Hindered Amines; III[1]. Highly Regioselective Syntheses of 1,3,3,5,5-Pentasubstituted 2-Piperazinones and their Nitroxyl Radicals

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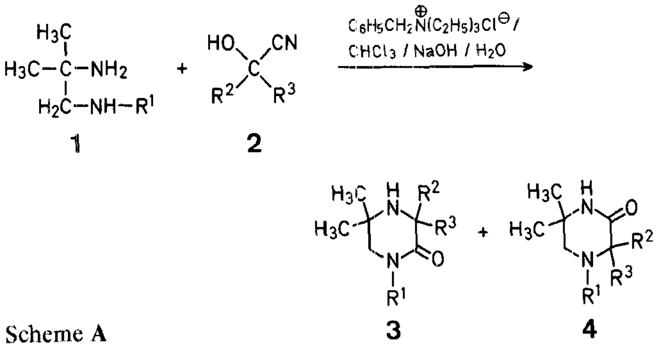
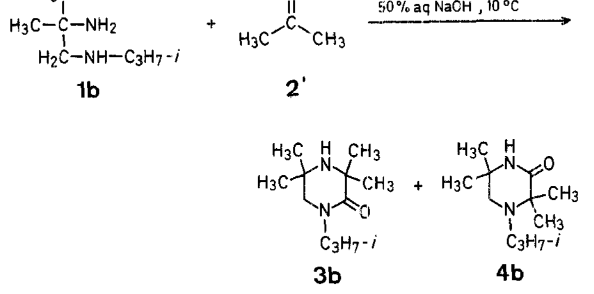
Hindered amines comprise a group of versatile compounds: their nitroxyl radicals have been used extensively as spin-labels in biological studies[2], their lithio-derivatives attract considerable interest in organic synthesis[3], and, industrially, they are known as the best type of polymer stabilizers against U.V.-degradation[4]. We recently reported a novel synthesis of 1,3,3,5,5-pentasubstituted-2-piperazinones **3** from the N^1,2,2-trisubstituted-1,2-propanediamine (**1**), a ketone, and chloroform in a strong base under phase-transfer-catalyzed condition[5]. A drawback to this synthesis is the substantial formation of the less hindered isomer **4** (10–30% of the total product). Although **3** can usually be isolated in pure form by simple recrystallization when solid, the yield drops tremendously when **3** with a bis-piperazinone structure (i.e., **3e, f**) is desired. Furthermore, the preparation of the nitroxyl radical requires highly pure **3** which is difficult to obtain when **3** is an oil and is contaminated with **4**. We found that one solution to this problem, without having to replace the more economical tetralkylammonium chloride as catalyst, is to employ the ketone cyanohydrin **2** instead of the ketone itself.



Scheme A

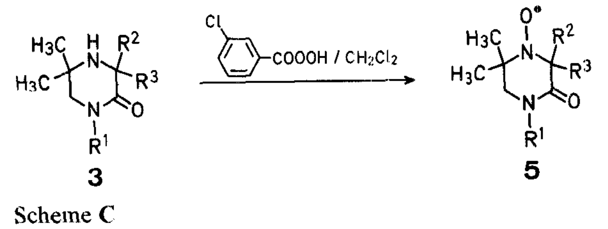
Only a trace amount of **4** could be detected by G.L.C. and ^{1}H-N.M.R. analysis and it can be removed by a simple recrystallization when **3** is solid. The oily **3a** made in this manner is oxidized smoothly with *m*-chloroperbenzoic acid to its nitroxyl radical in very good yield while the conversion of **3a**, made from acetone, fails due to the presence of impurities.

The reaction shown in Scheme **A** proceeds very slowly in the absence of a phase-transfer catalyst and no reaction in observed without chloroform. When chloroform containing only the ^{12}C-isotope is used in the reaction, the signals corresponding to the carbonyl carbons in **3** and **4** are absent in the ^{13}C-N.M.R. spectrum. We herewith propose that in this reaction, the cyanohydrin **2** is decomposed by sodium hydroxide to the corresponding ketone **2'** and cyanide ion. This is verified by using 40% aqueous sodium deuteroxide as base in the reaction. From the analysis of electron ionization mass spectra corrected to the natural abundance of ^{13}C, it was found that there was a 60% D-incorporation into the *gem*-dimethyl group ($R^2 = R^3 = CH_3$) at C-3 ($R^1 = t\text{-}C_4H_9$), which is comparable to the 45% D-incorporation from the acetone reaction. The formed ketone **2'** would then proceed to the products as described before[5], except that the ratio of **3**:**4** is greatly improved. Adding cyanide ion to the ketone reactions also improves the regioselectivity (Scheme **B**).



Catalyst (mol%)	Ratio of **3b** : **4b**
$C_6H_5CH_2\overset{\oplus}{N}(C_2H_5)_3Cl^{\ominus}$ (2)	86 : 14
$C_6H_5CH_2\overset{\oplus}{N}(C_2H_5)_3Cl^{\ominus}$ (2) + NaCN (3)	91 : 9
$C_6H_5CH_2\overset{\oplus}{N}(C_2H_5)_3Cl^{\ominus}$ (2) + NaCN (6)	95 : 5

Scheme **B**



Scheme C

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Compounds **3** are easily oxidized to the nitroxyl radicals **5** by treatment with *m*-chloroperbenzoic acid[6] (Scheme C).

1,3,3,5,5-Pentasubstituted 2-Piperazinones 3

Method A: using ketone cyanohydrin **2**: A mixture of N^1,2,2-trisubstituted-1,2-propanediamine **1** (0.1 mol), chloroform [0.2 mol; a large excess (500–900% of chloroform is used for **3i** and **3j**)], ketone cyanohydrin **2** (0.12 mol), and benzyltriethylammonium chloride (1.14 g, 0.005 mol) is stirred and cooled in a circulating bath. With stirring, 50% sodium hydroxide solution (0.5 mol) is added dropwise to keep the temperature between 0–5 °C. The mixture is then stirred at 5 °C until all **1** has been consumed (5–24 h) as determined by G.L.C. (2 ft × 2 mm column, 10% OV-17 on Chromosorb W, 50 °C, 20 °C/min, 230 °C). Dichloromethane (50 ml) and enough water are added to dissolve the solid. The two layers are separated and the aqueous layer is extracted with dichloromethane (2 × 50 ml). The combined organic layers are washed once with water (10 ml), dried with sodium sulfate, and concentrated. The solids are recrystallized and the oil is distilled (Table 1).

Method B: using ketone **2'** and sodium cyanide: A mixture of N',2,2-trisubstituted-1,2-propanediamine **1** (0.1 mol), chloroform (0.12 mol), ketone **2'** (0.2 mol), powdered sodium cyanide (0.29 g, 0.006 mol), benzyltriethylammonium chloride (0.45 g, 0.002 mol) and dichloromethane (50 ml) is stirred and cooled in a circulating bath. With stirring, 50% sodium hydroxide solution (0.5 mol) is added dropwise to keep the temperature below 10 °C, the mixture is then kept at 10 °C overnight, and worked up as described above (Table 1).

Nitroxyl Radicals (5) of 1,3,3,5,5-Pentasubstituted 2-Piperazinones 3:

A solution of **3** (10 mmol) in dichloromethane (50 ml) is stirred under argon while *m*-chloroperbenzoic acid (20 mmol; 30 mmol for **5i** and **5j**) is added in small portions in 30 min. The mixture is stirred at room temperature for 6 h before 5% sodium carbonate solution (300 ml) is added. The two layers are separated, the aqueous layer is extracted with dichloromethane (50 ml), the combined organic solutions are dried with sodium sulfate and concentrated. Solids are recrystallized and oils distilled (Table 2).

Table 2. Nitroxyl Radicals **5** from **3**

Product	Yield [%][a]	m.p. [°C] or b.p. [°C]/torr	Molecular formula[b]	I.R. ν[cm⁻¹] C=O	a_n [G]
5a	70	64–66°	$C_{11}H_{21}N_2O_2$ (213.3)	1650	14.3
5b	82	88–89°	$C_{11}H_{21}N_2O_2$ (213.3)	1630	14.2
5c	75	83–86°	$C_{12}H_{23}N_2O_2$ (227.3)	1650	14.3
5d	92	117–118.5°	$C_{14}H_{29}N_2O_2$ (247.3)	1650	14.3
5e	79	186–187°	$C_1H_{32}N_2O_2$ (368.5)	1650	—[c]
5f	81	180–181°	$C_{24}H_{44}N_4O_4$ (452.7)	1645	—[c]
5g	81	93–94°	$C_{12}H_{23}N_2O_3$ (243.3)	1645	14.2
5h	83	102–104°	$C_{14}H_{25}N_2O_2$ (253.4)	1620	14.0
5i	79	106–108°/0.3	$C_{12}H_{23}N_2O_2$ (227.3)	1650	14.1
5j	85	47–50°	$C_{14}H_{27}N_2O_2$ (255.4)	1650	14.4

[a] Yields are based on isolated pure product.

[b] The microanalyses are in satisfactory agreement with the expected results (C ±0.3, H ±0.1, N ±0.1) for all solids.

[c] Interaction between the two electron spins.

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Table 1. 1,3,3,5,5-Pentasubstituted 2-Piperazinones **3**

Product No.	R^1	R^2	R^3	Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr	Molecular formula[b]	I.R. [cm⁻¹][c] ν_{NH}	$\nu_{C=O}$	¹H-N.M.R. (CDCl₃)[d] δ [ppm]
3a	*n*-C_3H_7	CH_3	CH_3	70	118–120°/10	$C_{11}H_{22}N_2O$ (198.3)	3310	1635	0.91 (t, 3H); 1.20 (s, 6H); 1.36 (s, 6H); 1.3–1.8 (m, 3H); 3.20 (s, 2H); 3.36 (t, 2H)
3b	*i*-C_3H_7	CH_3	CH_3	61 (55)	81–84°	$C_{11}H_{22}N_2O$ (198.3)	3310	1610	1.09 (d, 6H); 1.18 (s, 6H); 1.35 (s, 6H); 3.08 (s, 2H); 4.94 (hept, 1H)
3c	*t*-C_4H_9	CH_3	CH_3	62	103–105°	$C_{12}H_{24}N_2O$ (212.3)	3300	1615	1.17 (s, 6H); 1.31 (s, 6H); 1.42 (s, 9H); 3.22 (s, 2H)
3d	C_6H_5	CH_3	CH_3	51	93–95°	$C_{14}H_{20}N_2O$ (232.3)	3310	1630	1.28 (s, 6H); 1.45 (s, 6H); 1.7 (br s, 1H); 3.19 (s, 2H); 7.30 (s, 5H)
3e[e]	—$(CH_2)_2$—	CH_3	CH_3	59 (60)	134–136°	$C_{18}H_{34}N_4O_2$ (338.5)	3300	1625	1.19 (s, 12H); 1.35 (s, 12H); 1.63 (s, 2H); 3.33 (s, 4H); 3.54 (s, 4H)
3f[e]	—$[C(CH_3)_2—CH]_2$—	CH_3	CH_3	75	126–128°	$C_{24}H_{46}N_4O_2$ (422.7)	3310	1620	1.17 (s, 12H); 1.32 (s, 12H); 1.33 (s, 12H); 1.5 (br s, 2H); 1.95 (s, 4H); 3.20 (s, 4H)
3g	—$C(CH_3)_2$—CH_2OH	CH_3	CH_3	51	83–85°	$C_{12}H_{24}N_2O_2$ (228.3)	3300	1595	1.16 (s, 6H); 1.31 (s, 6H); 1.35 (s, 6H); 1.2–1.6 (2 br s, 2H); 3.23 (s, 2H); 3.72 (s, 2H)
3h	*i*-C_3H_7	—$(CH_2)_5$—		63 (59)	77–78°	$C_{14}H_{26}N_2O$ (238.4)	3310	1605	1.97 (d, 6H); 1.15 (s, 6H); 1.3–2.3 (m, 11H); 2.88 (s, 2H); 4.91 (hept, 1H)
3i	*i*-C_3H_7	CH_3	C_2H_5	58	93–96°/1.2	$C_{12}H_{24}N_2O$ (212.3)	3310	1630	0.88 (t, 3H); 1.10 (d, 6H); 1.2 (br s, 1H); 1.19 (d, 6H); 1.35 (s, 3H); 1.4–2.1 (m, 2H); 3.03 (s, 2H); 4.98 (hept, 1H)
3j	*i*-C_3H_7	CH_3	*i*-C_4H_9	52	56–58°	$C_{14}H_{28}N_2O$ (240.4)	3305	1620	0.86 (d, 3H); 0.98 (d, 3H); 1.07 (d, 6H); 1.2 (br s, 1H); 1.19 (s, 6H); 1.34 (s, 3H); 1.3–2.3 (m, 3H); 3.06 (AB q, 2H); 4.97 (hept, 1H)

[a] All yields are of isolated **3** except **3i** and **3j** which were contaminated with trace **4**. The numbers are yields obtained from method A, using cyanohydrin while the numbers in parentheses represent yields from method B, using ketone and sodium cyanide.

[b] The microanalyses and mass spectra were in satisfactory agreement with the expected results (C ±0.3, H ±0.2, N ±0.3).

[c] Obtained on a Perkin-Elmer 467 spectrometer.

[d] Obtained on a Varian A-60 spectrometer.

[e] Bis-piperazinone structure.

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[1] For Part II, see: J. T. Lai, *J. Org. Chem.* **45**, 3671 (1980).

[2] (a) *Spin Labelling, Theory and Applications*, L. J. Berliner, Ed., Academic Press, New York, 1976.

(b) E. G. Rozantsev, *Free Nitroxyl Radicals*, Plenum, New York, 1976.

(c) E. G. Rozantsev, V. D. Sholle, *Synthesis* **1971**, 190, 401.

(d) J. F. W. Kenan, *Chem. Rev.* **78**, 37 (1978).

[3] R. A. Olofson, K. D. Lotts, G. N. Barber, *Tetrahedron Lett.* **1976**, 3779 and references cited therein.

[4] *Developments in Polymer Stabilization-1*, G. Scott, Ed., Applied Science Publishers, London, 1979, Chapters 7 and 8.

[5] J. T. Lai, *J. Org. Chem.* **45**, 754 (1980).

[6] E. J. Rauckman, G. M. Rosen, M. B. Abou-Donia, *Synth. Commun.* **5**, 409 (1975).