Synthesis of Substituted Pyrroles from Ketones

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A number of substituted pyrroles have been prepared through a four step reaction sequence based on the regiospecific alkylation of *N,N*-dimethylhydrazones with 2-iodomethyl-1,3-dioxolane.

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In a previous paper we reported the transformation of (+)-camphor into (+)-8,9,9-trimethyl-5,6,7,8-tetrahydroquinoline through alkylation of camphor-*N,N*-dimethylhydrazone with 2-(2'-bromoethyl)-1,3-dioxolane followed by cyclization of the iminoacetal derivative [1]. More recently we have expanded this new pyridoannelation procedure to other substrates in order to define the potential and limitations of the method [2].

Now we wish to report the use of this synthetic strategy in the preparation of substituted pyrroles.

As shown in the Scheme, the procedure entails a four-step reaction sequence involving alkylation of the *N,N*-dimethylhydrazones (DMH's) **1** with 2-bromo- or 2-iodomethyl-1,3-dioxolane (BMD or IMD), followed by acid catalyzed cyclization of the iminoacetal derivatives **2** and finally by hydrogenolysis of the N-N bond.

DMH's were metallated with lithium diisopropylamide in tetrahydrofuran/hexamethylphosphoric triamide (HMPT) at 0° and subsequently alkylated at -78° with BMD to give compounds **2**. The results are listed in Table I. The conversion (0-80%) greatly depends upon the nature of the DMH's (Table I) since the bromine in the α position to an acetal is not very reactive [3]. In the case of the DMH of (+)-camphor the use of BMD was unsuccess-

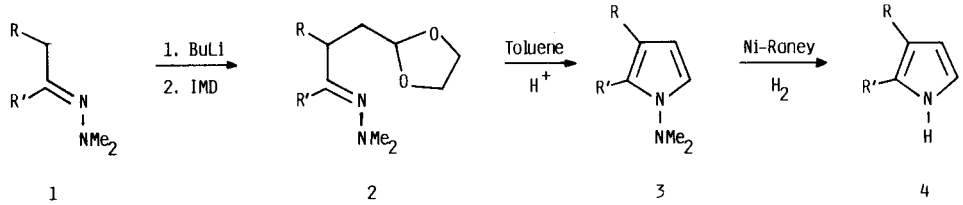
Table I

Results Obtained in the Alkylation of the DMH's with BMD and IMD

Entry	Alkylation with BMD		Alkylation with IMD	
	Conversion	Yield [a]	Conversion	Yield
a	50	87	100	91
b	70	93	100	95
c	75	50	100	95
d	80	85	100	92
e	50	90	100	94
f	0	0	85	92 [a]

[a] Yield based on reacted starting material.

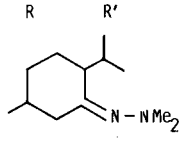
Scheme



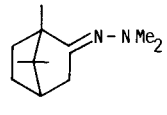
1 2 3 4

	R	R'
a	H	C_4H_9
b	H	C_6H_5
c	CH_3	C_2H_5
d	$-(CH_2)_4-$	

e



f



ful. This fact, probably due to the sterically hindered ketone prompted us to utilize the more reactive 2-iodomethyl-1,3-dioxolane (IMD). This reagent enhanced the conversion above 85% in the case of camphor DMH and gave quantitative conversion in the other cases (Table I).

The most outstanding features of the alkylation are the high positional selectivity towards the alkylation at the less substituted carbon [4] and the lack of side reactions that allow us to obtain the imino acetal in high yield in all cases either with BMD or IMD. It is noteworthy that for partial conversion it is possible to separate the iminoacetals **2** and the unreacted starting compounds **1** by simple fractional distillation.

Several reaction conditions were tested to achieve the pyrrole ring formation. Best results were obtained by refluxing compounds **2** in anhydrous toluene containing a few milligrams of *p*-toluenesulphonic acid. The yields and reaction times are reported in Table II. Sterically non-crowded dimethylaminopyrroles **3** (Entry a-d) are obtained in high yields, while these drop passing from moderately (Entry e) to very sterically-crowded pyrroles (Entry f). Also the reaction times detected in this stage are scattered over a wide range (Table II) depending on the structure of the aminoacetals **3**. High yields were obtained after prolonged heating, indicating the high thermal stability of these compounds.

Table II

Reaction Times and Yields in the Pyrroleannelation

Entry	Reaction time/hours	Yield
a	12	85
b	30	90
c	15	92
d	5	95
e	15	70
f	60	0

Previous attempts to achieve pyrrole anellation in other solvents, usually used in the cyclizative condensation of 1,4-dicarbonyl compounds with amines [5] gave poor formation of the pyrrole ring (25-35%).

The cleavage of the N-N bond with the removal of the dimethylamino group completes the synthetic Scheme. Hydrogenation over Raney-nickel catalyst has been reported by Severin *et al.* [6] as a very efficient method for the cleavage of the N-N bond of 2-aryl-1-dimethylaminopyrroles. Best results in the hydrogenation of the 2-phenyl-1-dimethylaminopyrrole (**3**) were obtained using T-1 Raney-nickel catalyst [7]. Thus the 2-phenylpyrrole (**4b**) was obtained in 85% yield. Variable results were obtained with this catalyst in the hydrogenation of the other dimethylaminopyrroles. In the hydrogenation of **3b** a 25% conversion to **4b** was achieved when the reaction was carried out at room temperature for 120 hours with a large amount of nickel catalyst. An attempt to perform the reaction at 80° brought about a faster formation of **4b** but a complex mixture of products was also obtained. Predictably compound **3e** was recovered unchanged. This behavior can be interpreted as the result of increased steric hindrance about the N-N bond. Finally neither reaction products nor starting materials could be detected after usual work-up in the case of **3c**.

In order to facilitate the hydrogenolysis of the N-N bond the quaternization of the *N,N*-dimethylamine group was attempted. Neither treatment of compound **3d** with excess of methyl iodide at reflux temperature nor trimethyloxonium tetrafluoroborate in dichloromethane provided the expected ammonium salts.

The method reported herein is particularly suited for regiospecific synthesis of aryl and alkyldimethylaminopyrroles from ketones. Also 2-phenylpyrroles can be profitably prepared.

EXPERIMENTAL

Boiling points are uncorrected. The gc controls were effected on a Perkin-Elmer 3920-B gas chromatograph, using 2 m x 2 mm column packed with 5% SE-30 on Chromosorb W and operating at a programmed temperature (between 100° and 300°). The products were separated by use of a Perkin-Elmer F-21 preparative scale gas chromatograph under the conditions and temperatures specified. The nmr spectra were obtained with a Varian T-60 spectrometer in tetrachloromethane solution using tetramethylsilane as an internal standard (δ = 0). Elemental analyses were performed on a Perkin-Elmer 240-B analyzer.

Materials.

All the ketones, *N,N*-dimethylhydrazine and 2-bromomethyl-1,3-dioxolane were commercial products (Fluka AG) and were used without further purification. (-)-(2*S*,5*R*)-menthone, $[\alpha]_D^{20}$ -24.98 (neat), was prepared from (-)-menthol through a conventional method [8]. 2-Iodomethyl-1,3-dioxolane was prepared according to Meyers *et al.* [9]. *N,N*-Dimethylhydrazones were obtained in high yield by reaction of the proper ketones with *N,N*-dimethylhydrazine in absolute ethanol according to a known procedure [10].

2-(Ethanediyldioxylethyl)-*N,N*-dimethylaminohydrazones (**2**). General Procedure.

To a solution of diisopropylamine (6.6 g, 0.065 mole) in THF (65 ml) a 1.6 *M* solution of *n*-butyllithium in *n*-hexane (47 ml) was added at -20°. After the addition was completed the solution was stirred at 0° for 15 minutes. A solution of **1** (0.065 mole) in HMPT (20 ml) was slowly added and stirring continued for 2 hours. The mixture was then warmed to 0° and stirring continued for 2 hours. The flask was cooled at -78° and 2-iodomethyl-1,3-dioxolane (14.1 g, 0.078 mmole) was slowly added. After 1 hour at -78° the reaction mixture was allowed to rise slowly to room temperature and then stirred for 12 hours. The reaction mixture was treated with water and extracted with ether. The dried and evaporated extract was fractionally distilled under reduced pressure to give pure **2**.

Compound **2a**.

This compound had bp 84° (0.3 mm Hg); nmr: 4.70 (1H, t), 3.97-3.63 (4H, m), 2.30 (6H, s).

Anal. Calcd. for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.27. Found: C, 63.38; H, 10.76; N, 12.03.

Compound **2b**.

This compound had bp 130° (0.3 mm Hg); nmr: 7.88-7.61 (2H, m), 7.50-7.26 (3H, m), 4.73 (1H, t), 4.03-3.73 (4H, m), 2.63 (6H, s).

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.85; H, 7.94; N, 11.53.

Compound **2c**.

This compound had bp 100° (0.5 mm Hg); nmr: 4.83 (1H, t), 4.03-3.75 (4H, m), 2.37 (6H, s).

Anal. Calcd. for $C_{11}H_{22}N_2O_2$: C, 61.65; H, 10.35; N, 13.07. Found: C, 61.32; H, 10.74; N, 13.23.

Compound **2d**.

This compound had bp 120° (0.5 mm Hg); nmr: 4.93-4.73 (1H, m), 3.90-3.60 (4H, m), 2.32 (6H, s).

Anal. Calcd. for $C_{12}H_{22}N_2O_2$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.42; H, 9.71; N, 12.35.

Compound **2e**.

This compound had bp 130° (0.2 mm Hg); nmr: 4.83-4.53 (1H, m), 4.00-3.60 (4H, m), 2.33 (6H, s).

Anal. Calcd. for $C_{16}H_{30}N_2O_2$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.17; H, 10.65; N, 9.96.

Compound **2f**.

This compound had bp 120° (0.05 mm Hg); nmr: 5.12-4.78 (1H, m), 4.11-3.78 (4H, m), 2.42 (6H, d), 1.11-0.78 (9H, m).

Anal. Calcd. for $C_{16}H_{28}N_2O_2$: C, 68.53; H, 10.06; N, 9.99. Found: C, 68.77; H, 10.22; N, 9.66.

Dimethylamino pyrroles (**3**): General procedure.

A solution of **2** (0.01 mole) in toluene (20 ml) containing *p*-toluenesulphonic acid (50 mg) was refluxed (reaction times are reported in Table II). After cooling, the mixture was treated with anhydrous potassium carbonate. Evaporation of the solvent and distillation *in vacuo* afforded pure **3**.

Compound **3a**.

This compound had bp 120° (40 mm Hg); nmr: 6.63-6.50 (1H, m), 5.77 (1H, t), 5.50-5.36 (1H, m), 2.27 (6H, s).

Anal. Calcd. for $C_{10}H_{16}N_2$: C, 72.24; H, 10.91, N, 16.85. Found: C, 72.42; H, 10.55; N, 16.53.

Compound **3b**.

This compound had bp 160° (40 mm Hg); nmr: 7.83-7.26 (5H, m), 7.10 (1H, t), 6.23 (2H, d), 2.80 (6H, s).

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.52; H, 7.23; N, 15.31.

Compound **3c**.

This compound had bp 105° (40 mm Hg); nmr: 6.81 (1H, d), 5.95 (1H, d), 2.75 (6H, s), 2.78 (3H, s), 1.10 (3H, t).

Anal. Calcd. for $C_9H_{16}N_2$: C, 71.01; H, 10.59; N, 18.40. Found: C, 71.16; H, 10.43; N, 18.21.

Compound **3d**.

This compound had bp 100° (0.5 mm Hg); nmr: 6.60 (1H, d), 5.77 (1H, d), 2.73 (6H, s).

Anal. Calcd. for $C_{10}H_{16}N_2$: C, 73.13; H, 9.82; N, 17.05. Found: C, 73.32; H, 9.64; N, 17.27.

Compound **3e**.

This compound had bp 120° (0.5 mm Hg); $[\alpha]_D^{25}$ -15.14 (c, 2.14 cyclohexane); nmr: 6.63 (1H, d), 5.80 (1H, d), 2.73 (6H, s).

Anal. Calcd. for $C_{14}H_{24}N_2$: C, 76.31; H, 10.98; N, 12.71. Found: C, 76.21; H, 10.85; N, 12.96.

General procedure for hydrogenation of **3**.

A low pressure Parr hydrogenator was used. The sample (0.001 mole) was suspended in 10 ml of methanol/water (3:1) and the Raney-nickel catalyst suspension (0.2 g) was added. The hydrogenation was carried at room temperature and 60 psi for 48 hours. The reduced mixture was filtered, the ethanol removed and the residue extracted with CH_2Cl_2. The organic solution was dried over anhydrous sodium sulfate, the solvent was removed and the products isolated by usual methods, depending on its physical properties.

Compound **4b**.

This compound was obtained in 85% yield, mp 130°; nmr 8.30-7.90 (1H, broad), 7.86-7.33 (5H, m), 7.10-6.90 (1H, m), 6.86-6.66 (1H, m), 6.62-6.40 (1H, m).

Anal. Calcd. for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78. Found: C, 84.14; H, 6.30; N, 9.70.

Compound **4d**.

In this case the hydrogenation was stopped after 120 hours. After the usual work up the oily residue was distilled to give 123 mg of a 3:1 mixture of **3d** and **4d**. This latter was identified after it was isolated in the pure state by preparative gc (2 m x 7 mm column packed with 5% SE-30 on Chromosorb A 70-80 mesh and heated at 129°); nmr: 7.2 (1H, broad), 6.21 (1H, t), 5.64 (1H, t), 2.73-2.26 (4H, m), 1.93-1.53 (4H, m).

Anal. Calcd. for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.64; H, 9.10; N, 11.60.

REFERENCES AND NOTES

[1] G. Chelucci, G. Delogu, S. Gladiali and F. Soccolini, *J. Heterocyclic Chem.*, **23**, 1395 (1986).

[2] G. Chelucci, M. Marchetti and S. Gladiali, submitted for publication.

[3] G. Stork, J. O. Gardner, R. K. Boeckman Jr. and K. A. Parker, *J. Am. Chem. Soc.*, **95**, 2014 (1973).

[4] A. Hosomi, Y. Araki and H. Sakurai, *J. Am. Chem. Soc.*, **104**, 2081 (1982).

[5] R. J. Sundberg in "Comprehensive Heterocyclic Chemistry", Vol **4**, Part 3, C. W. Bird and G. W. H. Cheeseman, eds, Pergamon Press, 1984, pp 329-330 and 361-363.

[6] Th. Severin and H. Poehlmann, *Chem. Ber.*, **110**, 491 (1977).

[7] X. A. Dominguez, I. Cavazos Lopes and R. Franco, *J. Org. Chem.*, **26**, 1625, 1961.

[8] A. S. Hussey and R. H. Baker, *J. Org. Chem.*, **25**, 1434 (1960).

[9] A. I. Meyers and N. Nazarenko, *J. Org. Chem.*, **38**, 175 (1973).

[10] G. R. Newkome and D. L. Fishel, *J. Org. Chem.*, **31**, 677 (1966) and references therein.