119899 Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1502-1503, November, 1997. Original article submitted June 26, 1997.

The two-phase water–dichloromethane system was used to prevent side-reactions of the reaction product [2, 3]. The product of radical substitution, which is less basic due to the presence of an additional electron-withdrawing substituent, does not form a salt with acid under the reaction conditions and may be extracted by organic solvents. We specifically used this technique for carrying out the reaction in the two-phase water–carbon tetrachloride system. The substrates were 2,6-dimethyl-3-nitropyridine (Ia), 2,5,6-trimethyl-3-nitropyridine (Ib), and 2,4-dimethyl-3-nitropyridine (Ic). These compounds were selected in order to examine the possibility of the radical introduction of an ethoxycarbonyl group at the α and γ positions of the 3-nitropyridine molecule and the effect of the number of alkyl substituents in the starting pyridine molecule. The difference in the structures of starting pyridines Ia-Ic did not have a significant effect on the homolytic ethoxycarbonylation and the yields of the ethyl esters of nitropicolinic IIa and nitroisonicotinic acids IIb and IIc did not exceed 40%.

The PMR spectra of IIa-IIc show signals for the ethoxycarbonyl protons at 4.40 (2H, q, CH_2) and 1.38 ppm (3H, t, CH_3) and lack signals for the γ-hydrogen atoms (IIa and IIb) and α-hydrogen atom (IIc) (~8-9 ppm) of the nitropyridine ring. The IR spectra of IIa-IIc show stretching bands for the ester carbonyl group at 1740 cm^{-1} and nitro group at 1330 and 1540 cm^{-1}.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for Vaseline mulls. The PMR spectra were taken on a Bruker AC-200 spectrometer for solutions in $CDCl_3$ with TMS as the internal standard.

Nitroethoxycarbonylpyridines (General Method). A sample of 3.4 g (0.03 mole) 30% hydrogen peroxide was added with stirring to 5.2 g (0.045 mole) ethyl pyruvate at from −15 to −5°C. The solution obtained was added dropwise with stirring to a mixture of 0.01 mole nitropyridine, 3 g concentrated sulfuric acid, 8 ml water, 8.3 g (0.03 mole) $FeSO_4 \cdot 7H_2O$, and 150 ml CCl_4, maintaining the temperature at from −10 to 0°C. After stirring for 15 min, the organic layer was separated and the aqueous layer was extracted with 50 ml CCl_4. The combined organic fractions were washed several times with water, dried over Na_2SO_4, and dried in vacuum. The residue was subjected to chromatography on a silica gel 40/100 column using 5:1 toluene–ethyl acetate as the eluent.

2,6-Dimethyl-3-nitro-4-ethoxycarbonylpyridine was obtained in 26% yield, mp 58-59°C (from heptane). PMR spectrum: 1.37 (3H, t, $CH_2\underline{CH_3}$), 2.60 (3H, s, 6-CH_3), 2.65 (3H, s, 2-CH_3), 4.39 (2H, q, $\underline{CH_2}CH_3$), 7.49 ppm (1H, s, 5-H). IR spectrum: 1332, 1560, 1740 cm^{-1}. Found: C, 53.79; H, 5.36;N, 12.37%. Calculated for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49%.

4,6-Dimethyl-3-nitro-2-ethoxycarbonylpyridine was obtained in 36% yield, mp 90-91°C (from heptane). PMR spectrum: 1.37 (3H, t, $CH_2\underline{CH_3}$), 2.38 (3H, s, 4-CH_3), 2.61 (3H, s, 6-CH_3), 4.41 (2H, q, $\underline{CH_2}CH_3$), 7.16 ppm (1H, s, 5-H). IR spectrum: 1340, 1545, 1740 cm^{-1}. Found: C, 53.74; H, 5.45; N, 12.48%. Calculated for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49%.

2,5,6-Trimethyl-3-nitro-4-ethoxycarbonylpyridine ($C_{11}H_{14}N_2O_4$) was obtained as an oil in 34% yield. PMR spectrum: 1.37 (3H, t, $CH_2\underline{CH_3}$), 2.31 (3H, s, 5-CH_3), 2.60 (3H, s, 6-CH_3), 2.68 (3H, s, 2-CH_3), 4.39 ppm (2H, q, $\underline{CH_2}CH_3$). IR spectrum: 1330, 1541, 1760 cm^{-1}. Mass spectrum, m/z (I_{rel}, %): M^+ 238 (37.2), 221 (28.7), 193 (86.2), 192 (100), 177 (12.7), 162 (57.4), 148 (15.4), 134 (47.3).

The authors express their gratitude to RFFI (Grant 96-03-32157a) for financial support of this work.

REFERENCES

1. T. Caronna, G. Fronza, F. Minisci, and O. Porta, J. Chem. Soc., Perkin Trans. II, No. 14, 2035 (1972).
2. G. Heinisch and G. Lotsch, Angew. Chem. Intern. Ed., **97**, 694 (1985).
3. G. Heinisch and G. Lotsch, Tetrahedron, **42**, 5973 (1986).