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8-METHOXYISOQUINOLINE DERIVATIVES THROUGH *ortho*-SELECTIVE METALATION OF 2-(3-METHOXYPHENYL)ETHYLAMINE

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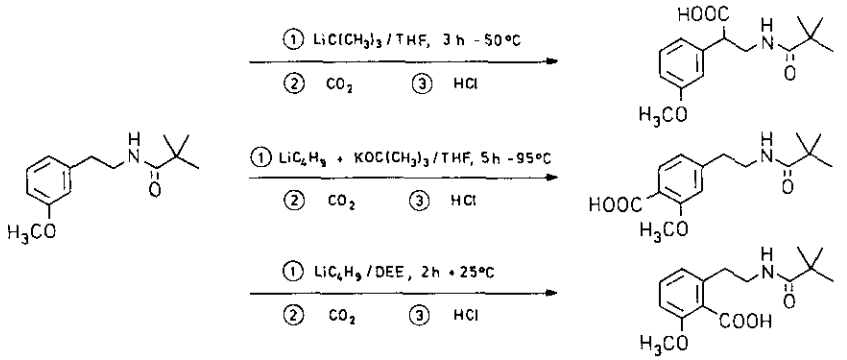
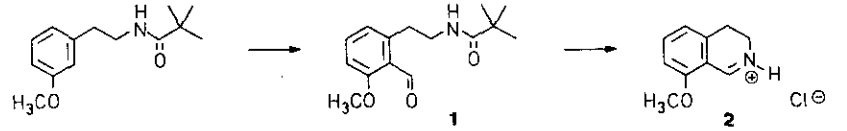
Summary : Butyllithium in diethyl ether smoothly metalates 2-*m*-anisyl-*N*-pivaloylethylamine at the aromatic position flanked by the two substituents. Subsequent reaction with *N,N*-dimethylformamide followed by acid catalyzed cyclization and reduction gives 8-methoxy-1,2,3,4-tetrahydroisoquinoline.

As reported in the preceding communication [1], 2-*m*-anisyl-*N*-pivaloylethylamine reacts with *tert*-butyllithium at the benzylic position and, after carboxylation, affords 2-*m*-anisyl-3-*N*-pivaloylaminopropanoic acid (77%, mp 138 - 139 °C). With our "superbasic" mixed metal reagent [2], however, the hydrogen/metal exchange occurs at the aromatic position which is adjacent to the methoxy group but distant from the alkyl sidechain (58% of the acid after carboxylation, mp 166 - 167 °C, recryst. from ethyl acetate). Finally, ordinary butyllithium preferentially abstracts a proton from the aromatic position which is *ortho* with respect to both substituents (61% of the acid after carboxylation, mp 128 - 129 °C, recryst. from ethyl acetate).



This reagent controlled site selectivity of the organometallic attack can be advantageously exploited in a simple synthesis of isoquinoline derivatives. If the intermediate resulting from metalation with butyllithium is treated with *N,N*-dimethylformamide, the aldehyde **1** is obtained which in acidic medium undergoes rapid cyclization. Simultaneous loss of the transient hydroxy function and the pivaloyl moiety led to 8-methoxy-3,4-dihydroisoquinoline hydrochloride (**2**·HCl) [3].



The heterocyclic compound **2** is a versatile intermediate for further transformations in the heterocyclic field. For example, it may be alkylated with methyl iodide affording 8-methoxy-2-methyl-3,4-dihydroisoquinolinium iodide (**3**, 71%, mp 185 - 186 °C, recryst. from ethanol) or reduced with sodium borohydride to give 8-methoxy-1,2,3,4-tetrahydroisoquinoline (**4**).

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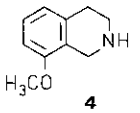

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Until now, the preparation of 8-methoxy-1,2,3,4-tetrahydroisoquinoline (**4**) has required lengthy and inefficient routes [4]. The Bischler-Napieralski type cyclization of *N*-formyl-2-*m*-anisylethylamine leads to 6- rather than 8-methoxy-3,4-dihydroisoquinoline [5].

Working procedure : 2-*m*-Anisyl-*N*-pivaloylethylamine [6] (10 mmol) was added to a solution of butyllithium (30 mmol) in hexane (20 mL) and diethyl ether (50 mL). After stirring the suspension 2 h at 25 °C, it was treated with dimethylformamide (60 mmol). After 1 h at 25 °C, a concentrated aqueous solution of ammonium chloride (20 mL) was added. The aldehyde **1** was extracted and purified by elution from silica gel with mixtures of ethyl acetate and hexane; 55%; mp 91 - 92 °C (recryst. from heptane). [7] - A solution of aldehyde **1** (5 mmol) in dichloromethane (10 mL) and 10% aqueous hydrochloric acid (20 mL) were vigorously stirred during 24 h at 25 °C. After evaporation of the aqueous phase to dryness, the 8-methoxy-3,4-dihydroisoquinoline hydrochloride demihydrate (**2**·HCl·$\frac{1}{2}$H$_2$O) remained as a colorless residue; 79%; mp 183 - 184 °C (dec.; recryst. from ethanol/diethyl ether)[7]. - The latter substance (3 mmol) was dissolved in ice-cold methanol (10 mL) which contained sodium borohydride (3 mmol). After 30 min at 0 °C, the solvent was evaporated, a 10% aqueous solution (10 mL) of sodium hydroxide was added and the 8-methoxy-1,2,3,4-tetrahydroisoquinoline (**4**) was extracted with dichloromethane (3 × 10 mL). This solvent was subsequently replaced by diethyl ether (10 mL). Anhydrous hydrochloric acid caused the precipitation of the **4** · HCl salt; 69%; mp 261 - 262 °C (dec.). [7, 8]

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REFERENCES

[1] Gy. Simig, M. Schlosser, *Tetrahedron Lett.* **32** (1991), preceding communication.
[2] M. Schlosser, *J. Organomet. Chem.* **8** (1967), 193; *Pure Appl. Chem.* **60** (1988), 1627.
[3] A similar reaction sequence has previously been employed to convert 2-(3,4-dimethoxyphenyl)-*N*-(trimethylsilyl)ethylamine with 45% yield into 7,8-dimethoxy-3,4-dihydroisoquinoline [C. Lamas, L. Castedo, D. Domínguez, *Tetrahedron Lett.* **29** (1988), 3865].
[4] R.A. Robinson, *J. Am. Chem. Soc.* **69** (1947), 1944; M. Okamoto, *Chem. Pharm. Bull.* **15** (1967), 168; A. Brossi, S. Teitel, *Helv. Chim. Acta* **53** (1970), 1779; F. Schenker, R.A. Schmidt, T. Williams, A. Brossi, *J. Heterocycl. Chem.* **8** (1971), 665; R.W. Gray, A.S. Dreiding, *Helv. Chim. Acta* **63** (1980), 315; M. Rey, T. Vergnani, A.S. Dreiding, *Helv. Chim. Acta* **68** (1985), 1828.
[5] J.M. Gulland, C.J. Virden, *J. Chem. Soc.* **1929**, 1793.
[6] Prepared by treating a 1 M solution of 2-*m*-anisylethylamine [T. Kametani, K. Kigasawa, M. Hiiragi, H. Ishimaru, *J. Chem. Soc. C* **1971**, 2632] 15 h at 25 °C with a slight excess of pivaloyl chloride and pyridine, followed by extraction and recrystallization from heptane; mp 44 - 46 °C [7].
[7] Elementary analyses and full spectroscopic data corroborate the identity and purity of all new compounds.
[8] D.S. Kashdan, J.A. Schwartz, H. Rapoport, *J. Org. Chem.* **47** (1982), 2638.

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