

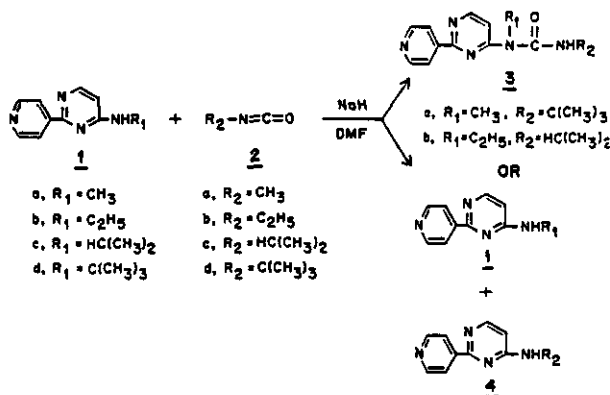
NOVEL REARRANGEMENT OF N'-ALKYL-N-ALKYL-N-[2-(4-PYRIDINYL)-4-PYRIMIDINYL]UREAS WITH SODIUM HYDRIDE

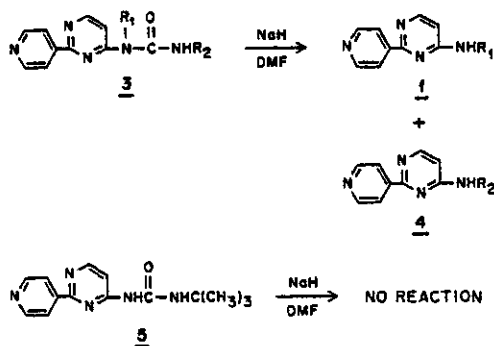
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Abstract - Treatment of N'-alkyl-N-alkyl-N-[2-(4-pyridinyl)-4-pyrimidinyl]ureas with sodium hydride in dimethylformamide gave mixtures of two N-alkyl-2-(4-pyridinyl)-4-pyrimidinamines.

We have recently reported¹ the synthesis and biological activity of N'-alkyl-N-alkyl-N-[2-(4-pyridinyl)-4-pyrimidinyl]ureas (3). These compounds were prepared by reacting the sodium salts of N-alkyl-2-(4-pyridinyl)-4-pyrimidinamines (1) with alkyl isocyanates (2) in dimethylformamide for 4-5 h. However, in one of the experiments involving N-ethyl-2-(4-pyridinyl)-4-pyrimidinamine (1b)¹ and isopropyl isocyanate, the reaction mixture was left at room temperature over the weekend and workup of this reaction gave a mixture of N-ethyl-2-(4-pyridinyl)-4-pyrimidinamine (1b)¹ and N-(1-methylethyl)-2-(4-pyridinyl)-4-pyrimidinamine (1c)¹ instead of N-ethyl-N'(1-methylethyl)-N-[2-(4-pyridinyl)-4-pyrimidinyl]urea. Similar results were obtained with other N-alkyl-2-(4-pyridinyl)-4-pyrimidinamines and alkyl isocyanates (Table 1). These results prompted us to speculate that it was the sodium salt of N'-alkyl-N-alkyl-N-[2-(4-pyridinyl)-4-pyrimidinyl]urea which was involved in this rearrangement. It was gratifying to discover that treatment of N'-alkyl-N-alkyl-N-[2-(4-pyridinyl)-4-pyrimidinyl]ureas with sodium hydride gave similar results. However, N'-(1,1-dimethylethyl)-N-[2-(4-pyridinyl)-4-pyrimidinyl]urea (5) which has a hydrogen instead of an alkyl substituent on the nitrogen failed to undergo this rearrangement and was recovered in almost quantitative yield. The mechanism of this rearrangement needs further investigation.





EXPERIMENTAL

N'-(1-Methylethyl)-N-ethyl-N-[2-(4-pyridinyl)-4-pyrimidinyl]urea (3b). A mixture of 8.5g (0.047 mol) of 1b, 2.4g (0.05 mol) of 50% NaH/oil, 5 ml (0.05 mol) of isopropyl isocyanate (2b) and 100 ml of dimethylformamide was stirred at ambient temperature for 5 h and then stripped. The brown residue was treated with 200 ml of 5% aqueous acetic acid and chilled. The resulting brown solid was filtered, washed with water, dried and then recrystallized from ether after treatment with charcoal to give 10.6g (87%) of colorless needles, mp 104-106 °C; ms: M+ at m/e 285 (C₁₅H₁₉N₅O); ¹H-NMR(CDCl₃): δ 9.88 (1H, s, NH), 8.04, 7.78 (4H, pyridine A₂B₂, J = 6.5 Hz), 8.62 (1H, d, H-6, J = 6HZ), 7.94 (1H, d, H-5, J = 6HZ), 1.36-1.32 (3H, m, -N-CH(CH₃)₂, -N-CH₂-CH₃) and 1.36-1.32 (9H, m, (-CH(CH₃)₂)₂, -NCH₂CH₃). Anal. Calcd. for C₁₅H₁₉N₅O: C, 63.14; H, 6.71; N, 24.54. Found: C, 62.82; H, 7.00; N, 24.76.

The general procedure for reacting N-alkyl-2-(4-pyridinyl)-4-pyrimidinamines (1) with alkyl isocyanates (2) in the presence of NaH is illustrated by the following example (Table I):

Reaction of N-Ethyl-2-(4-pyridinyl)-4-pyrimidinamine (1b) with Isopropyl Isocyanate (2c). A mixture of 14.1 g (0.075 mol) of 1b, 3.6g (0.075 mol) of 50% NaH/oil, 75 ml of dimethylformamide and 6.5 ml (0.075 mol) of isopropyl isocyanate was stirred for 30 min, left at ambient temperature for 104 h and then concentrated under reduced pressure. The residue was partitioned between 200 ml of 5% aqueous acetic acid and 200 ml of chloroform. The organic layer was stripped and the residue was separated by chromatography (silica gel) to give 5.7 g (36%) of 1c¹, mp 117-120 °C and 2.8 g (20%) of 1b¹, mp 122-124 °C.

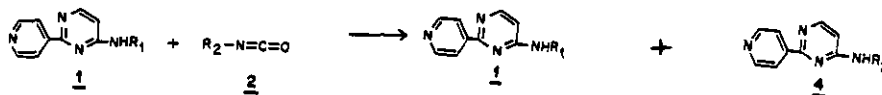
Reaction of N'-(1-Methylethyl)-N-ethyl-N-[2-(4-pyridinyl)-4-pyrimidinyl]urea (3b) with Sodium Hydride. A mixture of 6.5 g (0.02/mol) of 3b, 1.2 g (0.02 mol) of 50% NaH/oil and 50 ml of dimethylformamide was stirred until most of the sodium hydride had reacted and then left at ambient temperature for 96 h. The yellow mixture

was stripped and then partitioned between 200 ml of 2% aqueous acetic acid and 300 ml of chloroform. Removal of chloroform followed by chromatography on silica gel using 1% methanol in ether as the eluent gave 1.9 g (40%) of 1c¹, mp 117-120 °C and 1.6 g (36%) of 1b¹, mp 123-125 °C.

Reaction of N'-(1,1-Dimethylethyl)-N-methyl-N-[2-(4-pyridinyl)-4-pyrimidinyl]urea (3a) with Sodium Hydride. A mixture of 4 g (0.014 mol) of 3a¹, 0.7 g (0.014 mol) of 50% NaH/oil and 35 ml of dimethylformamide was stirred for 30 min, left at ambient temperature for 122 h and then stripped. The residue was partitioned between 100 ml of 3% aqueous acetic acid and 100 ml of chloroform. Evaporation of chloroform gave a white residue which was separated by chromatography on silica gel with 1% methanol in ether to give 1.15 g (36%) of 1d¹, mp 202-204 °C and 0.82 g (31%) of 1a¹, mp 148-150 °C.

Reaction of N'-(1,1-Dimethylethyl)-N-[2-(4-pyridinyl)-4-pyrimidinyl]urea (5) with Sodium Hydride. A mixture of 13.5 g (0.05 mol) of 5¹, 2.4 g (0.05 mol) of 50% NaH/oil and 150 ml of dimethylformamide was stirred for 30 min, left at ambient temperature for 122 h and then concentrated under reduced pressure. The residue was treated with 100 ml of 5% aqueous acetic acid and the white solid was filtered, washed successively with water and ether and dried to yield 13.1 g of 5¹.

Table 1



	Reactants		Products					
	<u>1</u>	<u>2</u>	<u>1</u>	<u>1</u>	<u>1</u>	<u>4</u>	<u>4</u>	<u>4</u>
	R ₁	R ₂	R ₁	% Yield	mp °C ¹	R ₂	% Yield	mp °C ¹
1	C ₂ H ₅	CH(CH ₃) ₂	C ₂ H ₅	32	123-125	CH(CH ₃) ₂	39	117-120
2	C ₂ H ₅	C(CH ₃) ₃	C ₂ H ₅	21	123-125	C(CH ₃) ₃	62	202-204
3	CH ₃	C(CH ₃) ₃	CH ₃	30	148-150	C(CH ₃) ₃	38	202-204
4	C(CH ₃) ₃	C ₂ H ₅	C(CH ₃) ₃	67	202-204	C ₂ H ₅	18	122-126
5	CH ₃	C ₂ H ₅	CH ₃	48	148-150	C ₂ H ₅	29	122-125

REFERENCE

1. G. Y. Leshar, B. Singh and Z. E. Mielens, *J. Med. Chem.*, 1982, **25**, 837.

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