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Synthesis of silylated β-enaminones and applications to the synthesis of silyl heterocycles

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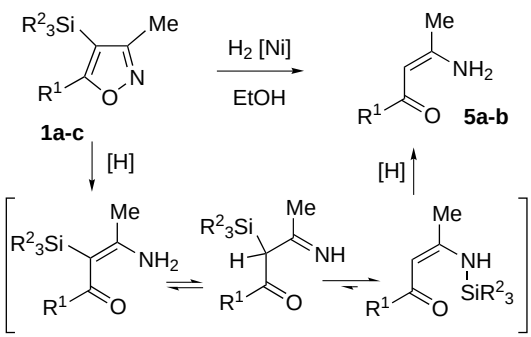
Abstract—Silyl β-enaminones have been synthesized by reductive cleavage of silylisoxazoles. These versatile synthons bearing the silyl group in different positions of the enamino ketonic system are of great interest in the construction of a variety of penta- and hexaheterocycles, which, in general, retain the silyl group attached at the ring or in a side chain. © 2001 Elsevier Science Ltd. All rights reserved.

β-Enaminoketones are versatile synthetic intermediates and have a large number of synthetic applications in organic chemistry.[1] They have, therefore, been the subject of attention by our research group, which has prepared differently substituted β-enaminoketones by catalytic hydrogenation of isoxazoles and studied their application in the synthesis of several heterocycles.[2] Likewise, reagents and methods based on organosilicon chemistry are an area of increasing interest in organic synthesis.[3] In connection with our current study concerning the preparation and synthetic utility of the organosilanes,[4] we decided to synthesize β-enaminones containing silyl groups in different positions of the enaminoketonic system[5] with the aim of creating through them a variety of penta- and hexaheterocyclic compounds bearing versatile silicon functionality.

In this communication we describe the synthesis of silylated β-enaminoketones by catalytic hydrogenation of 4- and 5-silylisoxazoles, as well as those resulting from the reductive cleavage of their 4- and 5-homologues. Furthermore, we have used these synthons as substrates in the synthesis of silylated pyrroles, pyrazoles, pyrimidines and pyridinones.

The starting 4-trimethylsilylisoxazoles **1a**,**b** were prepared by reaction of the corresponding lithio derivative with trimethylchlorosilane[6] and the 4-dimethylphenylsilyl isoxazole **1c** by coupling of the appropriate 4-iodo isoxazole with lithium dimethylphenylsilylcuprate.[4e] The 5-silylisoxazole **2** was obtained from the corresponding silylated acetylenic ketone by reaction with hydroxylamine,[7] the 4-silylmethylisoxazole **3** from the respective 4-chloromethylisoxazole by reaction with BuLi and trimethylchlorosilane and the 5-silylmethylisoxazoles **4a**–**d** by hydrogen–lithium exchange and quenching with the suitable chlorosilane.[6]

Although the Si–C bonds are stable toward catalytic hydrogenation, when the 4-silylisoxazoles **1a**–**c** reacted with hydrogen in EtOH and in the presence of Raney nickel,[8] the desilylated β-enaminoenones **5a** and **5b** were obtained. The reaction course was followed by NMR spectroscopy and HPLC chromatography and at no time was the desilylated isoxazole detected. This probably indicates that the initial C-silylated β-enaminone undergoes silyl rearrangement to nitrogen,[9] followed by the facile cleavage of the N–Si bond (Scheme 1).



Scheme 1. (a) $R^1 = Me$, $R^2{}_3 = Me_3$; (b) $R^1 = Ph$, $R^2{}_3 = Me_3$; (c): $R^1 = Me$, $R^2{}_3 = Me_2Ph$.

Keywords: silicon 2-aminopyrimidines; silicon β-enaminones; silicon pyrazoles; silicon 2-pyridones; silicon pyrroles.

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On the other hand, the catalytic hydrogenation of the 5-silylisoxazole **2** afforded the stable acylsilane derivative **6**, able to react regioselectively with hydrazines giving silylated pyrazoles.[10] When phenylhydrazine or semicarbazide was used as a nucleophile, we obtained the corresponding 5-silylpyrazoles **7a** and **7b**, while the reaction with methylhydrazine led to 3-silylpyrazole **8**. This latter result is very interesting because, as far as we know, general procedures for synthesizing *N*-alkyl-3-silylpyrazoles have not been previously described. Moreover, we have prepared 4-formylpyrrole **9** from **6** by the modified Knorr synthesis using Weinreb α-aminoamides (Scheme 2).[11]

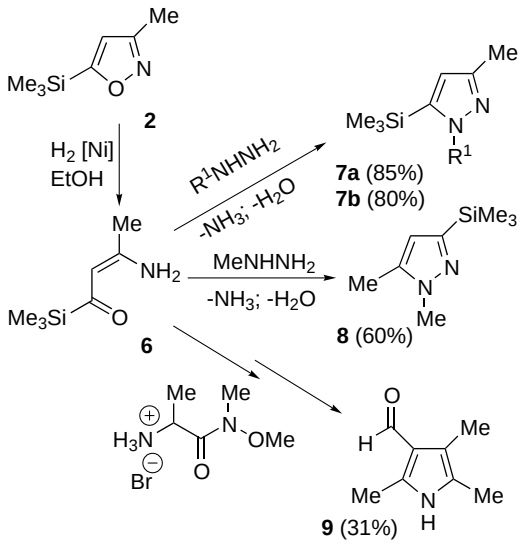
4-Formylpyrrole **9** was presumably formed by [1,4]-Brook rearrangement in the intermediate β-oxido acylsilane **10** resulting from cyclization, with concomitant elimination of R_3SiOH (Scheme 3).

This is a noteworthy result because 4-formylpyrroles are impossible to prepare by this method in the absence of the silicon group, since the necessary β-aminoacrolein undergoes 1,2-addition in its reaction with Weinreb α-aminoamides.

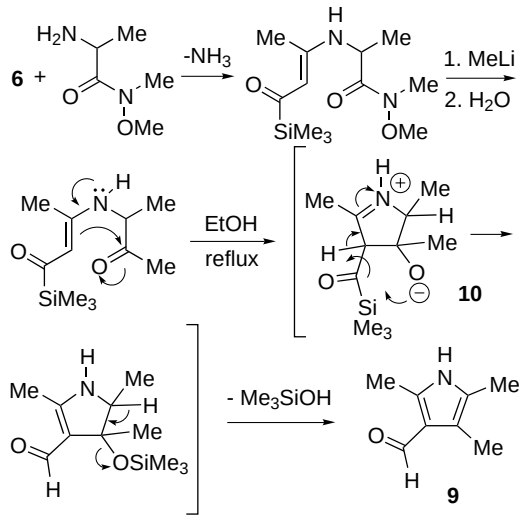
The silylated β-aminoenone **11**, obtained by reductive cleavage of 4-silylmethylisoxazole **3**, is very stable despite containing an allylsilane moiety and it was shown to be reactive toward semicarbazide and malononitrile,[10] giving the 4-silylmethylpyrazole **12** and the 5-silylmethyl-2-pyridone **13**, respectively (Scheme 4).

Conversely, the stability of the silyl β-aminoenones **14a–d** resulting from catalytic hydrogenolysis of 5-silylmethylisoxazoles **4a–d** depends on the nature of the silyl group. When this is trimethyl, the α′-silyl-β-enaminoketone **14a** is unstable in the acidic reaction medium. In its treatment with nucleophiles (hydrazine hydrochloride derivatives, cyanamide and malononitrile) desilylated heterocycles were obtained. Nevertheless, β-enaminones bearing silyl groups of minor nucleofugacity such as dimethylphenyl, diphenylmethyl and *tert*-butyldiphenyl furnished pyrazoles[10] **15e–g**, pyrimidine **16**, 2-pyridone **17**, and pyrrole[11] **18**, which retain the silyl group (Scheme 5).

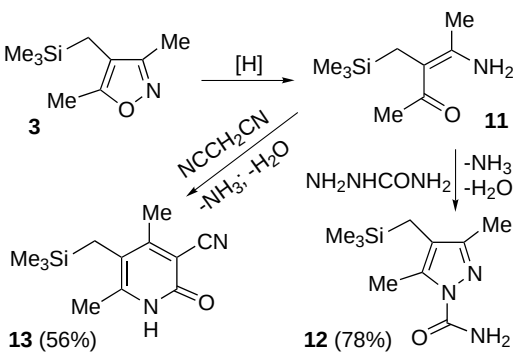
In conclusion, we have easily prepared β-enamino acylsilanes, α-silylmethyl β-enaminones and α′-silyl β-enaminones by reductive cleavage of 5-silyl-, 4-silylmethyl- and 5-silylmethylisoxazoles, respectively. Moreover, we have demonstrated that they are interesting synthons in the creation of pyrroles, pyrazoles, pyrimidines and pyridinones bearing arylsilane, arylmethylsilane and α-silyl ketone moieties. The known electrophilic *ipso*-substitution in heteroarylsilanes[4e,12] may permit the introduction through the silyl group of a variety of carbon or heteroatomic groups. Likewise, arylmethylsilanes[13] are synthetic equivalents of silicon-stabilized carbanions with wide synthetic possibilities. On the other hand, the synthetic utility of the α-silyl ketone moiety is particularly noteworthy since it is susceptible to nucleophilic attack at three sites. Halogen and oxygen nucleophiles[14] attack at the silicon atom generating, in mild conditions, enolate ions for aldol reactions. Nitrogen bases like LDA usually attack the α-hydrogen atom to give silicon-substituted enolates, which can be alkylated and used in Peterson reactions.[15] Carbon nucleophiles and hydrides usually



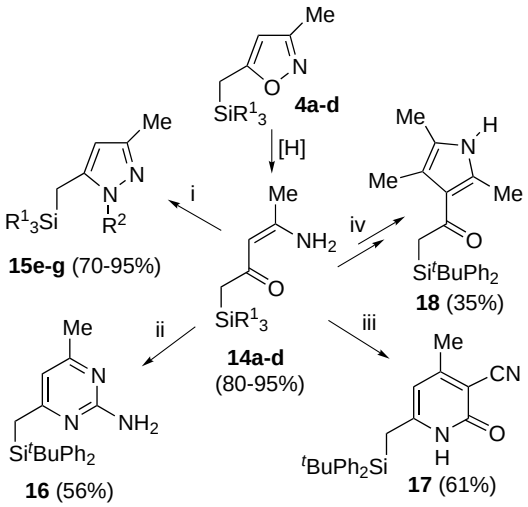
Scheme 2. (a) $R^1 = Ph$; (b) $R^1 = CONH_2$.



Scheme 3.



Scheme 4.



Scheme 5. i = R^2NHNH_2; ii = NH_2CN; iii = $NCCH_2CN$; iv = 1. *N*-methoxy-*N*-methylalaninamide, 2. MeLi, 3. EtOH, Δ.

attack at the carbonyl group affording β-hydroxysilanes,[16] precursors of stereospecific *Z*- or *E*-olefins. Furthermore, α-silyl ketones are also susceptible to thermal isomerization[17] to the versatile silyl enol ethers. Finally, dimethylphenylsilyl derivatives have an additional advantage since this group can be converted into a hydroxyl group.[18]

The synthetic possibilities of these silylated units will also be applied to the starting silyl β-enaminones and we will use the combined versatility of β-enaminones and silicon compounds in our future research.

Acknowledgements

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8. Hydrogenolysis of silylated isoxazoles. General procedure: A mixture of silylated isoxazol (20 mmol) and 1.0 g of Raney nickel in 10 mL of dry ethanol was stirred under 400 psi of hydrogen at rt for 24 h. Then, the catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The concentrate was chromatographed on silica gel using CH_2Cl_2/Et_2O (20:1) as eluent. The β-aminoenones **6**, **11** and **14a–d** were thus prepared (80–95%). *3-Amino-1-trimethylsilylbut-2-en-1-one* (**6**). Yield 91%. Mp 84°C (from hexane). IR (KBr) 3255, 3097, 1618, 1522, 1385, 1269, 1246, 867, 840, 752, 679 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.90 (s, 3H), 5.46 (s, 1H), 5.62 (br, 1H), 10.76 (br, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 2.95, 22.00, 102.19, 159.78, 225.08. Anal. calcd for $C_7H_{15}NOSi$: C, 53.45; H, 9.61; N, 8.91. Found: C, 53.38; H, 9.73; N, 9.00. *4-Amino-3-(trimethylsilylmethyl)pent-3-en-2-one* (**11**). Yield 89%. Mp 58°C (from hexane). IR (KBr) 3338, 2953, 1602, 1480, 1247, 851, 838 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H), 1.63 (s, 2H), 1.90 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ −0.67, 17.20, 22.24, 28.77, 101.80, 156.96, 197.13. Anal. calcd for $C_9H_{19}NOSi$: C, 58.32; H, 10.33; N, 7.56. Found: C, 58.56; H, 10.31; N, 7.40. *4-Amino-1-(methyl-diphenylsilyl)pent-3-en-2-one* (**14c**) Yield 90%. Mp 76°C (from hexane). IR (KBr) 3303, 3134, 1606, 1530, 1288, 1126, 1062, 777, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.69 (s, 3H), 1.75 (s, 3H), 2.54 (s, 2H), 4.76 (s, 1H), 4.93 (br, 1H), 7.26–7.61 (m, 10H), 9.56 (br, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ −4.04, 22.05, 34.29, 96.65, 127.68, 129.25, 134.49, 136.28, 159.51, 196.72. Anal. calcd for $C_{18}H_{21}NOSi$: C, 73.17; H, 7.16; N, 4.77. Found: C, 72.95; H, 7.22; N, 4.91.

9. An analogous tautomerism has previously been observed in the conversion of C-silyl Δ^1-pyrazolines to Δ^2-pyrazolines by 1,3 silyl migration: Bassindale, A. R.; Brook, A. G. *Can. J. Chem.* **1974**, *52*, 3474.
10. General procedure for the preparation of silylated pyrazoles, 2-aminopyrimidines and 2-1*H*-pyridones. A mixture of silylated β-aminoenone (2 mmol) and hydrazine hydrochloride derivative, cyanamide or malononitrile (3 mmol) was refluxed in 8 mL of dry ethanol. At the end of the reaction (monitored by TLC) the solvent was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2/H_2O. The organic layer was dried and concentrated. The residue was recrystallized from hexane/toluene (for pyridones) or chromatographed on silica gel using as eluent CH_2Cl_2/Et_2O (20:1–10:1) for pyrazoles or CH_2Cl_2/Et_2O (1:1) for 2-aminopyrimidines. The compounds **7a**,**b**, **8**, **12**, **13**, **15e**–**g**, **16** and **17** were thus prepared. *3-Methyl-1-phenyl-5-trimethylsilylpyrazole* (**7a**). Yield 85%. Bp 175–180°C/1.5 mmHg. IR (film) 1600, 1501, 1252, 844, 762, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 9H), 2.34 (s, 3H), 6.33 (s, 1H), 7.33–7.41 (m, 5H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ –0.62, 12.84, 115.65, 125.74, 127.83, 128.53, 142.28, 144.26, 148.74. Anal. calcd for $C_{13}H_{18}N_2Si$: C, 67.77; H, 7.88; N, 12.16. Found: C, 67.45; H, 8.00; N, 12.21. *1,5-Dimethyl-3-trimethylsilylpyrazole* (**8**). Yield 60%, bp 95–98°C/0.5 mmHg, IR (film) 1247, 842, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 9H), 2.25 (s, 3H), 3.80 (s, 3H), 6.13 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 1.13, 10.86, 35.90, 111.60, 138.16, 151.36. Anal. calcd for $C_8H_{16}N_2Si$: C, 57.09; H, 9.58; N, 16.64. Found: C, 58.21; H, 9.60; N, 16.41. *3,5-Dimethyl-4-(trimethylsilylmethyl)pyrazole-1-carboxamide* (**12**). Yield 78%. Mp 103–104°C (from hexane). IR (KBr) 3431, 3332, 1731, 1700, 1400, 863, 575 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 9H), 1.69 (s, 2H), 2.12 (s, 3H), 2.42 (s, 3H), 5.33 (br, 1H), 7.07 (br, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ –1.32, 12.30, 12.47, 12.86, 118.60, 137.38, 149.69, 152.65. Anal. calcd for $C_{10}H_{19}N_3OSi$: C, 53.29; H, 8.50; N, 18.65. Found: C, 53.57; H, 8.49; N, 18.40. *3-Cyano-4,6-dimethyl-5-(trimethylsilylmethyl)-2-pyridone* (**13**). Yield 56%. Mp 276–278°C (from hexane/toluene). IR (KBr) 2218, 1658, 858, 845 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 0.01 (s, 9H), 1.90 (s, 2H), 2.20 (s, 3H), 2.28 (s, 3H), 10.80 (br, 1H). ^{13}C NMR (75.4 MHz, DMSO-d_6) δ –0.64, 16.33, 18.13, 20.08, 100.18, 115.31, 116.76, 146.57, 158.45, 159.53. Anal. calcd for $C_{12}H_{18}N_2OSi$: C, 61.50; H, 7.74; N, 11.95. Found: C, 61.76; H, 7.65; N, 11.75. *1-Ethyl-3-methyl-5-((methyldiphenylsilyl)methyl)pyrazole* (**15f**). Yield 93%. Bp 200–205°C/1 mmHg. IR (film) 1540, 1427, 1113, 808, 733, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (s, 3H), 1.22 (t, $J=7.2$ Hz, 3H), 2.20 (s, 3H), 2.52 (s, 2H), 3.71 (q, $J=7.2$ Hz, 2H), 5.56 (s, 1H), 7.36–7.52 (m, 10H, Ar). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ –4.48, 13.27, 13.50, 15.29, 42.90, 104.06, 127.92, 129.60, 134.39, 135.48, 138.71, 147.00. Anal. calcd for $C_{20}H_{24}N_2Si$: C, 74.95; H, 7.55; N, 8.74. Found: C, 75.24; H, 7.50; N, 8.53. *5-(tert-Butyldiphenylsilyl)methyl)-3-methylpyrazole-1-carboxamide*. (**15g**) Yield 72%. Mp 108–110°C (from hexane). IR (KBr) 3401, 3236, 1698, 1395, 700, 488 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 9H), 2.04 (s, 3H), 3.36 (s, 2H), 5.21 (br, 1H), 5.50 (s, 1H), 6.81 (br, 1H), 7.30–7.55 (m, 10H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.07, 13.51, 18.43, 27.58, 109.03, 127.34, 129.13, 133.73, 136.04, 145.37, 150.09, 152.74. Anal. calcd for $C_{22}H_{27}N_3OSi$: C, 69.99; H, 7.21; N, 11.13. Found: C, 70.21; H, 7.32; N, 10.89. *2-Amino-4-((tert-butyldiphenylsilyl)methyl)-6-methylpyrimidine*. (**16**). Yield 56%. Mp 82–83°C (from hexane). IR (KBr) 2218, 1658, 858, 845 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 9H), 1.99 (s, 3H), 2.70 (s, 2H), 4.78 (br, 2H), 5.69 (s, 1H), 7.27–7.61 (m, 10H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.69, 23.48, 24.32, 27.74, 110.80, 127.39, 129.27, 133.61, 136.29, 162.26, 166.09, 169.94. Anal. calcd for $C_{22}H_{27}N_3Si$: C, 73.08; H, 7.53; N, 11.62. Found: C, 73.21; H, 7.40; N, 11.58. *6-((tert-Butyldiphenylsilyl)methyl)-3-cyano-4-methyl-2-pyridone* (**17**). Yield 61%. Mp 235°C (from hexane/toluene). IR (KBr) 2218, 1643, 1605, 701 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 1.02 (s, 9H), 1.98 (s, 3H), 2.80 (s, 2H), 5.36 (s, 1H), 7.37–7.52 (m, 10H), 12.03 (s, 1H). Anal. calcd for $C_{24}H_{26}N_2OSi$: C, 74.57; H, 6.78; N, 7.25. Found: C, 74.78; H, 6.69; N, 7.13.
11. The experimental procedure is the same as that described in Refs. 2b,c, except that the cyclization to pyrrol was carried out at reflux in ethanol. *3-(2-(tert-Butyldiphenylsilyl)acetyl)-2,4,5-trimethylpyrrole* (**18**). Yield 35% oil, $R_f=0.34$ (CH_2Cl_2/Et_2O, 20:1). IR (film) 3291, 1619, 1426, 1108, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 9H), 1.94 (s, 3H), 1.98 (s, 3H), 2.08 (s, 3H), 3.06 (s, 2H), 7.23–7.65 (m, 10H), 7.40 (br, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 10.36, 11.54, 14.13, 18.69, 27.73, 30.46, 114.14, 121.66, 123.24, 127.12, 128.92, 131.06, 133 96, 136.11, 197.31.
12. See for example: (a) Birkofer, L.; Stuhl, O. *Top. Curr. Chem.* **1980**, *88*, 62; (b) Pinkerton, F. H.; Thames, S. F. *J. Heterocycl. Chem.* **1972**, *9*, 67; (c) Pratt, M. J. R.; Pinkerton, F. H.; Thames, S. F. *J. Organomet. Chem.* **1972**, *38*, 29; (d) Fiorentino, M.; Testaferri, L.; Tiecco, M.; Troisi, L. *J. Chem. Soc., Chem. Commun.* **1977**, 317.
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