Polonovski-type Reaction Induced by *O*-Silylated Ketene Acetals

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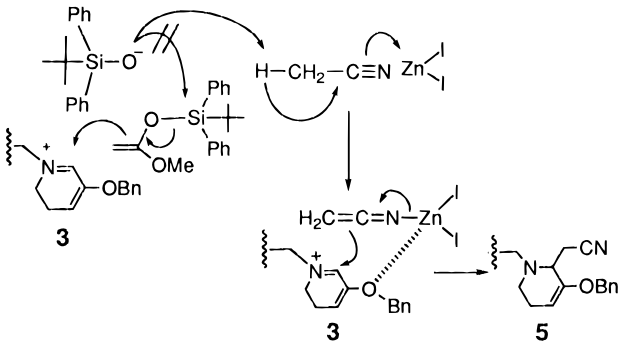
In 1927, Max and Michael Polonovski reported that the treatment of a tertiary amine *N*-oxide with acetic anhydride results in a rearrangement in which one of the alkyl groups attached to nitrogen is cleaved, and the *N*-acetyl derivative of the corresponding secondary amine and aldehyde are obtained.[1] This reaction has been widely used in alkaloid chemistry to create a carbon−carbon bond on the α-carbon to the nitrogen through an iminium ion intermediate.[2] On the other hand, it is known that the Polonovski-type reaction is induced by a silicon-activator (TBDMSOTf) and nucleophiles, but it is necessary to use a strong base such as alkyllithium.[3]

We have reported that *O*-silylketene acetal (SKA)[4] is an excellent reagent for the silicon-induced Pummerer-type rearrangement of various sulfoxides which under nearly neutral conditions gives high yields of α-siloxy sulfides.[5] A similar silicon-induced Polonovski-type reaction with tertiary amine *N*-oxides using the SKA treatment would provide a useful method for carbon−carbon bond formation to the α-carbon of the nitrogen of *N*-oxides. Therefore, we first examined the silicon-induced Polonovski reaction of *N*-oxides having an *N*-protected indole (**1**)[6] using SKA. Treatment of **1** with SKA (**2a**−**c**) (5 equiv) in the presence of a catalytic amount of ZnI_2 at 60 °C in acetonitrile gave carbon−carbon bond forming compounds, the (methoxycarbonyl)methyl adduct **4** and the cyanomethyl adduct **5** (Table 1). It has become apparent that the choice of silyl moiety in SKA influences the course of the reaction. Specifically, in the case of SKA (**2a**), bearing a *tert*-butyldimethylsilyl group, **4** was preferentially converted to **5** (Table 1, entry 1), whereas in the case of SKA (**2b**), bearing a *tert*-butyldiphenylsilyl group, only the cyanomethyl compound **5** was obtained (Table 1, entry 2). On the other hand, in the case of SKA (**2c**), bearing a trimethylsilyl group, no reaction occurred (Table 1, entry 3).

The following mechanism is proposed to account for these interesting behaviors. The oxygen atom of the *N*-oxide is first silylated by SKA, and then the hydrogen atom on the α-carbon to the nitrogen is removed by the *in situ* generated ester anion. The nucleophilic addition of SKA to the iminium intermediate **3** forms the adduct

Scheme 1. Speculation of Reaction Mechanism



4 (path A). It is thought that **5** is formed by nucleophilic addition of acetonitrile activated by ZnI_2 through path B. The formation of **5** was inhibited by the use of another solvent such as propionitrile. A convenient explanation of the control of this reaction course by the difference in the silyl part is depicted in Scheme 1. Namely, we suggest that the attack of the siloxy anion on the unreacted SKA is depressed by the steric repulsion in the case of using SKA **2b** whose silyl part is bulky. Consequently the enolate anion derived from SKA as a nucleophile is not formed (Scheme 1).

As can be seen in Table 1, SKA **2b** only acts during the activation of the *N*-oxide to the iminium ion intermediate, and the nucleophilic attack by the enolate anion does not occur. Therefore, we thought that it would be feasible to introduce various nucleophilic species on the α-carbon to the nitrogen by employing this remarkable feature. Consequently, we could achieve a regioselective carbon−carbon bond formation on the α-carbon atom of the heterocyclic nitrogen in the *N*-oxide **6** in good yields by addition of only the expected nucleophile (Table 2).

Finally, we could obtain the ring closed products **9a** and **9b** by way of intramolecular carbon−carbon bond formation of the *N*-oxides (**8a** and **8b**) by employing the bulky activator **2b** in the presence of trifluoroacetic acid or toluenesulfonic acid (Table 3).[7] The participation of SKA **2b** in this reaction is apparent from the fact that **9a** and **9b** are not formed by treatment only with trifluoroacetic acid (5 equiv) at 60 °C in propionitrile.

In conclusion, it has been found that the reaction of *N*-oxides and SKA **2b** shows a regioselective carbon−carbon bond formation on the α-carbon to the nitrogen of the tertiary amine *N*-oxide. The present silicon-induced Polonovski-type reaction provides a very useful carbon−carbon bond forming method due to the mild reaction conditions and simple procedure such as only mixing the desired nucleophile and SKA **2b** in propionitrile at 60 °C.

Experimental Section

General Procedure. All reactions were carried out under a positive atmosphere of dry nitrogen. Melting points are uncorrected. ^{1}H NMR spectra were measured in $CDCl_3$ on 200, 250, and 500 MHz spectrometers with $SiMe_4$ as the internal standard. E. Merck silica gel 60 (70−230 mesh ASTM) for column chromatography and E. Merck precoated TLC plates

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(3) (a) Tokitoh, N.; Okazaki, R. *Tetrahedron Lett.* **1984**, *25*, 4677. (b) Tokitoh, N.; Okazaki, R. *Chem. Lett.* **1985**, 241. (c) Tokitoh, N.; Okazaki, R. *Chem. Lett.* **1984**, 937. (d) Okazaki, R.; Tokitoh, N. *J. Chem. Soc., Chem. Commun.* **1984**, 192. (e) Tokitoh, N.; Okazaki, R. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3291.

(4) Kita, Y.; Yasuda, H.; Sugiyama, Y.; Fukata, F.; Haruta, J.; Tamura, Y. *Tetrahedron Lett.* **1983**, *24*, 1273.

(5) A review see: Kita, Y.; Shibata, N. *Synlett* **1996**, 289.

(6) (a) Lounasmaa, M.; Karvinen, E. *Tetrahedron* **1991**, *47*, 6371. (b) Lounasmaa, M.; Karvinen, E.; Koskinen, A.; Jokela, R. *Tetrahedron* **1987**, *43*, 2135.

(7) Results from a ^{1}H NMR study suggested that silylation on the nitrogen atom in the indole ring will occur with **5a** and **5b**. Therefore, the ring closure reactions successfully proceeded by the addition of acids that are not adequately nucleophilic (TFA or TsOH) to cleave the N-Si bond.

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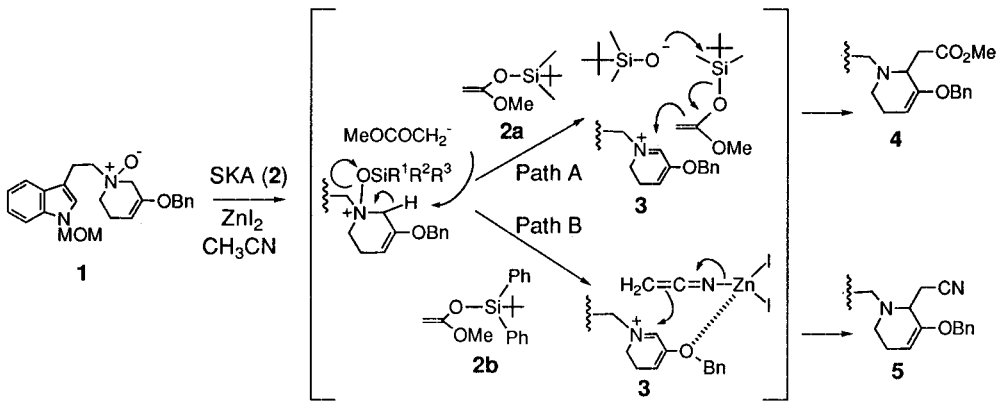
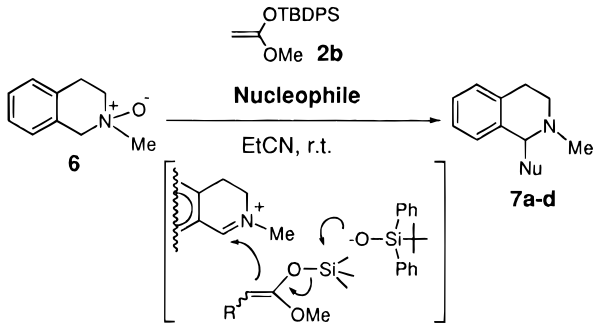
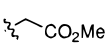
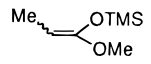
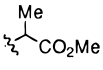
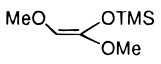
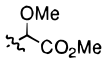
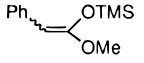
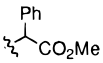
Table 1. Polonovski Reaction Induced by SKA 2



Entry	SKA*	$SiR^1R^2R^3$	Yield of **4** (%)	Yield of **5** (%)
1	**2a**		66	7
2	**2b**		0	54
3	**2c**	$SiMe_3$	No Reaction	

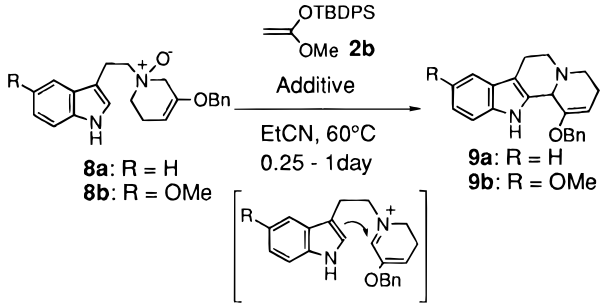
Table 2. Regioselective C−C Bond Formation on a Carbon Atom of the Nitrogen Heterocycle



nucleophile	Nu	yield(%) of **7**
		**7a:** 66
		**7b:** 71[a]
		**7c:** 68[a]
		**7d:** 72[a]

[a] A mixture of diastereomeric isomers.

Table 3. Intramolecular Nucleophilic Cyclization Induced by SKA 2b



R	additive	yield (%) of **9**
H	TFA	12
OMe	TFA or TsOH	32-34

with silica gel F254 for preparative TLC (PLC) were used. The known *N*-oxide **6**[3] and **8a**[6] were prepared by the reported methods.

***tert*-Butyl[(1-methoxyvinyl)oxy]diphenylsilane(2b).** This is prepared essentially following the published method:[4] pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.92 (s, 9 H), 2.94 (d, 1 H, J = 3.3 Hz), 3.05 (d, 1 H, J = 3.3 Hz), 3.26 (s, 3 H), 7.23−7.30 (m, 6 H), 7.55−7.60 (m, 4 H). MS *m*/*z* (%): 282 (M^+, 2), 195 (100). HRMS calcd for $C_{19}H_{24}O_2Si$ 312.1546; found 312.1561.

***N*-Oxide 1 and *N*-Oxide 8b.** These were prepared essentially following a published method.[6]

3-[2-[5-(Benzyloxy)-3,6-dihydro-2*H*-pyridinio]ethyl]-1-(methoxymethyl)-1*H*-indole *N*′-oxide (1): yellow oil. ^{1}H NMR ($CDCl_3$) δ: 2.38 (m, 1 H), 2.75 (m, 1 H), 3.22 (s, 3 H), 3.30−3.61 (m, 6 H), 3.94 (s, 2 H), 4.79 (dd, 2 H, J = 11.5 Hz), 4.92 (bs, 1 H), 5.40 (s, 2 H), 7.07 (s, 1 H), 7.13−7.62 (m, 9 H). MS *m*/*z* (%): 282 (M^+, 2), 195 (100). HRMS calcd for $C_{24}H_{28}N_2O_3$ 392.2100; found 392.2098.

3-[2-(5-(Benzyloxy)-3,6-dihydro-2*H*-pyridinio]ethyl]-5-methoxy-1*H*-indole *N*′-oxide (8b): yellow oil. ^{1}H NMR ($CDCl_3$) δ: 2.23 (m, 1 H), 2.68 (m, 1 H), 3.25−3.61 (m, 6 H), 3.78 (s, 3 H), 3.86 (s, 2 H), 4.69 (dd, 2 H, J = 11.5 Hz), 4.86 (bs, 1 H), 6.79 (dd, 1 H, J = 8.9, 2.5 Hz), 6.98 (s, 1 H), 7.13−7.62 (m, 7 H), 9.75 (bs, 1 H). MS *m*/*z* (%): 282 (M^+, 2), 195 (100). HRMS calcd for $C_{23}H_{26}N_2O_3$ 378.1943; found 378.1963.

(Methoxycarbonyl)methyl Adduct 4 and Cyanomethyl Adduct 5. A mixture of *N*-oxide **1** (196 mg, 0.5 mmol), SKA **2b** (470 mg, 2.5 mmol), and zinc iodide (15.9 mg, 10 mol %) in dry acetonitrile (7.3 mL) was stirred for 2 h at 60 °C. After concentration of the reaction mixture under reduced pressure, the residue was purified by flash column chromatography (AcOEt/hexane, 1:1) to give the (methoxycarbonyl)methyl adduct **4** (148 mg, 66%) and cyanomethyl adduct **5** (14.3 mg, 7%).

{3-(Benzyloxy)-1-[2-[1-(methoxymethyl)-1*H*-indol-3-yl]-ethyl]-1,2,5,6-tetrahydropyridin-2-yl}acetic acid methyl ester (4): pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.95 (m, 1 H), 2.35 (m, 1 H), 2.66−2.80 (m, 4 H), 2.85−2.99 (m, 4 H), 3.23 (s, 3 H), 3.56 (s, 3 H), 3.74 (bs, 1 H), 4.68 (d, 1H, J = 6.5 Hz), 4.75 (d, 1H, J = 6.5 Hz), 4.82 (bs, 1H), 5.40 (s, 2 H), 7.02 (s, 1 H), 7.14−7.61 (m, 8 H). IR (KBr) cm^{-1}: 1738. MS *m*/*z* (%): 448 (M^+, 13), 91 (100). HRMS calcd for $C_{27}H_{32}N_2O_4$ 448.2359; found 448.2357.

{**3-(Benzyloxy)-1-[2-[1-(methoxymethyl)-1*H*-indol-3-yl]-ethyl]-1,2,5,6-tetrahydropyridin-2-yl**}**acetonitrile (5):** pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 2.14 (m, 1 H), 2.34 (m, 1 H), 2.68 (m, 2 H), 2.71−3.08 (m, 6 H), 3.26 (s, 3 H, J = 2.5 Hz), 3.39 (t, 1 H), 4.78 (s, 2 H), 4.99 (bs, 1 H), 5.41 (s, 2 H), 7.15−7.62 (m, 10 H). MS m/z (%): 415 (M^+, 23), 91 (100). HRMS calcd for $C_{26}H_{29}N_3O_2$ 415.2257; found 415.2251.

C−C Bond Formed Products 7a−d. General procedure: A mixture of *N*-oxide **6** (16.3 mg, 0.100 mmol), SKA **2b** (96.3 mg, 0.308 mmol), and *O*-methyl-*O*-(trimethylsilyl)ketene acetal (58.9 mg, 0.403 mmol) in propionitrile (2 mL) was stirred for 2 h at 60 °C. After concentration of the reaction mixture under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt, 1:1) to give the C−C bond formed products **7a** (14.4 mg, 66%). The physical data for **7a**−**d** are summarized below.

(2-Methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid methyl ester (7a): pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 2.48 (s, 3 H), 2.61 (dd, 1 H, J = 15.6, 5.3 Hz), 2.84 (dd, 1 H, J = 15.6, 7.9 Hz), 2.59−3.19 (m, 4 H), 3.71 (s, 3 H), 4.15 (dd, 1 H, J = 7.9, 5.3 Hz), 7.05−7.17 (m, 4 H). IR (KBr) cm^{-1}: 1736. MS m/z (%): 282 (M^+, 2), 195 (100). HRMS calcd for $C_{13}H_{17}NO_2$ 219.1259; found 219.1264. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. found: C, 71.61; H, 7.85; N, 6.11.

2-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propionic acid methyl ester (7b) (as a mixture of diastereomeric isomers of 53:47): pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.03 (d, 3 H 53/100, J = 7.0 Hz), 1.17 (d, 3 H 47/100, J = 7.0 Hz), 2.41 (s, 3 H 47/100), 2.43 (s, 3 H 53/100), 2.63−2.84 (m, 4 H), 3.13−3.31 (m, 1 H), 3.60 (s, 3 H 47/100), 3.74 (s, 3 H 53/100), 3.78 (d, 1 H 53/100, J = 8.1 Hz), 3.87 (d, 1 H 47/100, J = 6.6 Hz), 6.95−7.17 (m, 4 H). IR (KBr) cm^{-1}: 1736. HRMS(FAB$^+$) calcd for $C_{14}H_{20}NO_2$ 234.1494; found 234.1490. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. found: C, 72.15; H, 8.32; N, 5.85.

Methoxy(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid methyl ester (7c) (as a mixture of diastereomeric isomers of 69:31): pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3 H 69/100), 2.45 (s, 3 H 31/100), 2.61−2.74 (m, 2 H), 2.83−2.92 (m, 1 H), 3.15−3.18 (m, 1 H), 3.28 (s, 3 H 31/100), 3.32 (s, 3 H 69/100), 3.63 (s, 3 H 31/100), 3.77 (s, 3 H 69/100), 3.81 (d, 1H 69/100, J = 5.5 Hz), 3.93 (d, 1H 69/100, J = 5.5 Hz), 3.99 (d, 1H 31/100, J = 4.0 Hz), 4.06 (d, 1H 31/100, J = 4.0 Hz), 7.09−7.24 (m, 4 H). IR (KBr) cm^{-1}: 1751. FABMS m/z (%): 250 ($M^+ + 1$, 92), 146 (100). HRMS(FAB$^+$) calcd for $C_{14}H_{20}NO_3$ 250.1443; found 250.1439.

(2-Methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenylacetic acid methyl ester (7d) (as a mixture of diastereomeric isomers of 73:27): white crystals. Mp 136−140 °C. ^{1}H NMR ($CDCl_3$) δ: 2.28 (s, 3 H 27/100), 2.46 (s, 3 H 73/100), 2.56 (bdd, 2 H 73/100, J = 16.5, 5.5 Hz), 2.60−2.63 (m, 1 H 27/100), 2.81−2.90 (m, 1H), 2.96 (ddd, 1 H 27/100, J = 16.5, 11.0, 6.1 Hz), 3.13 (ddd, 1 H 27/100, J = 12.8, 9.2, 5.0 Hz), 3.49 (ddd, 1H 73/100, J = 13.4, 11.0, 5.0 Hz), 3.83 (d, 1 H 73/100, J = 11.0 Hz), 3.89 (d, 1 H 27/100, J = 9.8 Hz), 4.12 (d, 1 H 73/100, J = 11.0 Hz), 4.31 (d, 1 H 27/100, J = 9.8 Hz), 5.96 (d, 1 H 73/100, J = 7.9 Hz), 6.64 (bt, 1 H 73/100, J = 7.0 Hz), 6.98−7.40 (m, 7 H). IR (KBr) cm^{-1}: 1736. HRMS(FAB$^+$) calcd for $C_{19}H_{22}NO_2$ 296.1650; found 296.1632. Anal. Calcd for $C_{19}H_{21}NO_2$: C,77.26; H, 7.17; N, 4.74. found: C, 77.15; H, 7.14; N, 4.66.

1-(Benzyloxy)-3,4,6,7,12b-hexahydroindolo[2,3-*a*]quinolizine (9a). A mixture of *N*-oxide **8a** (38.5 mg, 0.11 mmol), SKA **2b** (175 mg, 0.56 mmol), and trifluoroacetic acid (3 μL: 35 mol % against **8a**) in propionitrile (4 mL) was stirred for 19 h at 60 °C. After concentration of the reaction mixture under reduced pressure, the residue was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1) to give the ring closure product **9a** (4.4 mg, 12%): dark orange oil. ^{1}H NMR ($CDCl_3$) δ: 2.18 (m, 1 H), 2.34 (m, 1 H), 2.63 (m, 1 H), 2.74 (m, 1 H), 2.90 (m, 1 H), 3.01 (m, 1 H), 3.16 (m, 1 H), 3.30 (m, 1 H), 4.65 (s, 1 H), 4.88 (s, 2 H), 4.94 (bs, 1 H), 7.03−7.47 (m, 9 H), 8.42 (bs, 1 H).

1-(Benzyloxy)-9-methoxy-3,4,6,7,12b-hexahydroindolo-[2,3-*a*]quinolizine (9b). A mixture of *N*-oxide **8b** (5.0 mg, 0.013 mmol), SKA **2b** (20 mg, 0.064 mmol), and trifluoroacetic acid (1 μL: ca. 1 equiv against **8b**) in propionitrile (1 mL) was stirred for 12 h at 60 °C. After concentration of the reaction mixture under reduced pressure, the residue was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1) to give the ring closure product **9b** (1.6 mg, 34%): dark orange oil. ^{1}H NMR ($CDCl_3$) δ: 2.19 (m, 1 H), 2.34 (m, 1 H), 2.60 (m, 1 H), 2.75 (m, 1 H), 2.92−2.98 (m, 2 H), 3.16 (m, 1 H), 3.30 (m, 1 H), 3.84 (s, 3 H), 4.64 (bs, 1 H), 4.87 (s, 2 H), 4.96 (bs, 1 H), 6.76 (dd, 1 H, J = 8.8, 2.5 Hz), 6.93 (d, 1 H, J = 2.5 Hz), 7.07 (d, 1 H, J = 8.8 Hz), 7.23−7.41 (m, 5 H), 8.31 (bs, 1 H). MS m/z (%): 360 (M^+, 31.2), 79 (100). HRMS calcd for $C_{23}H_{24}N_2O_2$ 360.1836; found 360.1834.

Supporting Information Available: ^{1}H NMR spectra of **2b**, **4**, **5**, **7a**, and **9a**; HRMS spectra of **2b**, **4**, **5**, and **7a**; IR spectra of **4** and **7a**. (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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