Pergamon

Tetrahedron Letters, Vol. 35, No. 21, pp. 3545-3546, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0581-H

Sodium Trimethylsilanethiolate in Novel Cyclizations for Synthesis of Aromatic Heterotricyclic Compounds

Long-Li Lai,*,† Pen-Yuan Lin,† Wen-Hong Huang,† Min-Jen Shiao,†,‡ and Jih Ru Hwu*,†,§

Institute of Chemistry, Academia Sinica,
Nankang, Taipei, Taiwan 11529, Republic of China; and

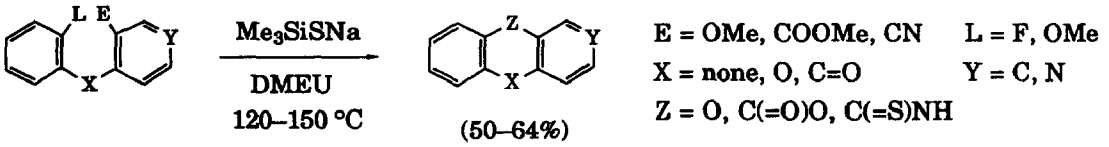
Organosilicon and Synthesis Laboratory,
Department of Chemistry, National Tsing Hua University,
Hsinchu, Taiwan 30043, Republic of China

Abstract: *A new method was developed for synthesis of aromatic heterotricyclic compounds in 50–64% yields from diaryls bearing a functionality including OMe, COOMe, and CN, and a leaving group (i.e., F and OMe) by use of Me_3SiSNa in 1,3-dimethyl-2-imidazolidinone at 120–150 °C.*

Many aromatic heterotricyclic compounds possess important biological activities;[1] some of them function as DNA intercalators.[2] The key steps for synthesis of those compounds often involve formation of the central ring.[3] Invention of new methods that can efficiently lead to aromatic heterotricyclic compounds would be beneficial to the development of biological chemistry.

Recently sodium trimethylsilanethiolate (Me_3SiSNa) has been utilized in demethylation of aromatic methyl ethers,[4–6] conversion of nitriles to thioamides,[5,7] and reduction of aromatic nitro compounds to amines.[5,8] Herein we report a new cyclization process involving the use of Me_3SiSNa for synthesis of heterotricyclic compounds (Scheme).

Scheme



We first generated Me_3SiSNa (~1.1 equiv) from $Me_3SiSSiMe_3$ (2.0 equiv) and NaOMe (1.1 equiv) in anhydrous 1,3-dimethyl-2-imidazolidinone (DMEU) at room temperature. To this solution was added diaryl **1**, **3**, **5**, or **7**; the resultant solution was heated at 120–150 °C in a sealed tube. After normal workup and purification with silica gel chromatography, the desired heterotricycles **2**, **4**, **6**, and **8** were obtained in 50–64% yields (see Table).

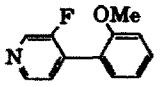
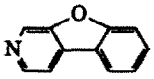
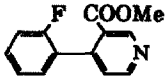
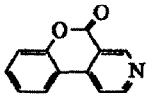
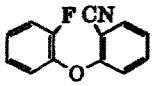
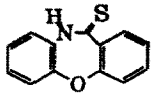
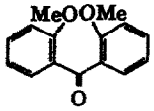
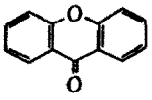
In the present conversion of **1** to **2** by use of Me_3SiSNa, *O*-demethylation followed by cyclization took place to form a five-membered ring. Use of the corresponding chlorine or bromine analog led to the desired product in <10% yields only. On the other hand, the success in the conversion of **3** to **4** demonstrates the feasibility of demethylation of a methyl ester with Me_3SiSNa and the efficiency of defluorinative cyclization to form a δ-lactone. Nucleophilic substitution on fluorobenzene also proceeded with a thioamide nucleophile, as indicated in the conversion of **5** to **6**. We generated the thioamide nucleophile (–C(=S)NH⁻)

‡Deceased April 5, 1993.

by reacting Me_3SiS^- with the cyano group in **5**.[5,7] The nitrogen, instead of sulfur, center in this nucleophilic moiety reacted with the fluorobenzene moiety to give the seven-membered lactam product **6** in 54% yield.

The methoxy group can function not only as an electrophile for Me_3SiS^- during *O*-demethylation, but also as a leaving group in cyclization. We found that, upon treatment with Me_3SiSNa, demethylation and demethoxylation occurred sequentially in dimethoxy benzophenone **7** to give **8** in 50% yield.

Table. Cyclizations of Diaryls by Use of 1.1 equiv of Me_3SiSNa in DMEU.

starting material		product		temp (°C)	time (h)	yield (%)
	**1**		**2**[9]	120	18	63
	**3**[10]		**4**[10]	150	5	64
	**5**		**6**	120	20	54
	**7**[11]		**8**[12]	150	24	50

Spectroscopic data and elemental analysis results of all products were consistent with published data for **2**, **4**, and **8**, or with the proposed structure **6** (mp 124–126 °C). Established methods were used for the preparation of starting materials **1**[10] (30%, mp 77–78 °C) and **5**[13] (52%, mp 44–46 °C).

Acknowledgments. *For financial support, we thank the National Science Council of Republic of China (Grants NSC 82-0208-M001-33 and NSC 83-0208-M007-101) and National Research Institute of Chinese Medicine.*

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(*Received in Japan* 10 *August* 1993; *accepted* 24 *January* 1994)