

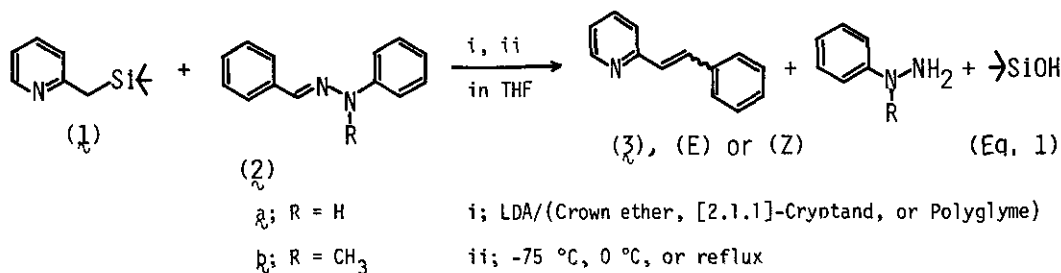
STEREOSPECIFIC SYNTHESIS OF (E)- OR (Z)- α -STYLBAZOLE FROM 2-(TRIMETHYLSILYLMETHYL)PYRIDINE AND BENZALDEHYDE PHENYLHYDRAZONES¹

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Abstract — In the presence of crown ethers, [2.1.1]-cryptand, di-, tri-, or tetraglyme, lithiated 2-(trimethylsilylmethyl)-pyridine reacts with benzaldehyde methylphenylhydrazone to give stereospecifically (E)- or (Z)- α -stylobazole in good yield.

In the course of our investigations on the reactions of α -silyl carbanions with carbonyl compounds or their analogs, we have reported that lithiated 2-(trimethylsilylmethyl)pyridine (**1**) reacted with imines to give (E)-2-alkenylpyridines stereospecifically in high yield.² Furthermore, lithiated **1** reacted with benzonitrile to give (E)-1-phenyl-2-(2-pyridyl)-1-(trimethylsilylamino)ethene under kinetically controlled conditions, while the Z-isomer was predominantly obtained under thermodynamically controlled conditions.³ These reactions are analogous to the Peterson reaction,⁴ in which there is no stereoselectivity due to the intermediate formation of a mixture of diastereomers.

As an extension of these investigations, we now wish to report a reaction of lithiated **1** with benzaldehyde phenylhydrazones, (**2a**) and (**2b**), to give (E)- or (Z)- α -stylobazole (**3**) in good yield (Eq. 1). In a typical run, **1** was lithiated with a



LDA/additive (crown ether, [2.1.1]-cryptand, or polyglyme) complex in THF at 0 (or -75) °C; the resultant carbanion of **1** was treated with a THF solution of **2** under the conditions indicated in the Table to give **3** stereospecifically. The results are shown in the same table. Benzaldehyde phenylhydrazone (**2a**) stubbornly resisted reacting with **1** even under reflux in the presence of 18-crown-6, the starting material, **2a**, being quantitatively recovered. However, the methylated derivative, **2b**, which has no acidic hydrogen, gave some hope of obtaining **3**. When a reaction mixture of **1** and **2b** was refluxed for 2.5 h in the absence of an additive, most of **2b** was consumed, however, the yield of (E)-**3** was low (34%). At low temperatures (0 or -75 °C), no reaction was observed regardless of the presence of a crown ether. On the other hand, when the reaction was carried out in the presence of 18-crown-6 under reflux

Table. Preparation of (E)- and (Z)- α -Stylbazoles (**3**) from 2-(Trimethylsilyl)methylpyridine (**1**) and Benzaldehyde Phenylhydrazones (**2**).

Entry	(2)	Additive ^{a, b)}	$\theta/^\circ\text{C}$	$t/\text{h}^{\text{c)}$	Conversion of (2), %	Yield of (3), % ^{d)}		E : Z
						E	Z	
1 ^{e, f)}	2a	18-C-6	reflux	2	0	0	0	-
2	2b	absent	-75	1	0	0	0	-
3	2b	absent	reflux	2.5	92	34	0	100 : 0
4	2b	18-C-6	-75	1	0	0	0	-
5	2b	18-C-6	reflux	4.5	58	74	0	100 : 0
6	2b	DB-18-C-6	0	1	0	0	0	-
7	2b	DB-18-C-6	reflux	2.5	45	89	0	-
8	2b	12-C-4	reflux	4	33	97	0	100 : 0
9	2b	15-C-5	reflux	3.5	63	68	0	100 : 0
10	2b	diglyme	reflux	3	71	37	0	100 : 0
11	2b	triglyme	reflux	0.5	48	85	0	100 : 0
12	2b	tetraglyme	reflux	3	82	72	0	100 : 0
13	2b	[2.1.1]-CRP	-80	1	10	0	27	0 : 100
14	2b	[2.1.1]-CRP	0	6.5	22	0	20	0 : 100
15	2b	[2.1.1]-CRP	reflux	1	83	87	7	92 : 8

a) Molar ratio, (**1**) : (LDA) : (**2**) : (Additive) = 1 : 1 : 1 : 0.015. b) Crown ether, cryptand, and dibenzo- are abbreviated as C, CRP, and DB-, respectively. c) The reaction reached equilibrium in the period indicated. d) The yield (determined by means of hplc) was based on the consumed **2**. e) Two equivalents of LDA were used. f) In the absence of an additive, **2a** did not give **3** at -75 °C.

for 4.5 h, (E)- β was formed stereospecifically in good yield (74%). Employing a variety of the other crown ethers and polyglymes (dibenzo-18-crown-6, 12-crown-4, 15-crown-5, tri-, and tetraglymes), (E)- β was also obtained stereospecifically in good yields (68 - 97%). Especially, 12-crown-4 quantitatively transformed the consumed β into (E)- β (97% yield) although the conversion of β was low (33%), and triglyme accelerated this reaction more strikingly than the other additives except [2.1.1]-cryptand did. When diglyme was used, the yield of (E)- β was very low (37%) in spite of the high conversion of β (71%).

On the other hand, when [2.1.1]-cryptand, which complexes with the lithium cation more tightly,⁵ was employed as an additive, only (Z)- β was obtained at low temperatures but in low yields (20 - 27%). However under reflux, (E)- β was predominantly formed in high yield (87%) together with a small amount of (Z)- β (7%). This fact suggests that the formation of (Z)- β is kinetically controlled, while that of (E)- β is thermodynamically controlled.

As each of the additives forms a complex with the lithium cation, the naked α -silyl carbanion with strong nucleophilicity should be generated.⁶ The results mentioned above are closely related to the complexation constants of these respective additives with lithium cation.⁵ A 1 : 1 complex of LDA/HMPT in THF⁷ was not suitable for a metalating agent in this reaction because decomposition of β (63% conversion) was observed even at room temperature [(E)- β was obtained in only 16% yield after 15 h]. The higher electron-density on the hydrazonomethyl carbon of β may be the reason why the anion of β was unreactive even in the presence of crown ether, and why β possesses lower reactivity than that of benzilidenanilin.²

Of particular utility are the results that this reaction is highly stereospecific, like the reaction of β with imines,² and that the yield of (E)- β is generally high. In addition, employing β , which exists only as a single isomer (E-form),⁸ gave only (Z)- β at -80 (or 0) °C in the presence of [2.1.1]-cryptand, while benzilidenaniline, which also exists only as a single isomer (Z-form), gave only (E)- β at -75 °C.^{2,9} In order to unravel why the high stereospecificity^{2,10} and the differences in the stereochemistry appeared, further investigation is now in progress.

To a THF (54 ml) solution of LDA prepared from diisopropylamine (20 mmol) and butyllithium (20 mmol) in hexane, 0.3 mmol of an additive in THF (10 ml) was added and stirred for 15 min at -75 (or 0) °C.¹¹ To the resultant solution, 20 mmol of β were added dropwise over 5 min. After an additional 10 min at this temperature, the mixture was treated with a THF solution of β (20 mmol). The resultant mixture was

stirred under the conditions indicated in the Table, then treated with water (60 ml), followed by complete extraction with ether. The dried and evaporated extract was analyzed by means of hplc. For comparison, an authentic sample of (*E*)- β ¹² was prepared by the method reported previously.²

ACKNOWLEDGEMENT

We are grateful to Mr. Nobuhiro Yano for his assistance in the experimental work.

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Received, 25th June, 1984