Convenient Syntheses of 1-Acyl-2-alkylhydrazines

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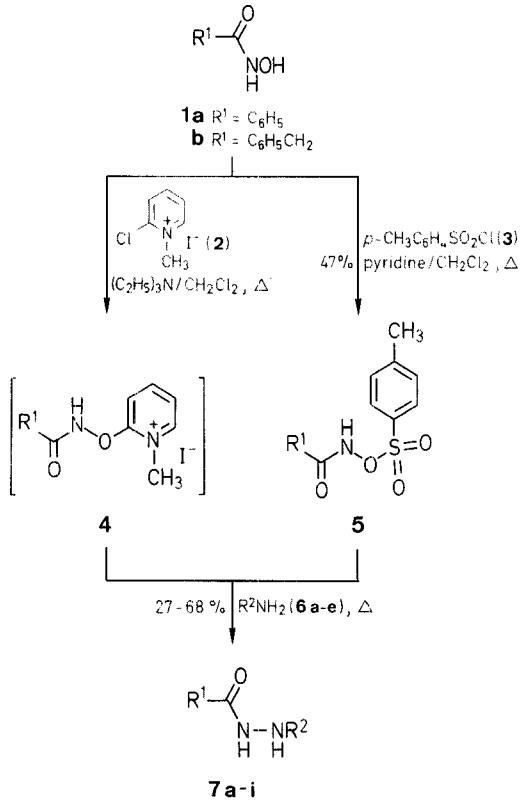
1-Acyl-2-alkylhydrazines **7** were prepared from hydroxamic acids **1** and amines **6** using 2-chloro-1-methylpyridinium iodide **2** or *p*-toluenesulfonyl chloride **3** in 27–68% yield.

In connection with our program directed toward the synthesis of fused aza-β-lactam, we required a convenient method for the preparation of 1-acyl-2-alkylhydrazines.

Although acylation of *N*-alkylhydrazines with carboxylic esters is the most convenient for the preparation of 1-acyl-2-alkylhydrazine, it is not easy to prepare arbitrary *N*-alkylhydrazines. We therefore tried a new synthesis of hydrazines through $N-N$ bond formation. In general, $N-N$ bond formation is achieved by the reaction of amines with chloroamines,[1] with hydroxylamine-*O*-sulfonic acid,[2] and the reaction of *O*-mesitylenesulfonyl-hydroxylamine with tertiary amines.[3] However, these methods can not be applied to our desired hydrazines.

We now report the convenient preparation of 1-acyl-2-alkylhydrazines **7** involving $N-N$ bond formation by the



6	R^2
a	n-C_4H_9
b	n-C_6H_{13}
c	c-C_6H_{11}
d	$C_6H_5CH_2$
e	C_6H_5

7	R^1	R^2
a	C_6H_5	n-C_4H_9
b	C_6H_5	n-C_6H_{13}
c	C_6H_5	c-C_6H_{11}
d	C_6H_5	$C_6H_5CH_2$
e	C_6H_5	C_6H_5
f	$C_6H_5CH_2$	n-C_4H_9
g	$C_6H_5CH_2$	n-C_6H_{13}
h	$C_6H_5CH_2$	c-C_6H_{11}
i	$C_6H_5CH_2$	$C_6H_5CH_2$

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Table. 1-Acyl-2-Alkylhydrazines **7** Prepared

Product	Method	Reaction Time (h)	Yield (%)	m.p. (°C) (solvent)	Molecular Formula[a]	IR (KBr) ν (cm^{-1})	MS m/e	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
7a	A	7	68	126–128	$C_{11}H_{16}N_2O$	3350 (NH),	192	0.87 (t, CH_3, 3H, J = 5.0 Hz), 1.15–1.51
	B	5	39	(benzene)	(192.3)	3290 (NH),		(m, 2 × CH_2, 4H), 3.15 (m, CH_2N, 2H),
						1640 (C=O)		3.35 (s, NH, 1H), 7.11–7.40 (m, C_6H_5,
								5H), 8.15 (br, NH, 1H)
7b	A	12	32	63–65	$C_{13}H_{20}N_2O$	3290 (NH),	220	0.80 (t, CH_3, 3H, J = 5.0 Hz), 1.08–1.65
	B	8	37	(ether)	(220.3)	1640 (C=O)		(m, 4 × CH_2, 8H), 1.87 (s, NH, 1H), 2.20
								(m, CH_2N, 2H), 7.05–7.40 (m, C_6H_5,
								5H), 7.53 (br, NH, 1H)
7c	A	12	57	237–239	$C_{13}H_{18}N_2O$	3260 (NH),	218	0.80–1.52 (m, c-C_6H_{11}, 11H), 3.00 (s,
	B	3	51	(benzene)	(218.3)	1630 (C=O)		NH, 1H), 6.85–7.31 (m, C_6H_5, 5H), 8.40
								(br, NH, 1H)
7d	A	10	65	163–164	$C_{14}H_{14}N_2O$	3260 (NH),	226	3.26 (s, NH, 1H), 4.28 (d, CH_2, 2H, J
	B	4	44	(benzene)	(226.3)	1630 (C=O)		= 7.0 Hz), 7.05–7.55 (s, 2C_6H_5, 10H),
								8.55 (br, NH, 1H)
7e	A	12	49	246–247	$C_{13}H_{12}N_2O$	3280 (NH),	212	3.28 (s, NH, 1H), 7.10–7.55 (m, 2C_6H_5,
	B	15	0	(chloroform)	(212.3)	3240 (NH),		10H), 8.67 (br, NH, 1H)
						1640 C=O)		
7f	A	13	35	103–104	$C_{12}H_{18}N_2O$	3300 (NH),	206	0.91 (t, CH_3, 3H, J = 5.0 Hz), 1.18–1.55
				(ether-hexane)	(206.2)	1630 (C=O)		(m, 2 × CH_2, 4H), 3.15 (m, CH_2N, 2H),
								4.30 (s, CH_2, 2H), 7.31 (s, C_6H_5, 5H),
								7.65 (br, NH, 1H)
7g	A	9	27	77–78	$C_{14}H_{22}N_2O$	3325 (NH),	234	0.89 (t, CH_3, 3H, J = 5.0 Hz), 1.10–1.92
				(ether)	(234.3)	3290 (NH),		(m, 4 × CH_2, 8H), 1.73 (s, NH, 1H), 3.21
						1630 (C=O)		(m, CH_2N, 2H), 4.41 (s, CH_2, 2H), 7.33
								(s, C_6H_5, 5H), 7.92 (br, NH, 1H)
7h	A	10	28	166–167	$C_{14}H_{20}N_2O$	3300 (NH),	232	1.10–2.05 (m, c-C_6H_{11}, 11H), 1.71 (s,
				(benzene)	(232.3)	1630 (C=O)		NH, 1H), 4.41 (s, CH_2, 2H), 7.31 (s,
								C_6H_5, 5H), 7.60 (br, NH, 1H)
7i	A	10	36	171–172	$C_{15}H_{16}N_2O$	3300 (NH),	240	1.67 (s, NH, 1H), 4.31 (s, CH_2, 2H), 4.40
				(benzene)	(240.3)	3260 (NH),		(s, CH_2, 2H), 7.30 (m, 2C_6H_5, 10H), 7.85
						1630 (C=O)		(br, NH, 1H)

[a] Satisfactory microanalyses obtained: C ±0.31, H ±0.38, N ±0.22.

reaction of hydroxamic acids **1** with amines **6** using activating reagents, such as 2-chloro-1-methylpyridinium iodide **(2)** and *p*-toluenesulfonyl chloride **(3)**.

The reaction of hydroxamic acid **1** with amines **6** was successfully carried out in the presence of **2** and triethylamine to give 1-acyl-2-alkylhydrazines **7** in 27–68% yield (Table). This reaction is considered to proceed *via* the intermediate **4**. Similarly, the reaction in the presence of **3** initially afforded the intermediate *O*-*p*-toluenesulfonylhydroxamic acids **5**, which were converted to **7** in 37–44% yield (Table). The structure of **7** was confirmed by IR ^{1}H-NMR and mass spectra. The use of other activating reagents, i.e. dicyclohexylcarbodiimide and diethyl azodicarboxylate-triphenylphosphine, was unsuccessful.

1-Acyl-2-alkylhydrazines 7; General Procedures:

Method A: A mixture of hydroxamic acid (**1**; 5 mmol), 2-chloro-1-methylpyridinium iodide (**2**; 5 mmol, 1.29 g), and triethylamine (10 mmol, 1.01 g) in anhydrous dichloromethane (15 ml) is refluxed for 0.5 h under nitrogen atmosphere. Amine **6** (10 mmol) is added dropwise to the mixture, which is refluxed for a period of time shown in the Table. The solution is washed with 1% aqueous sodium hydrogen carbonate (2 × 10 ml) and water (2 × 10 ml), dried with anhydrous magnesium sulfate, and evaporated to dryness. The residue is purified by recrystallization from benzene, chloroform and ether or column chromatography on silica gel with chloroform as the eluent.

Method B: To a stirred solution of benzoyl hydroxamic acid (**1a**; 5 mmol, 0.69 g) and pyridine (10 mmol, 0.79 g) in anhydrous dichloromethane (10 ml) is added dropwise a solution of *p*-toluenesulfonyl chloride (**3**; 5 mmol, 0.95 g) in anhydrous dichloromethane (5 ml) at room temperature. The mixture is refluxed for 0.5 h. Addition of water (15 ml) causes the intermediate **5** ($R^1 = C_6H_5$) to separate; yield: 0.70 g (47%); m.p. 181–183°C.

IR (KBr): ν = 3220 (NH), 1735 (C=O), 1305, 1195 cm^{-1} (SO_2).

The crude **5** ($R^1 = C_6H_5$) is used for further reaction without purification. To a stirred solution of **5** (1 mmol, 0.29 g) in anhydrous dichloromethane (10 ml) is gradually added a solution of amine (**6**; (3 mmol) in anhydrous dichloromethane (5 ml) at room temperature under nitrogen atmosphere. The mixture is refluxed for 0.5 h, washed with 1% aqueous sodium hydrogen carbonate (2 × 5 ml) and water (2 × 5 ml), dried with magnesium sulfate, and evaporated to dryness. The residue is recrystallized from benzene, chloroform and ether.

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