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

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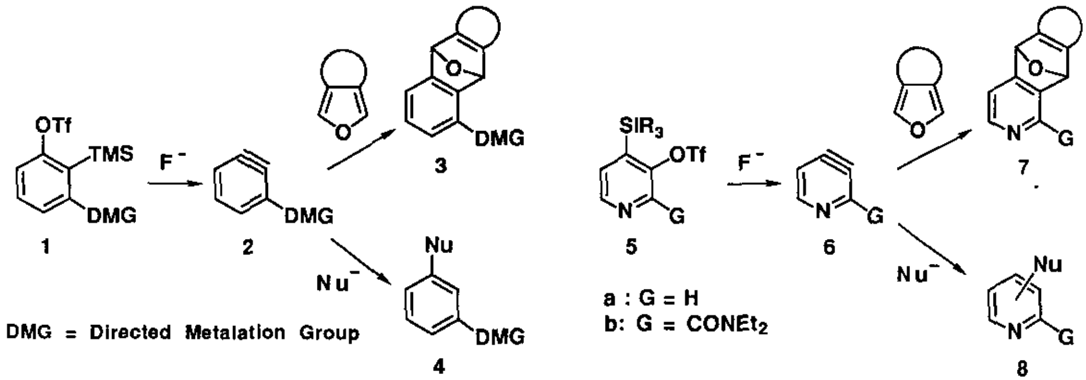
Abstract– 4-Trialkylsilyl-3-pyridyl triflates (**11a-b**), derived from **9** and **12** by directed ortho metalation chemistry, serve as useful precursors of 3,4-pyridynes (**6a-b**) and lead by cycloaddition and nucleophilic trapping reactions to products (**13a-b, 14a-b, 15, 16a-b**, and **17a-b**).

In the field of heteraryne chemistry,[1] the 3,4-pyridyne species has attracted considerable theoretical[2] and synthetic[3] interest. The classical methods of 3,4-pyridyne generation *via* thermolysis of diazonium carboxylate[4] and oxidative degradation of aminotriazole[5] have been supplemented by new procedures based on the original observations of halopyridine metal-halogen exchange and directed ortho metalation by Kauffmann,[6] Gribble,[3a] and Quéguiner.[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 coworkers[8] on the fluoride-induced generation of benzynes from *o*-silylaryl triflates[9] triggered our work[10] on the generation of substituted benzynes (**2**), derived from precursors (**1**) *via* directed ortho metalation strategies,[11] and their cycloaddition (**3**) and nucleophilic (**4**) reactivities (**Scheme** 1).

Scheme 1



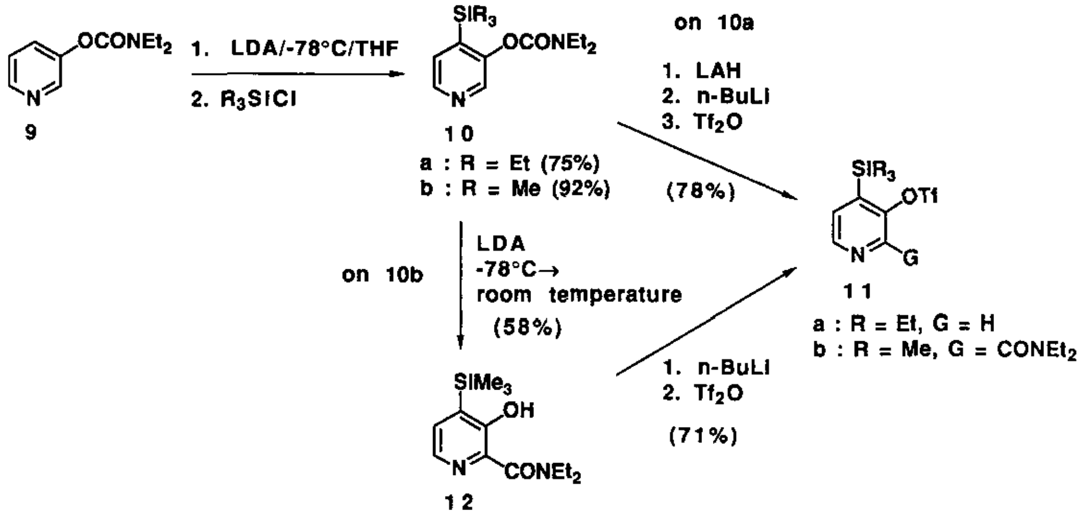
This paper is dedicated to Professor Emeritus Masatomo Hamana, a heterocyclic chemist *par excellence*, in celebration of his 75th birthday.

果州寿仁

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.[12]

Adopting the earlier general methodology for the synthesis of substituted pyridines *via* the powerful carbamate directed metalation group,[13] 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,[14] carbamate hydrolysis of **10a-b** under basic conditions[15] 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.[13] Thus LDA metalation of **10b** at -78°C and slow warming to room temperature afforded the migration product (**12**)[16] which was converted into the triflate (**11b**).

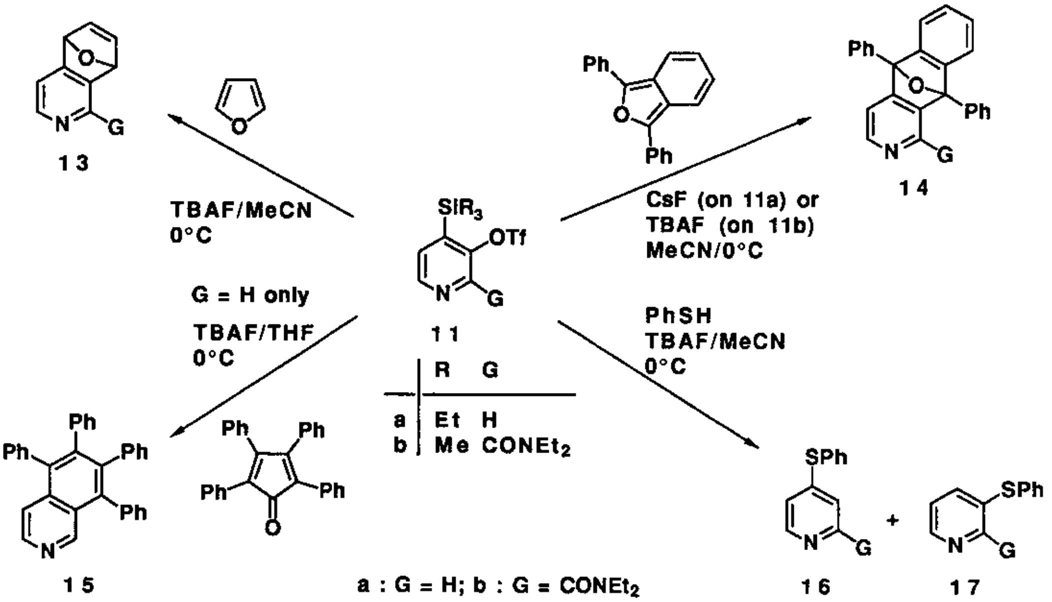
Scheme 2



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,[6,17] a 1:1 mixture of **16a** (42%) and **17a** (42%) was obtained from the reaction of **11a** with thiophenol. Also as expected,[18] the analogous picolinamide (**11b**) underwent regioselective addition to give **16b** in 55% yield. The isomer (**17b**) was not detected (<2%).

Scheme 3



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[12] 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.[19]

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