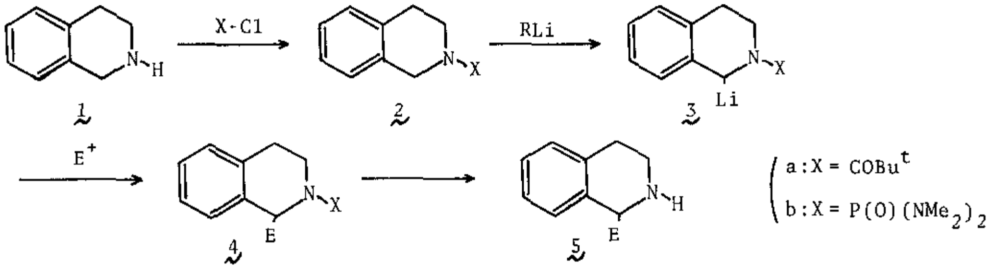
NEW SYNTHETIC METHODS OF 1-SUBSTITUTED 1,2,3,4-TETRAHYDROISOQUINOLINES

Masaaki Yoshifuji and Dieter Seebach
Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule
ETH-Zentrum, Universitätstrasse 16, CH-8092, Zürich, Switzerland

Two types of new synthetic reagents for preparation of 1-substituted 1,2,3,4-tetrahydroisoquinolines have been developed.



N-Pivaloyl-1,2,3,4-tetrahydroisoquinoline (2a: X = $\mathrm{COBu^t}$), prepared from tetrahydroisoquinoline (1) and pivaloyl chloride, was lithiated with tert-butyllithium at -78°C in THF in the presence of TMEDA and was allowed to react with various kinds of electrophiles to give 1-substituted N-pivaloyltetrahydroisoquinolines (4a). Removal of pivaloyl group was accomplished in refluxing benzene with exactly one equivalent of sodium bis(methoxyethoxy)aluminum hydride to give tetrahydroisoquinolines 5.

N-Bis(dimethylamino)phosphinyl-1,2,3,4-tetrahydroisoquinoline (2b: X = $\mathrm{P(O)(NMe_2)_2}$), prepared from 1 and the corresponding diaminophosphinyl chloride, was lithiated in THF at -78°C with n-butyllithium and was allowed to react with various kinds of electrophiles including s-alkyl halides, tosylate, epoxides, and (arene)tricarbonylchromium(0) to give the corresponding 1-substituted N-bis(dimethylamino)phosphinyl-1,2,3,4-tetrahydroisoquinolines (4b). Double alkylations and coupling reactions were achieved by the second lithiation and oxidation with iodine respectively. Cleavage of N-P bond to 5 was carried out in refluxing dilute hydrochloric acid.

The use of these reagents might be a useful extention to the methodology of isoquinoline synthesis. Amidation or phosphinoylation, lithiation, reaction with electrophiles and cleavage constitute an efficient sequence for 1-alkylation of the isoquinoline nucleus.