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

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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. 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, the Büchi enone transposition, Stevens' approach to the synthesis of vitamin B₁₂, and the Stork isoxazole annulation (eq 1). Isoxazoles can be prepared using a number of different approaches; however, few of these 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. 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. 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. 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 $X=Y^+$, 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 $N=O^+$

Scheme 1

(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 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 in 87% yield.

The synthesis of 4-silylisoxazoles is best achieved as described above using (t-butyldimethylsilylethynyl)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 with NOBF₄ in acetonitrile (-30°C, 30 min), addition of ca. 10 equiv of water (after warming to room temperature), and 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 NOBF₄ is distinctly superior to other nitrosating agents such as NOCl and NOHSO₄. 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 NOBF₄ 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 annihilation 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 thetrialkylsilyl substituent in annihilation 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 with NOBF₄ (CH₃CN, -30 → 25°C) and then bromine (25°C, 24 h) provided the bromoisoxazole 10 in 72% yield after chromatographic purification.
Further studies are underway in our laboratory to extend this general [3+2] annulation strategy to the synthesis of other classes of heteroaromatic compounds.

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REFERENCES AND NOTES

1. Dedicated to Professor Gilbert Stork on the occasion of his sixty-fifth birthday.
2. For examples, see pp. 127-130 of ref. 3, and (a) N.K. Kochetkov and S.D. Sokolov, Adv. Heterocycl. Chem., 1963, 2, 365; (b) B.J. Wakefield and D.J. Wright, Ibid., 1979, 25, 147.
11. Commercially available (e.g. Aldrich Chemical Co.).
13. For the preparation of this allene, see ref. 10.
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, CDCl₃) 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 calcld for C$_{10}$H$_{19}$NOSi 197.1236, found 197.1234.


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$_3$I (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


18. Isolated yields of products purified by distillation or chromatography (93-97% purity as determined by GLC analysis). IR, $^1$H 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).


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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