Alkylation of 1-Methyl-2-piperidones[1]

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The alkylation of 1-methyl- and 1,3-dimethyl-2-piperidone is reported in good yield.

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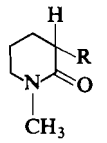
L'alkylation de la méthyl-1 et de la diméthyl-1,3-pipéridone est rapportée avec un excellent rendement.

In the course of our investigation which led to the development of a new stereoelectronic theory for the hydrolysis of amides[1] it was necessary to prepare *N*-dialkylated imidate salts. Some of those salts can be easily produced from the appropriate 3-alkyl-1-methyl-2-piperidones. The direct alkylation of 1-methyl-2-piperidones was therefore considered.

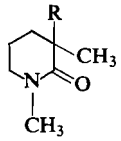
The α-alkylation of 1-methyl-2-pyrrolidone (3) and of *N*,*N*-dialkylamides (4) has been reported but the yields were moderate.[2] This is presumably due to the base used ($NaNH_2$) to produce the enolate salt of the amide function because when *n*-butyl lithium was used to generate the dilithioamide of secondary amide, high yield of α-alkylated secondary amides was obtained (6).

We would like to report the optimum experimental conditions that we have found for the alkylation reaction of *N*-methyl six-membered lactams.[3]

We have found that 1-methyl-2-piperidone (**1**) can be converted into **2** or **3** in high yield with the proper alkyl iodide. The lithium enolate of **1** was generated with lithium dimethylamide in benzene. A slight excess of the base and alkylating agent ensured complete alkylation. There were no detectable amounts of *O*-alkylated or bis-alkylated products. 1,3-Dimethyl-2-piperidone (**2**) could be further alkylated to give the bis-α-alkylated products **4** and **5** in excellent yield. Consequently, this method provides a convenient route to α-disubstituted-*N*-alkyl lactams.



1 R = H
2 R = CH_3
3 R = C_2H_5



4 R = CH_3
5 R = C_2H_5

We would like to point out that α-alkylation of an amide function has a great potential in organic synthesis. Generation of the lithium enolate with appropriate base seems easy. No side reactions occur presumably because the amide function does not react with its lithium enolate during its formation. Also, *O*-alkylation of the lithium enolate does not occur in normal conditions. The amide function is a versatile and fairly chemically stable functional group which is at the oxidation level of an acid. Still, it can be easily converted to the corresponding amine, acid, ester, and aldehyde function (10).

Experimental

The i.r. spectra were taken on a Perkin-Elmer 257 spectrophotometer; proton n.m.r. spectra were recorded on a Varian A-60 spectrometer. The chemical shifts are reported in δ-values relative to tetramethylsilane as internal standard. The vapor phase chromatographic (v.p.c.) analysis was done on a Varian aerograph model 90-P. Mass spectra were taken on a Hitachi-Perkin-Elmer RMU-6 mass spectrometer. Microanalyses were carried out by Mr. J. Tamas, Laboratoire de microanalyse, Université de Sherbrooke.

[1]References 1 and 2 and unpublished work by D. R. Patterson, this laboratory, 1974.

[2]For alkylation of amides having another stabilizing group in α-position, see ref. 5.

[3]Reaction of the lithium enolate salt of 1-methyl-2-piperidone has been reported during the course of this work (7); α-alkylation of β-lactams is known (8); for an example of α-alkylation of an α-alkyl-*N*-substituted lactam, see ref. 9.

Reagents

The alkyl iodides were washed with aqueous sodium thiosulfate, dried over anhydrous calcium chloride, and distilled. *N*-Butyl lithium in hexane (2.2 *M*) supplied by Alpha Products was used in all experiments. Benzene was dried over sodium hydride and distilled. 1-Methyl-2-piperidone (Chemical Procurement Laboratories) was dried over molecular sieves (type 4A, Fisher Scientific) and distilled. Dimethylamine was used as a solution in benzene: a solution of the amine ($\simeq 1.2$ *M*) was prepared by bubbling the gas for 4 h through benzene and this solution was diluted with an equal amount of benzene and the concentration was determined by titration (11).

1,3-Dimethyl-2-piperidone (2)

A solution of dimethylamine in benzene (33 ml, 39.6 mmol) was added dropwise to a magnetically stirred cold (ice bath) solution of *n*-butyl lithium in hexane (15 ml, 33 mmol) under an atmosphere of argon. The white slushy precipitate formed was stirred (ice bath) for 0.5 h. Addition of 1-methyl-2-piperidone (**1**; 3.5 g, 31.5 mmol) to this mixture gave a pale yellow homogeneous solution. The solution was heated for 1 h at 50–60 °C under vacuum (15–20 mm) to remove excess dimethylamine. Methyl iodide (4.68 g, 33 mmol) in benzene (10 ml) was then added to the cold (ice bath) magnetically stirred reaction mixture. Stirring was continued for 2 h at room temperature. Water (10 ml) was then added and the benzene layer was separated. The aqueous phase was then extracted with dichloromethane. The combined extract was washed with a small quantity of water and dried over sodium sulfate. The solvent was removed by distillation and the resulting oil was filtered through a column of silica gel with dichloromethane to yield after removal of the solvent, a pale yellow liquid (3.75 g). Distillation gave 1,3-dimethyl-2-piperidone (**2**; 3.25 g, 83%) which was shown to be pure (> 98%) by v.p.c.; b.p. 92–94 °C/5 mm (lit. (12) b.p. 113–114 °C/18 mm); i.r.: ν_{max} ($CHCl_3$) 1625 cm^{-1}; n.m.r.: δ($CDCl_3$) 1.25 (3H, doublet, CH_3—CH), 1.52–2.2 (4H, multiplets), 2.3–2.6 (1H, multiplet), 2.98 (3H, singlet, N—CH_3), and 3.2–3.5 (2H, multiplets); m.s.: *m/e* 127 (M^+), 112 ($M^+ - CH_3$).

1-Methyl-3-ethyl-2-piperidone (3)

The lithium enolate was generated from 1-methyl-2-piperidone (**1**; 3.5 g, 31.5 mmol) in benzene by the method described above. Ethyl iodide (5.14 g, 33 mmol) in benzene (10 ml) was added dropwise. The stirring was continued for 8 h at room temperature. Work-up as described above gave 1-methyl-3-ethyl-2-piperidone (**3**; 3.7 g, 85%) which was shown to be pure (> 98%) by v.p.c.; b.p. 78–79 °C/1 mm (lit. (13) b.p. 87–90 °C/2 mm); i.r.: ν_{max} ($CHCl_3$) 1625 cm^{-1}; n.m.r.: δ($CDCl_3$) 0.96 (3H, triplet, J = 6 Hz, CH_2—CH_3), 1.2–2.5 (7H, multiplet), 2.98 (3H, singlet, N—CH_3), and 3.2–3.5 (2H, multiplet); m.s.: *m/e* 141 (M^+), 126 ($M^+ - CH_3$).

1,3,3-Trimethyl-2-piperidone (4)

1,3-Dimethyl-2-piperidone (**2**; 2.4 g, 18.2 mmol) was converted into its lithium enolate by lithium dimethylamide in benzene prepared from *n*-butyl lithium (9 ml, 19.8 mmol) and dimethylamine (20 ml, 24 mmol) solutions. Methyl iodide (2.85 g, 20 mmol) in benzene (10 ml) was added to the cold reaction mixture. Stirring was then continued for 15 h at room temperature. Work-up as described above gave 1,3,3-trimethyl-2-piperidone (**4**; 2.3 g, 86%) which was shown to be pure (> 98%) by v.p.c.; b.p. 72–74 °C/1 mm (lit. (12) b.p. 106–107 °C/18 mm); i.r.: ν_{max} ($CHCl_3$) 1620 cm^{-1}; n.m.r.: δ($CDCl_3$) 1.21 (6H, singlet, two CH_3), 1.7–2.0 (4H, multiplet), 3.00 (3H, singlet, N—CH_3), and 3.2–3.5 (2H, multiplet); m.s.: *m/e* 141 (M^+), 126 ($M^+ - CH_3$).

1,3-Dimethyl-3-ethyl-2-piperidone (5)

1,3-Dimethyl-2-piperidone (**2**; 2.47 g, 19.5 mmol) was converted into its lithium enolate by lithium dimethylamide in benzene prepared from *n*-butyl lithium (10 ml, 2.2 mmol) and dimethylamine (22 ml, 26.4 mmol) solutions. Ethyl iodide (3.5 g, 22 mmol) in benzene (10 ml) was added to the cold reaction mixture. Stirring was then continued for 24 h at room temperature. Work-up as described above gave 1,3-dimethyl-3-ethyl-2-piperidone (**5**; 2.38 g, 80%) which was shown to be pure (> 98%) by v.p.c.; b.p. 80–82 °C/20 mm; i.r.: ν_{max} ($CHCl_3$) 1620 cm^{-1}; n.m.r.: δ($CDCl_3$) 0.83 (3H, triplet, CH_2—CH_3), 1.18 (3H, singlet, C—CH_3), 1.4–2.0 (6H, multiplet), 2.98 (3H, singlet, N—CH_3), and 3.3–3.5 (2H, multiplet); m.s.: *m/e* 155 (M^+), 140 ($M^+ - CH_3$).

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04. Found: C, 69.62; H, 10.81.

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