APPLICATION OF ALLENYLSILANES IN A REGIOCONTROLLED [3+2] ANNULATION ROUTE TO SUBSTITUTED ISOXAZOLES[1]

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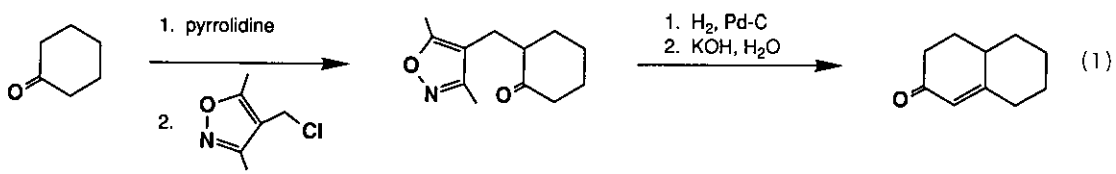
Abstract - Allenylsilanes react with nitrosonium tetrafluoroborate in acetonitrile at -30°C to provide 4-trialkylsilylisoxazole derivatives, which undergo in situ protodesilylation upon addition of water and heating to 70°C.

In recent years, isoxazoles have emerged as one of the most important classes of heteroaromatic compounds. A number of interesting isoxazoles occur in nature, and synthetic derivatives have found extensive application in medicine and in agriculture.[2,3] Equally significant is the role of isoxazoles as reagents and intermediates in a variety of ingenious synthetic methods, notable examples of which include the Woodward peptide-coupling reaction,[4] the Büchi enone transposition,[5] Stevens' approach to the synthesis of vitamin B_{12},[6] and the *Stork isoxazole annelation* (eq 1).[7] Isoxazoles can be prepared using a number of different approaches;[2,3] however, few of these



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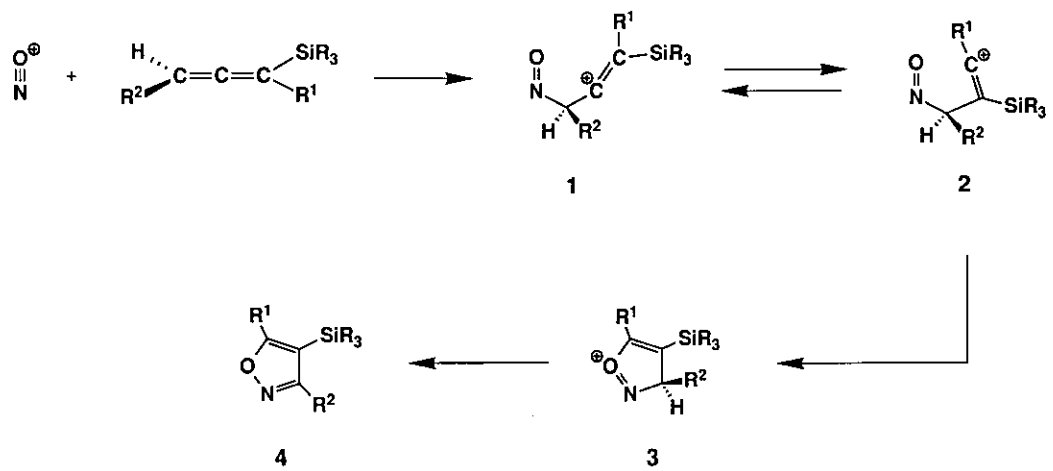
methods have proved to be general, and the synthesis of unsymmetrical 3,5-disubstituted (and 3,4,5-trisubstituted) derivatives remains a particularly vexing problem.[8] In this Communication we report a new, regiocontrolled [3+2] annulation route to isoxazoles which should be applicable to the preparation of a variety of highly substituted derivatives difficult to prepare employing previous methodology.

The reaction of allenylsilanes with electron-deficient olefins and acetylenes provides a powerful method for the synthesis of five-membered carbocyclic compounds.[9] Recently we have shown that aldehydes and N-acyl imine derivatives can participate as "heteroallenophiles" in a related [3+2] annulation route to five-membered *dihydroaromatic* heterocycles.[10] In principle it should be possible to extend this annulation strategy to the synthesis of *heteroaromatic* systems as well,

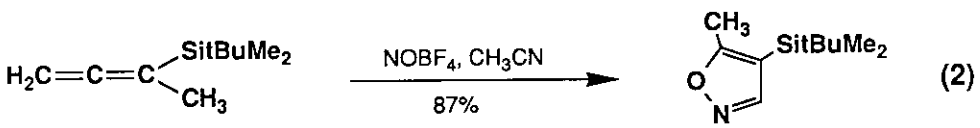
simply by employing various electrophilic species of the general form $X{\equiv}Y^+$, where X=RC or N and Y=O, S, or NR. Here we disclose the successful implementation of this strategy in a new route to substituted isoxazoles (Scheme 1). Thus, electrophilic addition of the heteroallenophile $N{\equiv}O^+$

Scheme 1



(as nitrosonium tetrafluoroborate)[11,12] at C-3 of an allenylsilane produces a vinyl cation (1) stabilized by hyperconjugative interaction with the adjacent carbon-silicon σ bond. A 1,2-trialkylsilyl shift then occurs affording an isomeric vinyl cation (2), which is intercepted by the nucleophilic nitroso group oxygen to generate 3. Deprotonation furnishes the aromatic isoxazole.

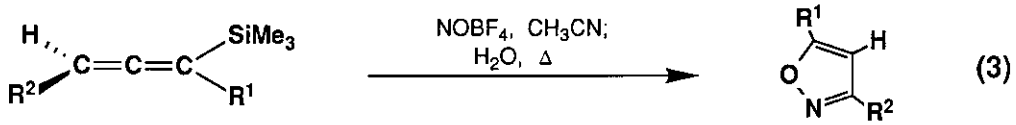
In a typical reaction the allenylsilane 5[13] was added in one portion to a suspension of 1.0 equiv of $NOBF_4$ in acetonitrile at -30°C. The resulting colorless solution was stirred at this temperature for 30 min and then poured into a mixture of ether and saturated aqueous sodium bicarbonate solution. Ether extraction followed by evaporative distillation provided the expected isoxazole 6[14,15] in 87% yield.



5 6 (2)

The synthesis of 4-silylisoxazoles is best achieved as described above using *(t-butyldimethylsilyl)allenes*. In contrast, the reactions of *(trimethylsilyl)allenes* with $NOBF_4$ produce the desired isoxazoles accompanied by 15-50% of the corresponding *desilylated* derivatives. The

(trimethylsilyl)allenes do find use, however, in a variant of our [3+2] annulation procedure that leads in one simple operation to 5-substituted and 3,5-disubstituted isoxazoles lacking the 4-silyl substituent (eq 3). Reaction of the allenylsilanes 7a-c[16] with $NOBF_4$ in acetonitrile (-30°C, 30 min), addition of ca. 10 equiv of water (after warming to room temperature), and



(3)

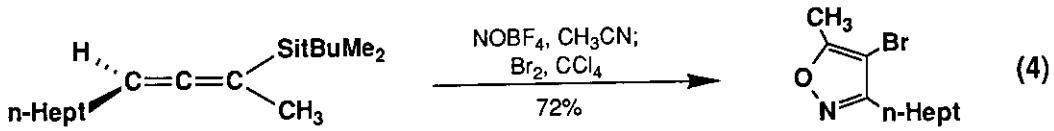
7a (R^1 = c-C_6H_{11}, R^2 = H)
7b (R^1 = c-C_6H_{11}, R^2 = CH_3)
7c (R^1 = CH_3, R^2 = CH_2CH_3)

8a[19] (66%)
8b[20] (63%)
8c[21] (59%)

further reaction at 65-70°C for 10-44 h (to complete desilylation) thus furnished the substituted isoxazoles 8a-c in 59-66% overall yield.[18]

In these annulations $NOBF_4$ is distinctly superior to other nitrosating agents such as NOCl and $NOHSO_4$. It should also be noted that the use of acetonitrile as solvent appears to be crucial to the success of the reaction. For example, in chloroform the allenylsilane 5 reacted with $NOBF_4$ to produce the desired isoxazole in only 33% yield as one component of a complex mixture of products.

As in earlier versions of our [3+2] strategy,[9,10] the new annulation method does not proceed efficiently when applied to allenylsilanes lacking substituents at C-1, and consequently the reaction can only be employed for the synthesis of isoxazoles substituted at the C-5 position of the heterocyclic ring. Nonetheless, this new annulation strategy should constitute a valuable addition to the methodology for the preparation of highly substituted isoxazoles, particularly unsymmetrical,disubstituted derivatives. Moreover, it should be noted that the trialkylsilyl substituent in annulation products such as 6 has the capacity to facilitate electrophilic substitution reactions at C-4 of the isoxazole ring. For example, sequential treatment (in one flask) of the allenylsilane 9[22] with $NOBF_4$ (CH_3CN, -30 → 25°C) and then bromine (25°C, 24 h) provided the bromoisoxazole 10 in 72% yield after chromatographic purification.



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9 **10**

Further studies are underway in our laboratory to extend this general [3+2] annulation strategy to the synthesis of other classes of heteroaromatic compounds.

ACKNOWLEDGMENTS

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14. IR (film) 2970, 2925, 2880, 2850, 1580, 1468, 1365, 1305, 1255, 1220, 1145, 945, 890, 840, 825, and 815 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 2.45 (s, 3 H), 0.87 (s, 9 H),

and 0.23 (s, 6 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 173.2, 154.6, 105.1, 26.1, 17.3, 13.1, and -5.6; MS, m/z 197 (M^+), 142, 141, 140, 111, 97, 86, 84, 75, 66, 59, 49, 43; HRMS, m/z calcd for $C_{10}H_{19}NOSi$ 197.1236, found 197.1234.

15. For previous studies of 4-trialkylsilylisoxazoles, see (a) R. Nesi, A. Ricci, M. Taddei, P. Tedeschi, and G. Seconi, J. Organomet. Chem., 1980, 195, 275; (b) L. Birkofer and R. Stilke, Chem. Ber., 1974, 107, 3717.

16. Allene 7a was prepared via the reaction of cyclohexylmagnesium chloride with the mesylate derivative of 3-trimethylsilyl-2-propyn-1-ol according to the procedure of Vermeer.[17] Sequential treatment of 7a with 1.1 equiv of n-BuLi (-78 → 0°C) and then 2.3 equiv of CH_3I (0 → 25°C) in THF provided the allenylsilane 7b [bp 74-76°C (1.5 mmHg)] in 54% yield. Allene 7c was prepared by the Vermeer method as described previously.[9b]

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18. Isolated yields of products purified by distillation or chromatography (93-97% purity as determined by GLC analysis). IR, ^1H NMR, ^{13}C NMR, and mass spectral data were fully consistent with the assigned structures. High-resolution mass spectra were obtained for all new compounds.

19. Bp 74-77°C (1.5 mmHg).

20. Mp 34-35°C (uncorrected).

21. For a previous synthesis of this compound, see H. Feuer and S. Markofsky, J. Org. Chem., 1964, 29, 935.

22. This allenylsilane [bp 90°C (0.4 mmHg)] was prepared in 89% yield by sequential treatment of 5 with 1.05 equiv of t-BuLi (-78°C, 0.5 h) and then 1.05 equiv of n-heptyl bromide (-78 → 25°C) in THF.

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