SYNTHETIC CONNECTIONS TO THE DIRECTED ortho METALATION REACTION.
3,4-PYRIDYNES FROM 4-TRIALKYLsILYL-3-PYRIDYL TRIFLATES

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Abstract—4-Trialkylsilyl-3-pyridyl triflates (11a-b), derived from 9 and 12 by directed ortho metallation chemistry, serve as useful precursors of 3,4-pyridynes (6a-b) and lead by cycloaddition and nucleophilic trapping reactions to products (13a-b, 14a-b, 15, 16a-b, and 17a-b).

In the field of heteraryne chemistry,1 the 3,4-pyridyne species has attracted considerable theoretical2 and synthetic3 interest. The classical methods of 3,4-pyridyne generation via thermolysis of diazonium carboxylate4 and oxidative degradation of aminotriazole5 have been supplemented by new procedures based on the original observations of halopyridine metal-halogen exchange and directed ortho metaltung by Kauffmann,6 Gribble,3a and Quéguiere.3b-c,7 Noteworthy is the lack of general approaches for substituted 3,4-pyridynes which is mainly due to poor accessibility of appropriately substituted pyridine precursors and/or their instability. The insightful studies by Kobayashi and coworkers8 on the fluoride-induced generation of benzynes from o-silylaryl triflates9 triggered our work10 on the generation of substituted benzynes (2), derived from precursors (1) via directed ortho metaltung strategies,11 and their cycloaddition (3) and nucleophilic (4) reactivities (Scheme 1).

This paper is dedicated to Professor Emeritus Masatomo Hamana, a heterocyclic chemist par excellence, in celebration of his 75th birthday.
Herein we report our preliminary results of a sequel study concerning the use of o-silylpyridyl triflates 5 for the generation of the corresponding 3,4-pyridynes (6) and their cycloaddition (7) and nucleophilic (8) reactions respectively.  

Adopting the earlier general methodology for the synthesis of substituted pyridines via the powerful carbamate directed metalation group, the 3-pyridyl carbamate (9) was sequentially lithiated with LDA and quenched with TMSCl or TESCl (triethylsilyl chloride) to furnish regiospecifically the 4-silylated products (10a) and (10b) in good to excellent yields. Since silylpyridines are sensitive to base-induced cleavage, carbamate hydrolysis of 10a-b under basic conditions was precluded. Although reductive carbamate cleavage of 10b was achieved using LAH, the resulting 3-hydroxy-4-trimethylsilylpyridine was unstable to desilylation under workup conditions. The TES derivative (10a), on the other hand, did not suffer from this problem and the analogous pyridinol was readily obtained and converted directly into the triflate (11a). The corresponding picolinamide (11b) was obtained by taking advantage of the previously established anionic ortho-Fries rearrangement. Thus LDA metalation of 10b at -78°C and slow warming to room temperature afforded the migration product (12) which was converted into the triflate (11b).

Treatment of 11a with an excess of furan in the presence of TBAF in acetonitrile at ice bath temperatures led to the cycloaddition product (13a) in modest yield (54%). Under CsF conditions in the presence of 18-crown-6, the cycloaddition of 11a with 1,3-diphenylisobenzofuran to give adduct (14a) proceeded in a similar yield (58%). In contrast to these reactions with electron-rich dienes, the analogous transformation of 11a with tetracyclone, an electron-deficient diene, led to the isoquinoline (15) in low yield (26%). Parallel observations were made in the reactions with the picolinamide 3,4-pyridyne precursor (11b) to give adducts (13b) (44%) and (14b) (17%) in yields which are lower presumably owing to steric effects from the carboxamide substituent.
Nucleophilic reactivity of 11a and 11b was probed with phenol and thiophenol. While phenol was ineffective in these reactions (<15% yields of products), thiophenol afforded good yields of substituted products (16a-b) and (17a-b). In consonance with previous observations, a 1:1 mixture of 16a (42%) and 17a (42%) was obtained from the reaction of 11a with thiophenol. Also as expected, the analogous picolinamide (11b) underwent regioselective addition to give 16b in 55% yield. The isomer (17b) was not detected (<2%).

In summary, silylpyridyl triflates (11a-b), prepared by taking advantage of 3-pyridyl carbamate directed ortho metalation chemistry, have been shown to serve as useful precursors for 3,4-pyridynes (6a-b) under neutral fluoride-induced conditions from which result synthetically useful yields of cycloaddition (13a-b, 14a-b, 15) and nucleophilic addition (16a-b, 17a-b) products. The use of 4-trialkylsilyl-3-pyridyl triflates for 3,4-pyridyne generation has advantage over 4-trimethylsilyl-3-bromopyridine in that using the latter intermediate a) yields of cycloaddition products (e.g. 13a) are lower and b) its synthesis is complicated by elimination and halogen dance reactions. Furthermore, the connection to aromatic metalation chemistry for the generation of a variety of other substituted 3,4-pyridyne precursors may be feasible by the described methodology.

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REFERENCES AND NOTES

16. 2-Deprotonation of 10b has been also achieved, a result which allows a general protocol for the synthesis of 2-substituted 3-pyridinols via 4-silyl protection: M. Tsukazaki and V. Snieckus, in preparation.
19. All new compounds show analytical and spectral (ir, nmr, ms, hrms) data in agreement with the assigned structures.

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