of (*R*)-(+)-**6** in 70% chemical yield and 86–91% ee.[18] This procedure also facilitated recovery of the chiral alcohol **17** for recycling. Assignment of the absolute configuration and assessment of the optical purity of (*R*)-(+)-**6** is based upon Ceder's correlation. This, then, represents an efficient chiral synthesis of (*R*)-(−)-sarkomycin which should be amenable to scale up if desired.

Acknowledgment. This investigation was supported by reasearch grants awarded by the National Cancer Institute (CA 17154) and the National Institute of General Medical Sciences (GM 25982) of the National Institutes of Health, DHEW.

Note Added in Proof. Another new regiospecific synthesis has recently been described: Marx, J. N.; Minaskanian, G. *Tetrahedron Lett.* **1979**, 4175.

Registry No. (±)-**1**, 72581-31-8; (*R*)-(−)-**1**, 489-21-4; (±)-**6**, 72581-32-9; (*R*)-(+)-**6**, 5709-99-9; (±)-**7**, 72581-33-0; (±)-**8**, 72525-94-1; (±)-**9**, 72525-95-2; (±)-**11**, 72525-96-3; (±)-**12**, 72525-97-4; (±)-**13**, 72525-98-5; (±)-**14**, 72542-01-9; (±)-**15**, 72525-99-6; (−)-**16**, 72526-00-2; butadiene, 106-99-0.

(18) Other Lewis acid catalysts such as $AlCl_3$ and $SnCl_4$ were inferior to $TiCl_4$ in terms of either chemical or optical yields.

(19) (a) Fellow of the Alfred P. Sloan Foundation (1976–1980); recipient of a Career Development Award (CA-00273) from the National Cancer Institute, NIH.

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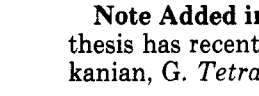
Hindered Amines. Novel Synthesis of 1,3,3,5,5-Pentasubstituted 2-Piperazinones

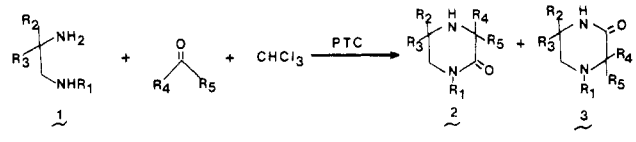
Summary: 1,3,3,5,5-Pentasubstituted 2-piperazinones (**2**) are prepared from easily available N^1,2,2-trisubstituted 1,2-ethanediamine (**1**), chloroform, and ketones in phase transfer catalyzed reactions and probably not through the dichlorocarbene intermediate.

Sir: Hindered amines, especially cyclic ones, are highly effective in the protection of polymers against ultraviolet light.[1] Their nitroxyl radicals are used extensively as spin labels in biological studies.[2] Their lithio salts, as strong and nonnucleophilic bases, are of considerable synthetic interest.[3] Although many types of hindered amines are known, only a few can be made practically, even in the laboratory.[2] In this communication, I wish to report a simple synthesis of novel 1,3,3,5,5-pentasubstituted 2-piperazinones[4] (**2**) from easily available N^1,2,2-trisubstituted 1,2-ethanediamines[5] (**1**), chloroform, and ketones in a phase transfer catalyzed (PTC) reaction.[6]

Table I. Synthesis of 2 and 3[a,b]

	R_1[c]	R_4	R_5	yield ratio[d,e] 2	3	mp[f] [bp],[g] °C
1a	*n*-C_3H_7	CH_3	CH_3	73	27	[118-121 (10 mm)]
b	*i*-C_3H_7	CH_3	CH_3	73 (52)	27	82-84
c	*i*-C_3H_7	$-(CH_2)_5-$		85 (67)	15	77-78
d	*i*-C_3H_7	CH_3	C_2H_5	70	30	[93-96 (1.2 mm)]
e	*t*-C_4H_9	CH_3	CH_3	74 (50)	26	103-105
f	*t*-C_8H_{17}	$-(CH_2)_5-$		76 (55)	24	102-103
g	Ph	CH_3	CH_3	87 (51)	12	93-95
h	$C(CH_3)_2CH_2OH$	CH_3	CH_3	80 (51)	20	83-85
i		CH_3	CH_3	68 (41)	32	53-55

[a] Yields are essentially quantitative by GC analysis. [b] All compounds gave satisfactory elemental analysis. [c] All R_2 and R_3 are CH_3 except for **1i**. [d] Determined by GC and/or ^1H NMR from different chemical shifts of ring methylene protons in **2** and **3**. [e] Numbers in parentheses are yields of pure **2**. [f] Of recrystallized **2**. [g] Of the mixture of **2** and **3**.



Under PTC conditions, chloroform is known to react with ketones, e.g., cyclohexanone, to form α-chloro- and α-hydroxycyclohexanecarboxylic acids,[7] secondary amines to form formamides,[8] and primary amines to form isocyanides.[9] However, the synthesis of **2** and **3** (see Table I) is remarkably selective. At ice-bath temperatures with 2–5% catalyst and a slight excess of chloroform, the reaction is complete overnight without detectable formation of these side products. Hydroxyl groups, which are reported to react with chloroform to form, e.g., chlorides,[10] under PTC conditions, do not interfere. This is important in spin-label studies when the nitroxyl radical is to be attached to a biological system. When **2** is solid, it can usually be isolated free from **3** after a single recrystallization. The following illustrates a general procedure: **1b** (50 mmol, Aldrich Chemical, 98% pure), chloroform (60 mmol), acetone (100 mmol), benzyltriethylammonium chloride (BTAC) (2 mmol), and 50 mL of CH_2Cl_2 are mixed and cooled while 50% NaOH (220 mmol) is added dropwise to keep the temperature below 5 °C. The reaction is stirred at 5 °C overnight and is worked up in the usual manner to obtain a clear oil which solidifies upon standing: IR (neat) 1610, 3310 (**2b**), 1665 (**3b**) cm^{-1}; ^1H NMR ($CDCl_3$) for **2b** δ 4.94 (hept, 1 H), 3.08 (s, 2 H), 1.50–1.30 (br, 1 H), 1.35 (s, 6 H), 1.18 (s, 6 H), 1.15 and 1.03 (d, 6 H); for **3b** δ 7.78 (br, 1 H), 2.78 (hept, 1 H), 2.59 (s, 2 H), 1.73 (s, 6 H), 1.35 (s, 6 H), 1.35 and 1.16 (d, 6 H).

(1) Patent literature has been flooded with this subject in recent years. See also: Ranby, B.; Rabek, J. F. "Photodegradation, Photo-oxidation and Photostabilization of Polymers"; Wiley: New York, 1975; pp 407–8.

(2) (a) "Spin Labeling, Theory and Applications"; Berliner, L. J., Ed.; Academic Press: New York, 1976. (b) Roaztsev, E. G. "Free Nitroxyl Radicals"; Plenum Press: New York, 1970.

(3) (a) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 581, 582. (b) Olofson, R. A.; Lotts, K. D.; Barber, G. N. *Tetrahedron Lett.* **1976**, 3779 and references cited therein.

(4) 3,3:5,5-Bis(pentamethylene)-2-piperazinone was prepared from a unique and complicated procedure: Egg, H. *Monatsh. Chem.* **1975**, *106*, 1167.

(5) Senkus, M. *J. Am. Chem. Soc.* **1946**, *68*, 10.

(6) (a) Weber, W. P.; Gokel, G. W. "Phase Transfer Catalysis in Organic Synthesis"; Springer-Verlag: New York, 1977. (b) Stark, C. M.; Liotta, C. "Phase Transfer Catalysis: Principles and Techniques"; Academic Press: New York, 1978.

(7) Kuhl, P.; Muhlstadt, M.; Graefe, J. *Synthesis* **1976**, 825.

(8) (a) Graefe, J.; Frohlich, I.; Muhlstadt, M. *Z. Chem.* **1974**, *14*, 34. (b) Makosza, M.; Kacprowice, A. *Rocz. Chem.* **1975**, *49*, 1627.

(9) Weber, W.; Gokel, G. *Tetrahedron Lett.* **1972**, 1637.

(10) Tabush, I.; Yoshida, Z.; Takahash, N. *J. Am. Chem. Soc.* **1974**, *96*, 3713.

0022-3263/80/1945-0754$01.00/0

Table II. Synthesis of 2 from 1 and 5[a]

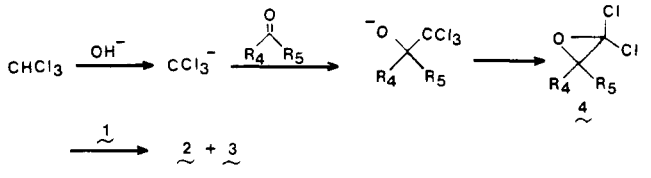
		yield ratio[b]	
	R_1	2	3
a	n-C_3H_7	85	15
b	i-C_3H_7	82 (60)	18
e	t-C_4H_9	90 (71)	10
g	Ph	85 (52)	15
h	$C(CH_3)_2CH_2OH$	90 (51)	10

[a] A 50% excess of 5 was used. Reactions were complete in 7 h. [b] Numbers in parentheses are yields of pure 2.

Recrystallization from pentane affords a 52% yield of **2b** as colorless needles: mp 82–84 °C; ^{13}C NMR ($CDCl_3$) δ 19.01 (q), 27.59 (q), 30.45 (q), 43.39 (d), 48.56 (s), 51.97 (t), 55.25 (s), 172.91 (s); mass spectrum, m/z 198 (M^+). Anal. Calcd for $C_{11}H_{20}N_2O$: C, 66.69; H, 11.12; N, 14.13. Found: C, 66.62; H, 11.19; N, 14.22.

An uncatalyzed reaction proceeds with only 12% conversion after 24 h under the same conditions. Powdered sodium hydroxide works as effectively as the aqueous solution while bromoform is less regioselective than chloroform, forming **2b** and **3b** in a 1:1 ratio from **1b**.

The generation of trichloromethide ion and its subsequent attack on carbonyl compounds are known to be very fast even at low temperature[11] while the syntheses involving dichlorocarbene require elevated temperatures to guarantee satisfactory yields.[12,13] We therefore believe the former is the reactive species and the mechanism is illustrated as follows in a simplified manner:



α-(Trichloromethyl)alkanols (e.g., **5**) which have been suggested to form the same oxirane intermediate **4** under basic conditions[14] react with **1** in similar fashion (Table II).

$$1 + \underset{5}{Me_2C(OH)(CCl_3)} \xrightarrow[50\%\ NaOH]{BTAC/CH_2Cl_2} 2 + 3$$

The piperazinones **2** are easily oxidized to their nitroxyl radicals by m-chloroperbenzoic acid in CH_2Cl_2[15] and reduced to the corresponding piperazines by $LiAlH_4$ in refluxing THF. The experimental details will be published later in a full paper.

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Registry No. **1a**, 72622-72-1; **1b**, 5448-29-3; **1e**, 38401-66-0; **1f**, 72622-73-2; **1g**, 5462-03-3; **1h**, 72622-74-3; **1i**, 72622-75-4; **2a**, 71044-00-3; **2b**, 71620-92-3; **2c**, 72622-76-5; **2d**, 72622-77-6; **2e**, 71764-81-3; **2f**, 72622-78-7; **2g**, 71620-94-5; **2h**, 71620-93-4; **2i**, 71764-80-2; **3a**, 71620-97-8; **3b**, 72638-40-5; **3c**, 72622-79-8; **3d**, 72622-80-1; **3e**, 72622-81-2; **3f**, 72610-24-3; **3g**, 72610-25-4; **3h**, 72610-26-5; **3i**, 72610-27-6; **5**, 57-15-8; acetone, 67-64-1; cyclohexanone, 108-94-1; butanone, 78-93-3.

(11) Merz, A.; Tomohogh, R. *Chem. Ber.* **1977**, *110*, 96.
(12) Reference 6b, p 281.
(13) Secondary and primary amines do proceed, although very slowly, to formamides and isocyanides, respectively, at ice-bath temperature.
(14) (a) Reference 7. (b) Weizmann, O.; Sulzbacher, M.; Bergmann, E. *J. Am. Chem. Soc.* **1948**, *70*, 1153.
(15) Rauckman, E. J.; Rosen, G. M.; Abou-Donia, M. B. *Synth. Commun.* **1975**, *5*, 409.

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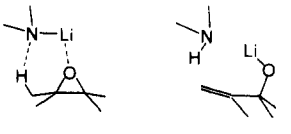
Asymmetric Induction. 3.[1] Enantioselective Deprotonation by Chiral Lithium Amide Bases

Summary: Optical yields as high as 31% have been observed as the result of the selectivity of a chiral base for enantiotopically related protons.

Sir: It is surprising that among the vast array of transformations that have been effected with concomitant induction of asymmetry there have been no reported cases of chiral bases showing selectivity between enantiotopic protons in prochiral molecules.[2] Of course it might be argued that a linear approach of a base along a carbon–hydrogen bond would provide but minimal opportunity for the development of discriminating interactions in the diastereomeric transition states. However, many of those transformations that are initiated by strong, anionic bases almost certainly involve complexation between the counterion of the base and the substrate, thus providing for a more ordered transition state than would be afforded by a simple, linear approach.

The rearrangement of epoxides to allylic alcohols as induced by lithium dialkylamide bases has been shown to be a process involving removal of a proton syn to the oxygen,[3] from which it may be inferred that the lithium atom is being transferred to the forming alkoxy group during deprotonation. Though it is tempting to represent this process by a cyclic, six-membered transition state, it is more likely that it involves an aggregate of the base.



We have been able to effect this rearrangement with a number of chiral, mono- and dialkyl, lithium amide bases with induction of asymmetry ranging from a low of 3% to a high of 31% ee. Table I provides a summary of our findings to date. These results represent, to the best of our knowledge,[2] the first example of enantioselective deprotonation.

It has been shown for cyclohexene oxides that deprotonation is highly selective for the syn proton that occupies the pseudoaxial orientation.[3] Thus in the present process, the enantiotopic proton selection involves a preferential reaction of the base with one of the rapidly equilibrating, enantiomeric conformations I and II.

In a typical experiment, the chiral amide base was formed from 4.4 mmol of the appropriate amine in tetra-

(1) For previous paper see: J. K. Whitesell and S. W. Felman, *J. Org. Chem.*, **42**, 1663 (1977).
(2) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, NJ, 1971; D. Valentine and J. W. Scott, *Synthesis*, 329 (1978).
(3) R. P. Thummel and B. Rickborn, *J. Am. Chem. Soc.*, **92**, 2064 (1970).

0022-3263/80/1945-0755$01.00/0