SYNTHESIS OF INDOLES FROM PYRIDINIUM SALTS.

4.* KETIMINES IN THE SYNTHESIS OF INDOLES FROM 3-NITROPYRIDINIUM SALTS

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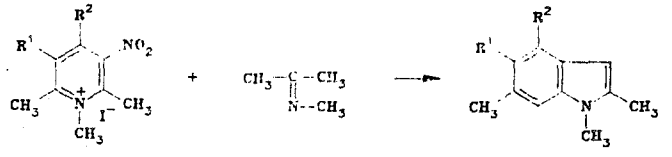
The possibility of using certain ketimines in place of mixtures of ketone and amine in the synthesis of indoles from 3-nitropyridinium salts has been demonstrated. The use of ketimines leads, in many cases, to increased yields of indoles and simplifies their isolation. It has been established that the rate of indole formation is considerably increased in polar aprotic solvents.

It has been shown previously, on a wide range of model compounds, that it is possible to prepare polyalkylindoles from salts of 3-nitropyridine [2-4]. In all cases the process involves the reaction of an excess of methylalkyl ketone and methylamine with the pyridine salt. The yield of indole when using acetone as the ketone component varies between 6 and 60% depending on the structure of the initial salt. The reaction is always accompanied by considerable resin formation as a result of self-condensation of the acetone in the basic medium and other side reactions and hence the only method of isolating the polyalkylindole is by column chromatography.

It is known that the reaction of ketones with primary amines leads to N-alkylketimines [5]. We have suggested that ready prepared ketimines could be used for the preparation of indoles from salts of 3-nitropyridine in place of a mixture of ketone and amine. We have carried out this suggestion using the example of the simplest N-alkylketimine — acetone N-methylimine (I) [6]. As initial salts of 3-nitropyridine, we selected IIa-d as models, providing a range of different numbers and locations of alkyl substituents. In all cases, in the reaction of salts II with ketimine I, we observed the formation of indoles, IIIa-d, which corresponded fully to the "molecular design" of the process which we proposed previously [3].



II (a-d) I III (a-d)

II, III a R^1=H, R^2=CH_3; b R^1=R^2=CH_3; c R^1=CH_3, R^2=H; d R^1=H, R^2=C_2H_5

The indoles IIIa [2] and IIId [3] were identical with those described previously. For proof of the structure of the indoles IIIb, c we used the technique (spectroscopic results, set out in the experimental section) which we developed previously [3].

The use of a pre-prepared imine makes it possible to examine the effect of the solvent on the rate and efficiency of the indole-formation process.† The salt IIa was used as an example to study the effect of polar aprotic solvents (Table 1). Since the reaction is not accompanied by resin formation the use of water-miscible solvents (such as DMF and pyridine, for example) permits considerable simplification of the procedure for separating the indole IIIa which is formed by simply diluting the reaction mixture with an equal volume of water (method B — see Table 1 and the experimental section). Up to 75% of the overall quantity of indole can be separated in this way and a further quantity obtained by chromatography.

*For Communication 3, see [1].

†In the framework of the present study, only indole formation was examined. A study of the products of concurrent reactions will be the subject of a further publication.

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TABLE 1. Effect of Solvent on the Yield of 1,2,4,6-Tetramethylindole (IIIa) from the Salt IIa and Imine I*

Solvent	Reaction time, days	Method of treatment**	Yield of indole, %
DMSO	1	A	55
Sulfolane	1	A	46
DMF	1	B	62
DMF	3	A	62
HMPA	1	A	51
Pyridine	1	A	56
Pyridine	3	A	62
Pyridine	7	B	62

*Reaction conditions: ratio of salt IIa:imine - 1:2.2, room temp., homogeneous medium.
**A = column chromatography; B = dilution with water.

TABLE 2. Effect of Solvent on the Yield of 1,2,4,5,6-Pentamethylindole (IIIb) from the Salt IIb and Imine I

Solvent	Reaction time, days	Yield of indole, %
DMF	1	55
Pyridine	1	48
Acetone	12	29
Chloroform	2,5	21
Triethylamine*	10	27
Dioxane	12	50
Benzene	8	26
Ethanol	6	18

*Ratio salt:imine = 1:1.2.

As can be seen from the results in Table 1, the use of polar aprotic solvents considerably accelerates the process of indole formation. In fact, when carrying out the reaction in DMF, one day proves to be sufficient to achieve a yield (60%) similar to that which requires 7 days by the earlier method [2]. The use of a less polar solvent (pyridine) requires 3 days to complete the reaction.

A wide range of solvents of different types and polarities was examined, using the salt IIb as an example (Table 2). In contrast to the work of [4] we used the pure salt IIb, free from the isomeric 1,2,6-trimethyl-4-ethyl-3-nitropyridinium iodide, which was prepared by selective synthesis of the pyridine salt from 2-methyl-2-butanol and acetic anhydride in the presence of sulfuric acid [7], conversion to the corresponding pyridine, nitration and quaternization. The proton NMR spectrum of the indole IIIb prepared from this salt showed that it was free e from 1,2,6-trimethyl-4-ethylindole and hence its melting point, 115-116°C, was considerably higher than that reported previously (59-60°C [8]). As in the preceding case, the most effective solvent was DMF, giving a yield of the indole (IIIb) some five times higher than that reported previously (11%, 7-15 days [4]). When a less polar solvent is used, the process is slowed and the yield falls. Protic solvents (ethanol) prove to be less effective.

Thus the use of the ketimine-DMF system would seem to provide the optimum conditions for conversion of 3-nitropyridinium salts to indoles. The use of this particular method makes possible an increase in the yield of indole IIId from salt IId from 43% [3] to 64%, and in the case of the salt IIc the yield of 1,2,5,6-tetramethylindole (IIIc), not previously reported, at 87% is the highest of all those presently known.

EXPERIMENTAL

Proton NMR spectra were run on T-60 and Brucker-360M instruments using TMS as internal standard. Carbon-13 spectra were obtained on a CFT-20 spectrometer. Mass spectra were recorded on a KB-2091 instrument with direct introduction of the sample into the ion source, the ionization energy being 70 eV and the temperature 200°C.

N-Methylacetonimine (I) was prepared by the method of [6]; mp 64-75°C. Proton NMR spectrum (DMSO-D_6, 360 MHz; δ, ppm): 1.76 (3H, m, syn-CH_3), 1.89 (3H, s, anti-CH_3, $J_{syn,anti}$ = 1.35 Hz), 2.93 (3H, q, N-CH_3, J_{syn,NCH_3} = 0.81 Hz).

1,2,4,6-Tetramethyl-3-nitropyridinium iodide (IIa) was prepared by the method of [9]. Proton NMR spectrum (DMSO-D_6; δ, ppm): 2.52 (3H, s, 6-CH_3), 2.73 (3H, s, 4-CH_3), 2.85 (3H, s, 2-CH_3), 4.09 (3H, s, N-CH_3), 8.15 (1H, s, 5-H).

1,2,3,4,6-Pentamethyl-5-nitropyridinium iodide (IIb) was prepared by synthesizing the 2,3,4,6-tetramethyl pyridinium salt by the method of [7], converting it, without isolation, into the corresponding pyridine, nitrating and quaternizing by the method of [4]. It was recrystallized from methanol and then from acetonitrile, mp 248°C (from acetonitrile). Proton

NMR spectrum (DMSO-D_6; δ, ppm): 2.46 (3H, s, 3-CH_3), 2.52 (3H, s, 2-CH_3), 2.75 (3H, s, 4-CH_3), 2.88 (3H, s, 6-CH_3), 4.23 (3H, s, N-CH_3).

2,3,6-Trimethyl-5-nitropyridine was prepared by nitration of the corresponding collidine by the method of [10], mp 52-53°C, bp 123°C (12 mm). From [10], bp 123°C (12 mm). Proton NMR spectrum (CCl_4; δ, ppm): 2.26 (3H, s, 3-CH_3), 2.44 (3H, s, 2-CH_3), 2.63 (3H, s, 6-CH_3), 7.85 (1H, s, 4-H).

1,2,3,6-Tetramethyl-5-nitropyridinium Perchlorate (IIc). A mixture of 8 g (48 mmole) 2,3,6-trimethyl-5-nitropyridine and 5 ml (52 mmole) dimethyl sulfate in 20 ml acetonitrile was heated at bp for 20 h. To the precipitated solid was added 5 ml 72% perchloric acid. The precipitate was filtered off and recrystallized from aqueous methanol. Yield 8.6 g (64%), mp 260°C (decomp). Proton NMR spectrum (DMSO-D_6); δ, ppm): 2.50 (3H, s, 3-CH_3), 2.77 (6H, br.s, 2- and 6-CH_3), 4.13 (3H, s, N-CH_3), 8.85 (1H, s, 4-H). Found (%): C 38.7, H 4.9. Calculated for $C_9H_{13}ClN_2O_6$ (%): C 38.5, H 4.7.

1,2,6-Trimethyl-4-ethyl-3-nitropyridinium iodide (IId) was prepared by the method of [3].

Polyalkylindoles IIIa-d (general method). The imine I was added with cooling and stirring to a mixture of the salt and solvent, and the mixture kept (in the case of nonhomogeneous mixtures, with stirring) for the time shown in Tables 1 and 2 and then treated by one of the following methods.

A. The reaction mixture was poured into a mixture of benzene and water, the aqueous layer extracted with benzene and the combined benzene extracts washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on 40/100 μm silica gel in a 1:3 benzene-hexane system.

B. An equal volume of water was added dropwise to the reaction mixture while cooling and stirring. After 10-20 min the indole precipitate was filtered off, washed with the minimum amount of water, and dried in air. The filtrate was treated in a manner similar to procedure A in order to isolate a further quantity of the indole.

1,2,4,6-Tetramethylindole (IIIa) was prepared from 1.54 g (5 mmole) salt IIa and 1 ml (10.6 mmole) imine I in 10 ml solvent. mp 83-84°C. From [2], mp = 82.83°C.

1,2,4,5,6-Pentamethylindole (IIIb) was prepared from 0.644 g (2 mmole) salt IIb and 0.42 ml (4.4 mmole) imine I in 5 ml solvent. mp 115-116 °C. Mass spectrum m/z (I, %): 188 (14), M^+ 187 (100), 186 (43), 173 (9), 172 (64), 171 (5), 170 (8), 157 (5), 156 (7), 128 (5). Proton NMR spectrum (acetone-D_6; δ, ppm): 2.19 (3H, s, 5(4)-CH_3), 2.33 and 2.34 (9H, 2 br.s, 2-, 4(5)-, and 6-CH_3), 3.55 (3H, s, N-CH_3), 6.09 (1H, m, 3-H, $J_{3,7}$ = 0.73 Hz, $J_{3,2\text{-}CH_3}$ = 0.90 Hz*), 6.90 (1H, m, 7-H, $J_{7,3}$ = 0.73 Hz*). Carbon-13 NMR spectrum (acetone D_6, δ, ppm): 12.59 (2-CH_3), 15.05 and 15.94 (4-CH_3 and 5-CH_3), 21.69 (6-CH_3), 29.34 (N-CH_3), 98.62 ($C_{(3)}$), 108.21 ($C_{(7)}$), 125.20 ($C_{(5)}$), 126.45 ($C_{(8)}$), 127.80 ($C_{(4)}$), 129.68 ($C_{(6)}$), 135.73 ($C_{(2)}$), 136.60 ($C_{(9)}$).

1,2,5,6-Tetramethylindole (IIIc) was prepared from 1.40 g (5 mmole) salt IIc and 1.42 ml (15 mmole) imine I in 10 ml DMF over a period of 1 day. Yield 0.75 g (87%), mp 110-112°C. Proton NMR spectrum (acetone-D_6; δ, ppm): 2.26 (3H, s, 5-CH_3), 2.33 (6H, s, 2- and 6-CH_3), 3.53 (3H, s, N-CH_3), 6.01 (1H, s, 3-H), 7.00 (1H, s, 7-H), 7.13 (1H, s, 4-H). Found (%): C 83.8, H 8.8. Calculated for $C_{12}H_{15}N$ (%): C 83.2, H 8.7.

1,2,6-Trimethyl-4-ethylindole (IIId) was prepared from 0.16 g (0.5 mmole) salt IId and 0.14 ml (1.5 mmole) imine I in 1 ml DMF over a period of 1 day. Yield 0.06 g (64%), mp 49-51°C. From [3], mp = 50-52°C.

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ISOINDOLES FROM PHTHALIMIDINES. N-ARYLISOINDOLES

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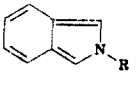
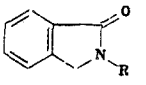
A convenient method was developed for the preparation of N-arylisoindoles by the reduction of the corresponding phthalimidines.

Several methods have been described for the preparation of N-arylisoindoles I, but none of them can be considered satisfactory [1]. Thus, we could not reproduce the synthesis of compound Ib via N-(4'tolyl)isoindoline N-oxide by the Polonskii reaction described in a brief communication [2]. Then we attempted to carry out the method of Wittig et al. [3], consisting in the reduction of phthalimidines IIa-d by lithium aluminum hydride. However, the main products of the reduction were the corresponding isoindolines, and the formation of trace amounts of isoindoles could be determined only chromatographically.



I



II

I, II a R=C_6H_5, b R=4'-$C_6H_4CH_3$, c R=4'-BrC_6H_4, d R=CH_3

We were able to obtain isoindoles Ia-d by the reduction of phthalimidines IIa-d with lithium bis(2-methoxyethoxy)aluminum hydride [4] used as a solution in benzene or toluene. As a rule, as a side product in the reaction, from 5 to 10% of the corresponding isoindoline was formed, which could be avoided by using its solubility in cold ether, which is better than that of isoindoles. N-arylisoindoles Ia-d could be obtained in yields from 70 to 80% by the proposed method (Table 1). All the synthesized isoindoles are colorless crystalline substances, and Ia-c are much more stable than Id.

In the proton NMR spectra of isoindoles Ia-d (Table 1), the 1,3-H protons gave a somewhat broadened singlet. The 4,7-H and 5,6-H protons in the spectrum gave two multiplets (Fig. 1). The components of one of them, located in a weaker field, were somewhat broadened because of interaction with 1,3-H protons (spin-spin coupling constant of 1 Hz [5]). We carried out a calculation with the PANIC iteration program to determine the values of the spin-spin coupling constants and to verify the indicated assignment of the proton signals (Fig. 1). The best correspondence between the calculated and experimental spectra was found with the chemical shifts indicated in Table 1 and the following values of the spin-spin coupling constants: $J_{1-7} = J_{3-4} = 0.8$; $J_{4-5} = J_{6-7} = 9$; $J_{5-6} = 6.3$; $J_{4-6} = J_{5-7} = 0.9$; $J_{4-7} = 0.77$ Hz. As shown by experiments, the nature of the substituent at the nitrogen atom of isoindole has practically no effect on the values of the spin-spin coupling constants of the protons of the isoindole fragment. As was accepted in [6], we tried to use the above-determined values of the spin-spin coupling constants of the vicinal protons of the carbocyclic part of isoindole as the aromaticity index. Our value of $J_{rel} = (J_{5-6}/J_{4-5}) = 0.7$ corresponds to the data for 2-methyl- and 1,3-diphenyl-2-methylisoindoles [1] and indicates partial localization of the bonds in the carbocyclic part of the molecule of the N-arylisoindoles.

The N-arylisoindoles have four absorption bands (Fig. 2), whereas the N-methyl derivative has only two distinct ones. In all the isoindoles, the long-wave absorption band at

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