ORGANIC LETTERS

2005
Vol. 7, No. 1
127−129

Rerouting Nucleophilic Substitution from the 4-Position to the 2- or 6-Position of 2,4-Dihalopyridines and 2,4,6-Trihalopyridines: The Solution to a Long-Standing Problem

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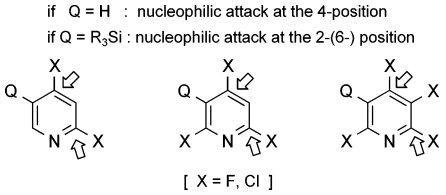
Received October 22, 2004

ABSTRACT



2,4-Difluoro-, 2,4,6-trifluoro-, and 2,3,4,6-tetrafluoropyridine undergo nucleophilic substitution preferentially if not exclusively at the 4-position. However, after the introduction of a trialkylsilyl group at C-3 or C-5, the halogen at the 6-(2-)position is displaced selectively. This synthetically valuable regiocontrol can also be realized with other halopyridines such as 2,4-dichloro- and 2,4,6-trichloropyridine.

Fluoropyridines and chloropyridines have two major reaction modes enabling the introduction of functional groups. They can be selectively lithiated to be subsequently combined with a huge variety of electrophiles.[1] Alternatively, the halogens, if located at activated centers, may be displaced by a manifold of nucleophiles such as alkoxy, amino, or cyano groups.[2,3] Whenever two or three halogens simultaneously occupy 2-(6-) and 4-positions, the reaction is found to occur preferentially or exclusively at the latter.[4] Previous attempts to reverse this order of priority met only limited success. The 4- to 2-substitution ratios were found to decrease from >10:1 to 1:1 or 1:2 when the substrates pentafluoropyridine, 3-chlorotetrafluoropyridine, and 3,5-dichlorotrifluoropyridine were treated with lithium or sodium oximates rather than with standard nucleophiles.[5]

We are now able to suggest a more rigorous and, at the same time, convenient approach to this regioselectivity issue. The approach is based on the accidental finding that bulky trialkylsilyl groups totally suppress the nucleofugal mobility of neighboring halogen atoms. Having scrutinized a series

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(3) Crampton, M. R. In *Organic Reaction Mechanisms*; Knipe, A. C., Watts, W. E., Eds.; Wiley: Chichester, **2003**; pp 275−286 and previous volumes of this series.

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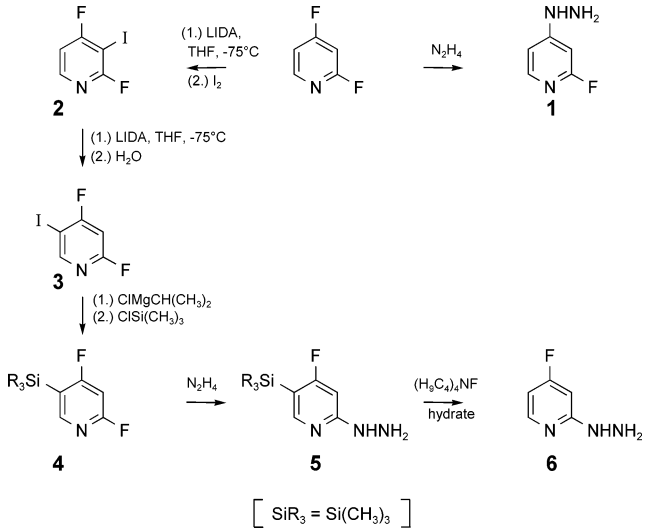
10.1021/ol047826g CCC: $30.25
Published on Web 12/10/2004

of different nucleophiles, we soon settled upon hydrazine as our favorite reagent. The resulting hydrazinopyridines[6] are unusually versatile intermediates. Other than being incorporated into pyrazoles[7] by condensation with 1,3-dicarbonyl compounds and reduced to aminopyridines by *NN*-cleaving hydrogenolysis,[8] they may lose both nitrogen atoms by dediazotation of a transient diazenylpyridine. The latter species can be generated by oxidation of the hydrazinopyridine with copper(II) sulfate[9] or by base-promoted 1,6-dehydrogenation of a tautomeric form of the halohydrazinopyridine.[10] In either case the hydrazino group is replaced by a hydrogen atom, whereas a bromine atom enters instead if the dehydrogenation of the hydrazinopyridine is accomplished with elemental bromine.[11]

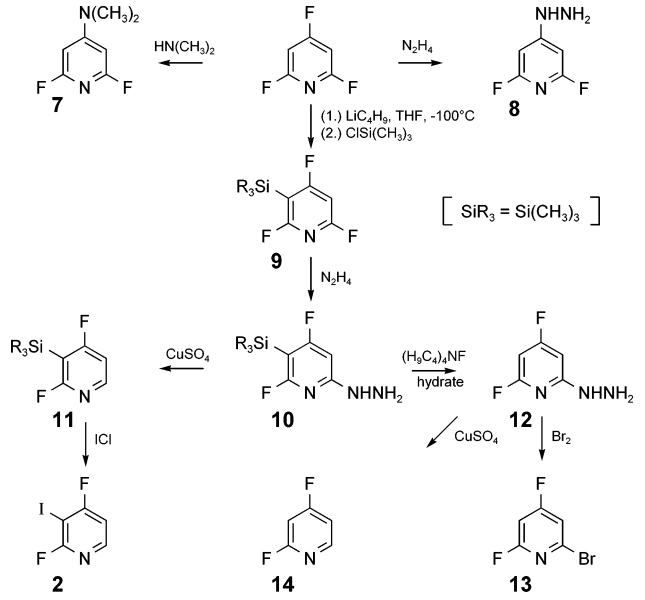
Prepared from the hydrazine compound **12** (see Scheme 2), 2,4-difluoropyridine reacted with hydrazine to afford

Scheme 1. Regiodivergent Substitution of 2,4-Difluoropyridine and 2,4-Difluoro-5-(trimethylsilyl)pyridine (**4**) with Hydrazine



2-fluoro-4-hydrazinopyridine (**1**; 73%) exclusively. 2,4-Difluoro-5-(trimethylsilyl)pyridine (**4**), made in three steps starting from 2,4-difluoropyridine through 2,4-difluoro-3-iodopyridine (**2**; see Scheme 1) and 2,4-difluoro-5-iodopyridine (**3**), exhibited toward hydrazine the same high degree

Scheme 2. Regiodivergent Substitution of 2,4,6-Trifluoropyridine and 2,4,6-Trifluoro-3-(triethylsilyl)pyridine



of regioselectivity, but this time in favor of the 2-position (Scheme 1). The resulting 4-fluoro-2-hydrazino-5-(trimethylsilyl)pyridine (**5**, 63%) was converted into the targeted 4-fluoro-2-hydrazinopyridine (**6**, 53%) by protodesilylation using tetrabutylammonium fluoride hydrate ("TBAF").

2,4,6-Trifluoropyridine[4b] underwent nucleophilic substitution solely at the 4-position, thus producing, for example, 4-(dimethylamino)-2,6-difluoropyridine (**7**; 86%) and 2,6-difluoro-4-hydrazinopyridine (**8**; 85%). On the other side, 2,4,6-trifluoro-3-(triethylsilyl)pyridine (**9**; from 2,4,6-trifluoropyridine by consecutive reaction with butyllithium and chlorotriethysilane in 84% yield) condensed with hydrazine at the 6-position to afford the key intermediate **10** (98%), which gave the 2,4-difluoro-3-(triethylsilyl)pyridine **11** (89%) by copper(II)-mediated dehydrogenating dediazotation and 2,4-difluoro-3-iodopyridine (**2**, 93%) by iododesilylation. The 2,4-difluoro-6-hydrazinopyridine (**12**), obtained by protodesilylation of intermediate **10** in 85% yield, provided 2-bromo-4,6-difluoropyridine (**13**, 71%) and 2,4-difluoropyridine (**14**, 51%[12]) through oxidation with elemental bromine and copper sulfate, respectively (Scheme 2).

The silencing of nucleophilic exchange centers in the vicinity of trialkylsilyl groups is a phenomenon that holds the promise of universal applicability. We have applied the method to 2,3,4,6-tetrafluoro-5-(trimethylsilyl)pyridine (**15**), 2,4-dichloro-5-(triethylsilyl)pyridine (**16**), and 2,4,6-trichloro-3-(trimethylsilyl)pyridine (**17**). Reaction with hydrazine and, except in the case of **16**, subsequent protodesilylation (producing the transient intermediates **18**−**20**) and oxidative dediazotation afforded the final products 2,4,5-trifluoropyridine (**21**), 4-chloro-3-(triethylsilyl)pyridine (**22**), and 2,4-

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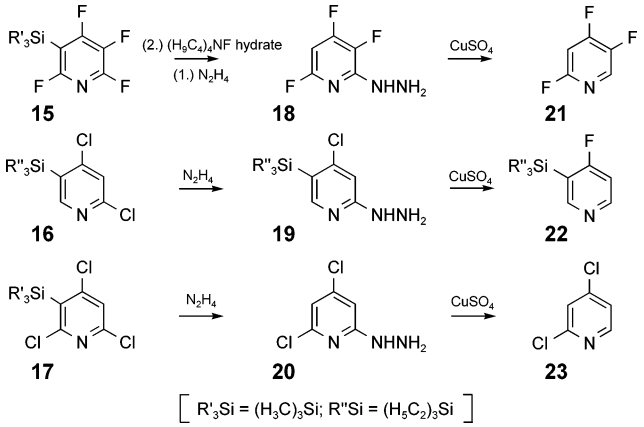
(12) In reality, the yield is high but almost half of the product is lost upon steam distillation because of its extreme volatility.

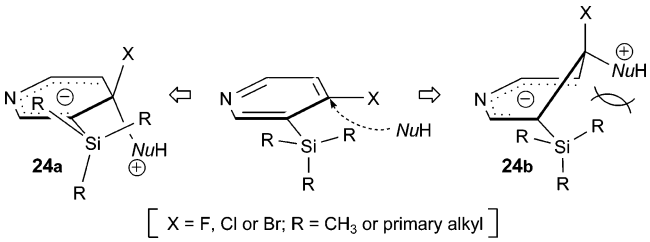
dichloropyridine (**23**) in, respectively, 65, 64, and 48% overall yields (Scheme 3).

Scheme 3. Regioselective Displacement of Halogen by Hydrazine in Tetrafluoro-5-(trimethylsilyl)pyridine (**15**), 2,4-Dichloro-5-(triethylsilyl)pyridine (**16**) and 2,4,6-Trichloro-3-(trimethylsilyl)pyridine (**17**)



It is by no means obvious how to rationalize how a bulky substituent shields neighboring halogen atoms against nucleophilic displacement so effectively. If one approximates the energy of the first transition state to that of the Meisenheimer-type adduct that emerges from it, one might rather have predicted a rate acceleration due to relief of internal strain. At first sight, this should occur when the nucleophile docks at the halogen-bearing carbon atom and thus transforms a trigonal center into a tetragonal center. The latter could nicely accommodate a silyl-bound alkyl group in a staggered arrangement (Scheme 4, **24a**). However, in reality the shrinking of the CCC angle from 120° to an estimated 112° must force the tetragonal center out of plane (**24b**). If, as we assume, the nucleophile approaches in the ring plane to occupy a quasiequatorial position (**24b**) rather than orthogonally to the ring plane to take an quasiaxial position, the bulky trialkylsilyl group will interfere with its trajectory and thus bar its access (Scheme 4).

Scheme 4. Two Alternative Images (**24a** and **24b**) of the Meisenheimer-Type Intermediate Generated upon Addition of a Nucleophile to a 4-Halo-3-(trialkylsilyl)pyridine



Acknowledgment. This work was financially supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (Grants 20-55′303-98, 20-63′584-00, and 20-100′336-02), and the Bundesamt für Bildung und Wissenschaft, Bern (Grant 97.0083, linked to the TMR project FMRXCT-970129).

Supporting Information Available: Typical experimental procedures and full characterization of compounds **1**−**17** and **20**−**23** by their physical constants, ^{1}H and ^{13}C NMR spectra, and elementary analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047826G