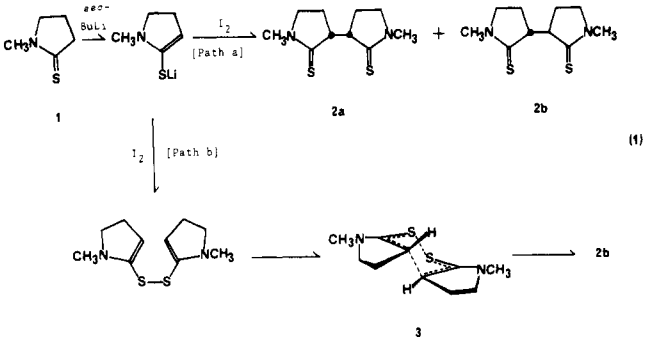
Stereoselective Coupling Reaction of Thioamides via a Dithia-Cope Rearrangement

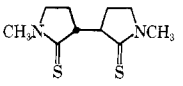
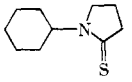
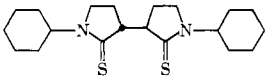
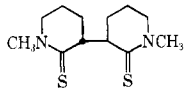
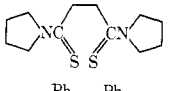
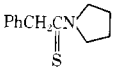
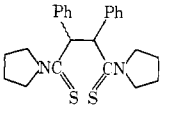
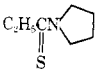
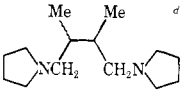
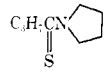
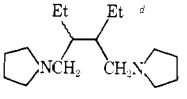
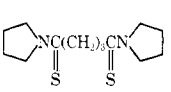
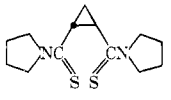
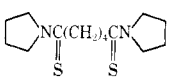
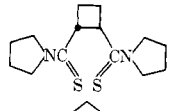
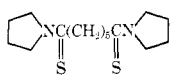
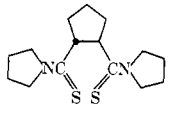
Sir:

While several studies have been reported on the coupling reaction of carbonyl compounds at the α position, so far we are aware, none of them have dealt with the subject of stereoselectivity at the coupling sites.[1] We wish to report the first example of stereocontrolled α coupling of thioamides to give *dl*-1,4-dithioamides, taking advantage of the stereoselectivity of the Cope-type rearrangement[2] of divinyl disulfides[3] (eq 1).



Thus the lithium thioenolate of 1-methylthiopyrrolidone **1**, generated by treatment with *sec*-butyllithium in THF at −30 °C under argon, was oxidized with 0.5 equiv of I_2[4] to give rise to 1,1′-dimethyl-3,3′-dithiopyrrolidone **2** as the sole product in 83% isolated yield. Two pathways to **2** merit consideration. Path a is the direct coupling between the α-carbon atoms and path b is the coupling between sulfur atoms followed by the Cope-type rearrangement. The exclusive formation of one isomer, either meso (**2a**) or *dl* (**2b**), evidently indicates that path b is responsible for this reaction. The product **2** has a sharp melting point (201–202 °C) and its NMR spectrum contains one singlet at δ 3.28 ($CDCl_3$) for the CH_3–N groups. The other protons are analyzable completely by spin decoupling. The product is expected to be the *dl* isomer **2b** by assuming that a Cope rearrangement proceeds through a chairlike arrangement[2] **3** as shown in eq 1. Actually the structure of **2** was de-

Table I. Stereoselective Coupling of Thioamides[a]

Entry	Thioamides	Products[b]	Yields,[c] %	Base (equiv)	Mass (M^+)	Mp or bp, °C
1			83	*sec*-BuLi (1.2)	228	201–202
2			69	*sec*-BuLi (1.2)	364	240–241
3			71	*sec*-BuLi (1.4)	256	138–138.5
4			54	LDA (1.1)		
5			64	*sec*-BuLi (1.2)	256	156–158
6			67 (8:2 *dl*:meso[e])	*sec*-BuLi (1.1)	408	>300[h]
7			62[f] (7:3 *dl*:meso[e])	*sec*-BuLi (1.2)	224	130–140[i] (0.5 mmHg)
8			43[f] (92:8 *dl*:meso[g])	*sec*-BuLi (1.2)	252	130–140[i] (0.1 mmHg)
9			53	*sec*-BuLi (3.0)	268	207.5–208
10			29	*sec*-BuLi (3.0)	282	128–129
11			55	*sec*-BuLi (2.4)	296	134–135

[a] Monoanions and dianions were generated using the indicated amount of *sec*-BuLi or lithium diisopropylamide at between −30 ~ −60 °C for 3 ~ 4 h and treated with 0.5 equiv of I_2 dissolved in THF for 4 ~ 14 h at −30 °C ~room temperature. [b] All products gave satisfactory analytical results and spectral data (IR, NMR, and mass). [c] Isolated yields. The yields have not been optimized in any case. [d] For the determination of the isomer ratio, the dithioamide was directly desulfurized to the diamine with $LiAlH_4$ in boiling THF. [e] The product ratio was determined on the basis of NMR peak integrations. [f] Overall yield for two steps. [g] The product ratio was determined by VPC. [h] Melting point of *dl* isomer. [i] Kugelrohr distillation.

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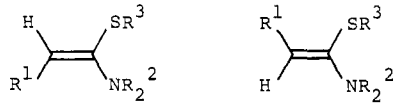
termined unambiguously to be **2b** by comparing the melting point (177–178 °C) of the dipicrate of 1,1′-dimethyl-3,3′-dipyrrolidine, which was obtained either by the reduction of **2** with Raney nickel W-2[5] or by the reduction of 1,1′-dimethyl-3,3′-dipyrrolidone[6] with $LiAlH_4$, with that of the meso isomer (mp 219–220 °C).[7] Similarly, 1-cyclohexylthiopyrrolidone and 1-methyl-δ-thiovalerolactam gave coupling products consisting of a single isomer.[8]

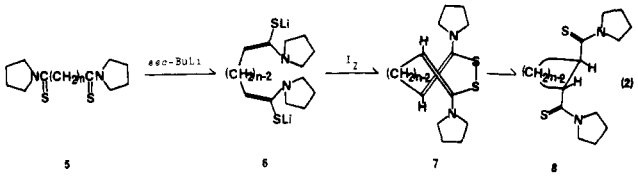
To obtain stereoselectivity in the coupling reaction of open-chain thioamides (entries 6, 7, and 8 for intermolecular coupling and entries 9, 10, and 11 for intramolecular coupling, Table I), the stereoselective formation of thioenolate (**4***E* or **4***Z*; R^3 = anionic charge) and its oxidative coupling with re-



4E 4Z

tention of configuration seem to be crucial. Brandsma and his co-workers[9] have reported the selective formation of **4***E* (R^3 = alkyl) by quenching the thioenolate, generated with sodium amide in ammonia, with alkyl halides. The thioenolate generated under our reaction conditions was treated with methyl iodide to give a mixture of ketene amino thioketal **4***E* and **4***Z* ($R^1 = R^3 = CH_3$; $R^2 = -(CH_2)_4-$) in a ratio of 92:8. These ketals were stable at room temperature but **4***E* isomerized gradually to the thermodynamically more stable form **4***Z* during distillation (120–130 °C (10 mmHg)). In accord with expectations based on these observations, the oxidative coupling of 1-thiobutyrylpyrrolidine afforded the *dl* isomer with 92% selectivity. Similarly 1-thiopropionylpyrrolidine and 1-thiophenylacetylpyrrolidine gave coupling products[10] in somewhat lower selectivity. The isomer distribution was determined by VPC and NMR analysis of the diamines derived by reduction with $LiAlH_4$ and/or Raney nickel W-2 (entries 7 and 8).

As illustrated in Table I, this reaction is also applicable to stereoselective intramolecular coupling which gives *trans*-cycloalkanedicarboxylic acid derivatives. That is, the cyclizations of dithioglutaryl-, dithioadipoyl-, and dithiopimeloylpyrrolidines were successfully performed to provide selectively the dithioamides[12] of *trans*-cyclopropane-, *trans*-1,2-cyclobutane-, and *trans*-1,2-cyclopentanedicarboxylic acids, respectively. Again in these examples the dianion intermediate **6** (eq 2), with the *E,E* configuration, seems to undergo the oxidative coupling with retention of configuration

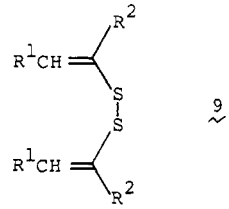


5 6 7 8 (2)

to give a racemic isomer **7** of 1,2-dithia-3, (ω-1)-*trans,trans*-cycloalkadiene,[14] which in turn rearranges to give **8** (eq 2).

The possibility that the alternate mechanisms (e.g., direct C–C coupling), which involve the isomerization of cis or cis,trans mixture of cycloalkanedithioamides to **8** by base or I_2 present in the reaction mixture, might be operative especially for $n = 3$ owing to the intermediacy of the highly strained **7**[15] cannot be totally discounted. However, the complete isomerization to give **8** under our reaction conditions seems to be unlikely, judging from the evidence given in ref 8. This leads us to believe that the mechanism depicted in eq 2 is responsible even for entry 9.

Finally it seems worthwhile to note that this dithia-Cope rearrangement proceeds at or below (−30 °C) room temperature, while the divinyl disulfides **9**[2,16] (R^2 = H, alkyl, or alkylthio group) generally require much higher temperatures (100–200 °C) to attain completion of the rearrangement.[17] For example, while **9** (R^1 = phenyl; R^2 = 1-pyrrolidine, entry



9

6) rearranges at room temperature, **9** (R^1 = phenyl; R^2 = SCH_3)[16c] has been reported to give thiophene derivatives after a [3.3] sigmatropic rearrangement at 100 °C for 3 h.

We are currently investigating the extention to the unsymmetrical coupling of thioamides and application to the synthesis of physiologically interesting compounds.

References and Notes

(1) (a) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 4605 (1971). (b) C. Chassin, E. A. Schmidt and H. M. R. Hoffmann, *ibid.*, **96**, 608 (1974). (c) Y. Ito, T. Konoike, and T. Saegusa, *ibid.*, **97**, 649 (1975); **97**, 2912 (1976); **99**, 1487 (1977). (d) T. J. Brockson, *Synthesis*, 396 (1975).

(2) S. J. Rhoads and N. Raulins, *Org. React.*, **22**, Chapter 1 (1975), and references cited therein.

(3) For the Cope rearrangement of divinylhydrazine dianions, see Z. Yoshida, T. Harada, and Y. Tamaru, *Tetrahedron Lett.*, 3823 (1976). For a comprehensive review, see G. B. Bennett, *Synthesis*, 589 (1977).

(4) Based on *sec*-butyllithium or lithium diisopropylamide used. Generally around an end of addition of THF solution of I_2, the reaction mixture was colored brown suddenly owing to the slight excess of I_2.

(5) G. R. Pettit and E. E. van Tamelen, *Org. React.*, **12**, 356 (1972).

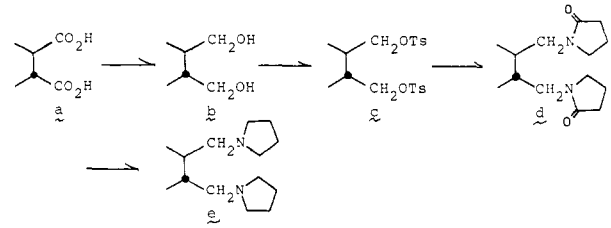
(6) Because methylation of **2** even with a large excess of CH_3I in refluxing acetone ceased at the stage of monomethylation, methylation, and subsequent hydrolysis with NaOH in EtOH were repeated twice to get 1,1′-dimethyl-3,3′-dipyrrolidone in 72% yield.

(7) K. Murayama, S. Morimura, Y. Nakamura, and G. Sunagawa, *Yakugaku Zasshi*, **85**, 130 (1965).

(8) For entry 1, the absense of **2a** in the reaction mixture was thoroughly checked by TLC using the authentic sample of **2a** (R_f 0.17 on silica gel plate, 5:1 benzene–ethyl acetate), which was obtained in 16% yield together with **2b** (R_f 0.34) in 56% yield by treatment of **2b** with 2 equiv of *sec*-butyllithium in THF at −40 °C for 4 h and then with H_2O. The NMR spectrum of **2a** showed a singlet at δ 3.26 ($CDCl_3$) for the CH_3–N groups. By treatment with 0.2 equiv of *sec*-butyllithium (room temperature for 4 h) or with NaOH in refluxing aqueous dioxane for 1 h, **2b** isomerized to **2a** only to a extent of <5%. No isomerization was observed by treatment with I_2 in THF at room temperature for 4 h.

(9) (a) P. J. W. Shuijl, H. J. T. Bos, and L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, **85**, 1263 (1966); (b) R. Gompper and W. Elser, *Justus Liebigs Ann. Chem.*, **725**, 64 (1969).

(10) The *dl* isomer of 1,1′-(2,3-dimethyltetramethylene)dipyrrolidine prepared in a sequence of reactions mentioned below showed the identical NMR, IR, and mass spectra with those of the main product in entry 7. *dl*-2,3-Dimethylsuccinic acid[11] was reduced to 1,4-diol (b) with $LiAlH_4$ in refluxing



a b c d e

THF (60% yield), followed by treatment with 2 equiv of *p*-toluenesulfonyl chloride in pyridine at 0 °C to give ditosylate (c) in 58% yield. By treatment of c with 2 equiv of sodium pyrrolidone in DMF at 100 °C was obtained 1,1′-(2,3-dimethyltetramethylene)dipyrrolidone d in 40% yield, which was reduced with $LiAlH_4$ in refluxing THF to give e in a quantitative yield.

(11) J. Cason and F. J. Schmitz, *J. Org. Chem.*, **28**, 555 (1963).

(12) The structures of the dithioamides of 1,2-*trans*-cyclobutane- and 1,2-*trans*-cyclopentanedicarboxylic acids were fully characterized by comparing the melting points and spectral data with those of the authentic samples prepared from 1,2-*trans*-cyclobutanedicarboxylic acid chloride (available from Aldrich) and 1,2-*trans*-cyclopentanedicarboxylic acid,[13] respectively.

(13) R. C. Fuson and W. Cole, *J. Am. Chem. Soc.*, **60**, 1237 (1938).

(14) G. M. Whitesides, G. L. Goe, and A. C. Cope, *J. Am. Chem. Soc.*, **89**, 7136 (1967).

(15) Compared with that of the corresponding hydrocarbon, the strain of **7** (n = 3) might be appreciably released owing to the longer C–S and S–S bonds. See ref 14 for *trans,trans*-1,5-cyclooctadiene.
(16) (a) J. Morgenstern and R. Mayer, *J. Prakt. Chem.*, **34**, 116 (1966); (b) H. Boelens and L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, **91**, 141 (1972); (c) F. C. V. Larsson, L. Brandsma, and S.-O. Lawesson, *ibid.*, **93**, 258 (1974).
(17) As an exception, **9** (R^1 = CH_3; R^2 = SCH_3)[16c] has been reported to rearrange at ~10 °C.

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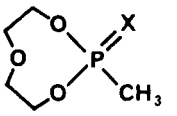
Conformational Study of Eight-Membered-Ring Organophosphorus Heterocycles

Sir:

In contrast to the numerous studies available concerning the conformation of five-[1] and six-membered[2]-ring phosphonite molecules, relatively little attention has been devoted to the corresponding seven-[3,4] and eight-membered rings. This paper describes some stereochemical and chemical features concerning the eight-membered rings **1** and **2**, a class of compounds which has received virtually no attention.[5] Particularly important questions to be answered in this area include the geometry and conformation of the ring system, the preferred orientation of the groups attached to the phosphorus, examination of a possible transannular phosphorus–oxygen interaction through the ring, and the possibility of a dimerization reaction as already observed for five-, six-, and seven-membered-ring phosphonites;[6] this dimerization would lead here to the formation of a sixteen-membered-ring crown ether.



1, X = lone pair; **2**, X = S

Compound **1** is prepared by reacting $CH_3P[N(CH_3)_2]_2$ and diethylene glycol in benzene under inert gas atmosphere. Compound **2** is readily obtained by direct addition of sulfur to a benzene solution of **1**.[7] Molecules **1** and **2** are identified by elemental analysis, ^1H, ^{13}C, and ^{31}P NMR spectroscopy.

The ^1H NMR spectra of molecules **1** and **2** have been recorded at 250 MHz and at 100 MHz with phosphorus decoupling. The spectra have been analyzed as ABCDX systems (X phosphorus) using the iterative program LAOCOON III. There is no evidence for the existence of long-range coupling constants between the ring protons. The results are shown in Table I. The ^{13}C and ^{31}P data are shown in Table II.

The dihedral angle ϕ between protons i and j on adjacent carbons can be calculated from vicinal coupling according to relation $J_{ij} = A\cos^2\phi + B\cos\phi$.[8] For each compound (**1** and **2**), spectral analysis leads to a set of four equations in three unknowns. Assuming a tetahedral HCH angle, the best fit yields the following results: **1**, A = 9.4, B = −0.9, ϕ = 60.8°; **2**, A = 9.2, B = −1.1, ϕ = 60.4°. Such angle values are indicative of a fixed staggered conformation around the C_4–C_5 and C_7–C_8 bonds.

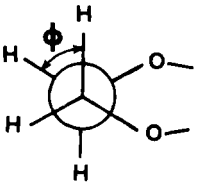
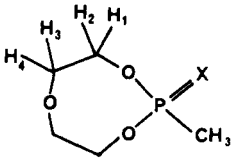


Table I. ^1H NMR Spectral Parameters of Molecules **1** and **2**

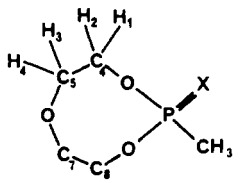


1, X = lone pair; **2**, X = S

	Chemical shift[a]				Coupling constants, Hz					
	H_1	H_2	H_3	H_4	$^2J(H_1H_2)$	$^3J(H_1H_3)$	$^3J(H_1H_4)$	$^3J(H_2H_3)$	$^3J(H_2H_4)$	$^2J(H_3H_4)$
1	4.00	3.69	3.73	3.25	−12.5	1.8	10.3	2.0	1.6	−12.9
2	4.66	3.24	3.54	2.98	−12.4	1.8	10.3	1.8	1.7	−13.5

[a] ^1H chemical shifts are in parts per million downfield from Me_4Si.

Table II. ^{13}C and ^{31}P NMR Spectral Parameters of Molecules **1** and **2**



1, X = lone pair; **2**, X = S

	Chemical shifts[a]				Coupling constants (Hz)						
	^{31}P	$^{13}C_{4,8}$	$^{13}C_{5,7}$	$^{13}CH_3$	$^3J(PH_1)$	$^3J(PH_2)$	$^4J(PH_3)$	$^4J(PH_4)$	$^2J(PC_4)$	$^3J(PC_5)$	$^1J(P^{13}CH_3)$
1	188.9	70.4	75.9	22.6	5.6	23.8	0.0	0.9	12.0	1.3	12.5
2	92.7	66.8	74.3	21.4	10.2	27.2	<0.3	<0.3	7.8	1.0	125.1

[a] ^{31}P chemical shifts are in parts per million with positive values downfield from external 85% H_3PO_4; ^{13}C chemical shifts are in parts per million downfield from Me_4Si.

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