# NOVEL AND REGIOSELECTIVE LITHIATION OF THE UNSYMMETRICAL HANTZSCH-TYPE 1,4-DIHYDROPYRIDINE BY PARTICIPATION OF THE NEIGHBORING SULFINYL GROUP

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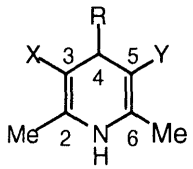
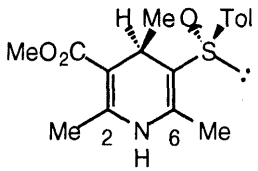
The C-6 methyl group of methyl (4*R*, $S_S$)-2,4,6-trimethyl-5-(*p*-tolylsulfinyl)-1,4-dihydropyridine-3-carboxylate (**2**) was found to be regioselectively lithiated by participation of the neighboring sulfinyl group, giving rise to the 6-modified Hantzsch-type compounds by treatment with *n*-butyllithium and the electrophiles.

**KEY WORDS** Hantzsch ester; lithiation; *p*-tolylsulfinyl group; neighboring group participation; regioselectivity; 1,4-dihydropyridine

The Hantzsch-type 1,4-dihydropyridines **1** (X, Y=electron withdrawing group) have been becoming attractive compounds from the viewpoint of their chemical and biological properties. Hence, development of the efficient derivatization of this type of compound as well as of the novel synthetic method is strongly demanded. Modification of the methyl group at C-2 or C-6 by use of the electron-withdrawing property of the neighboring group at C-3 or C-5 would be effective for further derivatization[1,2] since a series of new compounds is obtained from the sole starting material only by changing the electrophilic reagents. Particular interest has focused on the regioselectivity appearing in the unsymmetrical Hantzsch compounds **1** (X≠Y). However, only a few such examples have been reported, and all of these are dealing only with the 4-aryl derivatives **1** (R=Ar).[2]




**1**




**2**

We have already reported the synthesis of the 4-aryl and 4-methyl substituted novel Hantzsch-type 1,4-dihydropyridines **1** (X=$CO_2$Me, Y=S(O)Tol, R=Ar and Me) in optically active form and the biological activity of the 4-aryl derivatives as calcium channel antagonists.[3] The biological activities of the 4-methyl derivatives are of great interest as well since some of the 4-methyl derivatives are known to inhibit platelet aggregation and secretion.[4] Furthermore, from the viewpoint of organic chemistry, it is also interesting to know the differences in reactivity between the two methyl groups at C-2 and C-6 (ester vs. sulfinyl group). In this paper, we describe the first

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example of the regioselective lithiation of the C-6 methyl group of the Hantzsch-type compound **2** by the effect of the neighboring sulfinyl group.

Treatment of **2** with 2.1 eq of *n*-butyllithium and subsequently with Davis' reagent **3**[5] afforded the hydroxymethyl derivative **4** in good yield.[6] None of the regioisomeric compound was detected in the crude reaction mixture. The structure of **4** was suggested as shown from its spectral evidence[7] but was eventually confirmed after alternative synthesis of the isomer **7**. Compound **7** was obtained as a minor component by condensation of **5**[3] with **6**, as shown in Chart 1. The spectral properties of the product **4** obtained by direct oxidation were not identical with those of **7**.[7] This finding means that the C-6 methyl group is regioselectively lithiated and is quite noteworthy for the fact that the methyl group close to the ester group is exclusively lithiated under the same conditions in the case of the unsymmetrical Hantzsch ester **1** (X=$CO_2Et$, Y=CONHMe or $CONMe_2$).[2b] In our case, the carbanion at the C-6 methyl group is expected to be stabilized *via* formation of the chelation structure with the neighboring sulfinyl group (as illustrated in **8**), which is thought to be responsible for this regioselectivity.

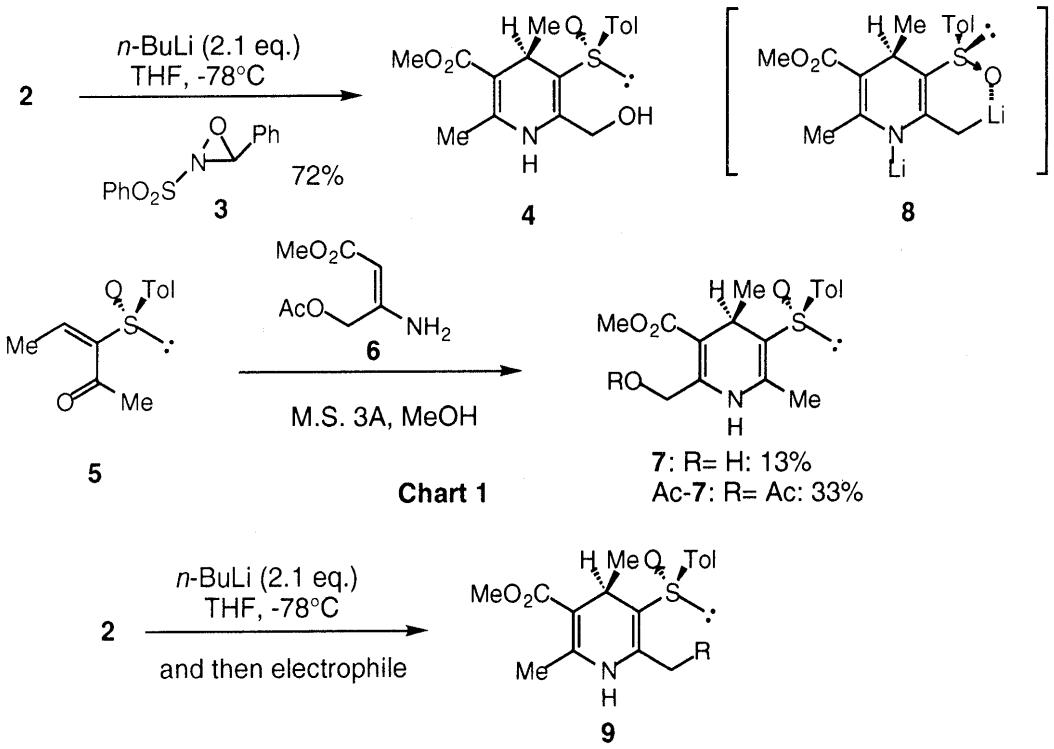


Chart 1

**Table 1**. Electrophilic Reaction of the C-6 Methyl Group of **2**

| Run | Electrophile | Product **9** | Yield (%) | R |
|---|---|---|---|---|
| 1 | MeI | **a** | 96 | Me |
| 2 | MOMCl | **b** | 83 | $CH_2OMe$ |
| 3 | MEMCl | **c** | 83 | $CH_2O(CH_2)_2OMe$ |
| 4 | acetone | **d** | 80 | $C(OH)Me_2$ |
| 5 | TMSCl | **e** | 66 | TMS |
| 6 | PhSSPh | **f** | 50 | SPh |

Other electrophiles were also examined under the same conditions, and the results are outlined in Table 1. The dianion **8** generated from **2** underwent not only formation of the C-C bond but also functionalization with the heteroatoms such as Si and S to afford **9a-f** in good to moderate yields.[8] Further investigation of this reaction and application to the other Hantzsch compounds possessing an ester and a sulfinyl group are under way.

## REFERENCES AND NOTES


1) For application to the symmetrical Hantzsch compounds **1**: (X=Y=ester) Aritomi J., Ueda S., Nishimura H., *Chem. Pharm. Bull.*, **28**, 3163-3171 (1980); (X=Y=ester) Kleinschroth J., Mannhardt K., Hartenstein J., Satzinger G., *Synthesis*, **1986**, 859-860; (X=Y=nitrile) Patterson J.W., *J. Heterocycl. Chem.*, **23**, 1689-1692 (1986).
2) For application to the unsymmetrical Hantzsch compounds **1**: a) (X=ester, Y=nitrile), Sircar I., Anderson K.R., Bonadies L., *Tetrahedron Lett.*, **29**, 6835-6838 (1988); b) (X=ester, Y=amide), Poindexter G.S., Licause J.F., Dolan P.L., Foley M.A., Combs C.M., *J. Org. Chem.*, **58**, 3811-3820 (1993).
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5) Davis F.A., Vishwakarma L.C., Billmers J.M., Finn J., *J. Org. Chem.*, **49**, 3241-3243 (1984).
6) Typical procedure for the preparation of **4** is as follows. A hexane solution of *n*-butyllithium (1.6 M, 1.37 ml, 2.08 mmol) was added dropwise to a stirred solution of **2** (333 mg, 1.04 mmol) in THF (10 ml) at -78°C and the whole was stirred for 30 min at the same temperature. A THF solution (5 ml) of **3** (333 mg, 1.27 mmol) was added dropwise to the above reaction mixture. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with sat. $NH_4Cl$ sol. and extracted with $CHCl_3$. The $CHCl_3$ layer was worked up as usual and the resultant residue was purified by silica gel column chromatography ($CH_2Cl_2$/AcOEt=1/2) to afford **4** as colorless crystals.
7) Spectral data for the 6- and 2-hydroxymethyl derivatives, **4** and **7**, are as follows. **4**: colorless crystals. mp 179-181°C ($Et_2O$). $[\alpha]_D^{26}$ +337 (*c*=0.66, $CHCl_3$). IR ν (KBr): 3295, 1684, 1490, 1251, 1096, 907, 809 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.28 (3H, d, *J*= 7 Hz, 4-Me), 2.25 (3H, s, 2-Me), 2.39 (3H, s, Ar-Me), 3.67 (3H, s, $CO_2Me$), 3.83 (1H, q, *J*= 7 Hz, 4-H), 4.42 (1H, d, *J*= 14 Hz, 6-CH), 4.92 (1H, br s, OH), 4.97 (1H, d, *J*= 14 Hz, 6-CH), 7.09 (1H, br s, NH), 7.28, 7.48 (4H, AA'BB', *J*= 8 Hz, aromatic). MS (EI) *m/z*: 335 ($M^+$, 3), 320 (75), 302 (100), 91 (54). *Anal.* Calcd for $C_{17}H_{21}NO_4S \cdot 1/6\ H_2O$ : C, 60.33; H, 6.35; N, 4.14; S, 9.47. Found: C, 60.35; H, 6.25; N, 4.04; S, 9.29. **7**: mp 144-146°C (MeOH). $[\alpha]_D^{19}$ +377 (*c*=0.56, $CHCl_3$). IR ν (KBr) : 3323, 1690, 1234, 1097 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 0.21 (3H, d, *J*= 7 Hz, 4-Me), 2.35 (3H, s, 6-Me), 2.41 (3H, s, Ar-Me), 3.65 (3H, s, $CO_2Me$), 3.81 (1H, q, *J*= 7 Hz, 4-H), 4.35 (1H, m, OH), 4.63, 4.65 (each 1H, AB in ABX, $J_{AX}$= $J_{BX}$= 6 Hz, $J_{AB}$= 16 Hz, 2-$CH_2$), 7.29, 7.51 (4H, AA'BB', *J*= 8 Hz, aromatic), 7.43 (1H, br s, NH). MS (EI) *m/z*: 320 ($M^+$-Me, 3), 163 (100), 134 (88). *Anal.* Calcd for $C_{17}H_{21}NO_4 \cdot H_2O$ : C, 57.77; H, 6.56; N, 3.96; S, 9.07. Found: C, 57.68; H, 6.47; N, 3.81; S, 8.71.
8) Satisfactory spectral data for the 6-modified Hantzsch compounds **9a-f** were obtained.


(Received November 22, 1995; accepted January 6, 1996)